Coronavirus occurrence and transmission over 8 years in the HIVE cohort of households in Michigan

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ABSTRACT

BACKGROUND

As part of the Household Influenza Vaccine Evaluation (HIVE) study, acute respiratory
infections (ARI) have been identified in children and adults over 8 years.

METHODS

Annually, 890 to 1441 individuals were followed and contacted weekly to report ARIs.
Specimens collected during illness were tested for human coronaviruses (HCoV) types
OC43, 229E, HKU1, and NL63.

RESULTS

In total, 993 HCoV infections were identified over 8 years, with OC43 most commonly
seen and 229E the least. HCoVs were detected in a limited time period, between
December and April/May, and peaked in January/February. Highest infection frequency
was in children <5 years (18 per 100 person-years), with little variation in older age
groups (range: 7 to 11 per 100 person-years). Overall, 9% of adult cases and 20% of
cases in children were associated with medical consultation. Of the 993 infections, 260
were acquired from an infected household contact. The serial interval between index
and household-acquired cases ranged from 3.2 to 3.6 days and the secondary infection
risk ranged from 7.2% to 12.6% by type.

21 CONCLUSIONS

22 Coronaviruses are sharply seasonal. They appear, based on serial interval and

23 secondary infection risk, to have similar transmission potential to influenza A(H3N2) in

24 the same population.

25   Coronaviruses, long known to infect a wide variety of species, have been recognized as

26   human respiratory pathogens for more than 60 years.[1–3] While animal coronaviruses

27   have been associated with severe disease in their respective hosts, human

28   coronaviruses (HCoV) were historically detected in mild respiratory illnesses.[4–6]

29   Therefore, the identification of Severe Acute Respiratory Syndrome (SARS) as caused

30   by a coronavirus of animal origin in 2002 was a surprise because of its epidemic

31   behavior as well as its severity.[7,8] Also a surprise was ultimate interruption of SARS

32   transmission by public health measures.[9] In 2012, another novel coronavirus of animal

33   origin emerged as the causative agent of Middle East Respiratory Syndrome (MERS).[10]

34   Unlike SARS, human-to-human transmission of MERS has been limited and sporadic

35   cases have continued to occur primarily in Saudi Arabia among those with contact with

36   camels.[11] The current outbreak of a novel coronavirus (SARS-CoV-2) has focused

37   attention back to this often forgotten and unstudied group of pathogens.[12]

38   HCoVs were first recognized when specimens from individuals ill with respiratory

39   illnesses were inoculated into organ cultures. One of these viruses is now known as OC

40   (organ culture) 43.[13] Another virus, 229E was first grown in primary human kidney

41   culture.[14] Because of the difficulties in isolating them, much of the initial work in

42   understanding their occurrence in was done by serology.[15,16] Following renewed interest

43   after the SARS epidemic, two additional coronaviruses, HKU1 and NL63, were identified

44   in the 2000's, first from persons with severe respiratory illnesses.[17–20]

45   Availability of reverse-transcriptase polymerase chain reaction (RT-PCR) has now made

46   it possible to detect infection easily for each of the 4 known human coronaviruses.

47   However, as data from population-based studies using molecular methods have

48 accumulated, minimal attention has been paid to these viruses, perhaps because there

49 was so little known about their role in respiratory illnesses. The Household Influenza

50 Vaccine Evaluation (HIVE) study is a longitudinal investigation of respiratory illnesses in

51 households with children in the Ann Arbor, Michigan area that has been ongoing since

52 2010. Here we report on the occurrence of the 4 HCoV types over an 8 year period.

53 **METHODS**

54 *Study Population*

55 The complete methods of the HIVE cohort have been published previously.[21]

56 Households were recruited from local households receiving primary care from the

57 University of Michigan Health Care System. From 2010-2011 through 2015-2016,

58 eligible households were those with 4 or more members at least 2 of whom were less

59 than 18 years old. In subsequent years, eligible households contained 3 or more

60 members including at least one child under 5 years (2016-2017) or under 10 years

61 (2017-2018). Each year in the spring or summer, households attended an enrollment or

62 re-engagement visit to collect or update the demographic characteristics for each

63 participant and household. Adult household members provided informed consent for

64 themselves and their children, and children 7 years or older also provided verbal assent

65 prior to participating. This study was reviewed and approved by the institutional review

66 board at the University of Michigan Medical School.

67 *Acute Respiratory Illness Surveillance*

68 HIVE participants were instructed to report the onset of two or more acute respiratory

69 illness (ARI) symptoms from anyone in the household, including: cough, fever or

70 feverishness, nasal congestion, chills, headache, body aches, or sore throat. Weekly

71 email and phone contacts were used to confirm the presence or absence of ARI in the

72 household. Beginning in 2014-2015 a separate set of age-specific symptom qualifiers

73 were provided for participants under 3 years of age, including: cough,

74 fever/feverishness, nasal congestion, trouble breathing, fussiness, decreased appetite,

75 and fatigue. Ill participants with 2 or more of the above symptoms attended an illness

76 visit within 7 days of illness onset where study staff interviewed them about their illness

77 and collected nasal and throat swabs (nasal only in children <3 years) combined in a

78 single vial of viral transport media. Study staff followed up with ill participants

79 approximately a week after their illness visit to collect additional information about the

80 course of the illness including participant report of whether they contacted a healthcare

81 provider regarding their illness.

82 Prior to the 2014-15 season, HIVE ARI surveillance periods were seasonal based on

83 the likely influenza season. For the first 4 study years, the annual surveillance periods

84 were October 1, 2010 through April 30, 2011; December 1, 2011 through May 10, 2012;

85 October 1, 2012 through May 13, 2013; and October 1, 2013 through April 30, 2014.

86 Surveillance resumed on October 1, 2014 and has been operating year-round since

87 then. New surveillance years are designated beginning July 1 and lasting until June 30

88 of the subsequent year.

89 *Laboratory Testing*

90 Respiratory specimens collected at illness visits were tested for detection of respiratory

91 viruses, including the four seasonal coronavirus types (229E, OC43, HKU1, and NL63).

92 For specimens collected prior to the 2016-2017 study year, testing was performed by

93 singleplex RT-PCR using primers and probes developed by the CDC Division of Viral

94 Diseases, Gastroenteritis, and Respiratory Viruses.[22] Specimens collected in the 2016-

95 2017 and 2017-2018 years were tested using the FTD Respiratory Pathogen 33

96 multiplex PCR kit (Fast Track Diagnostics, Luxembourg).

97 *Statistical Analysis*

98 Seasonal case counts of HCoV 229E, HKU1, NL63, and OC43 were used to assess

99 annual patterning of each type; counts were also summed by month across all seasons

100 combined to assess broad seasonality by type. Illnesses with multiple, coincident HCoV

101 detections were only counted once in analyses of overall HCoV infections, but each

102 HCoV type involved in coincident detection was also included in type-specific analyses.

103 Type-specific coronavirus incidence and corresponding 95% confidence intervals were

104 calculated by age group (<5, 6-11, 12-17, 18-49, and ≥50 years) and by study year.

105 Incidence was calculated as the number of type-specific coronavirus infections divided

106 by the total participant-time included during a specified time period. Because the

107 majority of the HCoV season was captured even in study years without year-round

108 surveillance, all participants were treated as contributing a full year of person time for

109 each study year in which they were enrolled.

110 For each study year, we defined household index cases as the first person in a

111 household to develop ARI with HCoV detection. Secondary cases were defined as

112 those who developed ARI with HCoV detection within 14 days following illness in a

113 household contact with the same type. The serial interval was calculated as the average

114   number of days from the illness onset a household index case to the illness onset of

115   secondary cases. Secondary infection risks were calculated as the proportion of

116   household contacts exposed to an index case who developed secondary infection. For

117   the purpose of these transmission analyses, only the first introduction of HCoV to a

118   household were considered.

119   We used latent class analysis to identify and compare classes of illness severity of

120   HCoV infection across age groups and the four HCoV types (Supplementary Materials).

121   For the latent items, we identified seven participant-reported potential markers of illness

122   severity including illness symptoms (cough, fever, fatigue, wheezing, and dyspnea),

123   missed work or school, and medically-attended illness (phone consultation, outpatient

124   care, and inpatient care). A priori, we anticipated three latent classes of severity to

125   represent mild, moderate, and severe illness; model diagnostics also confirmed that a

126   three-class model was most parsimonious. Latent class groups were then assigned to

127   each HCoV infection, not including cases with multiple coincident HCoV types detected.

128   Age-adjusted multinomial logistic regression models were then used to compare the

129   odds of being assigned to each latent class between the four HCoV types.

130   **RESULTS**

131   *Characteristics of the study population*

132   The number of individuals under study ranged from 895 to 1441, and the number of

133   households ranged from 209 to 340 over the 8 years (Table 1). Because of the

134   requirement that children be present in the household, the studied population tended to

135   be young, with relative absence of older adults. The numbers in the cohort varied from

136 year to year but the age structure remained similar in all years, due to combined

137 retention of existing households and recruitment of new households with young

138 children.

139 The number of ARIs reported also varied from year to year, mainly related to the

140 number of individuals on report but also the differential occurrence of influenza and

141 other respiratory viruses (Table 1). Overall, from 2010-11 through 2017-18, 7992 ARI

142 cases were reported to HIVE; 7469 had an illness visit with specimen collection and

143 were tested for respiratory virus detection (93%). The proportion of ARIs associated

144 with coronavirus identification varied between 8.3% during the major influenza year

145 2014-2015 to 16.3% in 2012-2013. Co-detection of multiple coronavirus types ranged

146 from 0.7% of all coronavirus ARIs in 2010-2011 to 14.2% in 2014-2015.

147 *Variation in identifying the four coronaviruses by seasons and years.*

148 There was distinct seasonality in the identifications of the viruses. In the first 5 of the 8

149 years, no surveillance was conducted from June to September. When year-round

150 surveillance was in place in the 2015-2016 through 2017-2018 study years, only 9

151 (2.5%) of the total 364 coronavirus-associated ARI occurred from June through

152 September. Combined over the 8 years, the number of identifications for each virus

153 increased in December, peaked in January or February, and began to decrease in

154 March (Figure 1). The seasonal similarity between the 4 types is striking, with only the

155 peak aggregate month differing between January and February.

156 Identification of each of the four coronaviruses types occurred in each of the 8 study

157 years, except for 2016-17, when no HKU1 viruses were identified (Table 1, Figure 2). In

158   prior community studies[16,23–25], there were suggestions of a cycling between 229E and

159   OC43, with major years followed by lesser years. Such a pattern appears to be present

160   for all types where relatively high incidence is not seen in consecutive years for a

161   specific type. Likewise, combinations of co-circulating types were not found to be

162   consistent from year to year.

163   *Occurrence of infections by age and illness characteristics*

164   Infection rates for common respiratory pathogens are highest in young children and

165   usually fall off with increasing age. With the exception of 229E, where incidence per 100

166   person-years was relatively low and did not vary by age, the incidence was consistently

167   highest among children less than 5 years (Figure 3). Among those older than 5 years,

168   incidence was relatively flat with little consistent variation with increase in age.

169   *Illness severity and outcomes*

170   Overall, 9% of adult cases and 20% of cases in children were associated with medical

171   consultation. However, medical consultation only captures one facet of overall illness

172   severity. Therefore, we used latent class analysis to categorize coronavirus case

173   severity based on participant-reported symptoms and actions taken during the course of

174   their illness (Supplemental Materials). Mild illnesses were primarily characterized by

175   cough and fatigue, those with moderate illnesses were additionally likely to have fever

176   and to miss school or work, and those with severe illness additionally were likely to have

177   wheezing, dyspnea, or to seek care for their illness. Of all single coronavirus detections,

178   59% were categorized as mild illness by latent class methods. Moderate and severe

179   illness were noted in 31% and 10% of coronavirus detections, respectively. HCoV

180 illnesses in children less than 5 years and adults older than 50 years were most likely to

181 be classified as severe. In age-adjusted multinomial regression models (Table 2), 229E

182 was associated with significantly higher odds of severe illness (versus mild) compared

183 to the three other HCoV types (OR: 1.82, 95%CI: 1.01-3.27). On the other hand, NL63

184 was associated with significantly lower odds of severe illness (versus mild) compared to

185 the other three types (OR: 0.59, 95%CI: 0.35-0.99).

186 *Household transmission*

187 Households present an ideal setting for determining the transmission characteristics of

188 respiratory viruses. Of the 993 HCoVs identified, 260 occurred within 14 days of

189 exposure to a household contact infected with the same type. The secondary attack risk

190 was 7.2% for 229E, 8.6% for HKU1, 10.6% for OC43, and 12.6% for NL63. The average

191 serial interval between the onset of illness in the household index case and onset of

192 illness in secondary cases was similar across (3.2 days for NL63 and HKU1, 3.3 days

193 for OC43, and 3.6 days for 229E). Consistent with overall patterns of incidence by age

194 (Figure 3), index cases were most frequently children with the exception of 229E where

195 adults 18 to 49 years were responsible for nearly half of the household introductions

196 (Table 3).

197 **DISCUSSION**

198 While HCoVs have been recognized for many years to be a cause of common

199 respiratory illnesses, documentation of their involvement has lagged behind that of other

200 agents, such as the rhinoviruses. This includes frequency of infection, illnesses

201 produced and transmission characteristics. We might not even know about the

202 existence of the two most recently identified viruses, NL63 and HKU1, if attention had

203 not been directed to HCoV following the occurrence of SARS. The development of the

204 RT-PCR test and the inclusion of the 4 types of HCoV in multiplex clinical testing

205 panels, mainly used in handling severe illnesses such as pneumonia, have resulted in

206 numerous reports of the involvement of these viruses in hospitalizations. While studies

207 of hospitalized patients have established the role of HCoV in causing lower respiratory

208 illness and the global circulation of these viruses, they are unable to shed light on the

209 frequency or seasonality of these viruses in the broader community. There are a few

210 exceptions which have followed HCoV infections over longer periods often in special

211 population groups. In particular, a recent study covered 9 years of Norwegian children

212 hospitalized with respiratory infection and found that coronaviruses were involved in

213 9.1% of episodes.[26] The highest frequencies were in young children, similar to the

214 infection rates demonstrated in the current study and also identical to it was the ordering

215 of frequency of types involved with OC43 the most common and 229E the least. While

216 the authors did not emphasize seasonality, it was clear that most of the infections

217 occurred in the winter months.

218 The regular appearance of all types of coronaviruses in the same months with minimal

219 circulation in the summer was a clear finding of this study. Unlike the influenza viruses

220 which peak at different times during the colder season from year to year and even the

221 rhinoviruses which are most common in the autumn and spring but are present year

222 round, the coronaviruses are sharply seasonal with little spread after May until

223 November or December. Our findings, on a larger scale, expand on the results a two

224 year study in childcare attendees suggesting a similar seasonal pattern.[27] It is of interest

225 that the SARS coronavirus outbreaks occurred during the same time period, with the

226 end of global outbreaks in the period of May-June 2003.[28] Whether such a time table

227 applies to the current circulation of SARS-CoV-2 is impossible to determine at this time.

228 Another notable finding in this community study was the fact that, in those above 4

229 years of age, HCoV infection rates were relatively consistent. Most agents causing

230 lower respiratory infections typically have falling incidence with increasing age,

231 sometimes with an increase in young adults.[29] However, it is clear that like other

232 respiratory viruses, HCoV infect people of all ages and infection only produces relative

233 immunity. The type-specificity of the protection is also not completely clear; although

234 frequent co-circulation of types and co-detection within individuals suggests that

235 protection is likely not highly cross-reactive. As with SARS and MERS, SARS-CoV-2

236 has most frequently infected adults to date.[30] Whether the relative sparing of children

237 has largely been driven by contact and exposure patterns or other factors remains

238 unclear. However, the frequency of infection in adults suggests that there is likely little

239 cross-protective immunity from prior seasonal HCoV infection.

240 The MERS coronavirus is limited in its potential for human to human transmission

241 except in the nosocomial setting.[11] Although the SARS coronavirus more effectively

242 transmitted human to human, transmission was interrupted by public health

243 interventions.[31] The seasonal HCoV viruses are clearly different in their transmission

244 characteristics given their continued seasonal circulation year after year. The serial

245 interval between cases and the secondary infection risk in the HIVE cohort was similar

246 to that previously found for A(H3N2).[32] Our secondary attack rates may reflect the

247 smaller household structure found in our region. A longitudinal study in Kenya found

248 overall attack rates as high as 34.0% over one season in a study of households of sizes

249 ranging to 37 members.[33]

250 The transition from pandemic to seasonal circulation is well established for influenza,

251 wherein, following an influenza pandemic, the novel virus becomes the new seasonal

252 virus, replacing the previous A subtype.[34] The four current HCoVs have been circulating

253 for decades, and it is unclear how they initially emerged or whether they replaced

254 previously circulating viruses.[35] Contrary to influenza, MERS and SARS, have not

255 become a fixed presence in seasonal respiratory illness circulation on a global scale.

256 Only time will tell if SARS-CoV-2 will become a continuing presence in the seasonal

257 HCoV landscape, continue with limited circulation as with MERS, or like SARS,

258 disappear from humans altogether.

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Table 1: Characteristics of the study population and counts of human coronavirus infections by study year: Household Influenza Vaccine Evaluation (HIVE) cohort 2010 – 2018.

	Season							
	2010-2011	**2011-2012**	**2012-2013**	**2013-2014**	**2014-2015**	**2015-2016**	**2016-2017**	**2017-2018**
Surveillance period	Oct 1 – Apr 30	Dec 1 – May 10	Oct 1 – May 13	Oct 1 – Apr 30	Oct 1 – Jun 30	Jul 1 – Jun 30	Jul 1 – Jun 30	Jul 1 – Jun 30
Households enrolled	328	213	321	232	340	227	209	293
Participants enrolled	1441	943	1426	1049	1431	996	895	1189
Age groups								
0-5	250 (17.4)	131 (13.9)	225 (15.8)	133 (12.7)	205 (14.3)	97 (9.7)	117 (13.1)	220 (18.5)
6-11	382 (26.5)	278 (29.5)	401 (28.1)	316 (30.1)	445 (31.1)	327 (32.8)	257 (28.7)	298 (25.1)
12-17	208 (14.4)	141 (15.0)	208 (14.6)	169 (16.1)	212 (14.8)	173 (17.4)	150 (16.8)	166 (14.0)
18-49	546 (37.9)	353 (37.4)	536 (37.6)	385 (36.7)	512 (35.8)	351 (35.2)	332 (37.1)	457 (38.4)
50+	55 (3.8)	40 (4.2)	56 (3.9)	46 (4.4)	57 (4.0)	48 (4.8)	39 (4.4)	48 (4.0)
ARI reports	1028	417	1227	706	1362	934	847	1401
HCoV positive cases, N (% of all ARI cases)								
All Types [a]	152 (14.8)	59 (14.1)	200 (16.3)	105 (14.9)	113 (8.3)	109 (11.7)	112 (13.2)	143 (10.2)
229E	7 (0.7)	20 (4.8)	8 (0.7)	45 (6.4)	8 (0.6)	3 (0.3)	46 (5.4)	12 (0.9)
HKU1	28 (2.7)	19 (4.6)	17 (1.4)	30 (4.2)	14 (1)	36 (3.9)	0 (0)	49 (3.5)
NL63	62 (6)	14 (3.4)	75 (6.1)	21 (3)	37 (2.7)	40 (4.3)	11 (1.3)	63 (4.5)
OC43	56 (5.4)	13 (3.1)	113 (9.2)	16 (2.3)	71 (5.2)	34 (3.6)	58 (6.8)	26 (1.9)

[a] Individual types sum to more than all types because coinfections were counted in each type, but only included as single cases in counts of all types.

Abbreviation: HCoV, human coronavirus.

Table 2. Odd Ratios and 95% confidence intervals from multinomial logistic regression models predicting illness severity from human coronavirus type and age group.

	Severity Group Odds Ratio (95% Confidence Interval) [a]				
HCoV Type	Mild	Moderate		Severe	
229E	ref	1.51	(1.00, 2.29)	1.82	(1.01, 3.27)
HKU1	ref	1.13	(0.77, 1.66)	1.51	(0.88, 2.59)
NL63	ref	0.88	(0.65, 1.20)	0.59	(0.35, 0.99)
OC43	ref	0.84	(0.62, 1.13)	0.87	(0.55, 1.37)
Age Group					
0 to 5 years	ref	1.46	(1.04, 2.04)	2.06	(1.27, 3.33)
6 to 11 years	ref	1.53	(1.11, 2.11)	1.02	(0.60, 1.72)
12 to 17 years	ref	0.99	(0.62, 1.61)	0.71	(0.31, 1.62)
18 to 49 years	ref	0.55	(0.40, 0.74)	0.59	(0.37, 0.94)
≥50 years	ref	0.63	(0.24, 1.61)	1.23	(0.40, 3.80)

[a] Odds ratios are relative to all other groups within category (i.e. 229E vs not, 0 to 5 vs not)

Abbreviation: HCoV, human coronavirus.

Table 3: Household index cases[a] by human coronavirus type and age group

	HCoV Type, N (column %)			
	229E	**HKU1**	**NL63**	**OC43**
Age groups				
0-5	13 (11.5)	38 (26.8)	45 (20.7)	82 (31.2)
6-11	21 (18.6)	35 (25.4)	78 (36.9)	65 (24.7)
12-17	16 (14.2)	9 (6.3)	24 (11.1)	24 (9.1)
18-49	54 (47.8)	56 (39.4)	64 (29.5)	83 (31.6)
50+	9 (8.0)	3 (2.1)	6 (2.8)	9 (3.4)

[a] Only index cases from the first introduction of each coronavirus type to a household per season are included.

Abbreviation: HCoV, human coronavirus.

Figure 1. Counts of human coronavirus (HCoV) infections over 8 study years by type and month of illness onset: Household Influenza Vaccine Evaluation Study 2010-2018.

Figure 2. Incidence per 100 person-years of human coronavirus (HCoV) infections by type over 8 study years: Household Influenza Vaccine Evaluation Study 2010-2018. Error bars represent 95% confidence intervals.

Figure 3. Incidence per 100 person-years of human coronavirus (HCoV) infections by type and age group over 8 study years: Household Influenza Vaccine Evaluation Study 2010-2018. Error bars represent 95% confidence intervals.
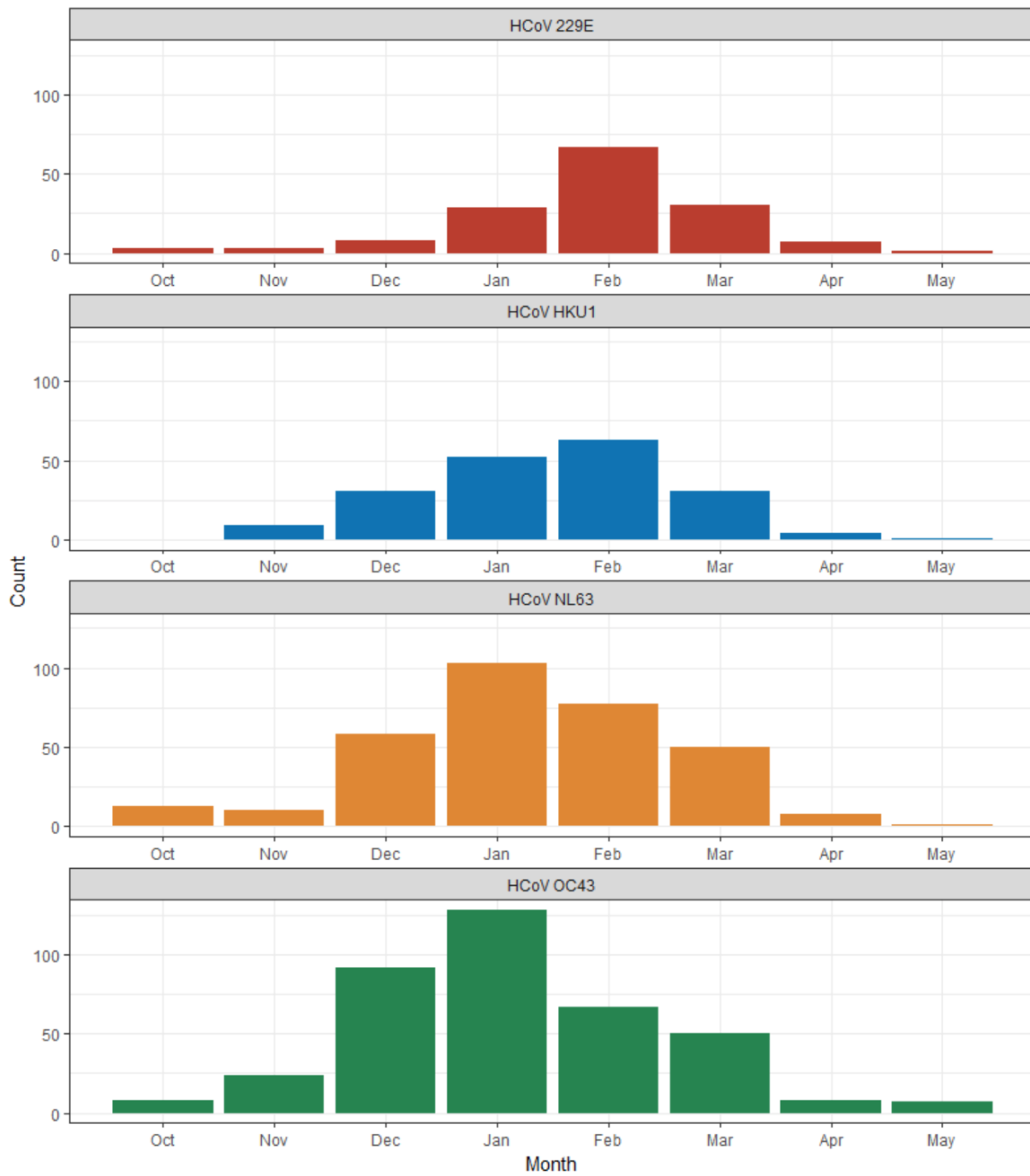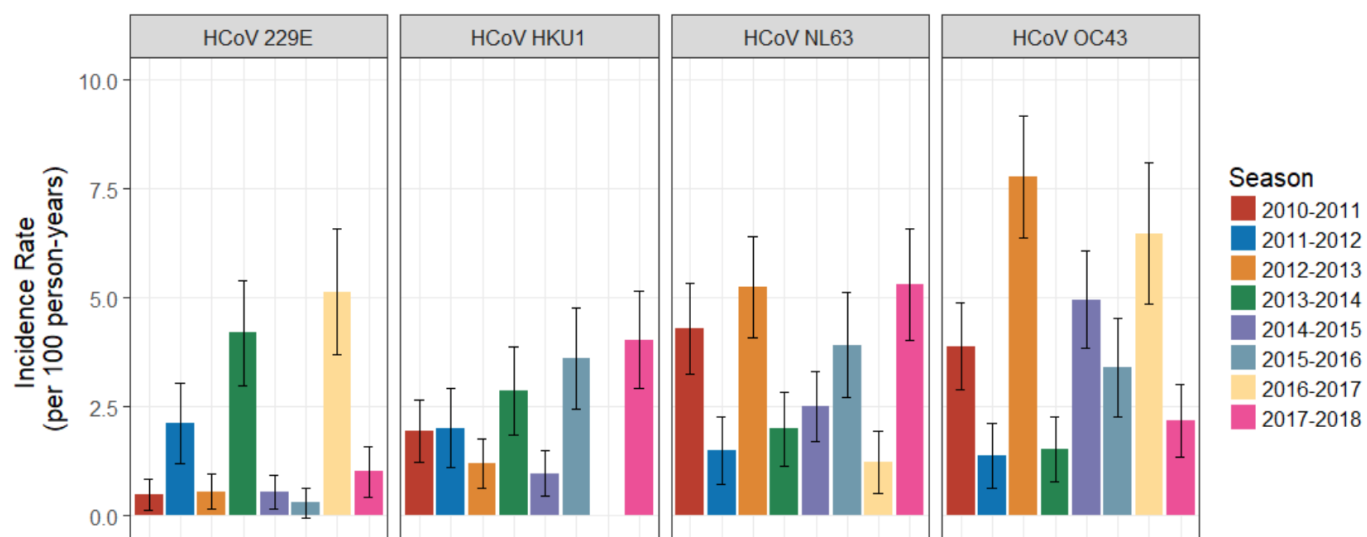
Figure 1

Figure 2

Figure 3