RESEARCH ARTICLE

REVISED Seasonality and immunity to laboratory-confirmed seasonal coronaviruses (HCoV-NL63, HCoV-OC43, and HCoV-229E): results from the Flu Watch cohort study [version 2; peer review: 2 approved]

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v2 **First published:** 30 Mar 2020, **5**:52
https://doi.org/10.12688/wellcomeopenres.15812.1
Latest published: 10 Dec 2020, **5**:52
https://doi.org/10.12688/wellcomeopenres.15812.2

Abstract

Background: There is currently a pandemic caused by the novel coronavirus SARS-CoV-2. The intensity and duration of this first and second waves in the UK may be dependent on whether SARS-CoV-2 transmits more effectively in the winter than the summer and the UK Government response is partially built upon the assumption that those infected will develop immunity to reinfection in the short term. In this paper we examine evidence for seasonality and immunity to laboratory-confirmed seasonal coronavirus (HCoV) from a prospective cohort study in England.
Methods: In this analysis of the Flu Watch cohort, we examine seasonal trends for PCR-confirmed coronavirus infections (HCoV-NL63, HCoV-OC43, and HCoV-229E) in all participants during winter seasons (2006-2007, 2007-2008, 2008-2009) and during the first wave of the 2009 H1N1 influenza pandemic (May-Sep 2009). We also included data from the pandemic and 'post-pandemic' winter seasons (2009-2010 and 2010-2011) to identify individuals with two confirmed HCoV infections and examine evidence for immunity against homologous reinfection.
Results: We tested 1,104 swabs taken during respiratory illness and detected HCoV in 199 during the first four seasons. The rate of confirmed HCoV infection across all seasons was 390 (95% CI 338-448)

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 10 Dec 2020	✓ report	✓ report
version 1 30 Mar 2020	? report	? report

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per 100,000 person-weeks; highest in the Nov-Mar 2008/9 season at 674 (95%CI 537-835) per 100,000 person-weeks. The highest rate was in February at 759 (95% CI 580-975) per 100,000 person-weeks. Data collected during May-Sep 2009 showed there was small amounts of ongoing transmission, with four cases detected during this period. Eight participants had two confirmed infections, of which none had the same strain twice.
Conclusion: Our results provide evidence that HCoV infection in England is most intense in winter, but that there is a small amount of ongoing transmission during summer periods. We found some evidence of immunity against homologous reinfection.

Keywords
HCoV-NL63, HCoV-OC43, HCoV-229E, SARS-CoV-2, public health, epidemiology, pandemic

This article is included in the Coronavirus (COVID-19) collection.

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Competing interests: ACH serves on the UK New and Emerging Respiratory Virus Threats Advisory Group. AMJ was a Governor of Wellcome Trust from 2011-18 and is Chair of the Committee for Strategic Coordination for Health of the Public Research.

Grant information: This study was supported by the Wellcome Trust through a Wellcome Clinical Research Career Development Fellowship to RA [206602] and funding to The Flu Watch Study. The Flu Watch study received funding from the Medical Research Council (MRC) and the Wellcome Trust [G0600511, G0800767 and MC_U122785833]. S.B. is supported by an MRC doctoral studentship [MR/N013867/1]. DL is funded by the National Institute for Health Research [DRF-2018-11-ST2-016]. This paper presents independent research. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Aldridge RW, Lewer D, Beale S *et al.* **Seasonality and immunity to laboratory-confirmed seasonal coronaviruses (HCoV-NL63, HCoV-OC43, and HCoV-229E): results from the Flu Watch cohort study [version 2; peer review: 2 approved]** Wellcome Open Research 2020, **5**:52 https://doi.org/10.12688/wellcomeopenres.15812.2

First published: 30 Mar 2020, **5**:52 https://doi.org/10.12688/wellcomeopenres.15812.1

REVISED **Amendments from Version 1**

We have updated the introduction to reflect the current UK context and have made edits throughout the manuscript in response to the peer review comments.

Any further responses from the reviewers can be found at the end of the article

Background

We write this paper during a pandemic caused by the novel coronavirus SARS-CoV-2. As of 30th November 2020, there were 62,363,527 confirmed cases and 1,456,687 deaths reported[1]. In the UK, 1,629,657 confirmed cases have been reported and 58,448 patients who tested positive for SARS-CoV-2 died within 28 days of a positive test[2]. The UK Government aims to reduce the spread of SARS-CoV-2 through mixture social distancing measures including asking people to stay at home and only go outside for food, health reasons or work where this absolutely cannot be done from home. In addition to social distancing measures, a national test, trace and isolate system is operational across the UK. The intensity and duration of the second wave in winter 2020/21 will be dependent on the effectiveness of these public health interventions, but will also be impacted by whether SARS-CoV-2 transmits more effectively in the winter than the summer. Mathematical models used to predict the transmission and impact of COVID-19 in the UK assume that the virus will produce an immune response that prevents reinfection in the short term[3].

Existing studies from outside the UK suggest that incidence of human coronaviruses in temperate climates is usually highest during winter, but spring and summer peaks and year-round circulation at varying levels have also been found[4–9]. There is minimal evidence regarding immunity and risk of repeat infection, but reinfection with common strains (HCoV OC43/229E) has been documented[10,11] and reinfection with SARS-CoV appears to be theoretically plausible as it has been shown that antibody titres appear to decline over time, with estimates for duration of protection up to three years[12].

Flu Watch is a cohort study measuring the community incidence and transmission of several respiratory viruses in England[13]. The study has the advantage of identifying mild cases of respiratory infection regardless of whether they lead to medical attendance and can therefore measure community incidence of infection over time and reinfection regardless of severity. We aimed to describe the community incidence and seasonal patterns of seasonal coronavirus strains, assess the frequency of reinfection with homologous and heterogeneous strains, and among participants with two confirmed HCoV infections, examine how likely we were to observe the number of homologous reinfections if participants had no immunity.

Methods

Study design and procedure

This study is based on analysis of data collected as part of the Flu Watch study, a prospective community cohort study of the transmission and burden of acute respiratory illness in UK households. The full study design and methodology has been described previously[13]. Follow-up occurred across three consecutive winter seasons (Nov-Mar 2006–2007, 2007–2008, 2008–2009), the summer and winter waves of the 2009 H1N1 influenza pandemic (May-Sep 2009, Oct-Feb 2009–2010) and 'post-pandemic' winter season (Nov-Mar 2010–2011).

Demographic data were collected at the start of each season and in this analysis we used age, sex, geographical region, quintile of Index of Multiple Deprivation 2007 (a composite measure of the socioeconomic status of small neighbourhoods)[14]. Throughout the season, participants were contacted weekly (via telephone or emailed online surveys) and asked to provide reports stating whether anyone in the household had experienced symptoms of acute respiratory illness. During all days of illness, participants were asked to report their symptoms and whether they took any time off work or study. In addition, we requested that all participants experiencing respiratory symptoms (including feeling feverish, headache, having muscle aches, cough, sore throat, runny nose, blocked nose, and sneezing) provide self-administered nasal swabs on the second day of illness. In the first season, participants received swabs via the post only when they reported illness (so swabs are likely to have arrived later than day two of illness) and swabbing began in late December 2006. In all subsequent seasons, participants received swabs at the beginning of follow up and we requested swabs for all illnesses regardless of when they occurred during follow up. Full details of sample handling and testing are provided elsewhere[13,15]. All swabs were tested for HCoV during the first four seasons, but only selected swabs were tested for HCoV in the pandemic and post-pandemic winter seasons. Table 1 summarises respiratory virus PCR testing across Flu Watch seasons.

We have published the full dataset used in this study (see underlying data).

Participants

Participants were randomly selected from participating general practice lists in England. All household members of each participant were invited. Households were recruited before each winter season. From 2008–2009, households that had previously participated were also re-invited to the study. Participants were eligible if all household members agreed to participate for the full season and adult household members (aged 16 years and older) agreed to provide blood samples for influenza-related research. Participants were not eligible if their household was larger than 6 people, if any household member suffered from terminal or severe illness or incapacity, or had heavy concurrent involvement in other research.

Outcomes

The primary outcome of interest in this study was PCR-confirmed coronavirus infection in participants. Three coronavirus strains were tested: HCoV-NL63, HCoV-OC43, and HCoV-229E.

Statistical analysis

We calculated the rate of PCR-confirmed coronavirus infection per 100,000 person-weeks. Follow-up began at the start of

Table 1. Respiratory virus PCR* testing on nasal swabs across Flu Watch seasons.

	Nov 2006 – Mar 2007	Nov 2007 – Mar 2008	Nov 2008 – Mar 2009	May 2009 – Sep 2009	Oct 2009 – Feb 2010	Nov 2010 – Mar 2011
HCoV**	✓	✓	✓	✓	partial	partial
Influenza A (H1N1)	✓	✓	✓	✓	✓	✓
Influenza A (H3N2)	✓	✓	✓	✓	✓	✓
Influenza A (H1N1pdm09)	n/a	n/a	n/a	✓	✓	✓
Influenza B	✓	✓	✓	✓	✓	✓
RSV***	✓	✓	✓	✓	✓	✓
hMPV****	✓	✓	✓	✓	✓	✓
Adenovirus	✓	✓	✓	✓	partial	partal
Parainfluenza virus	✓	✓	✓	✓	partial	partial
Rhinovirus	✓	✓	✓	✓	partial	partial

*Polymerase chain reaction **Human Coronavirus ***Respiratory syncytial virus ****Human metapneumovirus

each season and ended at the earliest of the final report of symptoms or the end of the season. We stratified rates by participants' age, sex, geographical region, quintile of Index of Multiple Deprivation 2007[14], and study season. We used a mixed poisson model to estimate rate ratios for confirmed HCoV. The dependent variable was the count of HCoV infections per season, the independent variables were participant characteristics at the start of each season plus an offset for the duration of follow-up, and the model was clustered by individual and household. For these descriptive analyses, we excluded the pandemic and post-pandemic winter seasons (2009–2010 and 2010–2011) as not all samples were tested for HCoV during these two seasons.

We used HCoV strains in participants with repeat infections to test the evidence for homologous immunity after infection. We started from a 'null' hypothesis of no immunity, and assumed that in this scenario the distribution of strains among participants with a second infection would be the same as in the entire cohort. If there is at least some immunity, we expected to see a pattern in which participants with a previous infection were less likely to have the same strain twice. For the eight participants with repeat infections, we created 100,000 simulations in which strain of the second infection (HCoV-NL63, HCoV-OC43, or HCoV-229E) was sampled with the probabilities observed in the entire cohort, and counted the number of homologous reinfections (zero to eight). We interpreted the proportion of simulations with as many or fewer homologous reinfections than in the observed data as evidence of immunity. In other words, the analysis attempts to examine the following question "is it likely that participants would have got more homologous reinfections if infection provided no immunity?" Figure S1 (extended data16 shows the first ten simulations and provides further detail of this method. For this analysis, we included data from the final two winter seasons (2009–2010 and 2010–2011).

We also estimated the percent of illnesses that were swabbed and tested for the relevant seasonal panel of viruses (see Table S1 extended data[16]) as well as for HCoV by season to aid interpretation of results.

Analysis was conducted using R version 3.6.2.

Ethics and consent

The ethical protocol for Flu Watch was approved by the Oxford MultiCentre Research Ethics Committee. (06/Q1604/103). Participants gave written informed consent (proxy consent for children).

Results

Approximately 10% of invited households agreed to participate in Flu Watch. Compared to the national population, the study population underrepresented young adults; people living in socially deprived areas, north England, west Midlands, and London; and people of non-white ethnic origin. We included 51,002 person-weeks of follow-up and 2,907 person-seasons in the first four seasons.

A total of 1,104 swabbed illnesses were tested for HCoV and 199 cases were confirmed in the first four seasons. This total

excludes six HCoV positive swabs (three in winter 2008–2009 and three in winter 2009–2010) as they were submitted without a participant ID. The percent of illnesses that were swabbed varied by season with lower adherence during Nov 2007 – Mar 2008 and May 2009 – Sept 2010 (61.5% and 57.0% respectively) and better adherence in the other seasons ranging from 83.6%–96.9% (see extended data 2 table S1). In the last two seasons when there was only partial testing (Oct 2009 – Feb 2010 and Nov 2010 – Mar 2011) the percent of illnesses swabbed and tested for HCoV was 14.0% and 24.5% respectively, which is why we did not report HCoV rates for these seasons.

We calculated an HCoV incidence rate of 390 per 100,000 person-weeks (95% CI 338–448) across the first four seasons. The maximum rate of HCoV was found in the 0–4 age group, with rate ratios lower in the 5–15; 45–64 and 65+ age groups compared to the 0–4 age group. Rates were similar in males and females, by geographical region, and by level of deprivation. Rates and rate ratios for participant characteristics are shown in Table 2.

Rates were higher in winter seasons than in the summer season of May-Sep 2009, during which four cases of HCoV were detected. Combining data across the first four seasons showed rates were highest in the month of February (759; 95%CI 580–975). Considering all respiratory viruses tested for, HCoV and influenza both peaked in winter and then declined, whereas hMPV, adenovirus, RSV, and rhinovirus showed no obvious winter peak, though this may relate to the small number of cases we detected (Figure 1).

Of 216 participants with a first confirmed HCoV infection during any of the six seasons, eight had a second confirmed HCoV infection (all eight were from different households). These participants are shown in Table 3. None of the eight participants had the same strain twice. No participants had a third confirmed HCoV infection. Based on simulations assuming no immunity, the probability of zero homologous reinfections in these eight participants was 3.48%, suggesting some evidence for immunity (Figure S2 extended data[16]).

Discussion

Our study shows that HCoV appears to follow a seasonal pattern in England, with peaks occurring during winter seasons and broadly at the same time as influenza. We collected data during one summer season that coincided with the start of the 2009 H1N1 influenza pandemic, and during this period we found a small amount of ongoing HCoV transmission. Our results provide some evidence of immunity against homologous reinfection.

Our results support existing evidence for seasonality of HCoV in England with reduced transmission during summer months. To our knowledge, this is the first published study of HCoV seasonality in England and the first to show continued transmission during summer months. A 2010 review[9] of HCoV-NL63 found that it broadly followed a winter seasonal distribution in temperate climates (Belgium, Canada, France, Germany, Italy, Switzerland) with greater variation in tropical climates with China (Hong Kong) showing a spring and summer distribution (one study) and peaks in autumn in Thailand and October in Taiwan. Two further studies have been published since this review. The first was a community surveillance study in Utah, USA, which showed a broadly winter seasonal pattern[8]. Another study of swab specimens from adults and children with fever and acute upper respiratory infection symptoms in Guangzhou, China, found transmission throughout the year with a peak in February[7].

Limited data exist on the immunising effect of previous infection with HCoV. Our data provide additional support for the immunising effect of infection in the short to medium term, but reinfection has been documented elsewhere. Our results should be interpreted with caution due to our sample size and the fact that we have not accounted for seasonal variations in strains, but it should also considered in the context of existing literature on immunity to HCoV, including community surveillance and experimental reinfection challenge studies. In a 1971 study of 937 medical students, reinfection with HCoV-229E was detected and infection with other respiratory viruses did not stimulate significant complement factor or neutralising antibody titre rises against HCoV-229E[10]. A combined paediatric hospital inpatient and household community surveillance study conducted in Kenya found second infections with HCoV-NL63 (20.9%), HCoV-OC43 (5.7%), and HCoV-229E (4.0%) over the six years of the study. This study provided evidence to rule out genotype switching as a possible mechanism for reinfection. Two studies have also demonstrated experimental HCoV reinfection in humans[17,18]. At the time of writing, one animal study has been conducted to examine the possibility of SARS-CoV-2 reinfection[19]. In this study, four 3- to 5-year old rhesus macaques were inoculated with SARS-CoV-2 and after the disappearance of symptoms, two were rechallenged and no viral load was detected. This study is important as it provides the only data we currently have on SARS-CoV-2, but it should also be interpreted with caution due to the fact that it is a primate study with a small sample size.

There are several additional limitations to our analysis and data. Our PCR data are reliant on participants sampling when symptomatic, which means that we will have not detected asymptomatic infection leading to underascertainment of such cases and as a result our estimates of rates will underestimate the true community burden. It is likely that we also received fewer samples from those who were minimally symptomatic. Our results therefore represent minimal burden estimates and we were unable to examine this further as we have no paired serological data on HCoV, although stored residual sera are available for this cohort and could be examined in future. Additionally, we were not able to calculate rates of confirmed HCoV infection in the final two winter seasons because not all swabs were tested for HCoV. Participants were advised to collect samples on day two of symptoms as Flu Watch was primarily set up to examine influenza and we are uncertain whether or not this is the optimum day for sampling those

Table 2. Baseline characteristics of study participants and HCoV PCR+ illness rates across the first four seasons (Nov-Mar 2006/7; Nov-Mar 2007/8; Nov-Mar 2008/9; May-Sep 2009).

Variable	Level	Individuals	Person-Seasons	Person-weeks	HCoV* PCR**+	HCoV PCR**+/100,000 person-weeks (95% CI)	Rate ratio (unadjusted)	Rate ratio (adjusted)
Total		1,847 (100.0%)	2,907	51,002	199	390 (338-448)		
Age group	0–4	111 (5.8%)	153	2,530	18	711 (422-1,124)	1	1
	5–15	272 (14.3%)	405	7,021	27	385 (253-560)	0.51 (0.27-0.96)	0.50 (0.26-0.94)
	16–44	537 (28.2%)	773	13,180	60	455 (347-586)	0.69 (0.39-1.20)	0.67 (0.38-1.17)
	45–64	650 (34.1%)	1,035	18,487	65	352 (271-448)	0.53 (0.30-0.94)	0.55 (0.31-0.97)
	65+	337 (17.7%)	541	9,784	29	296 (199-426)	0.45 (0.23-0.86)	0.48 (0.25-0.91)
Sex	Female	973 (52.7%)	1,543	26,986	105	389 (318-471)	1	1
	Male	874 (47.3%)	1,364	24,016	94	391 (316-479)	1.01 (0.76-1.34)	1.01 (0.76-1.34)
Region	East & East Midlands	318 (17.1%)	484	8,573	29	338 (227-486)	1	1
	London	116 (6.2%)	159	2,564	11	429 (214-768)	1.44 (0.65-3.18)	1.24 (0.56-2.76)
	North	273 (14.7%)	394	6,898	26	377 (246-552)	1.16 (0.63-2.14)	1.14 (0.61-2.12)
	South East	297 (16.0%)	479	8,179	22	269 (169-407)	0.85 (0.45-1.58)	0.83 (0.44-1.57)
	South West	698 (37.5%)	1,154	20,545	92	448 (361-549)	1.33 (0.82-2.17)	1.49 (0.91-2.44)
	West Midlands	159 (8.5%)	237	4,243	19	448 (270-699)	1.42 (0.73-2.78)	1.32 (0.67-2.59)
IMD*** 2007	1 - most deprived	99 (4.6%)	136	2,453	14	571 (312-958)	1	1
	2	284 (13.3%)	366	6,499	30	462 (311-659)	0.83 (0.38-1.81)	0.89 (0.41-1.95)
	3	534 (25.0%)	804	14,229	62	436 (334-559)	0.76 (0.37-1.55)	0.74 (0.36-1.53)
	4	513 (24.1%)	730	12,924	46	356 (261-475)	0.64 (0.31-1.33)	0.69 (0.33-1.44)
	5 - least deprived	409 (19.2%)	578	9,971	44	441 (321-592)	0.83 (0.39-1.73)	1.03 (0.49-2.16)
	Missing	293 (13.7%)	293	4,926	3	61 (13-178)	0.09 (0.02-0.33)	1.76 (0.30-10.21)
Season	Nov-Mar 2006/7	602 (20.7%)	602	10,751	42	391 (282-528)	1	1
	Nov-Mar 2007/8	779 (26.8%)	779	14,183	70	494 (385-624)	1.30 (0.85-1.99)	1.31 (0.85-2.02)
	Nov-Mar 2008/9	729 (25.1%)	729	12,315	83	674 (537-835)	1.68 (1.12-2.53)	1.68 (1.12-2.53)
	May-Sep 2009	797 (27.4%)	797	13,753	4	29 (8-74)	0.07 (0.03-0.21)	0.05 (0.01-0.21)
Month	Jan	1,737 (15.4%)	2,023	8,534	61	715 (547-918)		
	Feb	1,740 (15.5%)	2,033	8,040	61	759 (580-975)		
	Mar	1,722 (15.3%)	2,007	9,241	13	141 (75-241)		
	May****	681 (6.0%)	681	2,643	0	0 (0-140)		
	Jun ****	679 (6.0%)	679	3,346	3	90 (18-262)		
	Jul ****	649 (5.8%)	649	2,514	0	0 (0-147)		
	Aug	602 (5.3%)	602	2,941	0	0 (0-125)		
	Sep	670 (6.0%)	670	2,309	1	43 (1-241)		
	Nov	1,114 (9.9%)	1,280	3,050	4	131 (36-336)		
	Dec	1,666 (14.8%)	1,942	8,384	56	668 (505-867)		

* Human Coronavirus ** Polymerase chain reaction *** Index of Multiple Deprivation ****rates for May-Sep are based on data from 2009 alone*

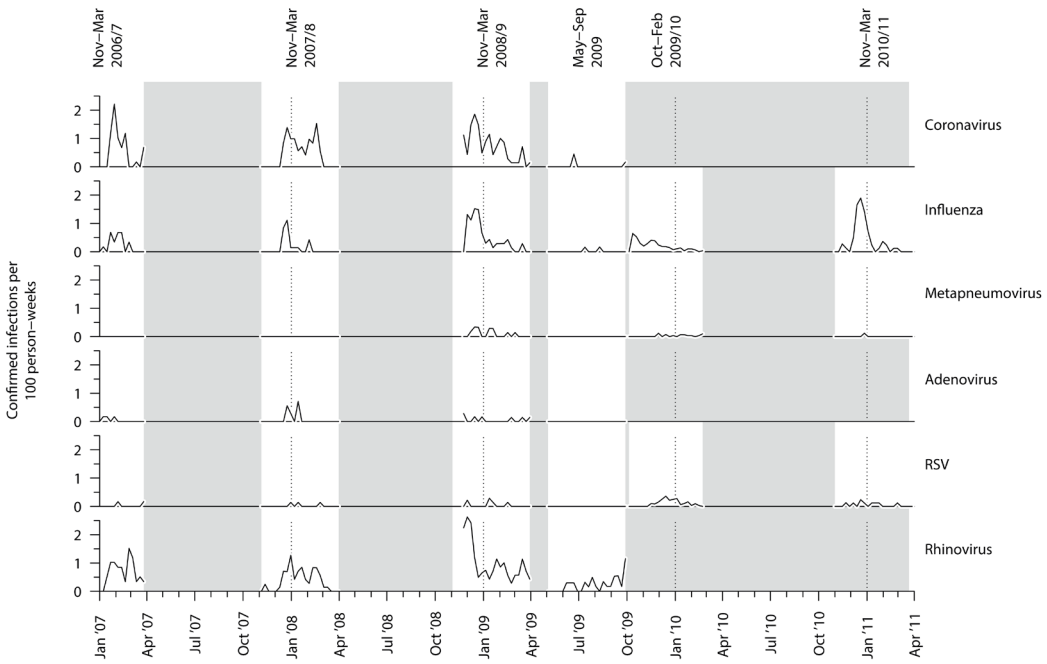

Figure 1. Weekly rates of PCR-confirmed viral respiratory diseases. PCR= Polymerase chain reaction, RSV = Respiratory syncytial virus.

Table 3. Participants with repeated confirmed coronavirus infections.

	First confirmed infection		Second confirmed infection		
Number	Week commencing	Strain	Week commencing	Strain	Weeks between infections
1	04-Feb-08	229E	19-Jan-09	NL63	50
2	24-Nov-08	NL63	21-Dec-09	229E	56
3	01-Dec-08	OC43	16-Mar-09	229E	15
4	15-Dec-08	OC43	02-Feb-09	NL63	7
5	22-Dec-08	NL63	09-Feb-09	OC43	7
6	22-Dec-08	OC43	09-Feb-09	NL63	7
7	12-Jan-09	NL63	22-Jun-09	229E	23
8	16-Feb-09	229E	21-Dec-09	OC43	44

with HCoV. We only have one year of data collection during summer, during which time adherence to swabbing was lower than winter periods. Our ability to confidently estimate the levels of transmission during the summer is limited as a result of this, as is our description of seasonality, although as we have discussed earlier, these results are consistent with the wider literature for HCoV transmission in temperate climates. A conclusive picture about the seasonal pattern of SARS-CoV-2 will require monitoring over several years to confirm. The generalisability of our results to SARS-CoV-2 has uncertainties, but given the lack of data on this novel virus, we believe that these data can help inform the public health response. At this stage in the pandemic, it appears to be the case that the clinical features of mild cases of SARS-CoV-2 are similar to NL63, OC43 and 229E, but the likelihood of developing severe disease or dying is much higher although considerably less than in SARS-CoV and MERS-CoV[20,21]. Finally, because of small numbers in sub-groups it has not been possible to stratify

our results socio-economic status or ethnicity despite the fact that they are increasingly recognised as important factors associated with COVID-19 outcomes.

In summary, our data provide additional support for a winter seasonal pattern of HCoV in the UK and that infection has an immunising effect against subsequent reinfection in the short to medium term. For COVID-19, in the context of intensive control measures it may prove difficult to assess the extent to which virus transmission is impeded by summer conditions. Comparing transmission the patterns in northern and southern hemispheres (where seasons are reversed) will be of help in providing early data on this. We also need further research to assess the strength and duration of immune protection following COVID-19 exposure. Whilst our results can help inform the response and modelling to SARS-CoV-2 in the UK, there are important research questions that need answering from community surveillance studies that are relevant to the policy and public health response. We urgently need to know the true extent of community transmission, including estimates of the asymptomatic fraction of SARS-CoV-2, the symptomatology in community cases and case hospitalisation rates in confirmed cases and how this varies over time and season. Additionally, we need to know what the duration of viral shedding is and whether there is evidence for repeat infection of SARS-CoV-2 in humans.

Data availability

Underlying data

UCL Discovery: Dataset: Seasonality and immunity to laboratory-confirmed seasonal coronaviruses (HCoV-NL63, HCoV-OC43, and HCoV-229E): results from the Flu Watch cohort study. https://doi.org/10.14324/000.ds.10093909[16]

This project contains the following underlying data:

- Aldridge_cov_seasonality_immunity_public_data_23_march_2020.csv (Flu Watch HCoV data)

Extended data

UCL Discovery: Dataset: Seasonality and immunity to laboratory-confirmed seasonal coronaviruses (HCoV-NL63, HCoV-OC43, and HCoV-229E): results from the Flu Watch cohort study. https://doi.org/10.14324/000.ds.10093909[16]

This project contains the following extended data:

- Aldridge_cov_seasonality_immunity_public_code_revised.R (Analysis replication code)
- Aldridge_Extended data 1.pdf (Pdf file containing Table S1 and Figure S1 and S2)
    - Table S1. Illnesses swabbed and tested for HCoV by season
    - Figure S1: First ten simulations to evaluate evidence of homologous immunity
    - Figure S2: Probability of number of homologous reinfections in 8 participants, with the assumption of no immunity

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 05 January 2021

https://doi.org/10.21956/wellcomeopenres.18155.r41796

✔ **David J. Muscatello**
School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia

I have no further comments to make. Thank you for addressing my concerns.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, influenza, time series analysis, infectious diseases.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 10 December 2020

https://doi.org/10.21956/wellcomeopenres.18155.r41797

✔ **Tom Wingfield**
Departments of Clinical Sciences and International Public Health, Liverpool School of Tropical Medicine, Liverpool, UK

The authors have responded fully to my comments and I am delighted to accept the current version of this article for indexing on Wellcome Open Research.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical infectious diseases (HIV/TB), epidemiology, social determinants and consequences of ill-health.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 10 June 2020

https://doi.org/10.21956/wellcomeopenres.17340.r38795

?

David J. Muscatello
School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia

In the context of the emerging COVID-19 pandemic, this article attempts to address two important questions - seasonality of human coronavirus infections in a temperate setting in the UK and the probability of re-infection by the same coronavirus in the time frame of a few years.

A positive of the FluWatch study is that it examined infection incidence in a more-or-less representative sample of the population. This is a very rare occurrence in infection incidence study designs.

The main limitation of the study is the limited number of non-winter seasons included - only one. A second limitation is that re-infection may have occurred during the periods during which follow-up did not occur - that is, the other missing summer seasons.

I have a few minor concerns:

- spelling of influenza should be lower case throughout - it is not a proper noun.
- Human Metapneumovirus should be spelled with a lower case m for the same reason - see footnote of Table 1.
- Abstract - I would prefer to see "100,000 person weeks" included next to all of the rate statistics in the result section. The highest rate is in February - should be clear that the highest average monthly rate was in Feb because I assume this was an average for Feb over the three seasons that included Feb.
- Background 2nd paragraph - could also reference this study[ref-1].

- Would be helpful if methods included the specific respiratory symptoms that triggered follow-up from the original study.

- Simulation description in methods could be explained better here and in the supplement. If I understand correctly, the aim was to compare the observed number of second homologous infections with the predicted number of second homologous infections. The predicted number was determined from 100,000 simulations that assumed that occurrence of a second homologous infection followed a distribution based on a null hypothesis that the probability of a second homologous infection was the same as the probability of the homologous strain occurring among all participants throughout the study period included. This simulation approach assumed that there was no residual immunity from a first infection. Thus, if the occurrence of the second homologous infection had a lower incidence than predicted then we might conclude that there is immunity to a second homologous infection. It's also not really clear why simulation was necessary when the simulation simply reproduces the distribution of infections observed in the study.

- The statement "The maximum rate of HCoV according to age was bimodal, peaking at ages 0–4 and ages 16–44" seems a bit of a stretch. All other age groups apart from 16-44 were lower than 0-4 based on adjusted RR, but 16-44 was not that much higher than all non-0-4 age groups.

- The results for monthly incidence are misleading e.g. in Table 2. May-Sep results are based on one season only. Remaining months based on three seasons. Are remaining months averages over 3 seasons? A footnote to the table could explain these issues.

- The authors have done well in stating that their results should be interpreted with caution. They could state more clearly that one important reason for this is that the summer results are based on one season only, and that's really insufficient to draw conclusions about seasonality which requires monitoring over several years to determine a seasonal pattern.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, influenza, time series analysis, infectious diseases.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 Nov 2020

Robert Aldridge, UCL, London, UK

Thanks very much for this helpful review - we appreciate the time you have taken to carefully read and provide constructive feedback on the article. We have tried to address all the points you have raised and below we include your comments alongside in our responses in bold italics. We have numbered each of our responses in order that we can cross-reference them across all of the reviews to this article.

Reviewer comment 4:

Spelling of influenza should be lower case throughout - it is not a proper noun.

Author response 4:

We have changed influenza to lower case throughout.

Reviewer comment 5:

Human Metapneumovirus should be spelled with a lower case for the same reason - see footnote of Table 1.

Author response 5:

We have changed Human Metapneumovirus in Table 1 footnote.

Reviewer comment 6:

Abstract - I would prefer to see "100,000 person weeks" included next to all of the rate statistics in the result section. The highest rate is in February - should be clear that the highest average monthly rate was in Feb because I assume this was an average for Feb over the three seasons that included Feb.

Author response 6:

We have added per 100,000 person-weeks to all rates in the abstract. The rate for the month Feb is not an average but is a rate calculated across all seasons using all cases in Feb as the numerator and person time at risk during Feb as the denominator.

Reviewer comment 7:

Background 2nd paragraph - could also reference this study[ref-1].

Author response 7:

[ref-1] did not appear to come through in the peer review response.

Reviewer comment 8:

Would be helpful if methods included the specific respiratory symptoms that triggered follow-up from the original study.

Author response 8:

We have added the following text to the methods section:
“In addition, we requested that all participants experiencing respiratory symptoms (including feeling feverish, headache, having muscle aches, cough, sore throat, runny nose, blocked nose, and sneezing) provide self-administered nasal swabs on the second day of illness.”

Reviewer comment 9:

Simulation description in methods could be explained better here and in the supplement. If I understand correctly, the aim was to compare the observed number of second homologous infections with the predicted number of second homologous infections. The predicted number was determined from 100,000 simulations that assumed that occurrence of a second homologous infection followed a distribution based on a null hypothesis that the probability of a second homologous infection was the same as the probability of the homologous strain occurring among all participants throughout the study period included. This simulation approach assumed that there was no residual immunity from a first infection. Thus, if the occurrence of the second homologous infection had a lower incidence than predicted then we might conclude that there is immunity to a second homologous infection. It's also not really clear why simulation was necessary when the simulation simply reproduces the distribution of infections observed in the study.

Author response 9:

In response to this comment, we have reviewed and edited our description of our approach to this part of the analysis in the methods section, to hopefully clarify our intention with this analysis:
“We used HCoV strains in participants with repeat infections to test the evidence for homologous immunity after infection. We started from a ‘null’ hypothesis of no immunity, and assumed that in this scenario the distribution of strains among participants with a second infection would be the same as in the entire cohort. If there is at least some immunity, we expected to see a pattern in which participants with a previous infection were less likely to have the same strain twice. For the eight participants with repeat infections, we

created 100,000 simulations in which strain of the second infection (HCoV-NL63, HCoV-OC43, or HCoV-229E) was sampled with the probabilities observed in the entire cohort, and counted the number of homologous reinfections (zero to eight). We interpreted the proportion of simulations with as many or fewer homologous reinfections than in the observed data as evidence of immunity. In other words, the analysis attempts to examine the following question “is it likely that participants would have got more homologous reinfections if infection provided no immunity?” Figure S1 (extended data16) shows the first ten simulations and provides further detail of this method. For this analysis, we included data from the final two winter seasons (2009–2010 and 2010–2011).”

Reviewer comment 10:

The statement "The maximum rate of HCoV according to age was bimodal, peaking at ages 0–4 and ages 16–44" seems a bit of a stretch. All other age groups apart from 16-44 were lower than 0-4 based on adjusted RR, but 16-44 was not that much higher than all non-0-4 age groups.

Author response 10:

We explored this issue further as per Author response 2 to Reviewer 1, but do not feel additional analysis is possible. As a result we have edited our description of these results in response to this reviewer comment 10 to:

“The maximum rate of HCoV was found in the 0–4 age group, with rate ratios lower in the 5-15; 45-64 and 65+ age groups compared to the 0–4 age group.”

Reviewer comment 11:

The results for monthly incidence are misleading e.g. in Table 2. May-Sep results are based on one season only. Remaining months based on three seasons. Are remaining months averages over 3 seasons? A footnote to the table could explain these issues.

Author response 11:

In Table 2 we have calculated the rate of HCoV PCR+ cases per 100,000 person-weeks. For each month we calculate this rate using the numerator as HCoV PCR+ cases and the denominator of Person-weeks across the whole month. The numerator and denominator for each month are each presented in Table 2 with the columns labelled, and the rate is specified as HCoV PCR**+/100,000 person-weeks
(95% CI) in the column header. It is correct that May-Sep results are based on one season only and remaining months based on all seasons.
In the discussion we previously noted that “We only have one year of data collection during summer, during which time adherence to swabbing was lower than winter periods. Our ability to confidently estimate the levels of transmission during the summer is limited as a result of this, as is our description of seasonality, although as we have discussed earlier, these results are consistent with the wider literature for HCoV transmission in temperate climates.”

In response to this reviewer comment 11 we have now added a footnote to Table 2 stating that: "****rates for May-Sep are based on data from 2009 alone".

Reviewer comment 12:

The authors have done well in stating that their results should be interpreted with caution. They could state more clearly that one important reason for this is that the summer results are based on one season only, and that's really insufficient to draw conclusions about seasonality which requires monitoring over several years to determine a seasonal pattern.

Author response 12:

In addition to the following text in the discussion:
"We only have one year of data collection during summer, during which time adherence to swabbing was lower than winter periods. Our ability to confidently estimate the levels of transmission during the summer is limited as a result of this, as is our description of seasonality, although as we have discussed earlier, these results are consistent with the wider literature for HCoV transmission in temperate climates."
We have added the following text in response to this point:
"A conclusive picture about the seasonal pattern of SARS-CoV-2 will require monitoring over several years to confirm."

Competing Interests: No competing interests were disclosed.

Reviewer Report 06 May 2020

https://doi.org/10.21956/wellcomeopenres.17340.r38640

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Tom Wingfield
Departments of Clinical Sciences and International Public Health, Liverpool School of Tropical Medicine, Liverpool, UK

This is a well-written and executed article by a team that is well experienced in the field and have a strong track record.

The findings are useful and highly topical amid the SARS-CoV-2 pandemic, especially with relation to the issue of immunity and re-infection.

I have a few minor comments:

1. It would be great to see some of the data disaggregated by IMD and also ethnicity (or if not individual ethnicity perhaps proportion of BAME people in LSOA from where swab sent) as it

is mentioned that these data are collected. This is highly pertinent to the evidence that is gathering about the differential impact of Covid-19 in BAME and amongst people of lower socioeconomic status. The issue of under-reporting in these groups is mentioned early in the manuscript and should also perhaps be mentioned in the limitations section.

2. Please can the authors comment/interpret the findings across age groups that are shown in Table 2 (lower HCoV PCR+ illness in older age groups compared to 0-4) and how these might be applied to help our understanding of SARS-CoV-2 transmission and illness, especially in light of potential lifting of lockdown measures including school closures.

3. Minor update to Covid-19 global/UK numbers will be required on re-submission of final version.

Congratulations to the authors on an interesting, important, topical, and highly readable piece. Thank you for considering me to review.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical infectious diseases (HIV/TB), epidemiology, social determinants and consequences of ill-health.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 Nov 2020

Robert Aldridge, UCL, London, UK

Thanks very much for this helpful review - we appreciate the time you have taken to

carefully read and provide constructive feedback on the article. We have tried to address all the points you have raised and below we include your comments alongside in our responses in bold italics. We have numbered each of our responses in order that we can cross-reference them across all of the reviews to this article.

Reviewer comment 1:

It would be great to see some of the data disaggregated by IMD and also ethnicity (or if not individual ethnicity perhaps proportion of BAME people in LSOA from where swab sent) as it is mentioned that these data are collected. This is highly pertinent to the evidence that is gathering about the differential impact of Covid-19 in BAME and amongst people of lower socioeconomic status. The issue of under-reporting in these groups is mentioned early in the manuscript and should also perhaps be mentioned in the limitations section.

Author response 1:

Thank you for these suggestions which we have considered carefully. Table 2 provides data by IMD, but unfortunately it has not been possible to stratify other results of the study (e.g. Figure 1 or Table 3) by ethnicity status or IMD due to low number of events in these groups. We have added the following note about this in the discussion:

“Finally, because of small numbers in sub-groups it has not been possible to stratify our results socio-economic status or ethnicity despite the fact that they are increasingly recognised as important factors associated with COVID-19 outcomes.”

Reviewer comment 2:

Please can the authors comment/interpret the findings across age groups that are shown in Table 2 (lower HCoV PCR+ illness in older age groups compared to 0-4) and how these might be applied to help our understanding of SARS-CoV-2 transmission and illness, especially in light of potential lifting of lockdown measures including school closures.

Author response 2:

Table 2 suggests that compared to the 0-4 age group, all other ages have a lower rate ratio of HCoV PCR+ illness. We are very cautious in our interpretation of this suggestion as the 0-4 age group also had the smallest number of events. In response to this reviewer comment we explored the possibility of modelling age as a continuous variable to improve our modelling approach. We also explored the possibility of including age with polynomials/splines. Unfortunately both of these approaches resulted in models that were more difficult to interpret and did not help with interpreting differences in HCoV PCR+ illness in older age groups compared to 0-4 as suggested. As a result, we do not think we can explore this issue further. However, we have edited the text describing these results as set out in response to Reviewer 2 comment 10.

Reviewer comment 3:

Minor update to Covid-19 global/UK numbers will be required on re-submission of final version.

Author response 3:

We have updated our analyses with the latest Covid-19 global/UK numbers and edited the text in the introduction in light of the current situation.

Competing Interests: No competing interests were disclosed.

Comments on this article

Version 1

Reader Comment 07 May 2020

Oswald Hotz de Baar, None, UK

Sirs,
From the outset when the Imperial study was presented the pattern of C19 infection seemed odd. Firstly 50% were believed to have had the disease with little or no symptoms and even those who were hospitalised generally recovered without recourse to intensive care. Reports from Diamond Princess also had an odd pattern with some spouses of infected people apparently never succumbed even though exposure must have been high. It looked to me as if a section of the population had acquired some immunity from a previous coronavirus infection. I would argue that this proposal is supported by what you have presented here. It would be nice to have some estimate of the proportion of the population likely to have been previously infected with one of these common cold coronaviruses when averaged over decades. I am not sure if you have sampled infants and young children although one might assume that resistance may have waned significantly after a few decades unless reinfection has occurred.
If it tiurns out that a significant proportion (say circa 50%) have been infected then there is a prima facia case that one or more of the common cold coronaviruses will provide some or good immunity and since its already wild registration should be rather easy.

Competing Interests: No competing interests were disclosed.