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Global seasonality of human seasonal coronaviruses: a clue for post-pandemic circulating season of SARS-CoV-2 virus?

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Brief summary: Human seasonal coronaviruses are found to be prevalent in winter months in most temperate sites, coinciding with influenza and respiratory syncytial virus season, but less seasonal in tropics and in temperate sites of China.

Abstract

Background

The ongoing pandemic of Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus could recur as seasonal outbreaks, a circulating pattern observed among other pre-existing human seasonal coronaviruses (sCoV). However, little is known about seasonality of sCoV on a global scale.

Methods

We conducted a systematic review of data on seasonality of sCoV. We compared seasonality of sCoV with influenza virus and respiratory syncytial virus. We modelled monthly activity of sCoV using site-specific weather data.

Results

We included sCoV seasonality data in 40 sites from 21 countries. SCoV was prevalent in winter months in most temperate sites except for China while sCoV tended to be less seasonal in China and in tropical sites. In temperate sites excluding China, 53.1% of annual sCoV cases (Interquartile range, IQR: 34.6–61.9) occurred during influenza season and 49.6% (IQR: 30.2–60.2) of sCoV occurred during respiratory syncytial virus season. Low temperature combined with high relative humidity was associated with higher sCoV activity.

Conclusions

This is the first study that provides an overview of the global seasonality of sCoV. Our findings offer clues to the possible post-pandemic circulating season of SARS-CoV-2 and add to the knowledge pool necessary for post-pandemic preparedness for SARS-CoV-2.

Key words

COVID-19, SARS-CoV-2, seasonality, human coronavirus, temperature, relative humidity

Introduction

The novel human coronavirus SARS-CoV-2 that emerged in Wuhan, China in December 2019 has since spread worldwide [1]. SARS-CoV-2 has caused over 3.6 million cases of Coronavirus disease 2019 (COVID-19) and over 250 thousand deaths as on 6th May 2020 [2]. It remains unclear which trajectory the transmission of SARS-CoV-2 will follow after the initial pandemic wave. One of the speculations is that SARS-CoV-2 will adapt itself to a seasonal circulation like the recent influenza pandemic H1N1/09 virus (H1N1pdm), which was later found to circulate annually in the same season as other existing seasonal influenza strains [3]. For human coronaviruses, there are four known seasonal coronaviruses (sCoV) that have been long circulating in human populations, including two alpha-coronaviruses, NL63 and 229E, and two beta-coronaviruses, OC43 and HKU1. Therefore, it is possible that once endemic, SARS-CoV-2, a beta-coronavirus will follow the same seasonal patterns as the sCoVs. In a recent modelling study projecting the post-pandemic transmission dynamics of SARS-CoV-2, Kissler and colleagues found that recurrent outbreaks of SARS-CoV-2 in the US would probably occur during wintertime, same as the sCoVs, after the initial pandemic wave [4]. However, the seasonality of these long-circulating sCoVs is still unknown on a global scale. To this end, we conducted a systematic review on the global seasonality of human sCoV.

Methods

Search strategy and selection criteria

This systematic review is registered with The International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42020182629). We searched Medline (Ovid), Embase (Ovid), Global Health (Ovid), Web of Science and three Chinese databases (CNKI, Wanfang and Chongqing VIP) for studies published between 1st January 1990 and 15th April 2020 that reported monthly or weekly activity of sCoVs (i.e. NL63, 229E, OC43 and HKU1). We also searched two

preprint databases (MedRxiv and BioRxiv) for preprints between 1st January 2020 and 15th April 2020. Detailed search strategy is in the Appendix. Selection criteria were applied as follows:

Inclusion criteria

- Studies reporting data on laboratory-confirmed incidence of human infection of coronaviruses for at least 12 consecutive months (or 52 weeks equivalent); AND
- Studies with stable testing practice throughout all years reported (e.g. studies should be able to conduct coronavirus tests in both winter season and other seasons with no interruption); AND
- Studies reporting virus results among residents in well-defined geographic locations; AND
- Studies reporting aggregated virus results at least on a monthly basis or, if possible, more frequently.

Exclusion criteria

- Studies focusing on SARS-CoV-1, SARS-CoV-2 or MERS-CoV-1; OR
- Studies reporting less than 25 coronavirus positive cases; OR
- Studies reporting respiratory infections only among those under special medical conditions (e.g. patients with chronic obstructive pulmonary disease or patients infected with human immunodeficiency virus); OR
- Studies focusing on specific settings other than the community (e.g. hospital, school, care-centre, etc.); OR
- Studies reporting a subset of data that were available elsewhere (corresponding original source of data was assessed for eligibility).

In addition to the literature search, we also searched for online datasets that were eligible for our review, using the keywords “coronavirus*”, “surveillance” and “seasonal*”.

Data extraction

Two reviewers (YL and XW) extracted the data from the literature, independently, using a template that was described elsewhere [5]. Briefly, we collected general information from each study including site, country, data source and test method. Geographical coordinates were extracted for the study site. For seasonality, we extracted monthly aggregated number of sCoV cases. We also extracted the monthly number of coronavirus cases by genus (i.e. alpha-coronavirus and beta-coronavirus) and by species (i.e. NL63, 229E, OC43 and HKU1). In order to compare the seasonality of sCoV with other two common respiratory viruses, influenza virus and respiratory syncytial virus, we also extracted monthly aggregated number of influenza and respiratory syncytial virus cases from each study, if available. For included studies where influenza virus and/or respiratory syncytial virus seasonality was not available, we searched studies that reported data from the same or a nearby site from our previous work on influenza virus and respiratory syncytial virus seasonality [5].

We also conducted quality assessment for each eligible study using a quality assessment form comprising three brief questions regarding data representativeness, test practice, and timely reporting as described elsewhere [5]. When two or more studies were available for a site, the study with higher quality score was retained with the rest being excluded and marked as duplicate data.

Data analysis

Description of seasonality of coronavirus

We aggregated the number of positives by month across years for each site and calculated annual average percentage (AAP) as a measurement of the strength of virus activity by the formula below:

$$AAP_i = \frac{n_i}{\sum_1^{12} n_i} \times 100\%$$

where i denotes the month i and n denotes the number of cases.

Relationship between coronavirus and influenza/respiratory syncytial virus

We plotted heat maps displaying the activity of sCoV, influenza virus and respiratory syncytial virus for each site sorted by latitude. In order to understand how the peak activity of each virus overlapped, we identified for each virus the top three months with highest AAP as the first step; we then calculated the cumulative AAP of another virus that occurred during these three months.

Coronavirus seasonality and meteorological factors

For each site, we extracted meteorological data from the site's nearest weather station provided by the US National Centers for Environmental Information using R package GSODR.[6] We modelled monthly AAP of sCoV activity with meteorological predictors, including mean-centred temperature, relative humidity and dew point, in a LOESS model as described elsewhere [5]. Details of the model are available in the **Appendix**. Briefly, we included two models based on the model selection results, one model with mean-centred dew point and relative humidity as predictors and the other with mean-centred temperature and relative humidity as predictors. Studies were eligible for this analysis if they reported >100 positive sCoV cases. We conducted two sets of models that excluded two temperate sites in China and included all sites, respectively. This was due to the observation that the sCoV seasonality in the temperate sites of China was less seasonal, different from the rest temperate sites. We did not model sCoV activity by genus or by species due to the paucity of data.

Software and data availability

All data analyses were conducted using R software (version 3.5.2)[7]. All the data in the study are made available in Edinburgh DataShare [8].

Results

We initially identified 2414 studies via our search. After excluding duplicates, we screened 1670 studies by title and abstract and screened 205 studies by full-text. A total of 40 studies were included in the final analysis. These studies represented 40 sites from 21 countries (**Figure 2** and

Figure S1). The number of positive sCoV ranged from 25 to 39573 across sites. Polymerase chain reaction (PCR) was used to detect sCoV in all the studies. Six of the 40 studies focused one or two particular sCoV species and therefore did not contribute to the results for the overall sCoV (all species). Details on these studies and their quality assessment are in **Table S1** and **Table S2**.

Global seasonality of sCoV

High activity of sCoV, as measured by AAP, was observed in winter months in most temperate sites (**Figure 3**), with the exception in China where sCoV activity tended to be year-round (**Figure S2**). No difference in study quality was observed between studies reporting sCoV in China and other studies. More variations in sCoV activity were observed in the tropical sites. No difference in timing of season was observed between alpha-CoV and beta-CoV. (**Figure 4** and **Figure 5**)

In the temperate sites excluding China, 53.1% of the sCoV cases (IQR: 34.6–61.9) occurred during influenza season (defined by the top three months with highest AAP) and 49.6% of the sCoV cases (IQR: 30.2–60.2) occurred during respiratory syncytial virus season. Less overlap was observed in the tropical sites as well as temperate sites in China between sCoV activity and influenza/respiratory syncytial virus activity (20% during influenza season and 29% during respiratory syncytial virus season). (**Figure S3**)

Meteorological factors and seasonality of sCoV

A total of 17 studies with >100 positive sCoV cases were included in our model (including two sites from temperate China). Low temperature with high relative humidity was found to be associated with higher expected proportion of sCoV cases; dew point was observed to have similar relationship with sCoV activity as temperature (**Figure 6**). Similar results were found from the model excluding two temperate sites from China (**Figure S4**).

Discussion

At the time of writing, more than 180 countries have been affected by COVID-19 [2] and it is timely and extremely important to understand the long-term future of SARS-CoV-2. Understanding of the global circulating season of sCoV, the genetic relative of SARS-CoV-2, might provide clues on the possible circulating season of SARS-CoV-2. In the present study, we described the month-by-month activity of sCoV in 40 sites from 21 countries. We found that sCoV occurred mainly in winter months in temperate sites except for China and was less seasonal in China and tropical sites. We highlighted high proportion of co-circulating sCoV cases during influenza virus and respiratory syncytial virus seasons, implicating the possibility of a substantial increase in the demand to healthcare system resources during wintertime.

Our findings have important implications in the control and prevention of COVID-19. The global seasonality of sCoV provides a clue for the possible circulating timing of SARS-CoV-2 after the initial pandemic. A modelling study reported that SARS-CoV-2 will likely enter into regular circulation starting from 2021 or 2022 in the US and synchronise with sCoV, if immunity to SARS-CoV-2 is not permanent [4]. Although it is not entirely clear how long the immunity to SARS-CoV-2 could last, a recent study showed that most convalescent plasmas obtained from individuals who recover from COVID-19 do not contain high levels of neutralizing activity [9]; of note, immunity to sCoV was reported to wane within one year [10].

We observed winter outbreaks similar for all species of sCoV in the temperate sites, suggesting that the SARS-CoV-2 epidemics might occur in winter months in temperate regions. Interestingly, the sCoV activity in the temperate sites of China was observed to be less seasonal, with high sCoV activity seen in summer, autumn and winter. In the temperate sites excluding China, there was substantial overlap between sCoV activity and activity of influenza virus and respiratory syncytial virus, with ~50% of annual sCoV cases occurring during influenza and respiratory syncytial virus season. This would pose a big challenge to the currently strained health-care systems if SARS-CoV-2,

which causes more severe illnesses than sCoV, circulates in the same season as influenza virus and respiratory syncytial virus, both of which represent substantial burdens in morbidity and mortality [11-13]. In addition, the seasonality of different species of sCoV in our study provides important baseline data for epidemiology and modelling studies in understanding the interaction between SARS-CoV-2 and sCoV; a recent study supported the cross-reactive T cell recognition between sCoV and SARS-CoV-2 [14].

However, it should be noted that the interpretation of our findings needs to be made in the context of several limitations in our study. First, although we found that seasonality of sCoV did not differ by virus species, we could not rule out the possible scenario where SARS-CoV-2 adapts itself to a distinct circulating season from other sCOVs. This might be a result of competition between viruses, for example, the observed negative interaction between influenza A virus and rhinovirus [15]. Second, none of the included studies reported seasonality results of sCoV by age group. Infectivity of sCoV is found to be higher in children [16] whereas that of SARS-CoV-2 is higher in adults [17]. The seasonality results from those studies including all ages were consistently highly influenced by the children group. Third, our findings are based on limited data, including only 20% (8/40) of studies reporting data in the tropics. Seasonality of sCoV in the tropics is still largely unknown, especially in Sub-Saharan Africa and in tropical America. Similarly, our model was mainly informed by the data from temperate sites (accounting for 88% [2/17] of data) and therefore, the model results should be interpreted with caution. Fourth, although most temperate sites excluding China showed winter outbreaks of sCoV in our study, this finding should not be generalised to other temperate sites where sCoV seasonality was underreported (e.g. Latin America).

One of the lessons learned from the history of influenza pandemics is its transition from pandemic to seasonal circulation and the replacement of existing strain(s) with the pandemic strain. Although it is not clear how the existing sCoV initially emerged or whether they had previously replaced any viruses, understanding the global seasonality of sCoV would undoubtedly offer some clues on the

possible post-pandemic circulating season of SARS-CoV-2 and contribute to the knowledge pool for the post-pandemic preparedness for SARS-CoV-2.

Author contributions

YL conceptualised the study. YL led the data collection with contribution from XW. YL led the data analysis and visualisation. YL led the data interpretation with inputs from XW and HN. YL wrote the first draft of the report. XW and HN reviewed the draft for intellectual contents. All authors approved the final report.

Financial support

None.

Potential conflicts of interests

YL reports grants from the World Health Organization and the Foundation for Influenza Epidemiology outside the submitted work. HN reports grants from the Foundation for Influenza Epidemiology, grants from Innovative Medicines Initiative, grants from the World Health Organization, personal fees from Bill and Melinda Gates Foundation, grants and personal fees from Sanofi, grants from National Institute of Health Research, personal fees from Janssen and personal fees from AbbVie, outside the submitted work. XW reports no conflicts of interests.

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Figure 1. PRISMA flowchart. *Other reasons include no full-texts (3) and review (1).

Figure 2. Study sites included in the analysis.

Figure 3. Heat maps of global monthly activity of sCoV, IFV and RSV. sCoV = seasonal coronavirus; IFV = influenza virus; RSV = respiratory syncytial virus. For each site, the results of IFV and RSV for the same site were presented for comparison. Y-axis shows the countries where the data were from and the latitude of sites, with reference. The numbers on the right side denote the total number of sCoV cases. Six studies that did not report sCoV (of all species) were excluded.

Figure 4. Heat maps of global monthly activity of (1) Alpha-coronavirus and (2) Beta-coronavirus. Y-axis shows the countries where the data were from and the latitude of sites, with reference. The numbers on the right side denote the total number of sCoV cases.

Figure 5. Heat maps of global monthly activity of sCoV by species. Y-axis shows the countries where the data were from and the latitude of sites, with reference. The numbers on the right side denote the total number of sCoV cases.

Figure 6. Model-predicted output of monthly activity of coronavirus against A. mean-centred dew point and relative humidity; and B. mean-centred temperature and relative humidity. AAP = annual average percentage. Only sites with ≥ 100 sCoV cases were included in the model.