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MAJOR ARTICLE

Global Seasonality of Human Seasonal Coronaviruses: A Clue for Postpandemic Circulating Season of Severe Acute Respiratory Syndrome Coronavirus 2?

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Background. The ongoing pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could recur as seasonal outbreaks, a circulating pattern observed among other preexisting human seasonal coronaviruses (sCoVs). However, little is known about seasonality of sCoVs on a global scale.

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

Results. We included sCoV seasonality data in 40 sites from 21 countries. sCoVs were prevalent in winter months in most temperate sites except for China, whereas sCoVs 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 cases 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 sCoVs. Our findings offer clues to the possible postpandemic circulating season of SARS-CoV-2 and add to the knowledge pool necessary for postpandemic preparedness for SARS-CoV-2.

Keywords. COVID-19; SARS-CoV-2; seasonality; human coronavirus; temperature; relative humidity.

The novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that emerged in Wuhan, China in December 2019 has since spread worldwide [1]. SARS-CoV-2 has caused >3.6 million cases of coronavirus disease 2019 (COVID-19) and >250 000 deaths as of 6 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 2009 influenza pandemic H1N1 virus, which was later found to circulate annually in the same season as other existing seasonal influenza strains [3]. For human coronaviruses, 4 known seasonal coronaviruses (sCoVs) have long been circulating in human populations, including 2 alphacoronaviruses (NL63 and 229E) and 2 betacoronaviruses (OC43 and HKU1). Therefore, it is possible that once endemic, SARS-CoV-2, a betacoronavirus, will follow the same seasonal patterns as the sCoVs. In a recent modeling study projecting the postpandemic transmission dynamics of SARS-CoV-2, Kissler and colleagues found that recurrent outbreaks of SARS-CoV-2 in the United States (US) would probably occur during wintertime, like 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 sCoVs.

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 3 Chinese databases (China National Knowledge Infrastructure, Wanfang, and Chongqing VIP) for studies published between 1 January 1990 and 15 April 2020 that reported monthly or weekly activity of sCoVs (ie NL63, 229E, OC43, and HKU1). We also searched 2 preprint databases (medRxiv and bioRxiv) for preprints between 1 January 2020 and 15 April 2020. The detailed search strategy is shown in the Supplementary Appendix. Selection criteria were applied as follows:

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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 (eg, 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, SARS-CoV-2, or Middle East respiratory syndrome coronavirus; OR
- Studies reporting <25 coronavirus-positive cases; OR
- Studies reporting respiratory infections only among those under special medical conditions (eg, patients with chronic obstructive pulmonary disease or patients infected with human immunodeficiency virus); OR
- Studies focusing on specific settings other than the community (eg, hospital, school, care center); 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 (Y. L. and X. W.) extracted the data from the literature, independently, using a template that was described elsewhere [5]. In brief, 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 (ie, *Alphacoronavirus* and *Betacoronavirus*) and by species (ie, NL63, 229E, OC43, and HKU1). To compare the seasonality of sCoVs with other 2 common respiratory viruses, influenza virus and respiratory syncytial virus (RSV), we also extracted monthly aggregated number of influenza and RSV cases from each study, if available. For included studies where influenza virus and/or RSV 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 RSV seasonality [5].

We also conducted quality assessment for each eligible study using a quality assessment form comprising 3 brief questions regarding data representativeness, test practice, and timely reporting as described elsewhere [5]. When 2 or more studies were available for a site, the study with the 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/RSV

We plotted heat maps displaying the activity of sCoV, influenza virus, and RSV for each site sorted by latitude. To understand how the peak activity of each virus overlapped, we identified for each virus the top 3 months with highest AAP as the first step; we then calculated the cumulative AAP of another virus that occurred during these 3 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 modeled monthly AAP of sCoV activity with meteorological predictors, including mean-centered temperature, relative humidity, and dew point, in a locally estimated scatterplot smoothing model as described elsewhere [5]. Details of the model are available in the Supplementary Appendix. In brief, we included 2 models based on the model selection results: 1 model with mean-centered dew point and relative humidity as predictors and the other with mean-centered temperature and relative humidity as predictors. Studies were eligible for this analysis if they reported >100 positive sCoV cases. We conducted 2 sets of models that excluded 2 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 other 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 (Figure 1). These studies represented 40 sites from 21 countries (Figure 2 and Supplementary Figure 1). The number of positive sCoVs ranged from 25 to 39 573 across sites. Polymerase chain reaction (PCR) was used to detect sCoV in all the studies. Six of the 40 studies focused on 1 or 2 particular sCoV species and therefore did not contribute to the results for the overall sCoVs (all species). Details on these studies and their quality assessment are in Supplementary Tables 1 and 2.

Global Seasonality of sCoVs

High activity of sCoVs, 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 (Supplementary Figure 2). No difference in study quality was observed between studies reporting sCoVs 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 alphacoronaviruses and betacoronaviruses (Figures 4 and 5).

In the temperate sites excluding China, 53.1% of the sCoV cases (interquartile range [IQR], 34.6%–61.9%) occurred during influenza season (defined by the top 3 months with highest AAP), and 49.6% of the sCoV cases (IQR, 30.2%–60.2%) occurred during RSV season. Less overlap was observed in the tropical sites as well as temperate sites in China between sCoV activity and influenza/RSV activity (20% during influenza season and 29% during RSV season; Supplementary Figure 3).

Meteorological Factors and Seasonality of sCoVs

A total of 17 studies with >100 positive sCoV cases were included in our model (including 2 sites from temperate China). Low temperature with higher relative humidity was found to be associated with higher proportion of sCoV cases; dew point

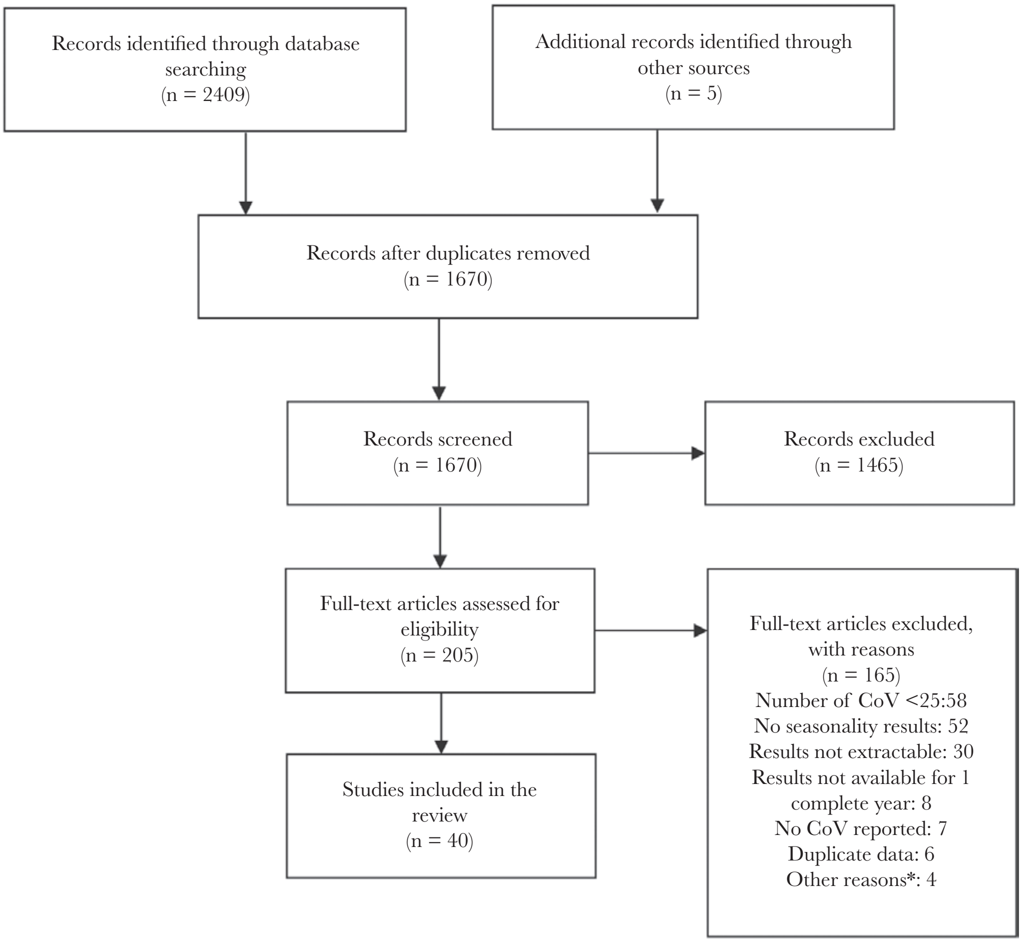

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. *Other reasons include no full texts (3) and review article (1). Abbreviation: CoV, coronavirus.

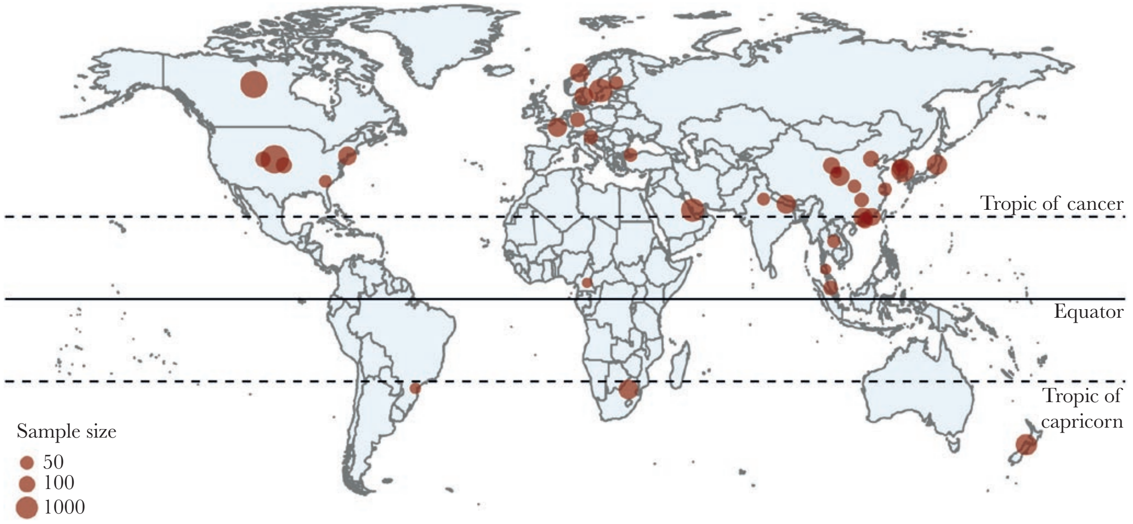

Figure 2. Study sites included in the analysis.

was observed to have similar relationship with sCoV activity as temperature (Figure 6). Similar results were found from the model excluding 2 temperate sites from China (Supplementary Figure 4).

DISCUSSION

At the time of writing, >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 sCoVs, the genetic relatives 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 sCoVs in 40 sites from 21 countries. We found that sCoVs occurred mainly in winter months in temperate sites except for China and was less seasonal in China and tropical sites. We highlighted a high proportion of co-circulating sCoV cases during influenza virus and RSV seasons, implicating the possibility

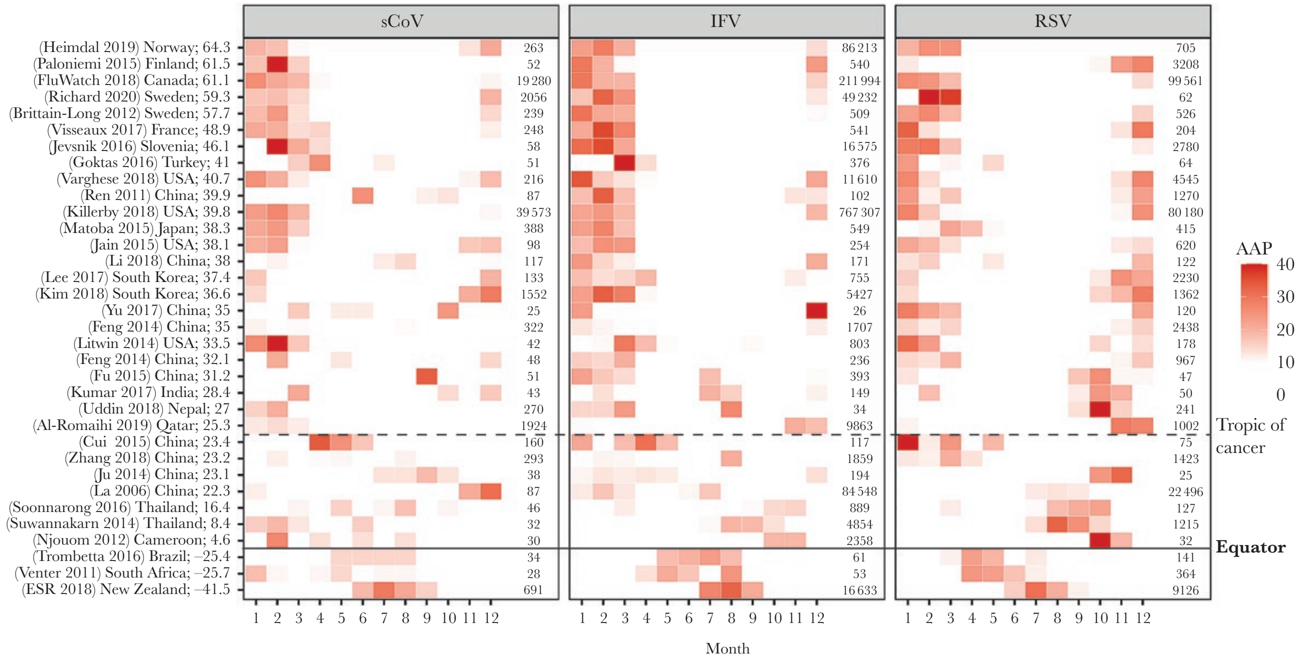

Figure 3. Heat maps of global monthly activity of seasonal coronaviruses (sCoVs), influenza virus (IFV), and respiratory syncytial virus (RSV). For each site, the results of IFV and RSV for the same site were presented for comparison. The y-axis shows the countries where the data were from and the latitude of sites (references are shown in the Supplementary Appendix). Numbers on the right side denote the total number of sCoV cases. Six studies that did not report sCoVs (of all species) were excluded.

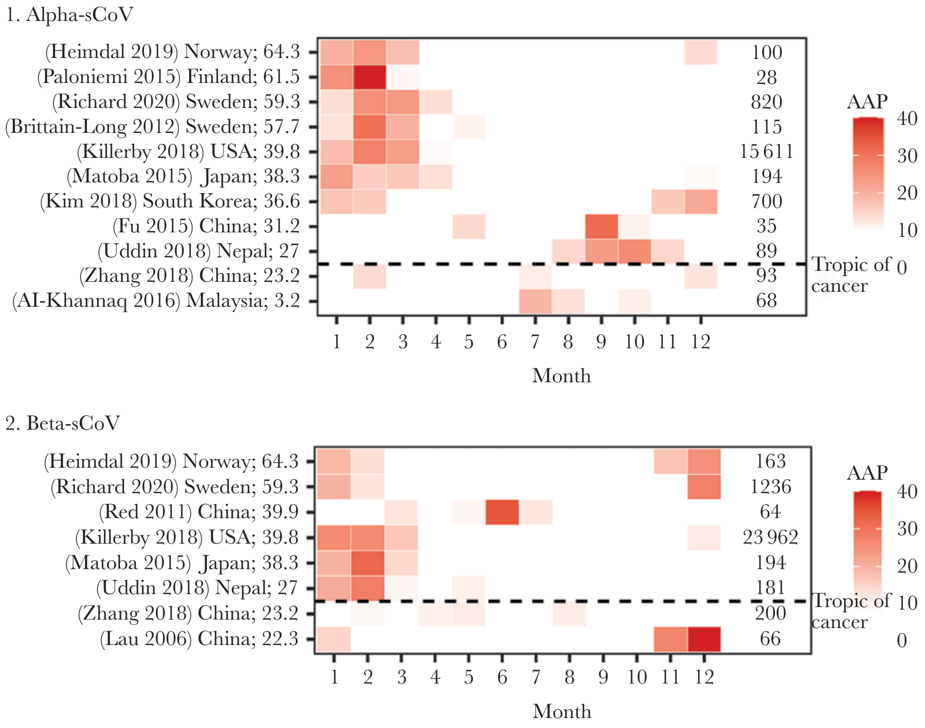

Figure 4. Heat maps of global monthly activity of alphacoronaviruses and betacoronaviruses. The y-axis shows the countries where the data were from and the latitude of sites (references are shown in the Supplementary Appendix). Numbers on the right side denote the total number of seasonal coronavirus cases. Abbreviations: AAP, annual average percentage; sCoV, seasonal coronavirus.

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 sCoVs provides a clue for the possible circulating timing of SARS-CoV-2 after the initial pandemic. A modeling study reported that SARS-CoV-2 will likely enter into regular circulation starting from 2021 or 2022 in the US and synchronize with sCoVs, 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 1 year [10].

We observed winter outbreaks similar for all species of sCoVs in the temperate sites, suggesting that the SARS-CoV-2 epidemics might occur in winter months in temperate regions. Interestingly, 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 RSV, with approximately 50% of annual sCoV cases occurring during influenza and RSV season. This would pose a big challenge to currently strained healthcare systems if SARS-CoV-2, which causes more severe illness than sCoVs, circulates in the same season as influenza virus and RSV, both of which represent substantial burdens in morbidity and mortality [11–13]. In addition, the seasonality of different species of sCoVs in our study provides important baseline data for epidemiology and modeling studies in understanding the interaction between SARS-CoV-2 and sCoVs; a recent study supported the cross-reactive T-cell recognition between sCoVs 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 sCoVs 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 sCoVs 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 pediatric group. Third, our findings are based on limited data, including only 20% (8/40) of studies reporting data in the tropics. Seasonality of sCoVs

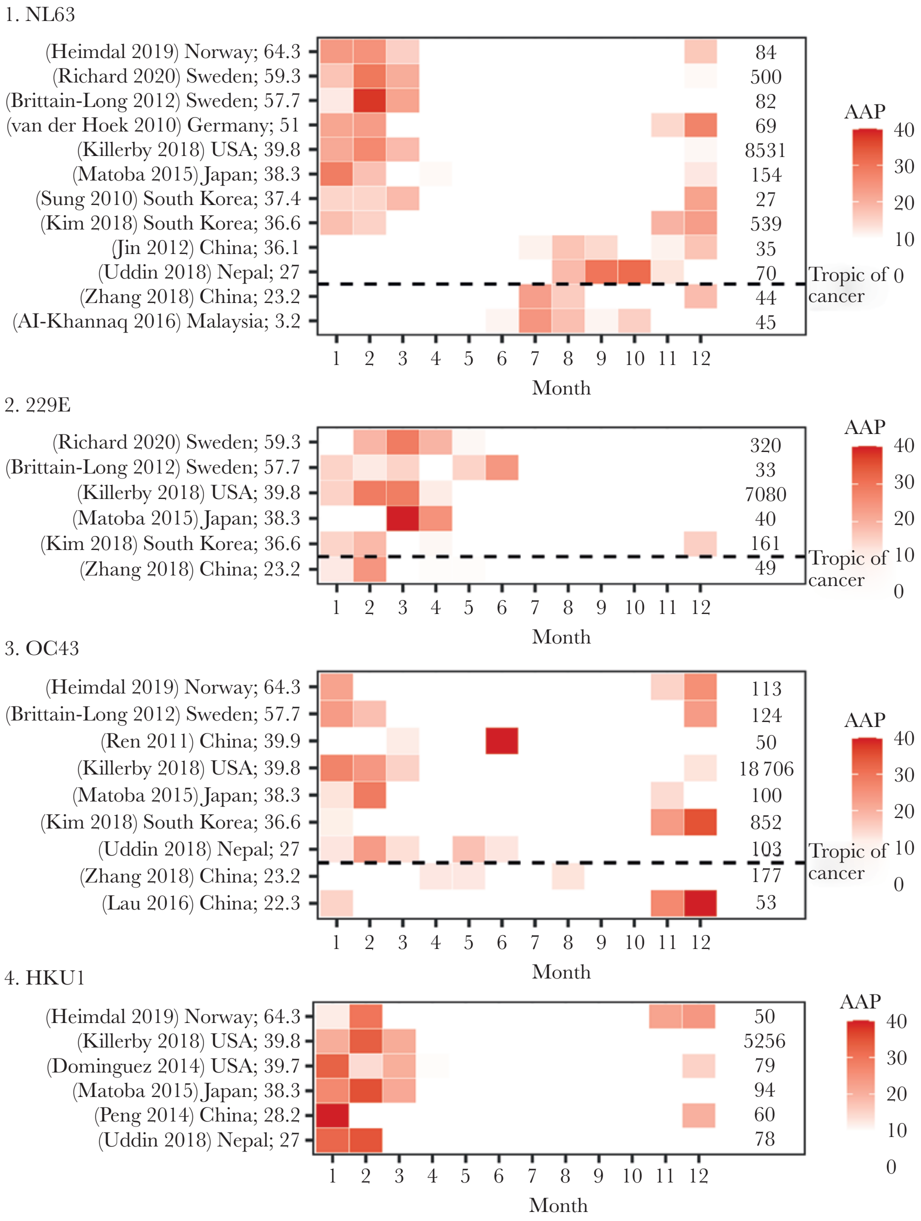

Figure 5. Heat maps of global monthly activity of seasonal coronaviruses (sCoVs), by species. The y-axis shows the countries where the data were from and the latitude of sites (references are shown in the Supplementary Appendix). Numbers on the right side denote the total number of sCoV cases.

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 sCoVs in our study, this finding should not be generalized to other temperate sites where sCoV seasonality was underreported (eg, 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 sCoVs initially emerged or whether they had previously replaced any viruses, understanding the global seasonality of sCoVs would undoubtedly offer some clues on the possible postpandemic circulating season of SARS-CoV-2 and contribute to the knowledge pool for the postpandemic preparedness for SARS-CoV-2.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are

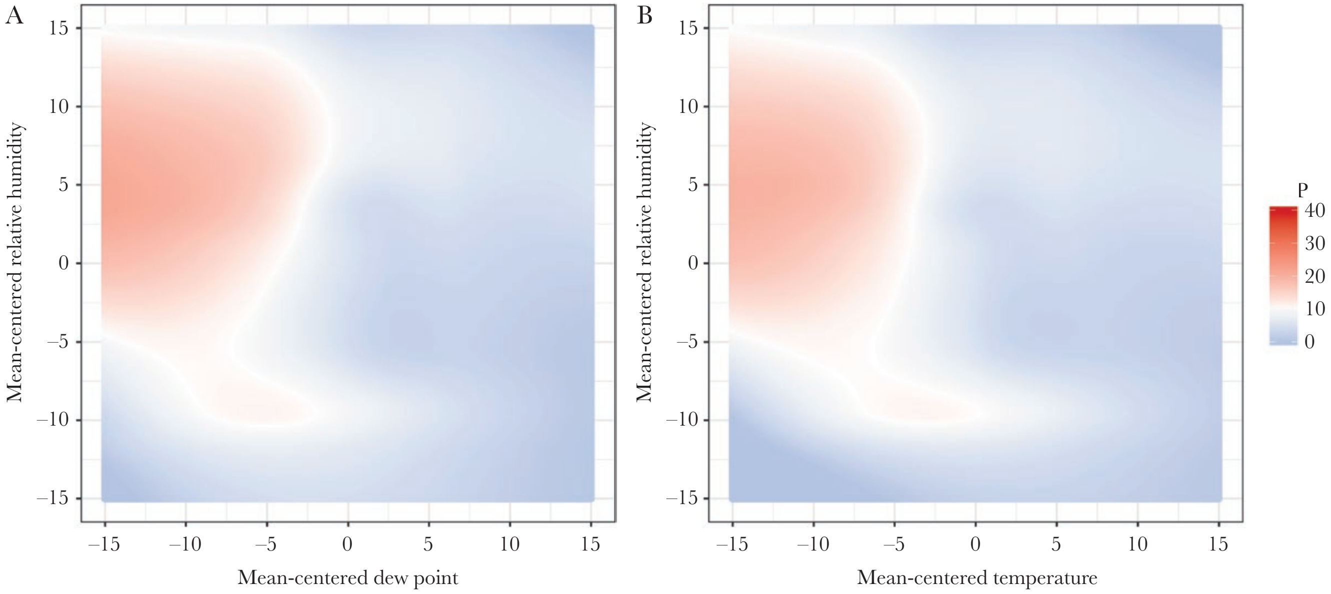

Figure 6. Model-predicted output of monthly activity of coronavirus against mean-centered dew point and relative humidity (*A*) and mean-centered temperature and relative humidity (*B*). Only sites with ≥100 seasonal coronavirus cases were included in the model. Abbreviation: AAP, annual average percentage.

not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Y. L. conceptualized the study; Y. L. led the data collection with contributions from X. W; Y. L. led the data analysis and visualization; Y. L. led the data interpretation with input from X. W. and H. N.; Y. L. wrote the first draft of the report; and X. W. and H. N. reviewed the draft for intellectual content. All authors approved the final report.

Potential conflicts of interest. Y. L. reports grants from the World Health Organization (WHO) and the Foundation for Influenza Epidemiology, outside the submitted work. H. N. reports grants from the Foundation for Influenza Epidemiology, the Innovative Medicines Initiative, the WHO, Sanofi, and the National Institute for Health Research, and personal fees from the Bill & Melinda Gates Foundation, Sanofi, Janssen, and AbbVie, outside the submitted work. X. W. reports no conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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