Reply to Letter by Li et al: Estimating the global epidemiology of endemic human coronaviruses: A cautionary note

Sema Nickbakhsh[1*], Antonia Ho[1], Diogo F.P. Marques[2], Jim McMenamin[2], Rory N. Gunson[3], Pablo R. Murcia[1]

[1]MRC-University of Glasgow Centre for Virus Research, Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK.

[2]Public Health Scotland, NHS National Services Scotland, G2 6QE Glasgow, UK.

[3]West of Scotland Specialist Virology Centre, NHS Greater Glasgow and Clyde, Glasgow, UK.

***Corresponding author:** Sema Nickbakhsh, MRC-University of Glasgow Centre for Virus Research, 646 Bearsden Road, Glasgow, G61 1QH, email: sema.nickbakhsh@glasgow.ac.uk

Disclaimer: Funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Letter to the Editor in reply to Li et al.

Word count: 744 words

To The Editor – We read with interest the Letter by Li et al. [1] reporting on the global prevalence of endemic human coronaviruses. The last decade has witnessed an expansion of global surveillance efforts in influenza and respiratory syncytial virus (RSV) infections, leading to an increased recognition of the importance of these viruses particularly in low- and middle-income settings [2]. However, a paucity of epidemiological research exists for other respiratory viruses, as highlighted by the WHO's Battle against Respiratory Viruses initiative [3].

Such knowledge is currently hindered by the lack of capacity of many diagnostic laboratories, including those of high-income countries, to simultaneously test for multiple viruses. These testing approaches are needed to accurately characterise the epidemiology of each respiratory virus, given their overlapping clinical presentations [4]. Furthermore, laboratories may employ different diagnostic methods for different viruses, from nucleic acid or antigen detection to virus culture, complicating reliable comparisons across viruses. In the absence of standardised surveillance, global comparisons of coronavirus epidemiology must be conducted with caution.

Li et al [1] included 128 studies in a systematic review describing the epidemiology of endemic coronaviruses. To enable valid comparisons, meta-analyses necessitate careful scrutiny of eligibility criteria to ensure standardisation of study design, including case definitions and denominator data, the period of observation, and stratification or adjustment by age and illness severity. Li et al. [1] have not described their study inclusion and exclusion criteria. Hence, it is not possible to examine the validity of their pooled estimates. In a similar vein, the comparison of our prevalence estimates [5] with that of Monto et al. [6] is not valid given the patient-based and community-based study designs respectively.

Studies by Monto et al. [6] provide a rare insight into the true community incidence of infections, however much respiratory virus epidemiology research relies on healthcare data. Li et al [1] do highlight the potential for bias in their study owing to small sample sizes. However, inter-country comparisons of infection prevalence will also be biased by disparities in healthcare infrastructures, clinical case definitions, and diagnostic laboratory methodologies. Test frequency denominator data are also critical because healthcare seeking and clinician testing behaviour may vary within and between countries and over time. It is important to consider that the clinical significance of respiratory virus detections is not always clear and may vary between populations. Furthermore, in contrast to that implied by Li et al. [1], patient-based studies may under-estimate prevalence in the general population owing to a high proportion of asymptomatic infections [7].

The temporal dynamics of viral respiratory infections further complicates the reliability of global comparisons of infection occurrence, as incidence varies across months and years. The drivers of respiratory virus seasonality are not well understood but are likely to be a complex interplay of weather-dependent virus survivability and transmissibility, social mixing behaviours, population immunity, underlying comorbidities, and the ecological landscape of cocirculating respiratory viruses and bacteria. The relative importance of each factor, and how this varies globally, remains unclear.

In temperate regions of the Northern Hemisphere, influenza, RSV, and endemic coronaviruses typically exhibit peak incidence in winter months. The comparability of our study with Monto et al. [6] in this respect reflects how the timing of peak healthcare burden mirrors peak incidence of infection in the community. However, in the tropics and subtropics, as well as temperate regions of the Southern

Hemisphere, seasonality is more complex; with respect to influenza, some locations experience multiple peaks with regular outbreaks coinciding with rainy seasons, whilst others experience a year-round incidence [8, 9]. Li et al. [1] presented the seasonal distribution of endemic coronavirus detections based on five (unspecified) pooled studies from the Northern Hemisphere. Although their findings of peak frequency in January/February is consistent with ours and that of Monto et al. [6], it is unclear which population sources and denominators informed their estimates [1]. Surveillance spanning entire calendar years is necessary for reliable comparisons of prevalence estimates geographically. It is unclear which seasons were captured by Li et al. [1].

In the context of the COVID-19 pandemic, it is currently unclear whether the causative virus, SARS-CoV-2, will establish endemicity. One modelling study predicts the peak occurrence of SARS-CoV-2 is possible in both summer and winter months for a range of scenarios governing population susceptibility and the duration of immunity [10]. Extrapolating from endemic human coronaviruses, it is likely that winter seasonality will be an important feature of the transmission dynamics of SARS-CoV-2 in temperate regions, if long-term persistence is established.

References

1. Li P, Liu J, Ma Z, Bramer W, M., Pepelenbosch M, P., Pan Q. Estimating global epidemiology of low pathogenic human coronaviruses relating to the COVID-19 context. The Journal of Infectious Diseases **2020**.
2. Bresee J, Fitzner J, Campbell H, et al. Progress and Remaining Gaps in Estimating the Global Disease Burden of Influenza. Emerging infectious diseases **2018**; 24:1173-7.
3. WHO. Research needs for the Battle against Respiratory Viruses (BRaVe). Available at: https://www.who.int/influenza/patient_care/clinical/BRaVe_Research_Agenda_2013.pdf?ua=1. Accessed 13 May 2020.
4. Nickbakhsh S, Thorburn F, B VONW, Mc MJ, Gunson RN, Murcia PR. Extensive multiplex PCR diagnostics reveal new insights into the epidemiology of viral respiratory infections. Epidemiology and infection **2016**; 144:2064-76.
5. Nickbakhsh S, Ho A, Marques DFP, McMenamin J, Gunson RN, Murcia PR. Epidemiology of seasonal coronaviruses: Establishing the context for COVID-19 emergence. J Infect Dis **2020**.

6. Monto AS, DeJonge P, Callear AP, et al. Coronavirus occurrence and transmission over 8 years in the HIVE cohort of households in Michigan. J Infect Dis **2020**.
7. Hayward AC, Fragaszy EB, Bermingham A, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. The Lancet Respiratory medicine **2014**; 2:445-54.
8. Bloom-Feshbach K, Alonso WJ, Charu V, et al. Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. PloS one **2013**; 8:e54445.
9. Moura FE. Influenza in the tropics. Current opinion in infectious diseases **2010**; 23:415-20.
10. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science **2020**.