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Letter to the editor

Transmission of SARS-CoV-2 from pre and asymptomatic infected individuals: a systematic review update

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To the Editor,

The transmission of SARS-CoV-2 is still incompletely understood, and the relative contribution and importance of transmission from individuals without COVID-19 symptoms remains unclear.

We previously reviewed the available evidence on transmission of SARS-CoV-2 from asymptomatic or presymptomatic individuals. We only included studies investigating the transmission from an asymptomatic or presymptomatic case (or cases) reporting the serial PCR cycle threshold readings, as well as viral culture, to establish the likelihood of the presence of replication-competent virus and/or genome sequencing in order to also establish a

probable common viral ancestry [1]. With searches to 31 March 2021, we included 18 studies; these studies provided probable evidence of transmission from asymptomatic or presymptomatic individuals. We were unable to quantify the likely fraction of transmission occurring from asymptomatic or presymptomatic individuals from the available studies.

We have updated our literature searches to 31 March 2022, following the same search strategy [1].

Although 12 months have passed since the previous search date for our review, we found only one additional eligible study investigating potential asymptomatic or presymptomatic transmission that used repeat PCR testing and genome sequencing [2]. This study reported three case studies of transmission presumed to be from identified individuals, whom, at the relevant time of exposure, were either asymptomatic (1 case) or presymptomatic (2 cases), with genome sequencing identifying no differences in single nucleotide polymorphisms between each index and linked secondary case [2].

Four other studies reporting the results of viral culture or genome sequencing of samples from asymptomatic or presymptomatic individuals along with repeat PCR testing data did not investigate the specific instances of presumed transmission, but provided evidence supporting our conclusions that individuals with no symptoms could be shedding a replication-competent virus, or a virus with similar gene sequences to that identified in those exposed to close contact. One of the studies, by Van den Besselaar et al., pointed out the difficulties in achieving a comprehensive symptom assessment in a nursing home, suggesting that the data on presumed asymptomatic or presymptomatic individuals need cautious interpretation [3].

These data are too limited to justify a full update for the review. It is surprising that so little new evidence on the transmission of SARS-CoV-2 from asymptomatic and presymptomatic individuals is available. Restrictions on movement and contact, designed to reduce transmission, appear to assume that transmission from asymptomatic and presymptomatic individuals is prevalent. We call for further research on the transmission from asymptomatic

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and presymptomatic individuals by using high quality methods to establish reliable evidence on the transmission of this virus.

Transparency declaration

TJ's competing interests are accessible at: <https://restoringtrials.org/competing-interests-tom-jefferson>. CJH holds grant funding from the NIHR, the NIHR School of Primary Care Research, the NIHR BRC Oxford and the World Health Organization for a series of living rapid review on the modes of transmission of SARs-CoV-2 reference WHO registration No2020/1077093. He has received financial remuneration from an asbestos case and given legal advice on mesh and hormone pregnancy test cases. He has received expenses and fees for his media work including occasional payments from BBC Radio 4 Inside Health and The Spectator. He receives expenses for teaching EBM and is also paid for his GP work in NHS out of hours (contract Oxford Health NHS Foundation Trust). He has also received income from the publication of a series of toolkit books and for appraising treatment recommendations in non-NHS settings. He is Director of CEBM and is an NIHR Senior Investigator. JMC holds grants from the Canadian Institutes for Health Research on acute and primary care preparedness for COVID-19 in Alberta, Canada and was the primary local Investigator for a *Staphylococcus aureus* vaccine study funded by Pfizer for which all funding was provided only to the University of Calgary. He is co-investigator on a WHO funded study using integrated human factors and ethnography approaches to identify and scale innovative IPC guidance implementation supports in primary care with a focus on low-resource settings and using drone aerial systems to deliver medical supplies and PPE to remote First Nations communities during the COVID-19 pandemic. He also received support from the Centres for Disease Control and Prevention to attend an Infection Control Think Tank Meeting. He is a member and Chair of the WHO Infection Prevention and Control Research and Development Expert

Group for COVID-19 and a member of the WHO Health Emergencies Programme Ad-hoc COVID-19 IPC Guidance Development Group, both of which provide multidisciplinary advice to the WHO and for which no funding is received and from which no funding recommendations are made for any WHO contracts or grants. He is also a member of the Cochrane Acute Respiratory Infections Working Group. AP holds grants from the NIHR School for Primary Care Research. IJO and EAS have no interests to disclose.

Author's contributions

TJ and CH designed the protocol and wrote the draft manuscript. ES, TJ, JC and CH extracted and checked screen and data. All authors contributed to the protocol and manuscript, and approved the final version.

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