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The Consequences of Isolating at Home

To the Editor—We welcome the first prospective study of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) household transmission in the United States (US) by Lewis and colleagues [1]. Household transmission of SARS-CoV-2 is an important contributor to R_0 and cannot be realistically addressed by continuous masking and social distancing. Use of data from contact tracing likely leads to an underestimate of household transmission [2]. Prospective studies like the one from Lewis et al, that test all household contacts regardless of symptoms at multiple points in time, are needed to measure the true household secondary attack rate (SAR).

The SAR of 29% among household contacts (55% among households) in [1] is impressive—double that of early estimates of approximately 10%–15% from studies that relied primarily on contact tracing data, and higher than the mean estimate of 19% (95% confidence interval, 15%–22%) found in a recent meta-analysis based on household data worldwide [3]. Even so, there is reason to believe the Lewis et al finding is not an outlier, and future estimates from the US may be even higher, due to 3 features of their study.

First, a key strength of the study is its completion during a shelter-in-place period when exposure of multiple household members to a common source was less likely. In our experience, multiple family members frequently test positive after attending a communal event (eg, barbecue, funeral, vacation, wedding). Such perihousehold transmission could boost the SAR in areas with significant community-level transmission [3, 4].

Second, key demographic groups affected by the pandemic were underrepresented in the population studied in Wisconsin and Utah. The population was largely non-Hispanic, white, and healthy: <10% had any cardiovascular disease, and none of the 188 household contacts were hospitalized [5]. Diabetes mellitus was seen in 5% of primary patients and 3% of household contacts (8 persons total), whereas a recent national US survey found a diabetes prevalence of 10.5% [6]. If the authors' finding that diabetic individuals are more susceptible to secondary infection holds true, this would translate to a higher SAR in the US population.

Finally, most households were tested after secondary transmission had already occurred, and testing was not performed frequently enough to reliably detect asymptomatic or mild cases with short-lived viral shedding. Households were sampled relatively late—a median of 11 days (interquartile range, 8–16) from symptom onset of the index case, and 83% of positive household contacts were already polymerase chain reaction positive at the initial household visit. Thus, actual secondary transmission was rarely observed. Secondary cases with mild illness may have tested negative by the initial visit, though they may have been captured via antibody testing [7]. Additionally, since samples were collected on study days 0 and 14, asymptomatic or mild cases that occurred and cleared in the 2 weeks between sampling may have been missed, as such cases may not seroconvert by day 14.

Clearly, household transmission happens frequently despite efforts to self-isolate, and new strategies are needed to prevent coronavirus disease 2019 transmission in the home. As access to SARS-CoV-2 testing improves, and especially if antigen-based at-home rapid testing becomes available, increased opportunities to interrupt household transmission should become possible.

Note

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Jessica T. Lin,[1] Katie R. Mollan,[2] and Carla Cerami[3]

[1]Institute of Global Health and Infectious Diseases, University of North Carolina, Chapel Hill, USA, [2]Gillings School of Global Public Health, University of North Carolina, Chapel Hill, USA, and [3]Medical Research Council Unit The Gambia, London School of Hygiene and Tropical Medicine, Fajara, The Gambia.

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Correspondence: J. T. Lin, Division of Infectious Diseases, University of North Carolina, 130 Mason Farm Road, Suite 2115, CB #7036, Chapel Hill, NC 27599, USA (jessica_lin@med.unc.edu).

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Asymptomatic Reinfection in 2 Healthcare Workers From India With Genetically Distinct Severe Acute Respiratory Syndrome Coronavirus 2

To the Editor—To et al [1] recently reported a case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

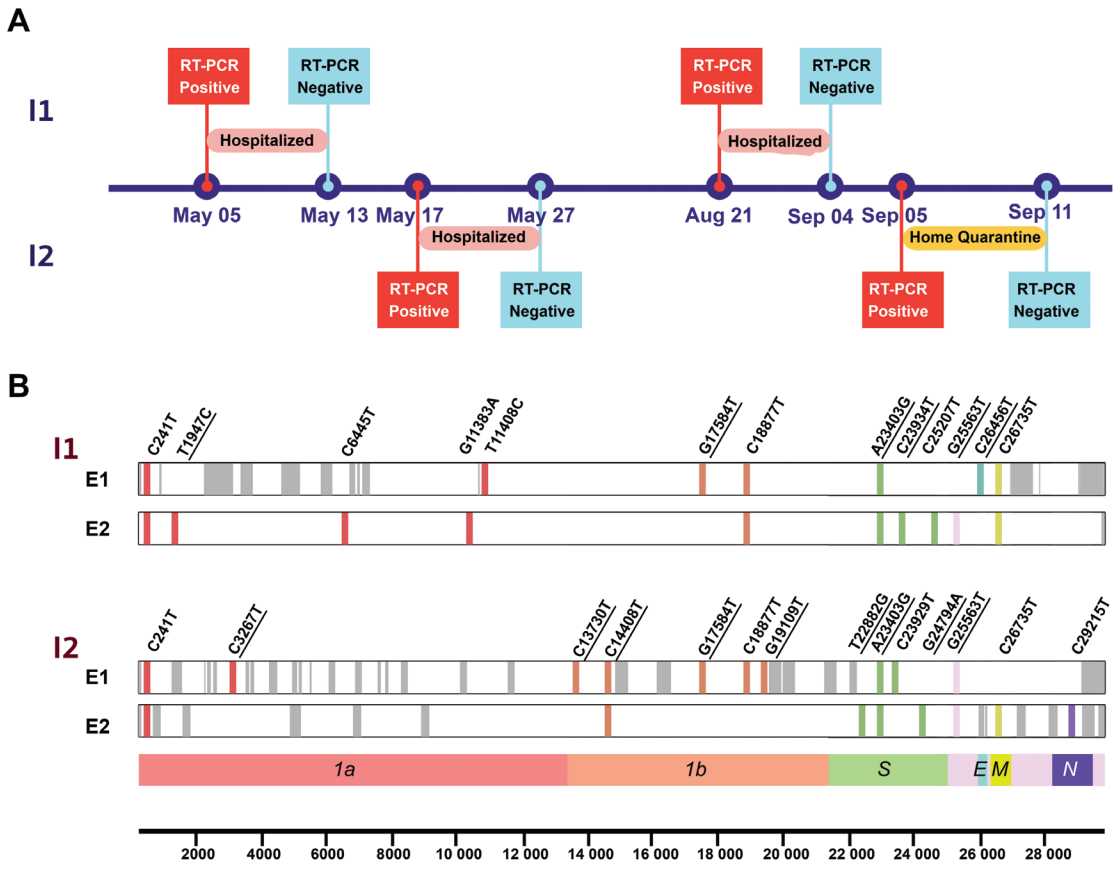

Figure 1. *A*, Timelines of severe acute respiratory syndrome coronavirus 2 in individuals I1 and I2. *B*, Genetic variants in isolates for the 2 episodes (E1 and E2) for individuals I1 and I2. Nonsynonymous variants have been underlined and the gaps in the genome are marked in gray. Abbreviation: RT-PCR; reverse-transcription polymerase chain reaction.

reinfection confirmed by genome sequencing. Additional reports of genetically characterized reinfections have emerged [2, 3], raising pertinent questions on the longevity of immune response in SARS-CoV-2 infection. In all previous reports, patients had symptoms in 1 or both of the episodes. Here we report asymptomatic SARS-CoV-2 reinfection in 2 healthcare workers detected during routine surveillance. The report highlights the possibility of undetected SARS-CoV-2 reinfections and the need for surveillance of SARS-CoV-2 reinfections in healthcare systems.

We describe 2 individuals, a 25-year-old man (I1) and 28-year-old woman (I2), both healthcare workers posted in the coronavirus disease 2019 (COVID-19) unit of a tertiary hospital in North India, who tested positive for SARS-CoV-2 by reverse-transcription polymerase chain reaction (RT-PCR) on 5 May 2020 and 17 May 2020, respectively. Though both individuals were asymptomatic, they were hospitalized as per institutional policy on 5 May and 18 May, respectively. Subsequently, they tested negative for SARS-CoV-2 by RT-PCR on 13 May and 27 May, respectively. After resuming duties in the hospital, the 2 individuals tested positive again for SARS-CoV-2 on 21 August and 5 September and further tested negative on the 14th and sixth days, respectively. Both individuals were again asymptomatic but had a higher viral load on the second episode of reinfection (cycle threshold values of 36 and 16.6 for I1 and 28.16 and 16.92 for I2 for the first and second episodes, respectively). The timeline of the 2 episodes of infection in the individuals are summarized in Figure 1A.

Since RNA from the nasopharyngeal/oropharyngeal swabs were archived, after informed consent (IHEC-CSIR-IGIB/IHEC/2020–21/01) the sequencing-ready libraries were prepared using capture-based (TWIST Biosciences) as well as amplicon-based (COVIDSeq, Illumina) approaches. The libraries were sequenced on 75 bp × 2 paired-end recipe on Illumina MiSeq. Genomes were assembled at an average of 13 684X coverage after merging the datasets, partially covering the SARS-CoV-2 reference genome (NC_045512.2) at 89.08% and 99.96%, respectively, for the 2 episodes for I1 and 85.60% and 92.14% for I2. Analysis of the genomes using a previously published protocol [4] for loci covered in both the genomes revealed 9 and 10 unique variant differences between the virus isolates from the 2 episodes of infection for I1 and I2, respectively (Figure 1B). Of the unique variants between the pair of samples, 7 variants each for the 2 individuals

mapped to predicted immune epitopes [5].

Taken together, our analysis suggests that asymptomatic reinfection may be a potentially underreported entity. Genetically distinct SARS-CoV-2 rules out persistent viral shedding or reactivation. Both individuals had a higher viral load during reinfection, highlighting the need for continuous surveillance. It is noteworthy that a genetic variant 22882T>G (S: N440K) found during reinfection in I2 possibly confers resistance to neutralizing antibodies [6]. To the best of our knowledge, this is one of the earliest reports of genetically characterized reinfection from India.

Notes

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Vivek Gupta,[1,a] Rahul C. Bhoyar,[2,a] Abhinav Jain,[2,3,a] Saurabh Srivastava,[1] Rashmi Upadhayay,[1] Mohamed Imran,[2] Bani Jolly,[2,3] Mohit Kumar Divakar,[2,3] Disha Sharma,[2,3] Paras Sehgal,[2,3] Gyan Ranjan,[2,3] Rakesh Gupta,[1] Vinod Scaria,[2,3] and Sridhar Sivasubbu[2,3]

[1]Government Institute of Medical Sciences, Greater Noida, India, [2]Council of Scientific and Industrial Research, Institute of Genomics and Integrative Biology, New Delhi, India, and [3]Academy of Scientific and Innovative Research, Ghaziabad, India

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[a]V. G., R. C. B., and A. J. contributed equally to this work.

Correspondence: V. Scaria, G. N. Ramachandran Knowledge Center for Genome Informatics, CSIR–Institute of Genomics and Integrative Biology, Sukhdev Vihar, New Delhi, India, 110025 (vinods@igib.in).

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Menopause Status and Coronavirus Disease 2019 (COVID-19)

To the Editor—We greatly appreciate the publication of this important research article, for its exploration of the connection of estradiol levels and menopausal status with outcomes from infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in women [1]. This study has been greatly needed from the inception of the coronavirus disease 2019 (COVID-19) pandemic. Sadly, unlike this research, most published data lacks stratification of women into pre- and postmenopausal categories, making the determinations made in this article an impossibility [2].

A pervasive lack of understanding of the myriad effects that estradiol plays throughout the female body has resulted in the exclusion of this critical information from consideration in much research and in the clinical care of women.

We advocate for the use of physiologically dosed human-identical transdermal estradiol as hormone replacement, combined with human-identical cyclic progesterone, recently menopausal women without contraindications. Our recommendations are based on a significant body of preclinical and clinical data [3]. This study's findings of a distinctly protective effect of estradiol in women with functioning ovaries is in complete alignment with our position and with science [4].

Estradiol has receptors on all innate and adaptive immune cells and is a key player in the immune response, which includes both proinflammatory and anti-inflammatory functions [5]. Estradiol (E2) is a modulator of the renin-angiotensin-aldosterone system, a major force in the instigation of the inflammatory response and in the resolution of inflammation [6]. E2 plays a major role in regulating lipid mediators and peptides involved in the processes needed for an optimal immune response, improving the likelihood of a successful outcome in the fight against an infectious agent such as SARS-CoV-2 [7].

The use of hormone replacement therapy gains further support from this excellent study. The harmful impact of ovarian senescence affects all organ systems, inclusive of the cardiovascular system, the neurological system, the gut, the musculoskeletal system, the genitourinary system, and now, in the age of the COVID-19 pandemic, its vital role with the immune system is clear [8].

Given the potential for serious, negative effects ensuing from a state of estradiol deficiency, heightened by the COVID-19 pandemic, not only should appropriate postmenopausal women be considered for hormone replacement therapy, but women being treated with aromatase inhibitors and estrogen receptor antagonists should be counseled on the risks and benefits of those drugs, personalized in each case, in light of the findings of this study.

Note

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