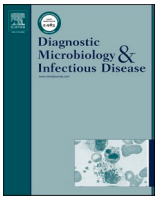
Diagnostic Microbiology & Infectious Disease 111 (2025) 116742

Contents lists available at ScienceDirect

Diagnostic Microbiology & Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio



Letter to the Editor

COVID-19 study quantifying daily viral loads confirms throat samples are key to early diagnosis

We appreciated the recent Letter by Todsen in *Diagnostic Microbiology and Infectious Disease*, highlighting the underappreciated role of the throat during early SARS-CoV-2 infection [1]. Unique longitudinal viral-load data from our COVID-19 household transmission study in Southern California strongly supports this point [2,3].

Between September 2020 and March 2022, 415 individuals from households where at least one member was recently diagnosed with COVID-19 were enrolled and collected daily nasal-swab, throat-swab, and saliva specimens for approximately 2 weeks. A subset of household contacts tested negative for SARS-CoV-2 at enrollment but later became infected (and continued daily specimen collection). Specimens from these individuals with incident infection provided an opportunity to quantify longitudinal viral loads in paired specimen types from the earliest stage of naturally acquired infection.

Quantitative, daily viral loads from paired specimens underscore the importance of the throat during early SARS-CoV-2 infection in humans. In 71 % (10 of 14) of individuals with incident infection, SARS-CoV-2 was detectable in the throat at least 1 day before the nose, with detection in the throat preceding the nose by a median of 2.5 days. Additionally, 64 % (9 of 14) of individuals reached high and presumably infectious viral loads in the throat before the nose [2]. Our data from naturally acquired infection of household contacts aligns with the SARS-CoV-2 human challenge study, in which infectious virions were detected in the throat at least 1 day before the nose for 67 % (12 of 18) of participants [4].

Testing the throat in addition to the nose increases clinical sensitivity during early infection. Using our quantitative viral load measurements, we predicted that COVID-19 antigen rapid diagnostic tests (Ag-RDTs) would exhibit up to 29.6 % higher clinical sensitivity during early infection when the throat and nose are tested, relative to testing the nose alone.[3] Two field evaluations including participants with early infections demonstrated similar (~20 %) increases in clinical sensitivity of the throat and nose with Ag-RDTs, compared to nose alone [5,6].

In contrast, two other field evaluations reported that throat and nose Ag-RDT was not superior to nose alone.[7,8] However, in one study, the high PCR positivity rate (83 %) among community members on the day of evaluation [7] suggests a population skewed towards later infection when the benefit of testing the throat is lower. In the other study,[8] clinical sensitivities were calculated against different references: nose-only Ag-RDTs were compared against nose-only PCR, while nose-throat Ag-RDTs were compared against nose-throat PCR. We have previously demonstrated that clinical sensitivity is overestimated when the nose alone is used as a reference, compared to both nose and throat [3].

We previously wrote a Correspondence in *Clinical Infectious Diseases* urging test manufacturers to validate their assays for use with throat swab specimens in the United States to enhance early detection [9]. We also encourage additional studies to observe early, longitudinal viral load dynamics in paired specimen types including throat swabs for other respiratory viral pathogens, such as influenza and RSV [10]. The throat appears to play an important role in early respiratory viral infection, and subsequently presents a unique opportunity for earlier detection of infection and more efficacious public-health and therapeutic interventions.

Funding Information

This work was supported by the Bill & Melinda Gates Foundation (grant INV-023124 to R.F.I.) and the Ronald and Maxine Linde Center for New Initiatives at the California Institute of Technology (grant to R. F.I.). A.V.W. is supported by the National Institutes of Health (NIH) F30AI167524 and NIH T32GM008042 to the UCLA-Caltech Medical Scientist Training Program.

CRediT authorship contribution statement

Alexander Viloria Winnett: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Natasha Shelby:** Writing – review & editing, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rustem F. Ismagilov:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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https://doi.org/10.1016/j.diagmicrobio.2025.116742
Received 23 January 2025; Received in revised form 7 February 2025; Accepted 11 February 2025
Available online 13 February 2025
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