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Letter

Chemosensory losses in past and active likely delta variant break-through COVID-19 cases

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Since its outbreak in China in December 2019, the COVID-19 pandemic has ravaged the world with more than 350 million cases and 5.5 million deaths (as of January 2022, WHO). While it has been documented that smell and/or taste losses are a hallmark symptom of COVID-19 and can present in isolation or preceding other symptoms,^{1,2} it remains unclear whether different variants, especially the widely circulating Delta variant, may cause similar or less impact on patients' chemosensory functions and whether vaccination can protect against smell and taste losses.

Since April 2021, we have recruited and tested 65 patients with prior confirmed or clinical probable diagnosis of COVID-19 (age 10–63 years old, median 24), as well as 123 controls without prior COVID-19 diagnosis (age 14–70 years old, median 35). Among them, 25 patients had active COVID-19 (symptom onset within 14 days) at the time of testing, and most of these (22/25) had been previously fully vaccinated (mRNA: 21, J&J: 1). All these active COVID-19 predominantly break-through cases occurred between August 1, 2020, and December 10, 2021, so they were likely infected by the Delta variant that dominated US infections during this period (~99%, CDC, see [Figure S1D](#)). We performed a brief nine-item scratch and sniff odor identification (ID) (NIH Toolbox Odor Identification Test)³ and whole mouth bitter intensity ratings of 1 mM quinine (NIH Toolbox)^{4,5} on all subjects. Among the sample set of likely delta-variant break-through cases, all (100%) have objec-

tive olfactory losses ([Figures S1A and S1B](#)) based on age- and gender-adjusted normative cutoffs,^{3,6} even though only 12/22 (54.5%) self-reported smell and/or taste losses.

The rest of the COVID-19+ cases (n = 40) occurred before April 17, 2021, and prior to the Delta surge in the US. The time between diagnosis and sensory testing for these patients was substantially longer, ranging from 21 days to 17 months (median = 6.5 months), and except for one patient, none were hospitalized for their disease. As such, they were considered mild cases and cleared of the virus by CDC standards at the time of testing. Thirty of these individuals, and an additional subject who was hospitalized, did not present with ongoing chemosensory losses, while nine others did self-report smell and taste losses at the time of testing. Eight of nine individuals in the sub-group with self-reported chemosensory loss were long-haulers with a diagnosis-to-testing time gap of 55–395 days (mean = 6.5 months); the time gap for the remaining subject was 21 days. Objective testing confirmed that this sub-group indeed has significant objective losses reflected in the Odor ID test ($p < 0.05$, one-way ANOVA with Tukey post-hoc), comparable to that of the active COVID-19 cohort. However, as shown in [Figure S1B](#), among the other 31 past COVID-19 patients who reported no ongoing smell and/or taste losses, 16 (52%) actually had objective olfactory losses, a proportion higher than the control group (33%, Fisher exact $p < 0.1$). We used a normative

lower 25% as the cutoff for odor ID, thus capturing a 33% (40 out of 123) incidence for olfactory losses among controls is expected. However, the tendency for a higher incidence of olfactory losses among past COVID-19 patients who reported no symptoms long after their infection (diagnosis-to-testing time gap of 102–785 days, median = 6.6 months) is intriguing and suggests that COVID-19 may have profound and long-term impact on sensory function not fully captured by self-reporting. For taste function, we also observed that COVID-19 patients with self-reported ongoing smell and/or taste losses rated quinine as less bitter ([Figure S1C](#)), although this difference is not statistically significant, potentially due to the small sample size.

These results demonstrate that (1) the Delta variant causes a high prevalence of acute chemosensory losses that cannot be completely protected by vaccination, and (2) the long-term chemosensory loss among pre-Delta variants is real and common. This is the case even when individuals are not aware of the loss, adding to the evidence that self-reported smell and taste losses are useful information, but may not be sensitive enough to capture the full spectrum of deficits due to COVID-19.^{7,8} A limitation of this study is that one group of experimental subjects had active infection of the likely Delta variant at the time of testing, while others had already recovered from SARS-CoV-2, and the variant that they were infected with is unknown.

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Thus, these cross-sectional data cannot be directly compared. In particular, they do not reveal the incidence of long-term chemosensory loss for individuals with likely Delta breakthrough cases, which will need to be determined through future studies. A second limitation is that the likely Delta variant infections were not confirmed with gene sequencing, but rather approximated through CDC population surveillance.

Obviously, by the time this report was completed, the Delta wave had subsided and the pandemic has been since dominated by the newly emerging Omicron variant and then the BA.2 sub-variant. Whether or not these new variants cause similar or different profiles of chemosensory losses is a new open question. We continued to collect objective chemosensory data on new infections in each new variant-dominant period. There have been several preliminary reports indicating a less-impacted chemosensory function in the Omicron period, but again these early reports were based on subjective self-reporting.^{9,10} These subjective reports in no way diminish the value of the objective data on chemosensory loss reported here for the Delta variant and among breakthrough infections. The pandemic landscape has been constantly shifting and it is difficult to foresee what the future holds. Perhaps the Delta variant will be eradicated, or it will come back again due to waning population immunity or its low cross-immunity with Omicron. Epidemiologists and public health experts have increasingly projected that SARS-CoV-2 could eventually become endemic. In an endemic stage, similar to flu, multiple COVID-19 variants may share the

circulation in seasonal and perennial fashions. This may present a challenge as well as an opportunity for us to use historical pandemic data to gauge the potential endemic impact.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.medj.2022.05.004>.

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AUTHOR CONTRIBUTIONS

C.T.S., K.Z., and S.P.T conceptualized the study and designed the experimental protocol; K.M., and AMO performed the experiments and collected all data; K.Z. performed the initial data analysis and initial draft of the manuscript; K.M. replicated the data analysis and replotted the figure; and K.M., K.Z., C.T.S, and S.P.T. had unrestricted access to all data and reviewed and edited the final article. All authors read and approved the final article and take responsibility for its content.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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