CORRESPONDENCE

Tracking the Emergence of SARS-CoV-2 Alpha Variant in the United Kingdom

TO THE EDITOR: As scientists, policymakers, and public health officials monitor newly emerging variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), data regarding the spread of previously identified variants are important in understanding the mechanisms through which such strains become dominant. Soon after the first case of infection with the B.1.1.7 (alpha) variant was identified in the United Kingdom in September 2020, researchers determined that the new variant had several genetic alterations: a N501Y mutation, which increased the viral binding affinity with angiotensin-converting–enzyme 2 receptor[1]; a H69del/V70del mutation, which was potentially associated with immune evasion and affected S-gene polymerase-chain-reaction (PCR) assays, resulting in S-gene target failure; and a P681H mutation, which potentially facilitated epithelial-cell entry.[2] Direct estimates of the potential of a variant for expansion and increased transmission are limited but have important implications for the global dissemination of these and future SARS-CoV-2 variants.

To investigate the expansion of the alpha variant in the United Kingdom, we performed a study using the national Covid-19 Infection Survey, a representative, longitudinal household sample.[3] Ethics approval for the study was provided by the ethics committee of South Central Berkshire B.

We analyzed questionnaire data and PCR test results from nose and throat swabs obtained during the period from September 28, 2020, to January 10, 2021. We used S-gene target failure as a proxy to identify the alpha variant. (Details regarding the analysis methods are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.)

A total of 381,773 participants from 189,766 households had a median of 4 results from nose or throat swabs (interquartile range, 3 to 6; simple range, 1 to 12) (Table S1 in the Supplementary Appendix). Of 1,690,793 samples, 17,963 (obtained from 14,195 participants from 10,506 households) were positive for SARS-CoV-2 (positivity, 1.06%; 95% confidence interval [CI], 1.05 to 1.08). Of the positive results, 9032 (50.3%) were triple-gene positive (i.e., indicating detection of all three regions of the SARS-CoV-2 genome tested: the ORF1ab region, the N [nucleocapsid] gene, and the S [spike protein] gene), 5258 (29.3%) had S-gene target failure (i.e., were alpha compatible), and 3673 (20.4%) had other combinations of genes detected. Starting in late November 2020, the samples with S-gene target failure made up an increasing percentage of positive results in most areas (Fig. S1). The most striking increase in positivity was from 15% to 76% during a 2-month period in London. Corresponding decreases in the cycle threshold (Ct) from approximately 30 to 20 (with lower values indicating higher viral loads) among samples with S-gene target failure at least partially reflected the expansion of the alpha variant in the population. Using finite mixture modeling, we determined that the infection subgroup with the highest viral load had a mean Ct of 16.1 (95% CI, 15.1 to 17.1) among samples with S-gene target failure, as compared with a value of 17.4 (95% CI, 16.9 to 18.0) among samples that were triple-gene positive (Fig. S2).

Population-level infection rates were consistent with both the expansion and increased transmissibility of the alpha variant, including during periods of national lockdown, when triple-gene–positive rates were either stable or decreasing. The timing of increases in infections with S-gene target failure varied greatly across geographic areas (Fig. 1 and Figs. S1 and S3), but the growth rate for S-gene target failure generally exceeded the corresponding rate for triple-gene–positive infections (relative difference, 6%; 95% CI, 4 to 7) (Fig. S4), which suggests addition and replacement. At the population level, growth rates for infections with S-gene target

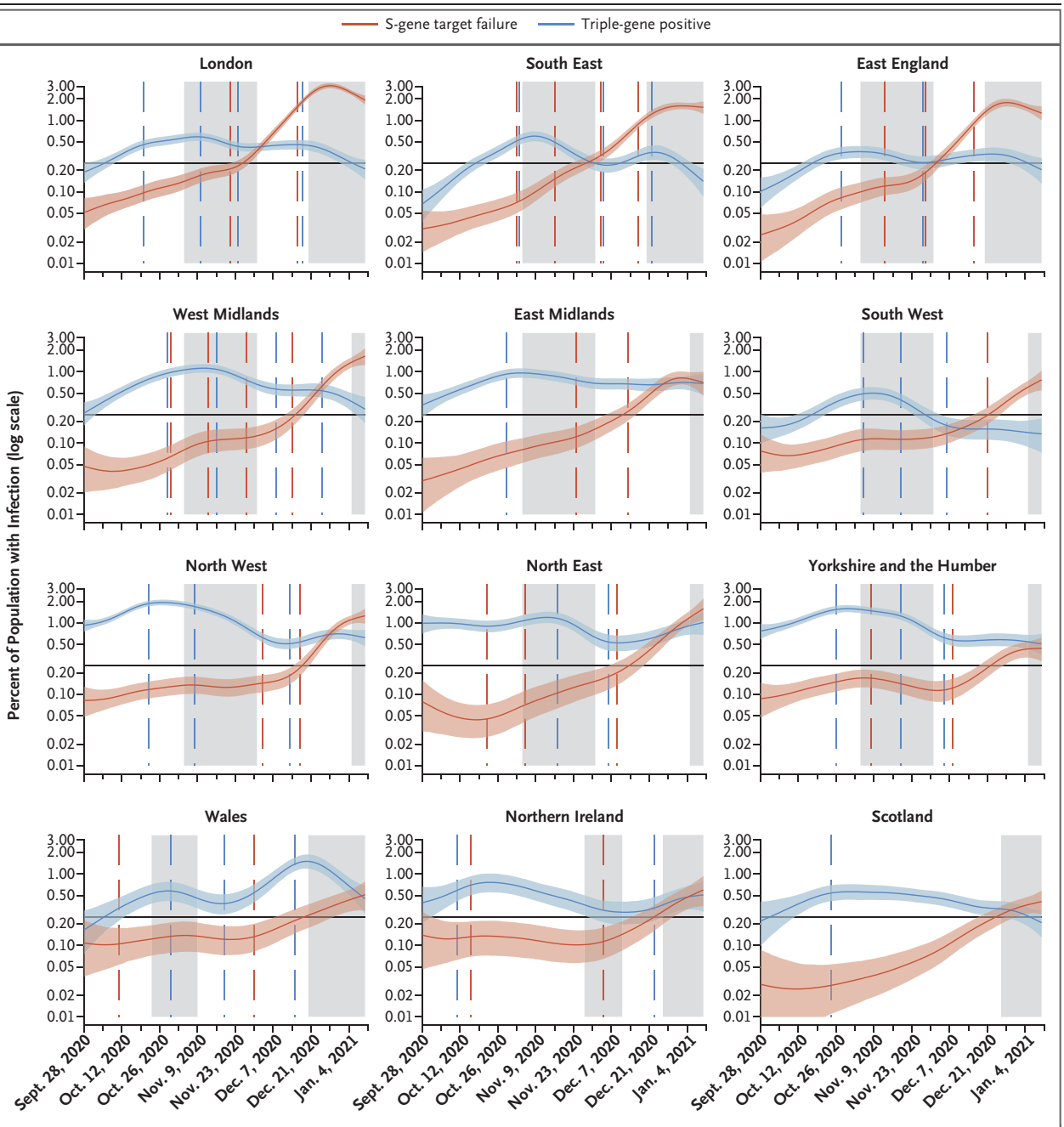

Figure 1. Percentage of Population with S-Gene Target Failure and Triple-Gene–Positive Infection in the United Kingdom during the Study Period, According to Geographic Area.

Shown is the percentage of the population that was estimated to be infected with SARS-CoV-2 with S-gene target failure (used as a proxy for identification of the alpha variant on the basis of findings that a mutation in the variant affected S-gene polymerase-chain-reaction [PCR] assays) or with all three SARS-CoV-2 genes detected. Shading around the data curves indicates the 95% credible interval. Gray shading indicates the time periods when national restrictions or stay-at-home orders had been issued for the majority of the region. The black horizontal line indicates the approximate positivity rate at the start of the surge in infections in most regions that are shown. The vertical dashed lines show the estimated changes in trend from the iterative sequential regression algorithm fitted on the log scale starting at the time of study initiation on September 28, 2020. The absence of a vertical dashed line indicates that there was no evidence that the trend in infection rates had varied during the study period at a level of evidence of $P<0.01$ for triple-gene positivity and $P<0.05$ for S-gene target failure. Additional data regarding other positive results (generally with a low viral load) are provided in Fig. S3 in the Supplementary Appendix.

failure accelerated as their prevalence increased, with initial marked increases occurring at a median positivity rate of 0.21% (simple range, 0.12 to 0.31) (Fig. S5). One explanation for why increases in rates generally became marked after the 0.21% positivity was exceeded could be heterogeneity in dispersion and super-spreading events, particularly involving asymptomatic persons with a high viral load,[4] plus chance variation. Although infections with S-gene target failure replaced triple-gene–positive infections faster for symptomatic infections (Table S2), absolute increases in positivity were relatively similar regardless of whether persons reported having symptoms (Fig. S6), which suggests that asymptomatic infections may have contributed substantially to the spread of the alpha variant. The growth rate for S-gene target failure was higher than that for triple-gene–positive infections by 5% (95% CI, 2 to 9) in children through high school age, as compared with 6% (95% CI, 4 to 7) in older persons, which suggests that children were not disproportionately affected (Fig. S7).

A limitation of our study is that not all the infections with S-gene target failure will have been caused by the alpha variant. However, our use of this proxy is supported by whole-genome sequencing (see the Supplementary Appendix). In addition, misclassification between the alpha variant and S-gene target failure would generally mean that our findings underestimate the true growth rates. Our analyses included geographic areas that had varying social restrictions during the study period. However, mathematical models that included only changes in behavior or contact patterns had a poor fit with the observed data, which supports the increased transmissibility of the alpha variant as the driving force behind the increased rates of infection.[5]

Our direct population-level analysis confirmed that the SARS-CoV-2 alpha variant was associated with a higher infection rate than other variants that were circulating in the United Kingdom during the study period. Careful monitoring for the emergence of such variants with enhanced transmissibility is needed.

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