Importance of epidemiological factors in the evaluation of transmissibility and clinical severity of SARS-CoV-2 variants

The SARS-CoV-2 delta (B.1.617.2) variant was first detected in India in December, 2020. Since then, the delta variant has rapidly become the main variant in some regions, including in the UK. As of July 27, 2021, the UK had reported the highest number of SARS-CoV-2 delta variant cases, with 167 856 patients.[1]

In *The Lancet Infectious Diseases*, Katherine Twohig and colleagues[2] report that patients infected with the delta variant had more than twice the risk of hospital admission and an increased risk of hospital attendance (emergency care attendance or hospital admission) compared with individuals infected with the alpha (B.1.1.7) variant. Importantly, Twohig and colleagues observed that among non-vaccinated patients, those infected with the delta variant were more than twice as likely as those infected with the alpha variant to be admitted to hospital. However, this study did not investigate whether there was an association between mortality and infection with the delta variant compared with the alpha variant. The findings of this study are important in the context of the worldwide spread of the delta variant and the barriers to achieving high vaccination rates against SARS-CoV-2 in many world regions.

Many pre-existing conditions, such as cardiovascular disease, chronic kidney disease, chronic lung diseases, diabetes, hypertension, immunosuppression, and obesity (body-mass index >30), predispose unvaccinated patients with COVID-19 to an unfavourable clinical course and increased risk of intubation and death.[3,4] The Centers for Disease Control and Prevention also included sex (male), age, sickle cell anaemia, cancer, severe asthma, and pregnancy as risk factors for severe COVID-19.[5] The consideration of demographic data, socioeconomic data, and comorbidities is important in large cohort studies because they might be confounding factors in the evaluation of the severity of outcomes related to the virus lineage. In Twohig and colleagues' study, patients infected with the delta variant were somewhat younger than patients infected with the alpha variant, and there was a higher proportion of Asian patients in the delta variant group compared with the alpha variant group.[2] The differences between the alpha variant and delta variant groups in ethnicity and age might affect the comparison analysis of hospitalisation and mortality outcomes. Moreover, the cause of death of patients and the vaccine status of dead patients are both additional important factors that could be considered in the comparison analysis.

The mutation affecting the spike proteins of delta variants enhances viral fitness by improving binding affinity to the angiotensin converting enzyme 2 (ACE2) receptor, leading to an increase in infectivity and transmission.[6] The organ expression of virus receptors (ACE2 and transmembrane protease serine 2) might substantially vary across ethnicities, with major differences between Asian and White populations,[7] which could explain, for example, why White people have been found to have a three times higher prevalence of chemosensory dysfunctions related to COVID-19 than Asian people.[8] Future studies could also clarify if the higher proportion of Asian people in the delta variant group is a coincidence or if there are ethnic variations in the risk of infection. Overall, the associations between variants, demographic characteristics, socioeconomic factors, and predisposing factors require large cohort studies to provide information that can guide more personalised patient care and monitoring.

In Twohig and colleagues' study, 32 078 (74·0%) of 43 338 patients were unvaccinated. At the time of data collection (March–May, 2021),[2] fewer people in the UK had been vaccinated, with only individuals considered to be at high risk being offered vaccines. Further studies are needed to determine both the risk of hospitalisation and death after vaccination according to lineage, and the potential mechanisms of immune evasion and the place of genetic interindividual differences in the disease development.[6] Vaccination features such as the number of doses might be important factors in patient outcomes; for example, Lopez Bernal and colleagues recently reported that there are modest differences in vaccine effectiveness against the delta variant compared with the alpha variant after the receipt of two vaccine doses.[9] Some studies are investigating the potential impact of the type of vaccine (adenovirus-vectored COVID-19 vaccine *vs* RNA vaccine) and the number of

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doses (one *vs* two doses for some adenovirus-vectored vaccines such as Ad26.COV2.S; Johnson & Johnson) on immune response and will help enhance the effectiveness of future vaccines.[10]

The most important finding from Twohig and colleagues' study is that outbreaks of the delta variant in unvaccinated populations might lead to a greater burden on health-care services than the alpha variant. This information is important for future decision making, providing additional arguments to strengthen vaccination programmes worldwide before the spread of a new variant with resistance to the vaccines.

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