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Letter to the Editor

The Delta SARS-CoV-2 variant has a higher viral load than the Beta and the historical variants in nasopharyngeal samples from newly diagnosed COVID-19 patients



Dear editor,

Following the publication of Tang et al.¹, we have previously shown that the Beta variant presented an intermediate relative viral load (VL) between the Alpha and the historical lineages in nasopharyngeal samples at diagnosis, a difference with historical lineages which may be associated with higher infectivity.²

In December 2020, novel SARS-CoV-2 variants emerged in India (B.1.617.1, B.1.617.2 and B.1.617.3) and led to a huge increase in positive cases³. B.1.617.2, known as the Delta variant, became rapidly the dominant variant and is now present in more than 124 countries, leading to a new surge in cases in France. To date, the Delta variant accounts for 90% of new cases in France. Recently, it has been shown in China that the relative VL of the Delta variant of quarantine contact cases (at their first positive RT-PCR) was strongly higher than the original 19A/19B lineage⁴. Moreover, it has been established that the Delta variant presented a transmissibility 40 to 60% higher than the Alpha variant⁵.

In order to evaluate the VL of the Delta variant in France, we measured and compared its relative VL with three other SARS-CoV-2 variants: the Alpha, the Beta and the historical (20A.EU2) SARS-CoV-2 variants, collected from four hospital laboratories in Paris area (Pitié-Salpêtrière, Bichat-Claude Bernard, Saint-Antoine/Trousseau and Avicenne hospitals) at their epidemic pic. A total of 738 RT-PCR SARS-CoV-2 positive nasopharyngeal samples collected at diagnosis were screened to assess SARS-CoV-2 viral lineages using the same method as in our previous study². Sanger sequencing of the receptor binding domain (RBD) was used to assess the variant type. The relative VL was assessed from CT values (for ORF1ab and N target genes) obtained by the TaqPath™ COVID-19 RT-PCR (ThermoFisher, Waltham, USA) and by linear regression in log₁₀ copies/ml with a standard curve realized from a SARS-CoV-2 positive nasopharyngeal sample quantified by Droplet-Digital™ PCR (Bio-Rad). Statistical analyses were performed with the STATVIEW software (ANOVA with a multiple comparison test).

We analysed the results from 738 SARS-CoV-2 infected patients (median age 51 years [27–67], sex ratio 48% men): 332 historical SARS-CoV-2, 249 Alpha, 98 Beta and 59 Delta variants. Concerning the ORF1ab target gene, the Delta variant presented a VL (median 7.83 log₁₀ copies/ml [6.3–8.83]) ten time higher than the historical variants (median 6.77 [5.04–7.88]) ($p < 0.0001$). A two-fold difference in the ORF1ab VL was also observed between the Delta variant and the Alpha and Beta variants (median 7.58 [5.79–8.69] and 7.42 [6.06–8.38], respectively) (Fig. 1A). For the N gene, the Delta variant (median 7.69 [6.58–8.94]) also presented a significantly higher VL (5-fold) than the historical variants (median 7.02 [5.26–8.15]) ($p < 0.0001$). We also observed a significant 2.5-fold

higher difference in VL levels between the Delta variant and the Beta variant (median 7.26 [6.10–8.37]) ($p < 0.05$). No statistical difference was found between the Delta and the Alpha (median 8.05 [6.13–9.08]) variants (Fig. 1B).

Our results showed significant differences of the relative VL between the Delta and the Beta and the historical variants. Indeed, the Delta variant has statistically higher nasopharyngeal VL at diagnosis than the Beta and the historical lineages. The Alpha and Delta variants had similar VL.

Further studies are required to confirm potential higher infectiousness and higher severity of the disease caused by these emerging variants. However, our study confirmed that the Delta variant presented a higher viral load, which could partially justify its rapid dominant position in France.

As previously, we focused on the relative VL in one swab per patient, which could be influenced by the variation of the nasopharyngeal swab technique. To limit sampling bias, we only collected samples from initial diagnostic swabs and we assessed Ct values using the same SARS-CoV-2 assay. We also collected samples during a variant specific target timing: we collected samples for each variant during their emergence phase.

We did not observe such a huge VL difference between the Delta variant and the historical variants as the one observed with the 19A/19B lineage⁴. However, this difference can be explained by the fact that all the historical variants studied here presented the D614G mutation, absent from the 19A/19B lineages, which is known to confer a better infectivity to the virus⁶.

Unlike the Alpha and the Beta variants, the Delta variant does not harbour the N501Y mutation in the Spike (S) protein which is known in the Alpha variant to enhance the affinity for ACE2⁷. However, the Delta variant carries three key S mutations, L452R, T478K and P681R which confer resistance to some neutralizing monoclonal antibodies and a possibly higher transmission⁸. Indeed, it has been shown that the L452R mutation leads to increased infectivity, though slightly lower than with the N501Y mutation, compared to historical lineages.⁹ Moreover, the L452R and the T478K possibly increase ACE2 binding and the stabilization of the ACE2-RBD complex and the P681R, present in the furin cleavage site, could enhance the transmissibility of the virus by its action on the S1-S2 cleavage.¹⁰ These mutations confer equally to the virus a resistance to neutralizing monoclonal antibodies by disrupting their binding ability to the RBD spike¹⁰ and could play a role in vaccine escape, which could explain its worldwide predominance.

Overall, our study brings evidence of increased infectivity of the Delta variant that could contribute to its fast worldwide propagation.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

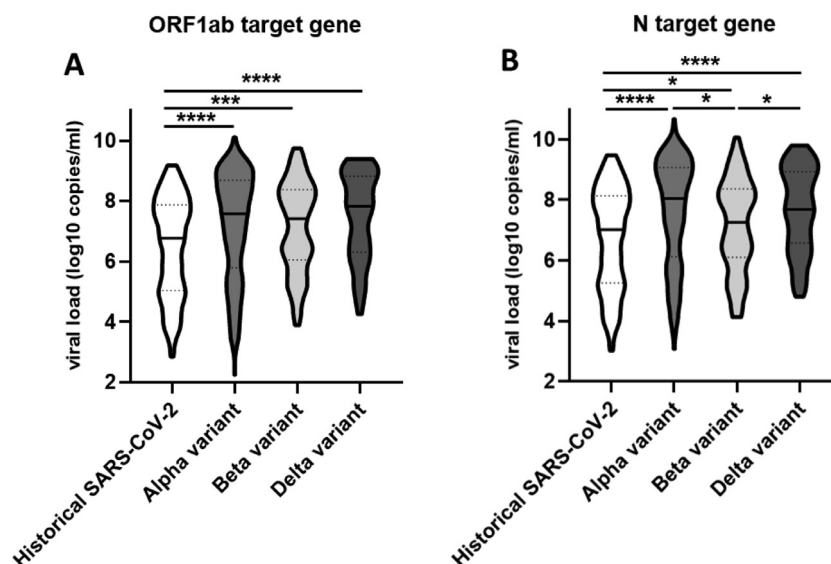


Fig. 1. Delta variant, similarly to the Alpha variant, is associated with a higher viral load than Beta and historical SARS-CoV-2 variants.

The graph presents the median and the quartiles of the relative VL in \log_{10} copies/ml of the four groups for the ORF1ab gene (A) and for the N gene (B). The median of the relative VL was higher for the Delta than the Beta and the historical SARS-CoV-2 variants. * $p < 0.05$, *** $p < 0.001$, **** $p < 0.0001$.

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