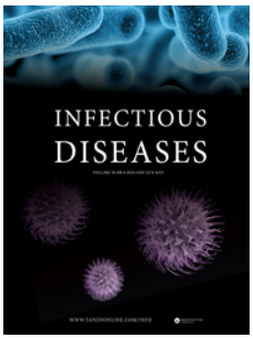

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COMMENT

Features of the SARS-CoV-2 KP.3 variant mutations

Dear Editor,

Recently, an increase in the number of SARS-CoV-2 cases has occurred, and since many are due to the new variant labelled KP.3, there is concern that this could, as often happens with new variants, spread new outbreaks and lead to critical situations. In this context, we have observed the main mutations that characterise the new variant in order to clarify the real danger associated with the mutations of the spike protein.

Such as KP.2, KP.3 is a descendant lineages of JN.1 and, as of 19 July 2024, is categorised as variants under monitoring (VUMs) due to their increasing prevalence worldwide [1].

In week 25 (ending on June 23), KP.3 accounted for 40.3% of sequences, up from 24.4% in week 22. KP.2 made up 16.7% of sequences in week 25, slightly down from 17.5% in week 22. Globally, their ancestor JN.1 remains the most frequently reported variant of interest (VOI), reported by 133 countries and representing 30.3% of sequences in week 25, down from 43.9% in week 22 [2]. Figure 1 provides a clear visualisation of the distribution of recent major variants of SARS-CoV-2, highlighting how these variants have spread globally, particularly showing the different concentration of KP.3 in different regions of the world. In particular, Figure 1A shows the time trend of the average daily prevalence of BA.2.86, JN.1, KP.2 and KP.3 variants globally from January to July 2024. JN.1 shows a peak of about 80% in early 2024, then gradually declines to about 30% in July. KP.3 emerges in mid-May 2024 with a rapid rise, surpassing JN.1 at the end of June and reaching over 40% in mid-July. KP.2 begins its growth just before KP.3 but remains at lower levels, hovering around 15%–20% in July. BA.2.86 maintains a very low and constant prevalence throughout the period in the last 6 months.

Figure 1B shows the estimated prevalence of the KP.3 variant over the past 60 days in different locations. Areas with the highest prevalence of KP.3 are coloured in green (between 5% and 10%), while those with lower prevalence are in lighter yellow (between 1% and 5%). In North America, Canada has a prevalence of 7%, while the United States records 3%. In Europe, the prevalence varies between 1% and 4%, with France and the United Kingdom at 4%, Spain, Iceland, Ireland and Belgium at 3%, Denmark and Sweden at 2%, and the Netherlands and Italy at 1%. Iceland, despite its isolated geographic location, shows a similar prevalence to many countries in continental Europe. In Asia, Thailand emerges with the highest prevalence in the region at 7%, followed by South Korea at 4%, Taiwan at 3%, and Japan and Malaysia at 2%. Australia has the highest prevalence among all the countries listed at 8%. These data indicate that the prevalence of KP.3 is lower than initially assumed, with significant variations among different regions and countries. The map highlights that the KP.3 variant has a global presence, but with relatively low and variable concentrations, suggesting that its spread may still be at an early stage or may be contained by local factors such as control measures or population immunity.

The KP.2 variant carries the spike mutations R346T, F456L, and V1104L, in addition to those from its ancestor [1]. The KP.3 variant shares the F456L and V1104L mutations with KP.2 but retains the wild-type configuration at site 346, lacking the R346T mutation. Additionally, KP.3 has a new mutation at site 493 (Q493E). KP.3 has recently attracted attention due to its role in the rising number of cases. Consequently, there are concerns that it may evade the host's immune system, aided by the new capabilities conferred by these mutations.

The F456L mutation in the spike protein of SARS-CoV-2 has been found in various lineages like XBB.1.5, EG.5, FL.1.5.1, XBB.1.16.6, and KP.2 [3]. It represents a key genetic change driving the convergent evolution of the virus's spike protein to evade immune responses from previous infections or vaccinations. The occurrence of

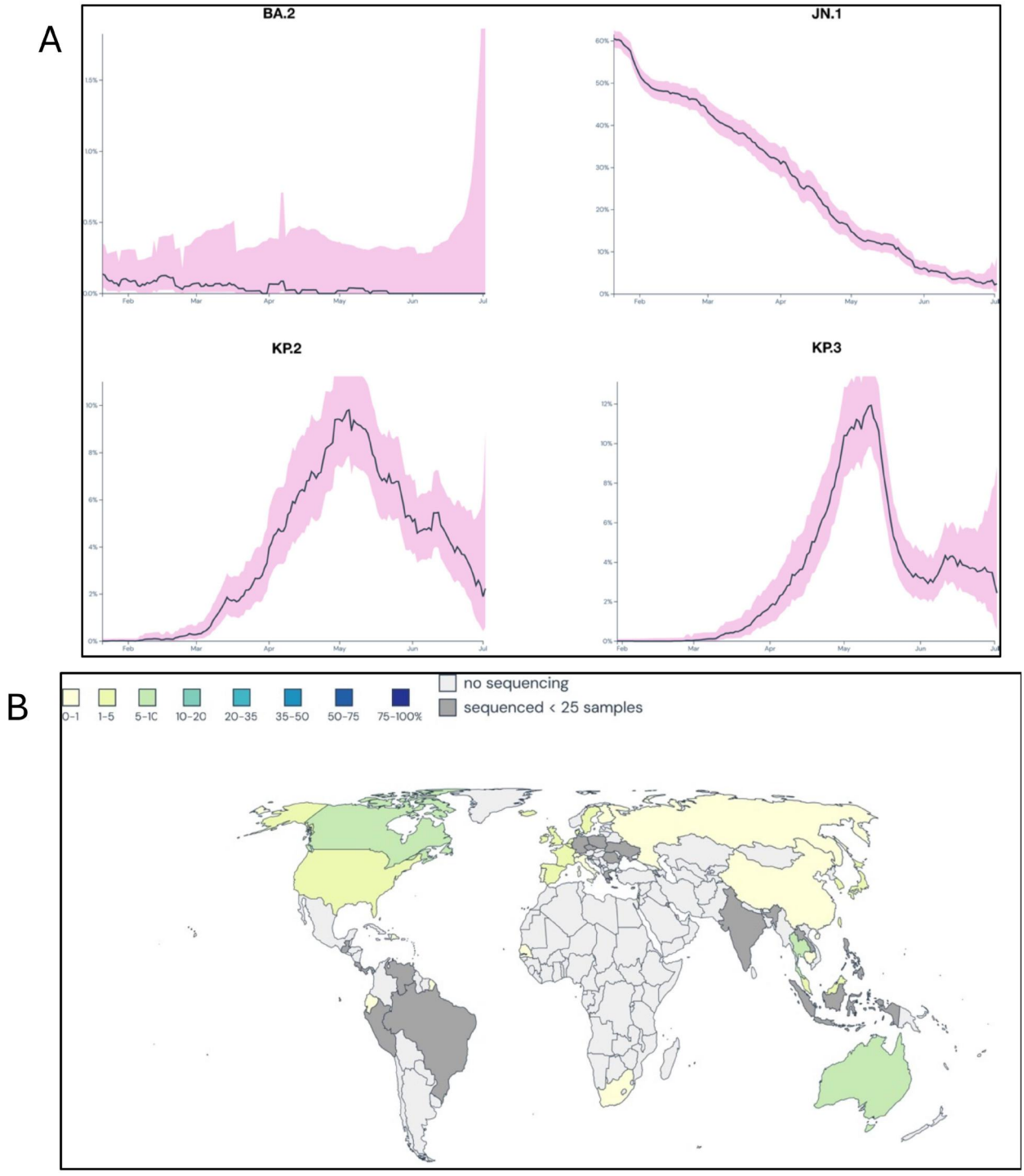

Figure 1. (A) Average daily BA.2.86, JN.1, KP.2 and KP.3 prevalence globally. Black line indicates 7-day moving average of percent of positive sequences; the pink shaded regions show 95% confidence region of a 7-day moving average. (B) Estimated KP.3 prevalence last 60 d by location [6].

the F456L mutation across multiple sublineages, often alongside the L455F mutation, is known as 'FLip' and significantly increases the spike protein's affinity for the ACE2 receptor. This adaptation helps the virus accommodate additional mutations for immune escape.

It should be noted that the combination of F456L and L455F has been observed to significantly increase ACE2 affinity [4]. However, in the case of KP.3, as well as KP.2, the F456L mutation is working alone due to the absence of L455F.

The Q493E mutation can also impact how effectively the virus evades neutralising antibodies. The effect of the Q493E mutation is often considered in the context of other mutations. For example, combinations of

mutations in the RBD can lead to synergistic effects, enhancing the virus's ability to bind ACE2, evade the immune response, or both.

The V1104L mutation is theorised to be critical in shaping the virus's evolution. Located within a T cell epitope, this mutation may enhance protein stability. Its presence in the Delta AY.36 lineage, a variant of interest, raises concerns about transmission, immune evasion, therapeutic response, and diagnostic detection. In summary, the V1104L mutation significantly impacts the ongoing evolution and adaptation of SARS-CoV-2.

The mutations characterising the KP.3 variant are theoretically dangerous, but only under specific conditions. Indeed, the presence of a mutation that previously caused significant changes in earlier variants does not necessarily represent an imminent threat. It is normal for new variants to initially show an advantage in spread compared to previous ones. In general, it is crucial to continually monitor these new mutations, but currently, there is no evidence indicating that KP.3 is a particularly concerning new variant.

The accumulation of mutations in emerging variants is a typical consequence of genetic drift, allowing the virus to continually adapt to the host. However, this does not always result in increased fitness or pathogenicity. T cells continue to provide significant protection against new variants of the virus, although there is some immune escape due to the emergence of new lineages. However, protection is maintained thanks to immunological memory, which is enhanced by hybrid immunity derived from antibodies produced by vaccines and previous infections. In conclusion, it is important not to assume that an increase in a virus's fitness automatically translates to greater contagion and danger. Often, the opposite is true: while higher fitness generally means greater contagiousness, it does not necessarily imply increased danger. In any case, to avoid misunderstandings and misinterpretations, continuous and uninterrupted monitoring of SARS-CoV-2 variants is essential, along with all of the other potential pathogens that can cause unexpected outbreaks [5].

Authors contribution

Francesco Branda: Conceptualisation, Formal analysis, Investigation, Resources, Data curation, Writing – Original Draft, Writing – Review & Editing. **Massimo Ciccozzi**: Conceptualisation, Formal analysis, Investigation, Resources, Data curation, Writing – Original Draft, Writing – Review & Editing. **Fabio Scarpa**: Conceptualisation, Formal analysis, Investigation, Resources, Data curation, Writing – Original Draft, Writing – Review & Editing.

Disclosure statement

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