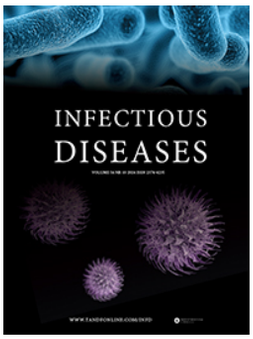

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On the new SARS-CoV-2 variant KP.3.1.1: focus on its genetic potential

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COMMENT

On the new SARS-CoV-2 variant KP.3.1.1: focus on its genetic potential

We recently published an integrated point of view on the main features of the new SARS-CoV-2 variant KP.3 [1], which has been spreading and raising concerns about its potential danger. As often happens, after a few weeks and considering the summer holidays, its descendants have emerged. Among them, KP.3.1.1 is causing particular concern; indeed, it was included among the currently circulating variants under monitoring (VUMs) on 19 July 2024 due to its increasing prevalence worldwide [2]. As of 31 July 2024, 1415 sequences of the KP.3.1.1 lineage have been identified [3]. Over the past 60 days, the prevalence of this lineage has varied significantly by location and reflects differences in sequencing efforts across countries. Germany reported the highest prevalence of 50% (1/2 cases). The Cayman Islands followed with a prevalence of 33% (29/87 cases). Spain reported a prevalence of 29% (568/1934 cases), while Iceland and Denmark showed prevalence rates of 27% (16/60 cases) and 24% (7/29 cases), respectively. Italy had a prevalence rate of 15% (10/66 cases) and Switzerland 14% (5/35 cases). Other notable prevalence rates include Sweden with 12% (13/110 cases), France with 9% (68/748 cases), and Ireland with 9% (37/427 cases). The United States had a prevalence of 5% (182/3627 cases). Lower prevalence rates were observed in Belgium (4%, with 1/23 cases), Israel (15/448 cases), Luxembourg (1/32 cases), the United Kingdom (69/2298 cases) with 3%, and Canada with 2% (47/2894 cases).

In this context, to assess the actual risk posed by this subvariant, we have focused on analyzing the primary mutations in the spike protein that characterize it and its potential impact.

In addition to the first ancestor of the clade, JN.1, it presents three new spike mutations and one deletion [4]. Specifically, it carries the F456L, Q493E, and V1104L mutations in the spike protein, along with the deletion of the serine in the site 31. The mutations F456L and V1104L are also shared with variant KP.2 [4]. The F456L mutation in the spike protein of SARS-CoV-2 has been detected in several lineages, including XBB.1.5, EG.5, FL.1.5.1, XBB.1.16.6, KP.3 and KP.2 [4]. This mutation is a crucial genetic change that contributes to the convergent evolution of the virus, enabling it to evade immune responses from prior infections or vaccinations. The presence of the F456L mutation, often occurring with the L455F mutation, across various sublineages is referred to as 'FLip'. This combination significantly increases the spike protein's affinity for the ACE2 receptor, facilitating the virus's adaptation to escape immune detection [5].

However, in the lineages KP.3.1.1 and previous carriers (KP.2 and KP.3), the F456L mutation appears on its own, as the L455F mutation is not present. The Q493E mutation may affect the virus's ability to escape neutralizing antibodies. Its impact is often assessed alongside other mutations, as combinations within the receptor-binding domain (RBD) can have synergistic effects, potentially enhancing the virus's binding affinity to ACE2, its evasion of the immune system, or both. The V1104L mutation is thought to play a crucial role in the virus's evolutionary trajectory. This mutation, located within a T cell epitope, might increase the stability of the protein. Its occurrence in the Delta AY.36 lineage, a variant of interest, raises concerns about increased transmissibility, immune evasion, the efficacy of treatments, and the accuracy of diagnostic tests. In conclusion, the V1104L mutation significantly influences the ongoing evolution and adaptation of SARS-CoV-2.

The deletion of the serine in the site 31 of the SARS-CoV-2 Spike protein is not known to be a particularly notable site in terms of mutations or deletions when compared to other regions of the protein. Most research and monitoring efforts have focused on mutations within the receptor-binding domain (RBD), such as N501Y, E484K, and K417N/T, which are critical due to their direct impact on the virus's ability to bind to the ACE2 receptor and evade immune responses. The significance of site 31 has not been highlighted in previous

studies or surveillance of past variants. Although any mutation in the Spike protein could potentially have effects depending on its context within the protein and in combination with other mutations, it should be pointed that this site has not been identified as a hotspot for critical mutations that significantly alter the virus's behavior, transmissibility, or immune evasion properties. Instead, the most impactful mutations have typically been those that directly affect the RBD or other regions known to interact closely with the immune system and host cell receptors.

Anyhow, considering that mutations carry out their action in concert with each other, it is important to highlight that KP.3.1.1 carries four Mutations of Interest (MoIs) – namely, K417N, S477N, N501Y, and P681R – and one Mutation of Concern (MoC), E484, which are shared with its predecessors and its ancestor BA.2.86 [6].

Each of these mutations individually poses potential risks. Specifically, among the MoIs, the P681R mutation was pivotal in the spread of Delta variants [7]. This particular spike mutation is located at a furin cleavage site, which serves as a demarcation between the S1 and S2 subunits of the spike protein. Theoretical models suggest that reverting the P681R mutation to its original wild-type form (P681) could significantly diminish viral replication, indicating that carriers might have greater pathogenicity compared to non-carriers. The P681R mutation seems to facilitate the cleavage of the spike protein into S1 and S2, potentially improving the virus's ability to penetrate host cells [7,8]. For the Delta variant, it has been shown that the virus with the P681R mutation exhibits higher pathogenicity than the original strain [8].

The MoC E484K has been identified in several viral variants, including the B.1.351 strain from South Africa and the P.1 strain from Brazil [9]. Variants with the E484K mutation tend to exhibit an enhanced ability to evade immune responses, including antibodies generated from previous infections or vaccinations [10]. Documented reinfections with variants carrying the E484K mutation have raised concerns about the durability of immunity provided by the immune system [10]. However, this specific evidence has not yet been directly observed in the current lineages.

The phylogenetic tree showed in Figure 1 depict the evolutionary path of variants collected from march to July 2024. From an evolutionary point of view, the KP.3.1.1 lineage does not appear to be particularly dangerous. Notably, the KP.3.1.1 lineage does not form a distinct monophyletic group, but clustered together with other relatives into the Next Strain Clade 24 C, along with its ancestor KP.3.

The clade of membership of KP.3.1.1 is dated 11 April 2024 (CI: April 10–13) showing a relatively level of divergence of 4.6×10^{-3}. In general, KP.3.1.1 displays evolutionary similarities to the recent JN.1, BA.2.86 and BA.2.86.1, KP.2 and KP.3, characterized by longer branches that suggest a relatively slow evolutionary rate.

Given its dating, this indicates that it circulated for at least three months before attracting significant attention and concern. These traits, coupled with the variant's extended period of circulation, imply that it currently poses no immediate increased risk but rather represents a new variant that has evolved through genetic drift. Bayesian Skyline Plot (BSP) reconstruction (Figure 2(A)), estimated on all available high-quality genomes of the variant KP.3.1.1 ($n = 585$), indicates a constant trend and a substantial lack of genetic variation during the time. Indeed, according to BSP, the genetic variability of KP.3.1.1 does not show any oscillations, neither increasing nor decreasing, indicating a consistent flattening over time. The reconstruction of lineages over time (Figure 2(B)) further supports the observation that there has been no increase in the number of haplotypes, even in recent times. This pattern does not suggest a lineage poised for a dramatic increase in population size and contagiousness. Rather, it is characteristic of an evolutionary lineage that has developed new traits compared to its immediate ancestor, but these traits do not currently provide a significant advantage that would lead to an unusually rapid expansion.

The mutations associated with the KP.3.1.1 variant may theoretically pose risks, but these concerns are conditional. The presence of mutations that previously led to significant changes in earlier variants does not automatically imply an immediate threat. It is common for new variants to initially exhibit increased transmissibility compared to their predecessors. While ongoing surveillance of these new mutations is essential, there is currently no evidence suggesting that KP.3 is an unusually worrisome variant.

The accumulation of mutations in new variants is a typical result of genetic drift, enabling the virus to adapt continuously to its host. However, this does not necessarily lead to enhanced fitness or pathogenicity. T cells continue to offer substantial protection against new virus variants, despite some immune evasion associated with emerging lineages. Protection is sustained through immunological memory, bolstered by hybrid immunity from both vaccines and previous infections. Therefore, an increase in a virus's

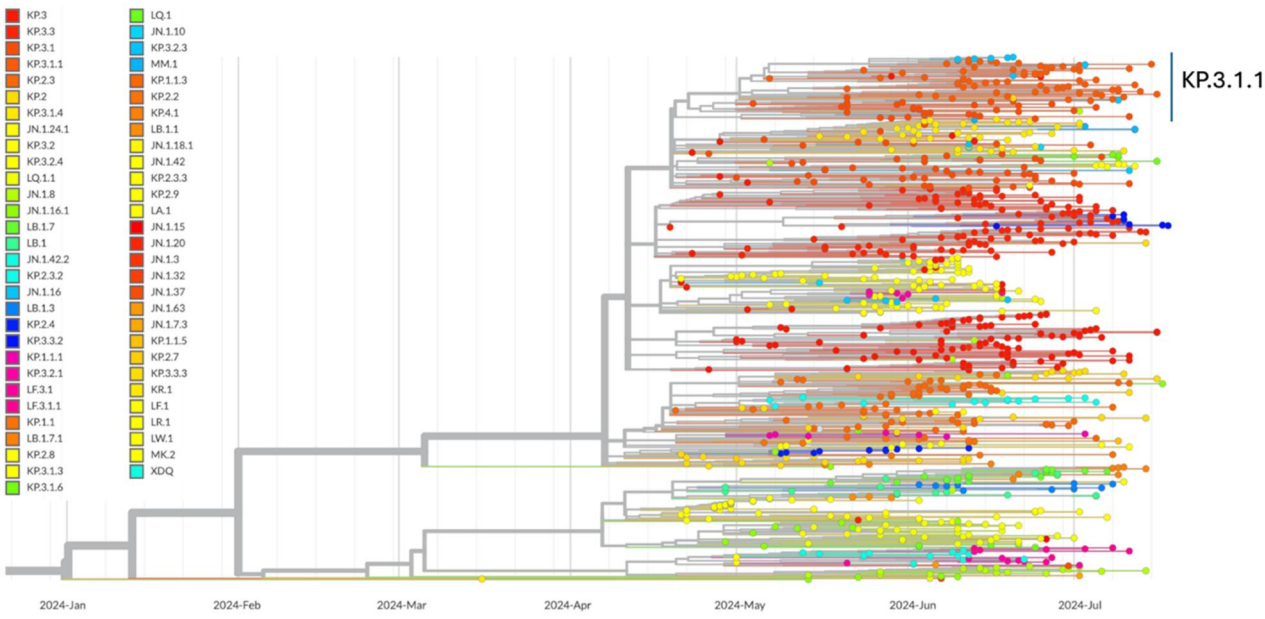

Figure 1. Phylogenomic time-scaled reconstruction by using 959 of 4.046 genomes collected between March and July 2024. The tree was created using nextstrain/ncov (https://github.com/nextstrain/ncov), with genomes filtered to ensure high quality and coverage. The resulting figure was then edited using GIMP 2.8 software, available at https://www.gimp.org/downloads/oldstable/.

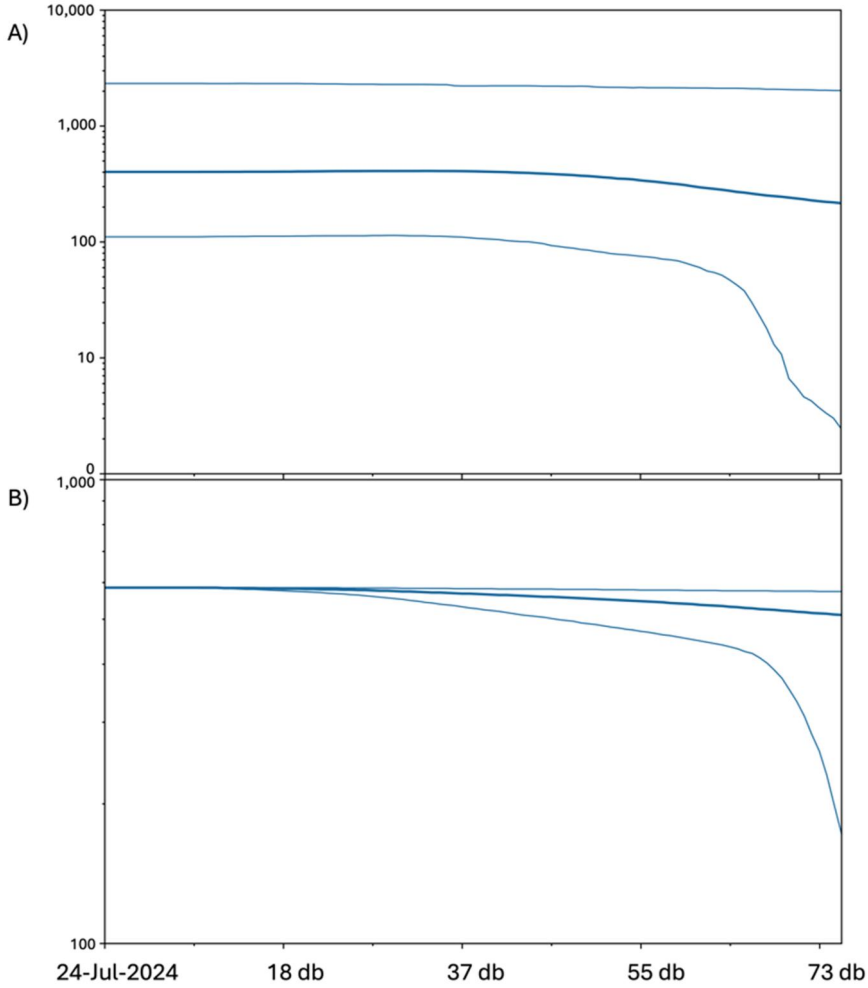

Figure 2. (A) Bayesian Skyline Plot of SARS-CoV-2 KP.3.1.1 variant. (B) SARS-CoV-2 KP.3.1.1 variant lineages through time. The viral effective population size and the number of lineages (y-axis) are shown as a function of days (x-axis). The scale of x-axis indicates the number of days before (bd) the 24 July 2024. Thin lines represent the 95% high posterior density (HPD) region. These plots have been reconstructed by using the software beast 1.10.4 10 [11].

fitness does not automatically correlate with higher contagion or danger. It is important not to mistakenly assume that an increase in a virus's fitness directly correlates with greater contagiousness and heightened danger. In fact, greater fitness often indicates higher transmissibility but does not always signify increased risk. If increased fitness directly equated to danger, highly contagious and deadly viruses like Ebola would exhibit extremely high fitness. However, this is not the case; Ebola has relatively low fitness precisely because its high lethality hampers its ability to spread widely.

In conclusion, to avoid misinterpretations, it is crucial to maintain ongoing and thorough monitoring of SARS-CoV-2 variants and other potential pathogens that could cause unforeseen outbreaks [12].

Author contributions

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

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