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EDITORIAL

Anticipating the future of the COVID-19 pandemic: insights into the emergence of SARS-CoV-2 variant JN.1 and its projected impact on older adults

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The initial instance of a severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was observed in December 2019 in the city of Wuhan, China. Subsequently, the virus disseminated expeditiously across the globe, precipitating the emergence of the COVID-19 pandemic. As of December 17, 2023, the protracted pandemic has documented an excess of 772.84 million confirmed cases and 6.98 million fatalities, following the reports disseminated by the World Health Organization (WHO). Globally, 67% of the total population was vaccinated with a complete primary series of a COVID-19 vaccine and 32% has been vaccinated with at least one booster dose, culminating in the administration of 13.5 billion doses [1]. Viruses, such as SARS-CoV-2, undergo continuous evolution due to alterations in their genetic code resulting from genetic mutations or viral recombination during genome replication. SARS-CoV-2 has exhibited a persistent pattern of mutation throughout the course of the pandemic, giving rise to variants that differ significantly from the original virus. The WHO and the Centers for Disease Control and Prevention (CDC) have recognized a multitude of variants, including variants of concern (VOCs) designated according to their time of emergence as alpha, beta, gamma, and delta. The most recent additions are the Omicron variant parent lineages including BA.1 and many other lineages that have acquired the F456L mutation [2, 3].

Following the emergence of BA.1 in November 2021, subsequent sublineages of the Omicron variant have disseminated widely [4–6]. Over 90% of the global human population has likely encountered infection with at least one Omicron subvariant, a phenomenon exacerbated by the absence of robust and enduring protection against novel viral acquisitions offered by prior infections or vaccinations [7–10]. This deficiency in immune resilience has provided a conducive milieu for the continued evolution and diversification of the virus.

All coronaviruses possess the inherent capability to engage in a natural process termed "recombination." This phenomenon emerges when two distinct lineages infect the same cellular entity simultaneously within an

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individual. This infrequent occurrence has the potential to impact the virus's characteristics, including its transmissibility, capacity to induce severe disease, and responsiveness to treatments or vaccines. It is noteworthy that, in numerous instances, recombinant viruses do not inherently acquire competitive advantages that contribute to their proliferation [11]. The XBB lineage, identified in September 2022, originated through the recombination of two BA.2-derived variants, gradually supplanting pre-existing Omicron strains. Characterized by heightened transmissibility rates and immune evasion properties, members of the XBB lineage have been responsible for initiating small waves of infections across numerous countries, albeit with a heterogeneous geographical distribution. For instance, the subvariant XBB.1.5 colloquially referred to as "Kraken" has been the prevailing strain for the majority of the year 2023 [12]. Notably, these variants are closely related and display a limited set of additional mutations in the spike protein, reflecting a stepwise accumulation of alterations. Convergent evolution may be associated with this process, as evidenced by the independent acquisition of mutations such as F486P or F456L in the receptor binding domain (RBD) of the Spike—a known repertoire of escape mutations for neutralizing antibodies [13, 14]. Furthermore, several other recombinant variants such as XBF or XBC have surged in frequency in specific regions of the world such as Australia and New Zealand and are characterized by the presence of the F486P substitution. This convergent evolutionary process is hypothesized to stem from shared selective pressure exerted by imprinted or hybrid immunity induced by Omicron infection and/or vaccination [15, 16].

Despite the fact that only four sequences were identified, in August 2023, the SARS-CoV-2 sublineage BA.2.86 was designated by the PANGO Network. The lineage earned its designation due to the presence of an exceptionally high number of mutations—34 in total—within the Spike protein and its detection across different continents during a much reduced genomic surveillance. At this time, the sublineage BA.2.86 was labeled by the WHO as a "variant under monitoring (VUM)" and nicknamed "Pirola" on social media to facilitate communication [17]. Nevertheless, current knowledge of clinical manifestations associated with the SARS-CoV-2 Omicron BA.2.86 variant is limited. Fever, cough, shortness of breath, generalized myalgia, malaise, and body fatigue have been reported as symptoms [18]. Disease appears to be more prevalent in females than males, with a notable predilection for older individuals, particularly those aged over 60. The majority of reported cases emanate from the UK, where the attack rate among residents reached 87% and 42.2% were symptomatic. Notably, no fatalities have been documented as a direct result of this new Omicron variant [19].

Then, much public attention was focused on the expanding EG.5.1 ("Eris") lineage, its descendant lineage named HK.3, and the so-called "FLip" sublineages harboring the Spike (S): L455F + F456L pair. On September 2023, the BA.2.86.1 sublineage was designated by the PANGO Network, harboring the additional ORF1a: K1973R mutation and the C12815T SNP. The JN.1 descendant harboring S: L455S was designated on September 29, 2023. JN.2 (ORF1a: Y621C), JN.3 (ORF1a: T2087I), BA.2.86.2 (ORF7a: E22D), and BA.2.86.3 (C222T, C1960T, T12755C), as well as the descendant of the latter JQ.1 (S: T95I), were designated on October 2023.

While BA.2.86 did not exhibit substantial evasion of humoral immunity or a pronounced growth advantage when compared to prevalent variants like EG.5.1 and HK.3, it did display notably elevated ACE2 binding affinity. This heightened binding affinity, combined with its distinct antigenic profile, may provide BA.2.86 with the capacity to accumulate immune-evasive mutations during periods of low-level population transmission [20–24]. There is an intricate relationship between specific mutations, ACE2 binding dynamics, and immune evasion strategies, underscoring the nuanced interplay of viral evolution in the context of host interactions.

The JN.1 variant has asserted itself as the predominant global strain. Its dominance has been associated with significant spikes in wastewater levels in various countries and a notable surge in hospitalizations in specific regions (e.g., the Netherlands, Singapore, Île-de-France). Although the 50% threshold has not yet been reached in the USA, it has been designated by WHO as a variant of interest last December 20 [25, 26]. A recent study analyzed the immune evasion potential of JN.1 employing pseudovirus-based neutralization assays with plasma from individuals recovering after XBB infection, who, despite having received three doses of inactivated vaccines, experienced breakthrough infections with XBB subvariants featuring the S486P substitution. An evident 2.1-fold reduction in 50% neutralization titers among

individuals reinfected with XBB following BA.5 or BF.7 infections and a 1.1-fold decrease in those recovering from XBB breakthrough infections heightened the immune escape capability of JN.1 compared to BA.2.86. Hence, JN.1 having inherited the antigenic diversity of BA.2.86 and acquired the strategic L455S mutation on the binding interface with human ACE2 rapidly achieved broad resistance against receptor binding domain class 1, 2, and 3 antibodies. However, the receptor binding domain showed a significant reduction in ACE2 binding affinity [20]. Even if JN.1 proves not to be particularly harmful, the key takeaway is the persistent emergence of concerning variants, introducing new paths for the virus to evolve. Currently, further evolution of JN.1 would be occurring, with the detection of the SLip variants by adding the Spike S456L mutation adjacent to L455S, showing no pause in the continuing evolution of SARS-CoV-2. These versions are progressively diverging from the initial strain that marked the onset of this pandemic nearly 4 years ago.

The antiviral Paxlovid, Remdesivir, and Molnupiravir continue to show activity against XBB-derived and BA.2.86 variants, suggesting that the current therapeutic tools remain effective [27].

After initial COVID-19 vaccination, the immune response diminishes with time [28]. In older individuals, factors such as immunosenescence and comorbidities can compromise the effectiveness of the immune response [29]. Successful evaluations of booster vaccination concepts have been conducted to address the declining immune response in healthy adults. Neutralizing antibody responses from individuals who had been administered three doses of the COVID-19 Pfizer BNT162b2 vaccine showed minimal neutralization activity against the recent XBB-derived or BA.2.86 variants. Although bivalent boosters temporarily elevated neutralization titers, their effectiveness was limited to a short duration. Six months post-boost, the sera's efficacy against EG.5.1.3 and BA.2.86.1 was hardly discernible. This substantiates reports suggesting that these two variants rank among the most immune-evasive viruses documented to date, despite some observed variations between studies [23, 24, 30–34].

Recently, COVID-19 vaccines have undergone updates that specifically target the spike protein of the SARS-CoV-2 XBB.1.5 subvariant. However, the full evaluation and reporting of their immunogenicity in humans are pending, especially in the context of emerging viruses that are rapidly gaining prevalence. Surprisingly, despite the substantial disparity in mutations between XBB.1.5, the designated target of the monovalent "updated" booster, and JN.1, there is noteworthy cross-reactivity. Preprint-published data from the Ho laboratory [35] suggest robust levels of neutralizing antibodies for the XBB.1.5 booster against JN.1, which serves as a valuable surrogate marker for protection against severe cases of COVID-19, including hospitalizations and deaths [35, 36]. Notably, the report from the Ho laboratory demonstrates that the administration of an updated monovalent mRNA vaccine from different manufacturers (Moderna or Pfizer) to uninfected individuals results in a significant boost in serum virus-neutralization antibodies. This boost is observed not only against XBB.1.5 (27.0-fold) and the EG.5.1 variant (27.6-fold) but also against crucial emergent viruses such as HV.1, HK.3, JD.1.1, and JN.1, showing increases in neutralization titers ranging from 13.3- to 27.4-fold. In individuals with a prior Omicron subvariant infection, the serum-neutralizing titers were boosted to the highest levels, ranging from 1504 to 22,978 serum virus-neutralizing titers (ID50), against all tested viral variants. Although immunological imprinting persisted for the updated vaccines, it was notably less severe compared to the previously authorized bivalent BA.5 vaccine [35].

A recent report highlighted that the survival benefit derived from primary vaccination diminishes after 6 months in older age groups, increasing the significance of booster protection. Thus, a decline in case fatality rate (CFR)—a valuable metric for detecting changes in mortality during the pandemic—was noted across all age groups, closely linked to the timeline of when each age group became eligible for primary vaccination and subsequently received the first booster. CFR exhibited an increase with age (0.3% for 50–59 years; 1.2% for 60–69; 4.7% for 70–79; 16.3% for 80 +), reaching its peak in the unvaccinated, albeit showing a reduction over time. The highest CFR was observed in the unvaccinated 80 + group before the vaccination rollout (30.6%). CFR consistently remained lowest in vaccinated populations within 6 months of their last dose, but it increased after more than 6 months elapsed since the last dose, across all age groups [37]. Coincidentally, a very recent study conducted in the Netherlands assessed the efficacy of

the XBB.1.5 monovalent vaccine in lowering hospitalizations and Intensive Care Unit (ICU) admissions among individuals aged 60 and above who had been previously vaccinated. The analysis encompassed a total of 2050 cases admitted to hospitals, with 295 (14.4%) among them having received the seasonal COVID-19 vaccine for 2023. The findings indicated a higher number of hospitalizations among individuals aged 75 and older compared to the 60–74 age group. The vaccine efficacy (VE) against hospitalization was 70.7% (95% CI: 66.6; 74.3), and VE against ICU admission was 73.3% (95% CI: 42.2; 87.6) [38].

These findings strongly support the official recommendation for widespread application of the updated COVID-19 vaccines as a crucial measure to enhance public protection and provide supporting evidence for the continued administration of booster doses, especially in older age groups.

Author contribution J.Q., M.V.D., and V.G. have contributed equally to conceptualization, writing, review, and editing.

Declarations

Competing interests The authors declare no competing interests.

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