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BA.2.12.1 is a new omicron offshoot that is a highly contagious but not severe disease

Dear Editor;

After the introduction of omicron (B.1.1.529) in Southen Africa in November 2021, the surge of a new omicron offshoot, BA.2.12.1, gained global attention due to breakthrough infections in fully vaccinated and boosted individuals in the northeastern U.S. Genetic recombination caused BA.2.12.1 virus to diverge from BA.2 (stealth Omicron) virus [1]. However, early studies revealed that BA.2.12.1 is about 25% more transmissible than BA.2 (https://newsinfo.inquirer.net/1599656/omicron-ba-2-12-1-in-ph-what-you-need-to-know). According to US Centers for Disease Control and Prevention (CDC) reports, BA.2.12.1 accounted for 36% of new COVID-19 sequenced cases during the week ending April 30th and is estimated to become the dominant COVID-19 variant within a few weeks in the United States [2]. The Philippines' ministry of health announced 17 BA.2.12.1 cases; of those, 16 are local cases while one has a history of travel to the U.S.A. However, BA.2.12.1 has been reported from at least 70 countries (https://newsinfo.inquirer.net/1599656/omicron-ba-2-12-1-in-ph-what-you-need-to-know).

Recent evidence showed that BA.2.12.1 infected cases were asymptomatic to mild symptoms like flu symptoms [3]. Because BA.2.12.1 primarily affects the upper respiratory tract and does not spread deeper into the lungs, it does not appear to cause more severe disease (https://newsinfo.inquirer.net/1599656/omicron-ba-2-12-1-in-ph-what-you-need-to-know).

Analysis of the nucleotide sequence for all identified SARS-CoV-2 Omicron sub-lineages e.g. BA.2.12.1, BA.2.13, BA.4, and BA.5 revealed that all bear the L452Q substitution that causes increased ACE2-binding affinity, stronger neutralization evasion, as well as higher transmissibility than BA.2 [3]. BA.2.12.1 even in fully vaccinated individuals has been identified in Delta, Kappa, Epsilon, and Lambda variants that elucidate the efficacy of this important variation in higher transmissibility or immune evasion of BA.2.12.1. Recent studies suggest that BA.2.12.1 has higher immune evasion activity against the plasma of 3-dose vaccines and BA.1 convalescent individuals [2]. In addition, the 69-70del, L452R, and F486V substitutions were also carried by the BA.4 and BA.5 variants that are dominant in South Africa [4]. BA2.12.1 displayed higher ACE2 binding affinities and lower S-trimer stability than BA.4 and BA.5, which resulted in higher transmissibility than other Omicron variants [2].

The genetic characteristics of omicron sub-lineages are constantly changing (Fig. 1); for example, XD was boosted by recombination between Delta and BA.1 mixed-infections, whereas XE was boosted by recombination between BA.2 and BA.1 [1]. The pressure selective due to vaccine or monoclonal antibodies or the presence of an animal reservoir can also be expected in the development of new omicron sub-lineages [5,6]. Cao et al. proposed that BA.2.12.1 evolved in response to the immune pressure induced by Omicron convalescent [2].

Yamasoba et al. suggested that recent therapeutic monoclonal antibodies don't work against omicron variants; however, the BA.2.12.1 valiant (harboring L452Q and S704L mutations) is more sensitive to sotrovimab than BA.2 [7]. However, Cao et al. suggested that Bebtelovimab and Cilgavimab could be nebulized into BA.2.12.1 variant [2]. Genetic substitutions in Omicron spike protein can influence transmission, infectivity, and immune escape that could be monitored over time. Rodino et al. demonstrated the partial ORF1ab gene target failure in Omicron BA.2.12.1 for faster tracking of the variant than the whole genome sequencing (WGS) method, which would be more applicable in developing countries with low incomes [8].

1. Further perspective

The surge of new Omicron sub-lineages, i.e., BA.4, BA.5, or BA.2.12.1 in South Africa, Europe, and the United States, has been a global serious threat. These new variants bear additional spike mutations that exhibit higher ACE-2 binding affinity, transmissibility, and immune evasion compared to BA.2. In addition, mixed infection with Omicron sub-lineage could be worse. BA2.12.1 can successfully infect fully vaccinated or boosted individuals. This suggests a strong possibility of new infection waves by BA.2.12.1, BA.4, or BA.5 in the world by continuing the current situation. Global surveillance and continuous monitoring of BA.2.12.1, as well as rapid tracking, vaccination, and the administration of effective monoclonal antibodies as prophylaxis for immune-compromised patients, remains an important step in the fight against novel Omicron sub-lineages before further global dissemination. Moreover, screening mixed infections, particularly in immune-compromised cases, is also a stone hacked step for control of genetic recombination between Omicron sub-variants.

Ethical approval

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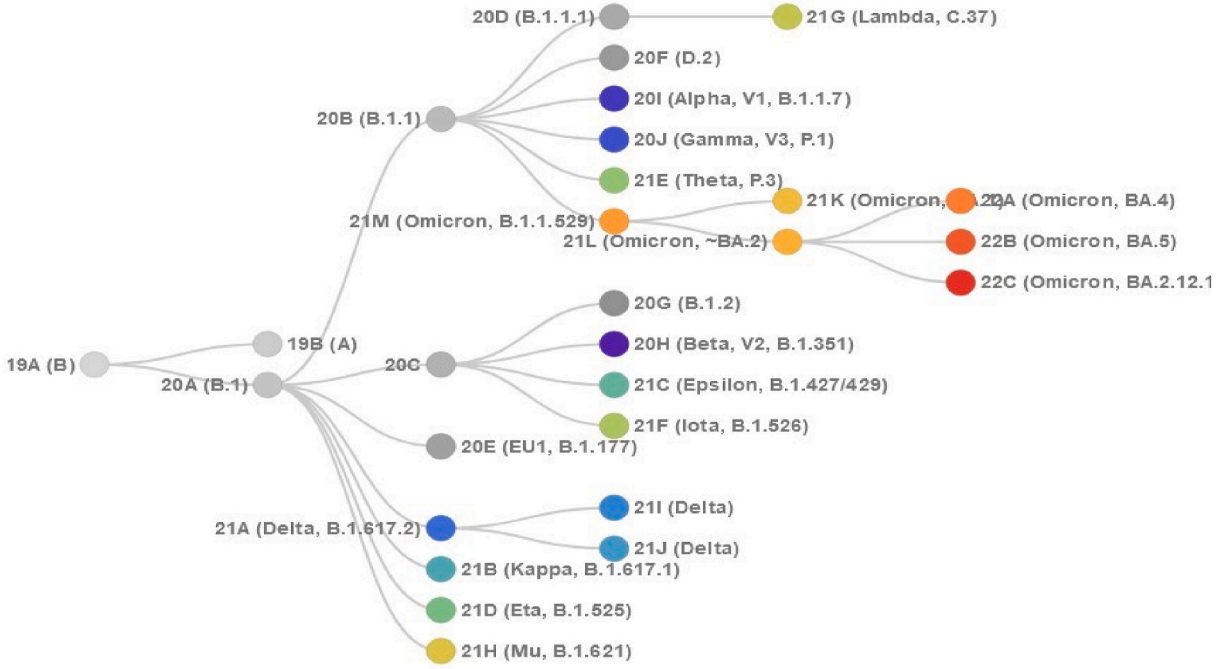

Fig. 1. Phylogenetic diagram of SARS CoV-2 evolution with their sub-linages.

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Declaration of competing interest

There is no conflict of interest.

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