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Highly mutated SARS-CoV-2 Omicron variant sparks significant concern among global experts – What is known so far?

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The new discovery of the highly mutated Omicron variant of concern (VOC) G.R./484A (B.1.1.529) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in South Africa on November 24, 2021, raised many questions [1,2]. As of December 3, 2021, the World Health Organization (WHO) reported Omicron Variant in 38 Countries in all six WHO regions and increasing trends in South Africa suggesting increased transmissibility (Fig. 1) [3]. More than half a million genome sequences have been submitted to the Global Initiative on Sharing Avian Influenza Data (GISAID) from all six continents to confirm variants until December 2021 [2]. It is now evident from the statement of the Dutch Health Ministry that the Omicron variant was present in Europe 10 days before its discovery in South Africa; however, there has been no established link to the variant's African origin [4]. Two of the cases found in the Netherlands were from samples tested on November 19 and 23, 2021, predating the alert from South Africa [4].

Furthermore, a recent report indicates that two patients tested positive with Omicron on November 13 and 18 in Hong Kong, China [5]. It is believed that the first passenger transmitted the virus to the other passenger despite being in a hotel quarantine in opposite rooms [5]. The United States also announced its first confirmed case on December 1, 2021, in California diagnosed in a traveller who returned from South Africa visit on November 22, 2021 [6].

The Omicron variant carries more than 50 mutations (Fig. 1), including 26–32 on the Spike protein alone, including amino acid substitution, deletion, and insertion [1,7]. Out of various mutations noted, only a dozen of them have been studied in the past. Therefore, it is early to have information on the other mutations and how they would affect the virus behaviour. The critical mutations in spike protein are G339D, S371L, S373P, S375F, K417 N, N440K, G446S, S477 N, T478K, E484A, Q493R, G496S, Q498R, N501Y, and Y505H [7]. These amino acid substitutions occur in the Receptor Binding Domain (RBD). Interestingly, this variant carries mutations found in other variants of concern (VOC); it has the deletion at spike position 69–70, similar to the Alpha variant that leads to the S gene dropout or S gene target failure [8]. It also has three key mutations similar to those found in Beta and Gamma variants that confer immune escape [8]. Additionally, it has a range of close mutations to the furin cleavage site similar to those present in the Delta variant [8]. Based on these mutations, it is thought that the Omicron variant may have similar characteristics to all other variants, at least at the molecular level [8].

All SARS-CoV-2 RT-PCR diagnostics currently detect this variant. One of the three target genes has been identified in several laboratories as missing from a commonly used PCR test (S gene dropout or S gene target failure) [1]. Therefore, this test can be used as an indicator for this variant while sequencing is carried out for confirmation. This method has allowed the detection of this variant at a higher rate than in previous outbreaks. Furthermore, more information is needed to identify the impact of this variant on other tests such as rapid antigen detection tests. Additionally, it is early to know about the effectiveness of the current treatment regimens but based on the preliminary evidence, IL-6 receptor blockers and corticosteroids will still be effective in managing patients who present with a severe form of the coronavirus diseases 2019 (COVID-19) caused by the Omicron variant [9].

It is still premature to have empirical scientific data to comment on the infectivity of the variant and its impact on vaccines efficacy/effectiveness. Because the mutations mimic some of the ones found in other variants, the Omicron would likely be highly infectious and transmissible. The spike protein mutations such as D614G, N501Y, and K417 N are thought to make the virus more infectious [10]. Similarly, the H655Y, N679K, and P681H mutations could increase the transmission of the virus (also found in Alpha and Delta variants) [7]. The antibodies produced for the natural infection are generally low in titer and dissipate quickly. Based on these concepts, it is more likely that we will see more reinfections with the omicron variant. The subsets of the population

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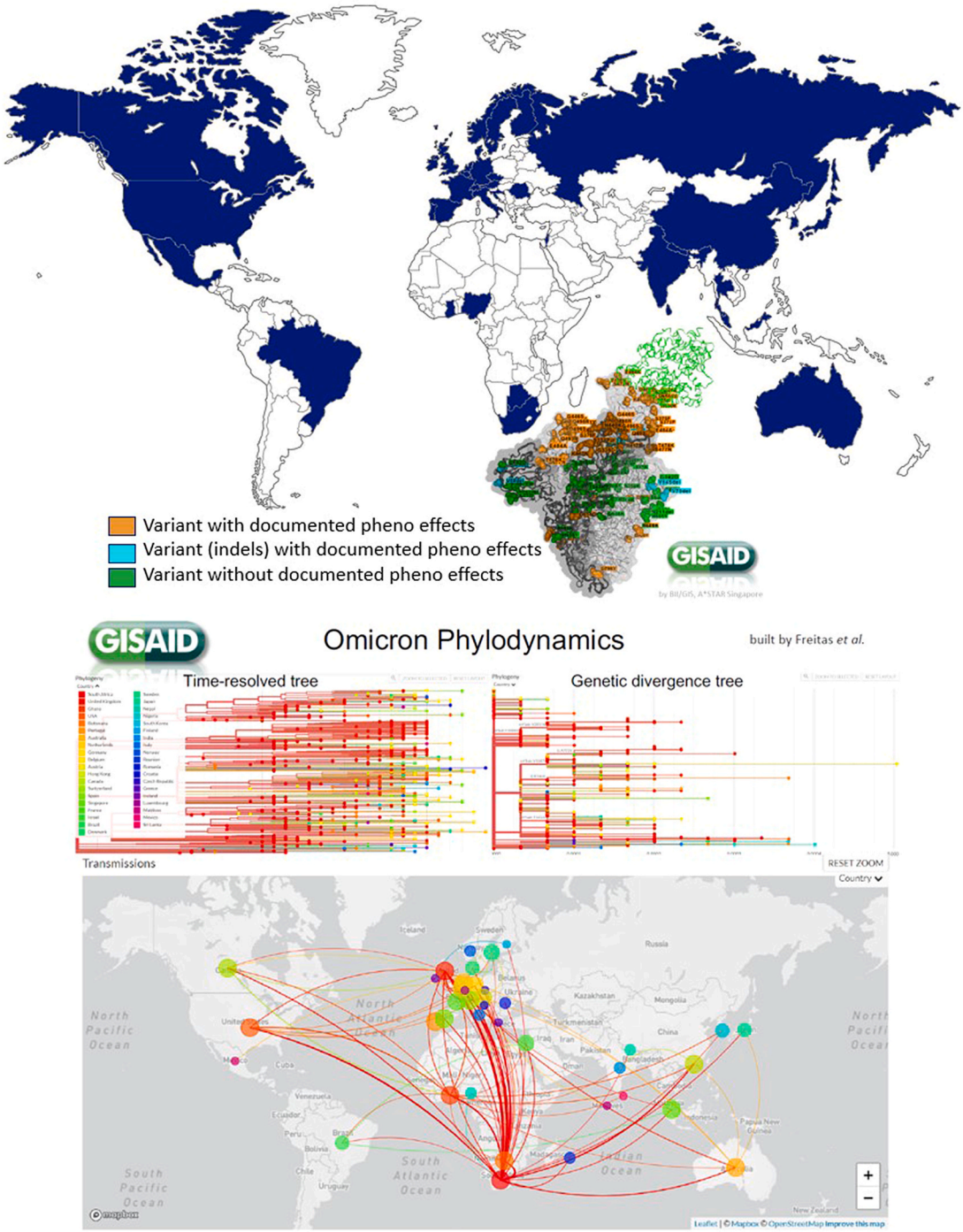

Fig. 1. Omicron variant of concern. Global case distribution, molecular characteristics and phylodynamics (by GISAID analyses), up to December 3, 2021 (https://www.gisaid.org/).
Total of cases per country: United States (40), Canada (28), Brazil (5), Japan (3), Switzerland (9), Spain (11), Portugal (13), France (11), Netherlands (27), Belgium (17), Luxembourg (1), Czech Republic (1), Croatia (1), Norway (14), Romania (2), Russia (2), Austria (17), Sweden (5), United Kingdom (334), Ireland (2), Italy (6), Germany (15), Denmark (5), Nepal (2), India (5), Maldives (1), Sri Lanka (1), Thailand (1), Malaysia (1), Singapore (6), South Korea (3), Hong Kong (13), Australia (22), Israel (12), Botswana (33), Ghana (33), Nigeria (6), Reunion (2), South Africa (398), Finland (1), Mexico (1). Updated on December 8, 2021.

with no vaccination status are more likely to be predisposed to the infection and suffer from a more severe form of the disease than vaccinated individuals in whom partial immunity is conferred by T-cell mediated response. Based on the report from the physicians and primary care providers in South Africa, it is known that the clinical presentation is similar to other COVID-19 variants. However, the severity of the cases will be more apparent in the coming days [8]. Initially, identified individuals affected in South Africa were cohorts of young university students with mild symptoms, including fatigue [9]. Finally, the WHO officials mentioned that early indications suggest most omicron coronavirus cases are mild [1].In a recently published data, population-level data from South Africa suggests that unlike with the Beta and Delta variant, there is an increased reinfection risk that is temporarily associated with the Omicron variant [11].

The original trials of vaccines performed in 2020–2021 clearly show the efficacy against infection with SARS-CoV-2. However, the vaccine

effectiveness with the arrival of a new variant, Omicron, remains unclear. Although the vaccine produces a whole array of antibodies, there are still many unknown mutations associated with the Omicron variant; therefore, partial immune escape may be expected. Interestingly, mRNA vaccines provide protection mediated by T-cells. The response may still provide partial protection even if mutations favour the virus to escape from antibodies, significantly decreasing the severity and hospitalization rate [12]. Data from South Africa shows reports of breakthrough infections with the Omicron variant in people vaccinated with the Pfizer vaccine [13]. However, preliminary data suggest that the vaccines are still effective in preventing severe disease, with those unvaccinated having an increased chance of developing severe symptoms, according to the reports from Israel [14]. The WHO also iterated in their technical report that vaccinations are still effective in preventing severe disease and death [1]. In the meantime, all three companies that produce the FDA-approved vaccinations (Johnson & Johnson, BioNTech/Pfizer, and Moderna) have released statements confirming that they believe their vaccines would still produce protection against severe disease and that variant-specific vaccination and boosters are under development [15–17]. BioNTech anticipates results about vaccine effectiveness against the Omicron variant in less than two weeks to determine the need for a variant-specific vaccine [17].

The Centers for Disease Control and Prevention (CDC) will tighten measures for people arriving in the United States that will require travellers to present a negative PCR test one-day prior to departing [18]. Furthermore, they are debating whether to enforce new measures that will require all travellers arriving in the United States to self-quarantine for seven days, regardless of vaccine status, PCR result, or country of departure [18]. The WHO has advised those over the age of 60 not to travel amid concern of the new variant [18]. The CDC has reinforced their recommendations for vaccinated people to get the booster vaccine six months after the second dose of Pfizer-BioNTech or Moderna and just two months after Johnson & Johnson's Janssen vaccine [19]. CDC guidelines stated that people above the age of 50 should get the booster, and people above 18 may get it but have now stated people over 18 should get the booster amid the new variant spread [19]. The U.S. public health laboratories have also increased full-genome analysis to 20,000, four-fold from the previous year [20]. The NIH has strengthened its recommendations for people to wear masks, especially as the Omicron variant could be spreading in the U.S. now [21]. The WHO has recommended countries to apply an evidence-informed and risk-based approach to travellers and not to close borders, stating its unlikely to prevent the spread of the Omicron variant [22].

VOC, such as Alpha (B.1.1.7 from the United Kingdom), Beta (B.1.351, from South Africa), and Gamma (P.1, Brazil), Delta (B.1.617.2, India), are associated with increased transmissibility, increased virulence, and decreased effectiveness of public health and social measures [23–28], but with the recent Omicron variant (B.1.1.529, South Africa), urgent data is needed about that.

In addition to Omicron and the rest of VOCs, interest also remained in the role of the Variants of Interest (VOI), especially present and originated in Latin America, such as the Lambda (C.37-Peru) and Mu (B.1.621-Colombia). These present changes in the genome, affecting the characteristics of the virus such as its transmissibility, the severity of the disease it causes, and its ability to escape the action of the immune system; in addition, they may pose a new risk to the global public health [23,24].

The new Omicron variant of COVID-19 has been detected in more than 40 countries on five continents (Fig. 1), in Africa in South Africa, Ghana, La Reunion (France), Nigeria and Botswana, in Asia in Japan, South Korea, Russia, Nepal, India, Sri Lanka, Thailand, Malaysia, Maldives, Singapore, Hong Kong, in the Middle East in Israel, in the Americas in Canada, United States, Mexico and Brazil [2], and Oceania in Australia [25–28].

The European Centre for Disease Control and Prevention (ECDC) had recorded 337 confirmed cases of the Omicron variant of COVID-19 in 21 countries of the European Union and European Economic Area (EU/EEA) (Fig. 1), namely in Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Liechtenstein, the Netherlands, Norway, Portugal, Romania, Spain, and Sweden. In addition, the confirmed cases have a history of travel to African countries [28–30].

In Latin America, Brazil confirmed on November 30, 2021 (Fig. 1), the first two infections with the omicron variant of the coronavirus, detected by COVID-19 testing, in a 41-year-old man and his 37-year-old wife, who were in South Africa [30–34]. In Mexico, the first case was confirmed on December 4, 2021, in a 51-year-old South African who arrived in Mexico on November 21, 2021 [35].

Finally, more studies are needed to understand better its transmissibility, immunity escape potential, clinical presentation and severity of the disease, and the role of other available diagnostic and therapeutic countermeasures.

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