frontiers | Frontiers in Virology

TYPE Opinion
PUBLISHED 23 December 2022
DOI 10.3389/fviro.2022.1077155

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Viral Diversification and Evolution, a section of the journal Frontiers in Virology

RECEIVED 24 October 2022
ACCEPTED 02 December 2022
PUBLISHED 23 December 2022

CITATION
Mohapatra RK, Mahal A, Kutikuppala LVS, Pal M, Kandi V, Sarangi AK, Obaidullah AJ and Mishra S (2022) Renewed global threat by the novel SARS-CoV-2 variants 'XBB, BF.7, BQ.1, BA.2.75, BA.4.6': A discussion.
Front. Virol. 2:1077155.
doi: 10.3389/fviro.2022.1077155

Renewed global threat by the novel SARS-CoV-2 variants 'XBB, BF.7, BQ.1, BA.2.75, BA.4.6': A discussion

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KEYWORDS

SARS-CoV-2, COVID-19, novel variants, omicron, XBB sub-variant

Introduction

Despite the numerous preventive and curative measures *in vogue* post the onset of the recent pandemic, the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) continues evolving to more critical and infectious variants (1, 2). The reasons attributed to facilitating the transmission include, among others, low vaccination rate, overcrowding defying social distancing, poor compliance to personal hygiene like masking and hand sanitisation, and increased immunodeficient and susceptible population. Such situations favour viral replication and increased mutation risk leading to the emergence of novel variants (3). Omicron mutants allegedly primarily had altered spike protein that facilitated evasion of the innate immune capabilities n individuals including in the vaccinated ones thereby rendering Omicron and its sub-lineages more infectious (4, 5). The currently used vaccines may not necessarily restrict infections and thus might not restrict the transmission, which could invariably contribute to the emergence of variants (6). Omicron variant is currently the most predominant SARS-CoV-2 variant completely replacing all preceding variants like, among others,

alpha, beta, gamma and delta. The unique mutations of the Omicron variant at the receptor binding domain (RBD) enhanced the transmissibility of the virus as well as its immune escape mechanisms. The mutated spike protein could provide resistance against vaccination and monoclonal antibody (mAb) therapy (7). Most available mAb therapies target the spike protein of the earlier SARS-CoV-2 variant. As the latest Omicron variants and the numerous sub-lineages demonstrably have significantly altered spike protein attributed to mutations, their efficacy of vaccines and mAbs is questionable. The USFDA recommended the use of Bebtelovimab/Etesevimab that has demonstrated efficacy against most of the recent Omicron sub-lineages including BA.1.1, BA.2, BA.4 and BA.5. However, Bebtelovimab is unavailable outside the USA, and also its efficacy against the XBB, BQ.1 and their descendants is yet to be confirmed (8).

Novel SARS-CoV-2 variants

The XBB (BA.2.10 strain), an Omicron subvariant, was detected in August simultaneously in nations like Singapore, Australia, Denmark, Bangladesh, India, the US and Japan. Despite a rise in cases in Singapore, currently there is no proof of the subvariant leading to serious effects. With the WHO identifying Omicron as a 'variant of concern', the second generation Omicron variants and their descendants are treated similar as in the earlier cases. The percentage of the Omicron subvariant (XBB) strain cases has grown during the past month in Singapore. Up to 54% of local XBB cases between October 3 and 9, 2022, it is currently the most prevalent subvariant in Singapore. However, it is not more fatal than the earlier variants although it is extremely contagious. As per the Singaporean health authority, the current COVID-19 wave would peak by mid-November there amid the growing concern about the 'immunity-evasive' XBB strain (https://www.bloomberg.com/news/articles/2022-10-13/xbb-bf-7-ba-5-1-7-new-covid-variants-renew-threats-to-the-world?leadSource=uverify%20wall). As of now, the XBB variant has been reported in nine Indian states with more than 500 cases. The numbers may not represent the real picture since the access to COVID-19 diagnosis and sequencing of SARS-CoV-2 in most health centres in India is limited. As per the data of the Indian SARS-CoV-2 Consortium on Genomics (INSACOG), the XBB sub-lineage accounts for more than 50% of the recently sequenced Indian samples (https://weather.com/en-IN/india/coronavirus/news/2022-11-01-covid-19-faqs-xbb-variant-infiltrates-9-indian-states). In the ongoing Indian festivities, maintaining strict vigilance especially towards variants like BF.7, BQ.1 in India is suggested. BQ.1 is an offshoot of Omicron variant, related to BA.5. Both BF.7 and BQ.1 sub-variants are mutated making them contagious by evading immunity. Further, clinicians may misdiagnose it due to the prevailing influenza in the region with the onset of winter. Recent available data hint at the dominance of XBB and BQ.1 variants in India and Singapore. The BQ.1 being currently responsible for most cases in the UK, South Africa, Germany, the US, Australia and South Korea, XBB variants may have spread to more than 15 countries and might have contributed to the increasing cases in the US, Australia and South Korea. Analysing the recent trends, soon the BQ.1 variant replacing by XBB in most countries throughout the world is predicted.

Unique mutations

The recent rise in infections in Singapore demonstrate that most cases were due to XBB (BA.2.10) strain (more than 50%) followed by BA.2.75 (24%) and BA.5 (21%) (https://health.economictimes.indiatimes.com/news/industry/singapore-monitoring-xbb-covid-strain-very-closely-health-minister/94804128). As per the WHO (9), XBB is a hybrid/recombinant variant that potentially emerged from BA.2 (BA.2.10.1 and BA.2.75) sub-lineages, *i.e.*, BJ1 and BM.1.1.1, with a break in S1 and unique mutations of BA.2+ (S:V83A, S:Y144, S:Q183E, S:H146Q, S:V213E, S:G252V, S:R346T, S:G339H, S:L368I, S:G446S, S:V445P, S:N460K, S:F486S, S:F490S), and it could apparently become the next dominant variant. The currently circulating Omicron lineages that include BA.2.3.20, BA.2.75.2, BM.1.1.1, BR.2, CA.1, BN.1, BQ.1.1, BU.1 and XBB demonstrate unique mutations (R346, K444, N450, L452, V445, G446, N460, F490, F486 and R493) on the RBD that reinforce their immunity-escape mechanism and increase transmissibility. The XBB and BQ.1.1 exhibited the strongest resistance to mAbs that target RBD and increased ACE2-binding affinity (10).

Vaccines and mAb therapy

The S gene analysis revealed that there is a significant difference in the representative codons among different variants of concern (11). The S gene of SARS-CoV-2 variants like alpha, beta, gamma and delta differ from the Omicron variant. Omicron variant emerging during the early stages of the pandemic and the remaining ones that stayed undetected until discovered later in South Africa is also hypothesised (11). Given the occurrence of unique mutations in the spike and RBD of the SARS-CoV-2 Omicron and its lineages, the efficacy of the current vaccines and the mAb therapies is uncertain (12). A bivalent vaccine that consisted of the spike proteins of the original SARS-CoV-2, and the Omicron BA.4 and BA.5 manufactured by the Moderna and Pfizer-BioNTech was recently approved by the USFDA (13). The currently available vaccines and mAb therapies for SARS-CoV-2 variants are listed in Table 1. Thus, the spread of such variants could contribute to increased infection that in turn could affect nations and their

TABLE 1 Currently available vaccines and mAb therapies against SARS-CoV-2 variants.

	Name	Clinical data	Reference
Vaccine	The Pfizer/BioNTech Comirnaty vaccine	65.5% (95% confidence interval; 63.9–67.0) at 2–4 weeks, dropping to 8.8% (95% CI; 7.0–10.5) at 25 or more weeks	14
	SII/COVISHIELD/AstraZeneca/ AZD1222 vaccines	48.9 (95% CI; 39.2–57.1) at 2–4 weeks, dropping to -2.7 (95% CI; -4.2 to -1.2) at 25 or more weeks	14
	Janssen/Ad26.COV 2.S vaccine developed by Johnson & Johnson	55% (95% CI; 22–74) in 13 days after 2nd dose, 74% (95% CI; 57–84) in 14–27 days, 72% (95% CI, 59–81) at 1–2 month	15
	Moderna COVID-19 vaccine (mRNA 1273)	75.1 (95% CI; 70.8–78.7) at 2–4 weeks, dropping to 14.9 (95% CI; 3.9–24.7) at 25 or more weeks	14
	Sinopharm COVID-19 vaccine	67% (95% CI; 52–78%), 0.33 (95% CI; 0.22–0.48)	16
	Sinovac-CoronaVac vaccine	6.3% (95% CI; 5.3–7.3) after 180 days of vaccination	17
	BBV152 COVAXIN vaccine of Bharat Biotech	~26-fold reduction in neutralisation titre (FRNT50) against Omicron	18
	Nuvaxovid (NVX-CoV2373) vaccine	82.7% (95% CI: 73.3–88.8)	19
	Moderna COVID-19 vaccine (mRNA 1273)-bivalent	492.1 (95% CI; 431.1–561.9) with mRNA-1273 booster, 727.4 (95% CI; 632.8–836.1) mean titre of neutralising antibodies against Omicron BA.4/5 subvariants 28 days after mRNA-1273.214 booster	20
mAb	Bebtelovimab	Effective against Omicron BA.1, BA.1.1, BA.2, BA.4, BA.5	21–23
	Bamlanivimab	Ineffective against Omicron	21–23
	Casirivimab	Effective against Omicron	21–23
	Cilgavimab	Moderately effective against Omicron	21–23
	Etesevimab	Ineffective against Omicron	21–23
	Imdevimab	Moderately effective against Omicron	21–23
	Sotrovimab	The US COVID-19 treatment guidelines panel recommends against Omicron BA.1, BA.2, BA.4, BA.5	21–23
	Tixagevimab	Moderately effective against Omicron	21–23
	Bamlanivimab+ Etesevimab	The US COVID-19 treatment guidelines panel recommends against Omicron BA.1, BA.1.1, BA.2, BA.4, BA.5	23
	Tixagevimab+ Cilgavimab	Moderately effective against Omicron BA.1, BA.1.1, BA.2, BA.4, BA.5	21–23
	Casirivimab+ Imdevimab	The US COVID-19 treatment guidelines panel recommends against Omicron BA.1, BA.1.1, BA.2, BA.4, BA.5	23
	Bebtelovimab+ Etesevimab	Effective against Omicron BA4, BA5	21

economies. It is prudent to reevaluate the current vaccines and improve the vaccination strategies to counter the variant and its lineages. An IgG antibody was synthesised that could block cell-virus fusion region, the COVID19-SF5 (24). The IgG antibody cross-reacted with six cell-adhesion facilitating spike protein sites. It is imperative that such antibodies are used in therapeutics to block infections, restrict viral replication and minimise the mutations.

It is evident that most of the recent variants have demonstrated significant mutations in the S region attributed to selective pressure on the survival of the virus against effective immune responses and vaccines. Future interventions must necessarily target such S variations that increase the virus's resistance and infectivity (25). Understanding its evolution and predicting future viral variants is very important in public health perspective. Thermodynamics to increase the understanding of virus evolution was suggested (26, 27). The Gibbs energy of binding correlates well with the fusion and entry of the virus in to the host cells, and the Gibbs energy of growth correlates with the viral replication in the host. Thermodynamics implicate that the current SARS-CoV-2 virus could continue to evolve and develop as more pathogenic and more infective variants compared to native counterparts that are more infectious although less pathogenic. An urgent need to collaborate to develop broad-spectrum SARS-CoV-2 vaccines and mAb drugs is sensed.

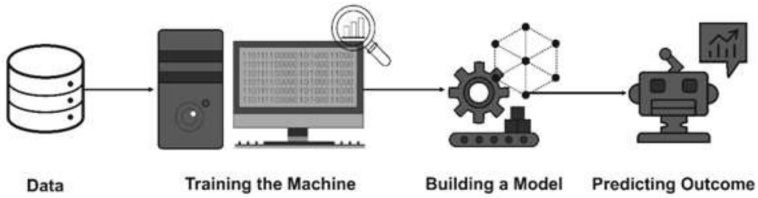

FIGURE 1
Architecture of Artificial Intelligence (AI) system (reproduced from 29).

Public health measures

Health experts in India advised against letting the guard down on the fight against the pandemic in face of the new variant that is anticipated to spread faster through the market places and the festival times. People taking preventative measures including following the government-recommended vaccination schedules and the COVID-appropriate behaviour in the public is suggested. The governments and administrations should ensure infection prevention measures like use of masks, and restricting public gatherings, among others to minimize transmission. Special attention may be extended to the Comorbid population with compromised immunity and flu-like symptoms. As both XBB and BQ.1 variants possess mutations that enable them to evade vaccine-related immunity and expedite transmission, people may further be prone to reinfection (10, 28).

With regard to the surveillance and readiness to counter the Omicron variants, it seems the Artificial Intelligence approach in line with the IoT (Internet of Things) could provide teeth to the drive. Artificial intelligence based machine learning approach shall pave an effective way to find solutions to such a burgeoning global menace as it is dependent on numerous dependent and interdependent factors and systemic issues that could be beyond human comprehension (29). An increasing need to apply machine learning techniques to accurately predict is felt. Without expressly programmed, machine learning could be elevated to artificial intelligence wherein the machine gains knowledge with experience. The data related to the pandemic could be analysed through various machine learning classifiers (Figure 1). Dataset is trained using machine learning classifiers and analysed based on the training. Healthcare system will appreciate this strategy and adopt it sooner or later for the common good.

Author contributions

RM: conceptualised, updated and edited the draft. LK, AO, AM: Teamed up during the first draft. VK, AS: Updated the manuscript. SM: Teamed up during drafting and edited. All authors have critically reviewed and approved the final draft.

Acknowledgments

The authors are thankful to their respective institutions to provide necessary institutional facilities and encouragement.

Conflict of interest

Author AM was employed by Guangzhou HC Pharmaceutical Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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