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COMMENTARY

Strategies to tackle SARS-CoV-2 Mu, a newly classified variant of interest likely to resist currently available COVID-19 vaccines

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ABSTRACT

Several severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants have recently been reported in many countries. These have exacerbated the coronavirus disease 2019 (COVID-19)-induced global health threats and hindered COVID-19 vaccine development and therapeutic progress. This commentary discusses the potential risk of the newly classified Mu variant of interest, seeming a highly vaccine-resistant variant, and the approaches that can be adopted to tackle this variant based on the available evidence. The SARS-CoV-2 B.1.621 (Mu variant) lineage has shown approximately ten times higher resistance to neutralizing sera obtained from COVID-19 survivors or BNT161b2-vaccinated people than the parenteral B.1 lineage. Several urgent and long-term strategic plans, including quick genomic surveillance for uncovering the genetic characteristics of the variants, equitable global mass vaccination, booster dose administration if required, and strict implementation of public health measures or non-pharmaceutical interventions, must be undertaken concertedly to restrict further infections, mutations, or recombination of the SARS-CoV-2 virus and its deadly strains.

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As with all emerged viruses, SARS-CoV-2 is generating new variants by adapting to the environment through random genomic mutations, inclusions or deletions, and recombination of its geneticmaterial.[1,2] Genomic alteration might affect the pathogenesis, transmissibility, illness severity, morbidity, and mortality of thevirus.[3] During the inception of the ongoing pandemic, there was a modest level of genomic variation, suggesting that vaccination could bring its long-term resolution.[4] However, the current situation suggests otherwise, as even single amino acid modifications in the genetic material of the virus are resulting in new variants that challenge current-vaccines.[5] To date, several mutations have been reported in the SARS-COV-2 spike (S) protein, particularly within the receptor-bindingdomain (RBD) and N-terminal domain (NTD), enhancing the affinity toward the host cellular receptor angiotensin-converting enzyme-2 (ACE-2). Subsequently, these mutations may render the virus more virulent and transmissible. In addition, the new strains may become more resistant to monoclonal and polyclonal antibody-based therapies and infect recovered patients and vaccinated people. Thus, emerging SARS-CoV-2 variants and mutants have become the dominant strains globally within a shortperiod.[3,5–8]

Since autumn 2020, SARS-CoV-2 variants have begun to emerge in many countries and spread worldwide quickly. The Centers for Disease Control and Prevention (CDC) has defined these virulent strains as variants of concern (VOCs), variants of interest (VOIs), and variants of high consequence(VOHC).[9] A novel variant is classified into one of these categories based upon its impact on transmission, disease severity, diagnostics, vaccine efficacy, andtherapeutics.[3] According to the WHO working definitions, VOIs present specific genetic mutations that are assumed to affect transmissibility, disease severity, diagnostics, treatment, or immune protection, and might create a deadly pandemic cluster of cases or huge epidemiologicalimpacts.[10]

The recent rapid worldwide surge in the number of SARS-CoV-2 infections has intensified the damage caused by the ongoing COVID-19 pandemic. This is mainly due to the emergence of variants such as B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617 (Delta), B.1.617.2 (Delta-plus), B.1.525 (Eta), and B.1.429 (Epsilon).[6,11–16] Recently, AY 4.2, a subvariant of the Delta variant, has emerged. This subvariant possesses two mutations in the spike protein (A222V and Y145) that promote host cell invasion. The subvariant has been reported in the UK, Russia, and Israel, with investigations examining whether the strain has higher transmissibility, increased infectivity, and/or is deadlier than previous strains, and whether it may spreadwidely.[17–19]

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Furthermore, a new SARS-CoV-2 lineage, B.1.621, also known as the Mu variant, was first traced in Colombia in January of2021, and defined by the WHO as VOI on August 30,2021.[10] The outbreak of the Mu variant has spread in South America and several European countries, and another sub-lineage of this VOI, B.1.621.1, has already spread to more than 20countries.[9] The infection rate of this strain was shown to be 39% and 13% in Colombia and Ecuador, respectively, as of August 31,2021.[20] The SARS-CoV-2 lineage, B.1.621, bears mutations in T95I, Y144T, Y145S and the insertion 146 N in the NTD; R346K, E484K, and N501Y in the RBD; and P681H in the S1/S2 cleavage site of the S protein.[21] The WHO has maintained this VOI under special monitoring because, according to preliminary data, it may be highly resistant to current vaccines due to the large number ofmutations.[22] However, evidence from sizable experimental data is too limited to make robust conclusions. More stringent investigations are required to clearly understand the genomic characteristics, biological implications, and epidemiological impacts of the variations of B.1.621 and its sub-lineage.

Based on a small-scale study, Uriu et al.[23] showed that the Mu variant was 10.6 times more resistant to convalescent sera from 13 COVID-19 survivors (affected from April to September, 2020) and 9.1 times more resistant to the sera obtained from 14 BNT162b2-vaccinated people, than the parental SARS-CoV-2 strain (B.1 lineage). Until now, the Beta (B.1.351) VOC has been considered the most resistant strain.[24] Alarmingly, however, the Mu variant shows more resistance to convalescent serum-mediated neutralization than Beta pseudoviruses($p = .031$).[25] In addition, Messali et al.[26] challenged the Mu variant with 37 sera retrieved from 37 BNT162b2-immunized individuals and demonstrated that the neutralization of the lineage B.1.621 is significantly lower than that of the B.1 strain. Compared to the delta variant, the Mu variant is also prominently resistant to inactivated vaccine-elicitedantibodies.[27] Consequently, it is uncertain, and perhaps unlikely, whether global herd immunity against this new variant is possible. Nevertheless, proper genomic surveillance and global epidemiological data are needed to collect enough evidence for the assessment of the actual infectivity of this VOI. Considering the impact of the Mu strain on vaccine-induced antibodies, an evaluation of the protective efficacy of the currently available COVID-19 vaccines against the Mu variant is sorelyneeded.[27]

COVID-19 vaccine development and mass vaccination have been an extraordinary success in global history; however, the long-term effect of COVID-19 vaccines remains unclear due to viral mutations and the emerging of variants of interest or concern with enhancedvirulence.[7,28,29] Recently, vaccines such as BNT162b2, mRNA-1273, Sputnik V, mRNA vaccines, AZD1222, and CoronaVac were found to be safe and effective at preventing severe COVID-19 disease, hospitalization, and mortality against most of the VOCs, although with varying degrees ofeffectiveness.[30]

To tackle the impacts of the newly emerged SARS-CoV-2 variants, including the potentially more resistant Mu variant, to the currently available vaccines, several global and local public health strategic plans and measures must be undertaken. The standard operating procedure (SOP) might consist of the following approaches to break the chain of infection caused by the SARS-CoV-2 virus or its various types of emerged variants.

(1) Rapid genomic surveillance needs to be extensively performed to reveal all potential polymorphic sites of the emerging novel SARS-CoV-2 lineages. Furthermore, the virus-host interactions and dynamics related to viral evolution need to be immediately investigated to understand the enhanced pathogenicity of the emerged VOCs and VOIs.[31] The mechanisms whereby the virus mutates or its genetic characteristics vary might be elucidated by integrating epidemiological data with laboratory experiments or genomic evidence.[32] Despite the disparity in genomic surveillance between countries due to socio-economic, political, and epidemiological cofactors, several approaches, such as rapid identification, enough staffing, and efficient training, might enhance genomic surveillance.[33]
(2) Quick and equitable global mass vaccination might be the most strategic approach to achieve herd immunity and thus tackle viral mutation and the emergence of new variants.[34–36] Since the virus may mutate in susceptible populations due to slow or delayed vaccination, ramping up of the immunization drive through highly efficacious vaccines should be fostered worldwide. In addition, the development of newer, more effective, and safer vaccines, including nucleic acid-based, protein subunit-based, and adenoviral vector-based vaccines, are urgently needed to keep up with viral mutation. Vaccine updates through the incorporation of the required modifications in the viral gene sequences may also be a good strategy against viral alterations, tackling the public health concerns posed by emerging SARS-CoV-2 variants.[37] However, the consequences of gene modification and adverse effects must be monitored during the post-vaccination period.
(3) Collaboration among world-leading public health organizations such as the WHO, Gates Foundation, Coalition for Epidemic Preparedness Innovations (CEPI), Global Alliance for Vaccines and Immunizations (GAVI), and COVID-19 Vaccines Global Access (COVAX) program, as well as the implementation of needful programs must move forward to ensure universal access to COVID-19 vaccines and effectively control the spread of SARS-CoV-2 infection and the ongoing pandemic.[29,35,38]
(4) The evaluation of the efficacy of existing COVID-19 vaccines against newly emerged variants should be strengthened by observational studies checking vaccine breakthrough and sequencing a huge number of SARS-CoV-2 viral isolates worldwide.[27,39]
(5) A booster dose of the COVID-19 vaccine might be another alternative solution for rendering full protection against VOIs or VOCs, according to the current data.[40]
(6) The potential risk of newly emerged VOCs or VOIs must be resolved by adopting several stringent public health measures or non-pharmaceutical interventions, such as social isolation or distancing, face mask use,

hand hygiene, movement restriction, and avoidance of social gatherings.[41–43] Moreover, treatments that might potentiate the evolution of variants must be avoided, the compulsory use of vaccine certificates during travel must be ensured, and targeted vaccination strategies must be adopted to shield against community transmission of the potential variants.[39,44] Furthermore, the identification and characterization of emerging variants and the establishment of a global genomic and epidemiological data repository must be coordinated globally to tackle the newly emerged strains, including the latest classified Mu variant.[27,29,39]

Collectively, all the above-mentioned measures must be given utmost priority to stop the spread of the virus and tackle the ongoing COVID-19 pandemic effectively.[3,45–52] The emerging SARS-CoV-2 variants have caused a rapid surge in COVID-19 cases worldwide and are affecting vaccine efficacy to varying degrees. Thus, an understanding of the molecular mechanisms of viral transmission and evolution is sorely needed. Moreover, immunological correlates of protection and immune escape mechanisms leading to the evasion of immunity conferred by prior SARS-CoV-2 infection need to be investigated. We must keep the pace with the emergence of SARS-CoV-2 variants by designing strategies for improving the next generation of SARS-CoV-2 vaccines. This can be addressed by incorporating the necessary modifications in the currently available vaccines and a vaccination schedule with booster doses, and/or designing new vaccines with higher efficacy along with multiple antigen-based vaccines (multivariant vaccines), mutation-proof vaccines, and monoclonal antibodies.[53–58] These advances might be needed under a scenario in which SARS-CoV-2 variants with higher transmissibility, virulence, and lethality continuously emerge.

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Author contributions

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