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INVITED COMMENTARY

Variants of SARS Coronavirus-2 and Their Potential Impact on the Future of the COVID-19 Pandemic

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Abstract

The emergence of SARS-CoV-2 variants of concern (VOCs), especially the sweeping spread of the delta variant, and differing public health management strategies, have rendered global eradication of SARS-CoV-2 unlikely. The currently available COVID-19 vaccines, including the inactivated whole virus vaccines, mRNA vaccines, and adenovirus-vectored vaccines, are effective in protecting people from severe disease and death from COVID-19, but they may not confer good mucosal immunity to prevent the establishment of infection and subsequent viral shedding and transmission. Mucosal vaccines delivered via intranasal route may provide a promising direction, which, if given as a third dose after a two-dose series of intramuscular vaccination, likely promotes mucosal immunity in addition to boosting the systemic cell-mediated immunity and antibody response. However, immunity induced by vaccination, and natural infection as well, is likely to wane followed by re-infection as in the case of human coronaviruses OC43, 229E, NL63, and HKU1. It is a challenge to prevent and control COVID-19 worldwide with the increasing number of VOCs associated with increased transmissibility and changing antigenicity. Nevertheless, we may seek to end the current pandemic situation through mass vaccination and gradual relaxation of non-pharmaceutical measures, which would limit the incidence of severe COVID-19. Repeated doses of booster vaccine will likely be required, similar to influenza virus, especially for the elderly and the immunocompromised patients who are most vulnerable to infection.

Key words: SARS-CoV-2, mutation, VOC, vaccination

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Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has infected 214 million people and caused more than 4.4 million deaths as of 29 August, 2021 [1]. Since its first detection in humans in December of 2019, the rate of evolution of SARS-CoV-2 has proceeded at approximately two mutations per month in global human isolates [2]. These mutations have been found throughout the SARS-CoV-2 genome [3]. However, the phenotypic implications of many of these mutations have not been defined, except for those affecting the surface spike protein, which is responsible for cell entry through binding to the host receptor angiotensin converting enzyme 2 (ACE2) [4] and subsequent fusion of the viral lipid envelope with the host cell membrane [5].

Although SARS-CoV-2 is suspected to have originated from bat SARS-related coronaviruses and to have passed through an unknown intermediate mammalian host

before jumping to humans [6,7], definitive evidence remains lacking [8]. The mutation T372A in the spike receptor binding domain (RBD) has been proposed to be a key mutation in the adaption of SARS-CoV-2 to infect humans, because this mutation has been found only in SARS-CoV-2 but not in closely related viruses such as the bat SARS-related coronavirus RaTG13 [9].

Another important example of spike mutation resulting in better adaptation of the virus to humans is the spike D614G, which was not isolated from the initial outbreak. SARS-CoV-2 strains with the D614G mutation were first found in late January 2020 [10] and are now found in nearly all strains globally. Phenotypic studies have shown that the D614G variant replicates more readily in primary human bronchial airway tissue, has greater transmissibility, and results in higher viral titer in nasal wash samples in a hamster model [11,12]. However, it does not affect disease severity or significantly change the neutralizing activity of convalescent sera [13,14]. A structural study has shown that the D614G mutation confers a more open conformation on the spike protein, thus enabling it to bind ACE2 more efficiently [15].

Subsequently, another important spike mutation emerged, N501Y, which has been selected in viral adaptation experiments in Balb/c mice [16]. The structure of the complex between the ACE2 receptor and N501Y spike protein ectodomain has been determined through cryogenic electron microscopy, which showed that Y501 inserts into a cavity at the binding interface near Y41 of ACE2. This additional interaction confers greater ACE2 affinity on the N501Y mutant and is likely to contribute to its increased infectivity [17].

Recently, the spike P681R mutation has been found to facilitate the cleavage of the spike protein and to enhance the fusion between the viral envelope and host cell membrane, thus leading to prominent syncytial formation in cell culture experiments. Moreover, the 681R mutant induces greater weight loss than the 681P wild type in hamster model [5].

Although few genetic mutations at the receptor binding domain were observed in the early months of the pandemic, by late 2020, many SARS-CoV-2 variants of concern (VOCs) or variants of interest (VOIs) had emerged. The WHO defines SARS-CoV-2 VOCs as variants with higher transmissibility or detrimental changes in COVID-19 epidemiology; increased virulence or changes in clinical disease presentation; or decreased effectiveness of public health and social measures, or available diagnostics, vaccines, and therapeutics [18].

Several notable variants that fit the VOC definition have emerged, including B.1.1.7 (alpha variant); B.1.351 (beta variant), P.1 (gamma variant), and B.1.617.2 (delta variant). They were first reported in the United Kingdom, South Africa, Brazil, and India, respectively. These variants usually demonstrate higher transmissibility and consequently have rapidly replaced the existing lineages. Some of these variants share critical mutations in the spike protein RBD among the constellation of nucleotide changes in their genomes [19]. For example, N501Y is present in B.1.1.7, B.1.351, and P.1, whereas E484K is present in B.1.351 and P.1 in addition to N501Y and D614G. E484K is a key mutation affecting the antigenicity of the spike protein [20]. The increased transmissibility of these viruses may be associated with better binding of their RBD to human ACE2 [4]. However, the delta variant has dominated the pandemic, as of August 2021. Unlike the original prototype virus, which has a mean basic reproductive number R_0 of 2.79, the mean R_0 of the delta variant is 5.08 [21]. The delta variant also shows a decrease in vaccine effectiveness, presumably because the spike mutations result in 2- to 10-fold lower neutralizing antibody titers [22,23].

The emergence of the highly transmissible delta variant has sparked a debate regarding the correct strategy for pandemic control, ranging from a "zero COVID-19 policy" to a more relaxed mitigation approach. The former strategy has been successfully adopted in several places such as mainland China, Macau SAR, Hong Kong SAR, Australia, and New Zealand. In the Hong Kong SAR, the prevalence rate of COVID-19 is 0.16%, which is far lower than those in the United Kingdom (10%) and the United States (11%) at the time of writing [1,24]. The ability to achieve such a low incidence is largely attributed to the early implementation of border control and testing and quarantining of entrants, universal masking and social distancing, isolation of all confirmed cases in hospitals, rapid and comprehensive contact tracing, restriction of movement, and testing of all premises resided in or visited by confirmed cases [25,26]. With stringent measures, even a delta variant outbreak in mainland China, which started in July 2021, was successfully eliminated in August 2021. However, the social and economic effects of such drastic non-pharmaceutical measures for epidemic control are enormous and may not be sustainable in the long run. These measures are aimed not at eradicating SARS-CoV-2 but at buying time to achieve high levels of vaccine-induced immunity in the population. However, the arrival of the delta variant has dramatically changed the game. Approximately 40% and 60% of vaccinated individuals in Hong Kong SAR were inoculated with CoronaVac (Sinovac) and BNT162b2 (Comirnaty, BioNTech), respectively [27]. In test-negative case-control studies, the effectiveness of CoronVac and BNT162b2 vaccines against the delta variant is found to be 59% and 88%, respectively [28,29], compared with 65.9% and 95% respectively against the prototype virus [30,31]. On the basis of mathematical calculation, the critical vaccination level to achieve herd immunity would increase from between 67% and 98% when R_0 was 2.79 previously, to between 91% and 136% when the R_0 of the presently circulating delta variant is 5.08 [32]. These apparently absurd percentages indicate that although both the inactivated whole virus vaccine and mRNA vaccine are effective in providing personal protection against severe disease and death from lung infection, neither is highly effective against asymptomatic or mildly symptomatic upper respiratory tract infections, which may result in substantial viral shedding and transmission

[33,34]. These findings are not unexpected, given the viral loads observed in the upper respiratory tracts of vaccinated non-human primates challenged with the prototype virus [35]. In Israel, which has a vaccination rate above 70%, the epidemic resurged after the border was reopened, and social distancing measures were relaxed [36,37]. The virus is likely to continue to circulate even among the vaccinated population and subsequently infect the unvaccinated population, which constitutes most hospital admissions and deaths.

Although we have no crystal ball to predict whether another worse virus variant will come, the chances are high that SARS-CoV-2 will continue to circulate globally, similarly to the other coronaviruses causing common colds. Several precedents exist: the human coronavirus OC43 might have jumped to humans from bovine species in the 1890s; HKU1 might have jumped from rodents in the 1950s, 229E in the 1820s; and NL63 might have jumped from bats between 1200 and 1460 [38]. When most of the population has some degree of protection from neutralizing antibodies and cell mediated immunity, life may gradually return to normal with the reopening of borders and the relaxation of social distancing. However, as with the case of other human coronaviruses, frequent re-infection may occur following a predictable pattern, e.g., every 12–24 months due to waning immunity [39]. It is likely that the elderly and the immunosuppressed will require booster dose of vaccine when their level of protection goes down with time, perhaps as another annual vaccination similar to the case of seasonal influenza.

Although a third booster dose of vaccine is likely to improve the systemic protection and, indirectly the mucosal protection, the existing vaccines confer poor mucosal immunity in the upper respiratory tract. Further studies must be performed to understand why the nasopharyngeal mucosa is sub-optimally protected despite high serum neutralizing antibody levels. Several mucosal vaccines administered by intranasal sprays are now in clinical trials, including two adenoviral vector COVID-19 vaccines and the influenza virus vector NS1 deleted vaccine carrying the spike RBD [40–43]. These mucosal vaccines could easily be modified to carry the spike of the delta variant and are likely to constitute the second wave of COVID-19 vaccines for boosting the mucosal immunity of people who were already vaccinated with inactivated whole virus, mRNA, or adenoviral vector vaccines. Intranasal sprays are generally much more acceptable to the general population. Many people have been apprehensive about receiving injectable vaccines, because life-threatening adverse effects have been reported in rare cases, such as myopericarditis after mRNA vaccination, or dural venous sinus thrombosis with thrombocytopenia after adenoviral vector vaccination [44–47].

Novel SARS-CoV-2 variants will continue to emerge. Recently, genomic recombination has been found in the B.1.1.7 lineage viruses, thus suggesting the possibility of a sudden emergence of novel variants that dramatically differ from existing strains [48]. Global efforts in continual genomic surveillance are required for the early detection of novel variants. Antigenic characterization, similar to that performed for influenza virus, will be required to detect strains with antigenic drift. Furthermore, animal surveillance will also be important, because reverse zoonosis of SARS-CoV-2 is not an isolated event. Novel variants may arise in animals, as observed in mink-associated human COVID-19 cases [49,50].

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