

Voice Series

COVID-19 Special Collection

Part 1: Interview with clinicians: COVID-19 mutation and current breakthrough in vaccine development

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As we look back on the rough year of 2020, with the emergence of a novel coronavirus (COVID-19), we were faced with many uncertainties, with no known standard treatments or available vaccines. Scientists and clinicians work around the clock to understand and combat this virus. So far, tremendous progresses have been made especially in genetically identifying this virus, which in turn leads to rapid development of drugs and vaccines.

With 3 Food and Drug Administration– and 4 China Food and Drug Administration–approved COVID-19 vaccines so far and many more in the pipelines, we are now faced with the dilemma of weighing the effectiveness of these vaccines versus their side effects. The questions that were asked frequently is: should I get vaccinated? In this two-part interview, *BIO Integration* first interviewed the team of clinicians who were deeply involved in the writing of “The Guidelines for the Diagnosis, Treatment, Prevention and Control of Coronavirus in Adults in China” during the COVID-19 outbreak. This team, led by Professor Shanping Jiang, along with team member Tiantian Tang, now discusses SARS-CoV-2 mutation and progress in vaccine development with *BIO Integration*.

EE: What is SARS-CoV-2 mutation? How does it mutate? How will the mutation affect the preventive and control measures in this current situation? Will there be another wave of COVID-19 outbreak?

SJ and TT: Virus mutation refers to changes in the genetic materials within the viral genome due to various factors. Similar to other viruses, SARS-CoV-2 can undergo different forms of mutation during the transmission process. The Global Initiative on Sharing Avian Influenza Data database classifies SARS-CoV-2 into several major clades according to its marker mutations, which include clade L (Wuhan variant), clade S (markers C8782T and T28144C), clade V (markers G11083T and G26144T), clade G (markers C241T, C3037T, and A23403G), etc. [1].

Spike protein D614G mutation is typically seen in SARS-CoV-2, in which the virus variant undergoes non-synonymous mutation at nucleotide position 23403 in the genome, resulting in the substitution of aspartic acid (D) with glycine (G) at amino acid position 614 of the virus’s spike protein. At present, this mutant strain has become the dominant variant of SARS-CoV-2 in the global pandemic [2, 3]. Compared with the D614 strain, the G614 variant has stronger infectivity and virus stability, but there is no evidence that the mutation is associated with the severity of the disease. It is also unlikely that the mutation will affect the efficacy of the vaccines [2-4].

Another typical mutation in the spike protein is the N501Y variant, in which asparagine (N) at amino acid position 501 is replaced with tyrosine (Y). The N501Y variant belongs to the B.1.1.7 lineage. In addition to N501Y, this lineage also includes other mutations such as spike protein 69-70del and P681H. Lineage B.1.1.7, also known as SARS-CoV-2 VOC 202012/01 (variant of concern, year 2020, month 12, variant 01), was reported in the UK on December 14, 2020, and is highly infectious [5]. Another variant, 20H/501Y.V2, first appeared in the UK on September 20, 2020, and was subsequently reported in South Africa and other countries. The amino acid position 501 on the spike protein is one of the key sites that directly interact with angiotensin-converting enzyme 2 (ACE2) receptor. Currently, there is no officially published research data to confirm whether the variant has higher transmissibility in the population or whether it is related to the severity of the disease.

The mutation rate of SARS-CoV-2 in the population is calculated to be at around 8×10^{-4} per site per year [6, 7]. Because of the relatively low evolution rate of SARS-CoV-2 and the highly efficient human-to-human transmission, it was suggested the virus may have already adapted to the human population by the time the large-scale outbreak occurred [4, 8]. The virus mutation has placed a huge pressure upon public pandemic controls. In response, the World Health Organization (WHO) calls on countries and scientists to actively cooperate with the organization, to strengthen the monitoring of virus mutation, to establish an epidemiological model of virus transmission, and to provide the technical support needed in assessing the effect of virus mutation on the risk of reinfection, diagnostics, vaccination, and transmission rate [9].

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EE: Are current body temperature checks and nucleic acid tests reliable? Can these measures effectively prevent and control COVID-19?

SJ and TT: Pathogenic diagnosis of SARS-CoV-2 includes two methods: the detection of the virus itself (via the presence of viral nucleic acid or antigen) and the detection of the human body's immune response to the viral infection (via the presence of antibodies or other biomarkers). The detection of viral nucleic acid and viral antigen is the most powerful evidence to confirm viral infection. Currently, the sensitivity of virus nucleic acid detection can reach up to 89.1% (95% confidence interval [CI], 84.0%–92.7%) with specificity of 98.9% (95% CI, 98.0%–99.4%) [1]. The positive detection rate of viral nucleic acid test differs in different types of respiratory specimens. Compared with upper respiratory tract specimens (such as nasopharyngeal swabs, oral swabs, sputum), there is higher detection rate and viral load of SARS-CoV-2 in lower respiratory tract specimens (such as bronchoalveolar lavage fluid and tracheal aspirate) [2]. However, it is not feasible to collect lower respiratory tract specimen when screening a large population. Furthermore, the positive detection rate of viral nucleic acid test varies across the disease course. During the first 7 days after disease onset, the positive detection rates of nasopharyngeal swabs, oropharyngeal swabs, and sputum were 80% (95% CI, 66%–91%), 75% (95% CI, 60%–88%) and 98% (95% CI, 89%–100%), respectively, whereas between 8 and 14 days, the positive detection rates were 59% (95% CI, 53%–64%), 35% (95% CI, 27%–43%), and 69% (95% CI, 57%–80%), respectively. Fourteen days after disease onset, the positive detection rates of nasopharyngeal swabs, oropharyngeal swabs, and sputum were 36% (95% CI, 18%–57%), 12% (95% CI, 2%–25%), and 46% (95% CI, 23%–70%), respectively [3]. Among the upper respiratory tract specimens, it is evident that the positive detection rate of viral nucleic acid in nasopharyngeal swabs is higher than that in oropharyngeal swabs. The *Guideline for the Diagnosis, Treatment, Prevention and Control of Coronavirus in Adults in China* [4] recommends nucleic acid testing as the first choice for pathogenic diagnosis of the acute phase SARS-CoV-2 infection. Nucleic acid testing is recommended in the following population:

suspected SARS-CoV-2 infection with symptoms of acute respiratory infection; suspected SARS-CoV-2 infection without respiratory tract symptoms, clustered cases of pneumonia infection; close contacts with confirmed COVID-19 patients; cases needed to rule out SARS-CoV-2 infection in the differential diagnosis (evidence level 1a, A). In terms of sampling methods, the guideline recommends nucleic acid testing of nasopharyngeal swabs in the following cases: within 7 days of symptom onset, asymptomatic cases, and mild cases. Meanwhile, nucleic acid testing of sputum and lower respiratory tract specimens such as tracheal aspirate is recommended for the following: late stage in disease course; acutely severe cases; critical cases.

For suspected cases with negative nucleic acid testing results, the guideline recommends the addition use of antigen testing as auxiliary diagnosis during acute phase of infection (evidence level 1a, A). The target analyte for antigen detection is usually the nucleocapsid (N) of SARS-CoV-2 virus. Antigen testing has an average sensitivity of 56.2% (95% CI, 29.5%–79.8%) and an average specificity of 99.5% (95% CI, 98.1%–99.9%) [4].

When there is a high degree of clinical suspicion of SARS-CoV-2 infection but the results of nucleic acid and antigen testing are negative, the guideline recommends the detection of antiviral-specific immunoglobulin (Ig) M or the use of paired sera samples from the acute and convalescent phases to detect virus-specific IgG antibodies to assist diagnosis (evidence level 4, C). In humans, after SARS-CoV-2 infection, IgM appears first, and the median time of detection is 5 days after symptoms onset [5, 6]; followed by the appearance of IgG, and the median time of detection is 14 days after symptoms onset, which can last at least 6 months [7]. Detection of IgM antibodies helps to determine whether the viral infection is in the acute phase. The use of serological methods to detect IgM antibodies in combination with nucleic acid testing 5 days after the onset of symptoms can increase the early diagnosis rate from 50% to >90% [6]. IgG antibody detection requires the use of paired sera samples in the acute and convalescent phases. The first serum sample should be collected as soon as possible (preferably within 7 days after the onset of the disease). The second serum sample should be collected

within 2–4 weeks after the onset of the disease. It is used to assess the dynamic changes in serum antibody titers, which is helpful in retrospectively determining whether the individual has been infected with SARS-CoV-2 virus. SARS-CoV-2 infection can be diagnosed when SARS-CoV-2-specific IgG antibody is tested positive, or when the IgG antibody titer in the convalescent phase is four times higher than that in the acute phase. We need to note that the antigenic components used during the detection of SARS-CoV-2 antibodies may cross-react with other pathogens. Non-specific reactions may occur between the antigenic components with certain molecules in human such as rheumatoid factors, heterophilic antibodies, complements, lysozymes, etc. Other factors, including hemolysis, bacterial contamination, and improper storage, can lead to false-positive results. Therefore, the guidelines specifically emphasize that the positive result of antibody testing must

be taken in consideration, along with the epidemiological history, clinical manifestations, and imaging examinations when making the clinical diagnosis.

An observational study published online on January 27 in the *New England Journal of Medicine* showed that mild to moderate cases of COVID-19 patients requires 7 days (95% CI, 5–10) to achieve virus clearance by viral culture detection (from the day of disease onset). The duration of disease onset to virus clearance time, by real-time reverse transcription–polymerase chain reaction (RT-PCR) detection is up to 34 days (95% CI lower limit, 24 days). As the disease course progresses and with increasing RT-PCR cycles, the positive rate of virus culture gradually decreases, suggesting that the infectivity of the residual virus in the patient’s body also decreases [8]. This result is important in guiding the application of nucleic acid testing in the prevention and control of pandemic.

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EE: Where are we at with the treatments for COVID-19? Are these measures still effective as the virus continues to mutate?

SJ and TT: Currently, the development of targeted drugs for COVID-19 is progressing slowly. Although many drugs or therapies have been trialed and tested in the treatment of COVID-19, but according to the current WHO guideline, only glucocorticoids are strongly recommended in hospitalized patients with critical COVID-19 [1].

Glucocorticoid is one of the most widely used broad-spectrum anti-inflammatory drugs in clinical practice. It has a strong inhibitory effect on innate immunity and adaptive immunity, which may reduce the level of systemic inflammation in critical COVID-19 patients by inhibiting the release of cytokines and inducing lymphocyte apoptosis.

The team from the University of Oxford published the RECOVERY trial in the *New England Journal of Medicine* on July 17, 2020, which included a total of 6425 (critical and

non-critical) hospitalized COVID-19 patients [2]. This trial evaluated the effect of a 10-day course of oral or intravenous dexamethasone at a dose of 6 mg once daily on patient prognosis, of which 2104 patients received the dexamethasone treatment and 4321 patients received conventional treatment. The results suggest that systemic glucocorticoids may reduce the 28-day mortality in patients who received mechanical ventilation (n=3883; risk ratio [RR], 0.64; 95% CI, 0.51–0.81) and those on oxygen therapy (n=1007; RR, 0.82; 95% CI, 0.72–0.94), but not in non-critical patients who do not require respiratory support, as it may increase the risk of death within 28 days for such patients (n=1535; RR=1.19; 95% CI, 0.91–1.55). To date, this is the largest study on the effects of glucocorticoids on the prognosis of patients requiring different degree of respiratory support. Furthermore, this study provides significant guidance on the selective clinical application of glucocorticoids.

A meta-analysis by the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group was

published in JAMA on October 6, 2020. The study included 7 prospective randomized clinical trials with a total of 1703 patients, of which 678 patients received glucocorticoid treatment while 1025 patients received conventional treatment or placebo treatment. The results suggest that systemic glucocorticoid therapy can significantly reduce the 28-day all-cause mortality in critically ill COVID-19 patients (odds ratio, 0.66; 95% CI, 0.53–0.82) [3].

The key to halting progression of COVID-19 is to fight against the imbalance of immunity during the disease course. Besides glucocorticoids with broad-spectrum anti-inflammatory effects, the search for potential therapeutic drugs in biological agents acting on various targets of the inflammatory networks is a hot topic of research. Tocilizumab, a monoclonal antibody against the interleukin 6 receptor, is one of the famed potential drugs. On February 11, 2021, the RECOVERY trial website (<http://www.recoverytrial.net>) released a brief online news report on the clinical efficacy of tocilizumab [4]. This clinical study—the largest population of tocilizumab participants (n=2022) to date—revealed that tocilizumab can reduce the mortality rate, length of hospitalization, and risk of mechanical ventilation in hospitalized COVID-19 patients who require oxygen therapy and have significant inflammatory response. It is important to note that 82% of the patients in the study group received systemic glucocorticoid therapy such as dexamethasone, which means that the clinical benefit of tocilizumab was built upon the beneficial use of glucocorticoids. Currently, the trial results have yet to be officially published, but many are looking forward to it.

The RECOVERY trial led by University of Oxford is a multi-arm, open-label randomized controlled trial. As of February 22, 2020, a total of 37,412 patients from 178 research centers have been enrolled. In addition to the above-mentioned glucocorticoids and tocilizumab therapies,

the study has verified the efficacy of hydroxychloroquine, convalescent plasma, azithromycin, and lopinavir-ritonavir on COVID-19 patients. Baricitinib, a JAK kinase inhibitor that was included the study on February 2, 2021, is also highly anticipated because of its powerful anti-inflammatory effect [5].

A recent study published in *Science* showed that plitidepsin, a novel drug in multiple myeloma treatment, may be a potential therapy in COVID-19 [6]. A research led by University of California, San Francisco (UCSF), and Icahn School of Medicine at Mount Sinai (ISMMS) revealed that plitidepsin can effectively inhibit SARS-CoV-2 in human alveolar cell lines in vitro, and its antiviral activity (IC₉₀=0.88 nM) was 27.5 times as potent as the control drug remdesivir [6]. In a mouse model expressing human ACE2, researchers have observed that prophylactic injection of plitidepsin before the viral infection can significantly reduce SARS-CoV-2 viral load in the lungs [6]. Theoretically, plitidepsin interferes with the translation process in eukaryotic cells by targeting the binding site of the host protein eEF1A (a eukaryotic translation elongation factor). The host protein eEF1A is the key protein manipulated by SARS-CoV-2 that enables the hijacking of host cells, which allows a large number of viral replications to take place. This is different from viral protease inhibitors because, theoretically speaking, SARS-CoV-2 would not easily acquire resistance to plitidepsin through mutation. In fact, the research team had cooperated with scientists from the UK to evaluate if plitidepsin can inhibit the mutant strain B.1.1.7 that was spreading recently. According to the results published on bioRxiv, a preprint server, plitidepsin also has antiviral activity against the B.1.1.7 strain [7]. PharmaMar, the developer of plitidepsin, had completed the phase I/II clinical study (APLICOV-PC; NCT04382066) for the treatment of COVID-19 [8]. The phase II/III trial is currently underway.

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EE: What is the progress in COVID-19 vaccine development? Which vaccine is more promising? How safe and effective is the COVID-19 vaccine? For vaccines that are approved, are the clinical trial data sufficient to prove its safety and efficacy? What is the significance of vaccinating the whole population? Does the physically weak population need to be vaccinated? How safe are these vaccines to the frail population?

SJ and TT: As of February 19, 2021, according to the WHO tracker of COVID-19 candidate vaccines [1], there are currently 181 candidate vaccines in pre-clinical development and 70 in clinical development, of which 27 are in phases II/III and III. Vaccine platform technologies include inactivated virus, viral vector, protein subunit, nucleic acid vaccines (including DNA and mRNA), virus-like particle, live attenuated vaccines, etc. [2]. **Table 1** presents more information on vaccines that are currently in phase II/III clinical trials.

The results of the phase III clinical trial of the viral vector vaccine ChAdOx1 (AZD1222) jointly developed by AstraZeneca and University of Oxford were published online in *Lancet* on December 8, 2020 [3]. This is the first COVID-19 vaccine to officially release their phase III clinical data. A total of 23,848 participants were enrolled in the study, of which 11,636 participants were included in the data analysis. The results showed that different vaccine dosages have varying vaccine efficacies. The vaccine efficacy of the first study group (receiving a half-dose followed by a standard dose, with the two doses at least 1 month apart, n=2741) was 90.0% (95% CI, 67.4%–97.0%) tested 14 days after the last dose. In the first study group, there were 3 cases of COVID-19 in the vaccine group and 30 cases in the control group. The vaccine efficacy of the second study group (receiving two standard doses at least 1 month apart, n=8895) was 62.1% (95% CI, 41.0%–75.7%) tested 14 days after the last dose. In the second group, there were 27 COVID-19 cases in the experimental group and 71 cases in the control group. The overall analysis across the two study groups revealed that the vaccine efficacy was 70.4% (95% CI, 54.8%–80.6%). WHO COVID-19 Vaccines Global Access Facility (COVAX) listed viral vector vaccine ChAdOx1 for emergency use on February 15, 2021 [4].

The phase III trial results of the mRNA vaccine BNT162b2 developed by Pfizer and BioNTech was published online on December 10, 2020, in the *New England Journal of Medicine* [5]. A total of 43,548 participants aged 16 years and older were enrolled in the study and randomly assigned in a 1:1 ratio to the vaccine group (BNT162b2, 30 µg/time, intramuscular injection, 0+21 days) or the placebo group. More than 7 days after the second dose of vaccine/placebo injection, there were 8 COVID-19 cases

in the vaccine group and 162 cases in the placebo group. The vaccine efficacy was 95% (95% CI, 90.3%–97.6%). COVAX listed mRNA vaccine BNT162b2 for emergency use on January 22, 2021 [6].

The mRNA vaccine mRNA-1273 developed by Moderna has completed phase III clinical trials. The trial results were pre-published online in the *New England Journal of Medicine* on December 30, 2020 [7]. This randomized, controlled, double-blind study included a total of 30,420 participants, who were randomly assigned in a ratio of 1:1 to the vaccine group (mRNA-1273, 100 µg/time, intramuscular injection, 0+28 days) and the placebo group. The results showed that there were 185 COVID-19 cases in the placebo group and 11 cases in the vaccine group. Two weeks after the second dose, the vaccine efficacy was 94.1% (95% CI, 89.3%–96.8%; P<0.001).

Currently, the China National Medical Products Administration (NMPA) has granted conditional market approval of two COVID-19 vaccines, that is, the inactivated virus vaccines developed by Sinopharm (dated December 31, 2020) [8] and by Sinovac Life Sciences, Co., Ltd (dated February 6, 2021) [9]. The epidemic situation in China is different from other countries; therefore, the vaccination strategy shifted from emergency use to focus on vaccinating key populations first. It is recommended that individuals who are designated to receive vaccination “should be inoculated as soon as possible, “in line with the overall strategy of controlling external “imported cases” and preventing internal “rebound of COVID-19 cases” [10]. As of midnight of February 9, China reported to have vaccinated a total of 40.52 million people nationwide [11].

At this stage, the contraindications of the COVID-19 vaccine in China are implemented in accordance with the vaccine’s instruction manual. Common contraindications include those who are allergic to vaccines or its components, those who suffer from acute diseases, those who are in the active acute phase of chronic diseases, those who are febrile, and pregnant women [10]. In fact, because people of all ages are susceptible to SARS-CoV-2 virus, mass vaccination is required to form herd immunity and block transmission. According to the *Guidelines for Clinical Evaluation of COVID-19 Preventive Vaccines (Trial)*, an ideal candidate vaccine should be suitable for all ages, including pregnant and breastfeeding women, or at least it should be suitable for adults including the elderly [12]. China will continuously improve on the prevention and control strategies based on the epidemiologic characteristics of the epidemic, the safety and efficacy of the vaccines, and the supply of vaccines. China will also arrange the vaccination of various populations in an orderly manner, to reach the ultimate goal of establishing an immunity barrier in the population by vaccinating the majority of the people [10].

Table 1 Vaccines Currently in Phase II/III Clinical Development (as of February 19, 2021) [1]

Vaccine platform description	Number of doses	Schedule (days)	Route of administration	Country	Developers	Phase	Trial registries
Inactivated virus	2	0+14	IM	China	Sinovac Research and Development, Co., Ltd	Phase III	NCT04456595
Inactivated virus	2	0+21	IM	China	Sinopharm+China National Biotech Group, Co.+Wuhan Institute of Biological Products	Phase III	ChiCTR2000034780
Inactivated virus	2	0+21	IM	China	Sinopharm+China National Biotech Group, Co.+Wuhan Institute of Biological Products	Phase III	NCT04560881
Viral vector (Non-replicating)	1-2	0+28	IM	UK	AsiraZeneca+University of Oxford	Phase III	NCT04400838; ISRCTN89951424
Viral vector (Non-replicating)	1	0	IM	China	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase III	NCT04526990
Viral vector (Non-replicating)	2	0+21	IM	Russia	Gamaleya Research Institute; Health Ministry of the Russian Federation	Phase III	NCT04530396
Viral vector (Non-replicating)	1-2	0 or 0+56	IM	USA	Janssen Pharmaceutical	Phase III	NCT04505722
Protein subunit	2	0+21	IM	USA	Novavax	Phase III	NCT04611802
RNA	2	0+28	IM	USA	Moderna+National Institute of Allergy and Infectious Diseases (NIAID)	Phase III	NCT04649151; NCT04470427
RNA	2	0+21	IM	Germany, USA	Pfizer/BioNTech+Fosun Pharma	Phase III	NCT04368728
Protein subunit	2-3	0+28 or 0+28+56	IM	China	Anhui Zhifei Longcom Biopharmaceutical+Institute of Microbiology, Chinese Academy of Sciences	Phase III	ChiCTR2000040153
RNA	2	0+28	IM	Germany	CureVac AG	Phase III	NCT04652102; NCT04674189
Inactivated virus	2	0+28	IM	China	Institute of Medical Biology+Chinese Academy of Medical Sciences	Phase III	NCT04659239
Inactivated virus	2	0+21	IM	Kazakhstan	Research Institute for Biological Safety Problems, Rep of Kazakhstan	Phase III	NCT04691908
DNA	2	0+28	ID	USA, China	Inovio Pharmaceuticals+International Vaccine Institute+Advaccine (Suzhou) Biopharmaceutical, Co., Ltd	Phase II/III	NCT04642638
DNA	2	0+14	IM	Japan	AnGes+Takara Bio+Osaka University	Phase II/III	NCT04655625
DNA	3	0+28+56	ID	India	Zyudus Cadila	Phase III	CTRI/2020/07/026352
Inactivated virus	2	0+14	IM	India	Bharat Biotech International Limited	Phase III	NCT04641481; CTRI/2020/11/028976
Protein subunit	2	0+21	IM	China, UK, USA	Clover Biopharmaceuticals Inc./GSK/Dynavax	Phase II/III	NCT04672395
Protein subunit	2	0+28	IM	USA	COVAXX+United Biomedical Inc	Phase II/III	NCT04683224
Virus-like particles	2	0+21	IM	Canada	Medicago Inc.	Phase II/III	NCT04636697

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