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COVID-19 Vaccine: Critical Questions with Complicated Answers

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Abstract

COVID-19 has caused extensive human casualties with significant economic impacts around the globe, and has imposed new challenges on health systems worldwide. Over the past decade, SARS, Ebola, and Zika also led to significant concerns among the scientific community. Interestingly, the SARS and Zika epidemics ended before vaccine development; however, the scholarly community and the pharmaceutical companies responded very quickly at that time. Similarly, when the genetic sequence of SARS-CoV-2 was revealed, global vaccine companies and scientists have stepped forward to develop a vaccine, triggering a race toward vaccine development that the whole world is relying on. Similarly, an effective and safe vaccine could play a pivotal role in eradicating COVID-19. However, few important questions regarding SARS-CoV-2 vaccine development are explored in this review.

Key Words: COVID-19, Vaccine, Vaccine backfires, Vaccine safety

INTRODUCTION

Humans have a long history of battling against the viruses. The constant battle between viruses and scientists has been recognized as a key driver of medical advances. In this series of battles, the latest one is the outbreak of a novel coronavirus, COVID-19, originating in the Wuhan region of China in late December 2019 (Ratan *et al*., 2020). COVID-19 has affected at least 216 countries, areas or territories around the world. So far, there had been approximately 54 million 301 thousand 156 cases and one million 316 thousand 994 deaths confirmed globally due to this deadly virus by November 16, 2020 (World Health Organization, 2020). Prior to the emergence of Severe Acute Respiratory Syndrome CoV-2 (SARS-CoV-2), there were six human CoVs (HCoVs), including that which caused the SARS global outbreak that started in November 2002 in the Guangdong province of China. After that epidemic, China reported more than 8,000 cases of disease and 774 deaths with a case-fatality rate of 7%. A decade later in 2012, Middle East respiratory syndrome CoV (MERS-CoV) first emerged in Saudi Arabia, with a total of 2,494 laboratory-confirmed cases and 858 deaths with a case-fatality ratio of 34.4% (Corman *et al*., 2018; Peeri *et al*., 2020). However, COVID-19 has caused a pandemic that has compelled the global economy to grind to a halt. A vaccine remains the best option for restoring normal life and global economies. This has triggered a vaccine development race. According to Mullard's report (Mullard, 2020), as of 11 November 2020, there were 259 COVID-19 vaccine projects going on around the world. Of those, there were 79 protein, 16 virus-like particle, 22 DNA, 33 RNA, 36 non-replicating and 20 replicating viral vector, 15 inactivated and four live-attenuated, and 35 other vaccines can-

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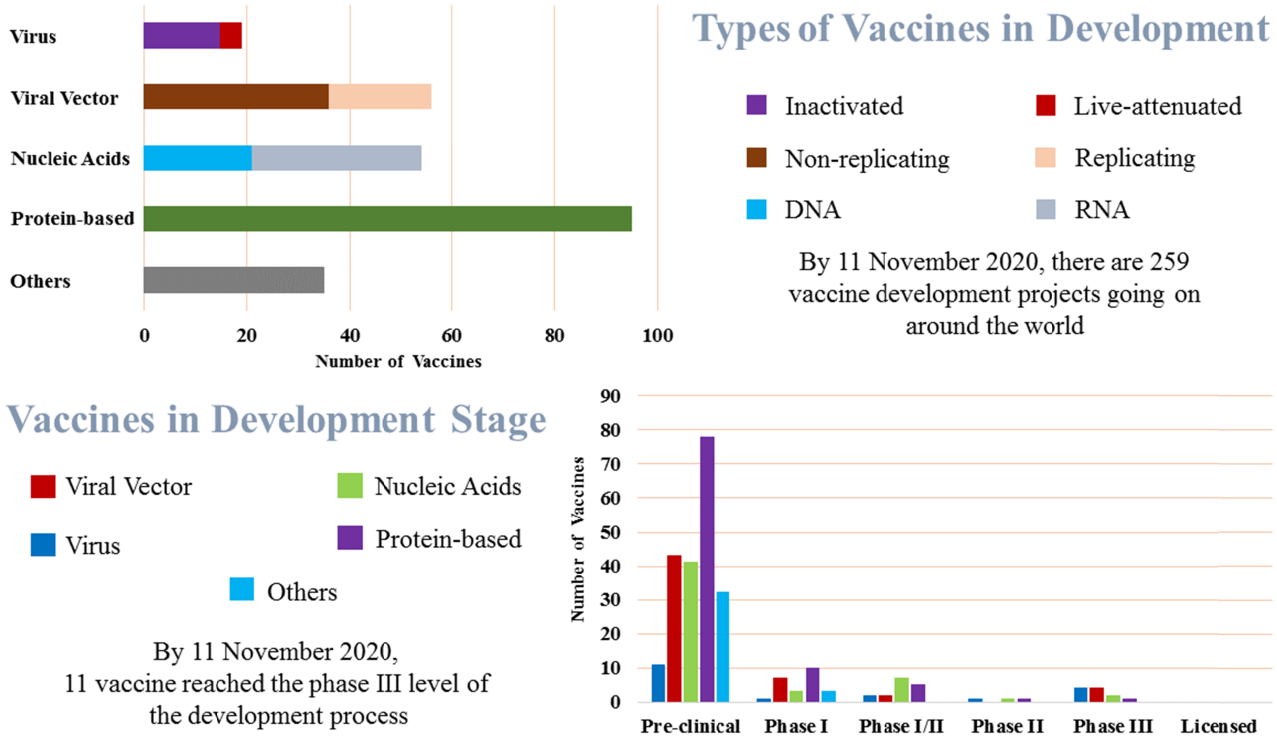

Fig. 1. State of the vaccine race for COVID-19.

didate in development pipeline. Among them, 204 were still in the preclinical stage; 11 candidates were reached phase III clinical trial stage, and the remaining were in between these stages (Fig. 1) (London School of Hygiene and Tropical Medicine, 2020).

A vaccine introduces the structure and biological agents of a specific virus to antigen-presenting cells of the host, which engulf it and pass portions of it to activate helper T (Th) cells. The Th cells then trigger other immune responses i.e., activation of B cells and cytotoxic T (Tc) cells. B cells produce antibodies that can prevent the virus from infecting cells, while Tc cells recognize and kill cells that are infected with the virus, that help the surveillance cells of the body to track the virus for long periods (Fig. 2B). In principle, understanding the etiology, epidemiology, pathogenesis and immunobiology of the infection is of the utmost importance for the development of vaccines (Zepp, 2010). Thus, a few simple questions, although complicated to answer, have arisen regarding the basic principles of vaccines that need to be resolved with regard to COVID-19 vaccine development. Here, we aim to address those simple questions.

STRUCTURE AND PATHOPHYSIOLOGY OF COVID-19

SARS-CoV-2 is a β-coronavirus belonging to the Sarbecovirus subgenus of the Coronaviridae family, and is enveloped with non-segmented positive-sense RNA virus (Zhu *et al*., 2020). In broad terms, the genome of this virus can be divided into two parts. The first open reading frame (ORF 1a/b) comprises two-thirds of the total viral genome (~30 kb) and encodes 16 non-structure proteins. This ORF 1a/b has the genetic function to roll-out the viral replication that controls the production of cellular proteins and keeps evading the immune system of the host. The remaining portion of the genome codes for four basic structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein, and several other accessory proteins (Guo *et al*., 2020). The crucial part of SARS-CoV-19 and COVID-19 infection begins when the S protein of this pathogen binds to angiotensin-converting enzyme 2 (ACE2), a cellular receptor of the host (Fig. 2A). After binding to the ACE2 receptor, the conformation shift in the S protein enables fusion of the viral envelope with the cell membrane via the endosomal pathway. Then, the virus enters the cell and releases its RNA. This RNA then goes through transcription, translation, and replication. In this production line, RNA is translated into replicase polyproteins pp1a and 1ab, and those are then severed by viral proteinase into small products. Polymerase by discontinuous transcription yields a sequence of subgenomic mRNAs that are eventually transformed into specific viral proteins. Subsequently, in the endoplasmic reticulum and Golgi apparatus, viral proteins and genome RNA are packaged into the virion and then transported through vesicles to be released from the cell (Shereen *et al*., 2020).

TYPES OF VACCINE

The Coalition for Epidemic Preparedness Innovations (CEPI), a multilateral and multinational stakeholders foun-

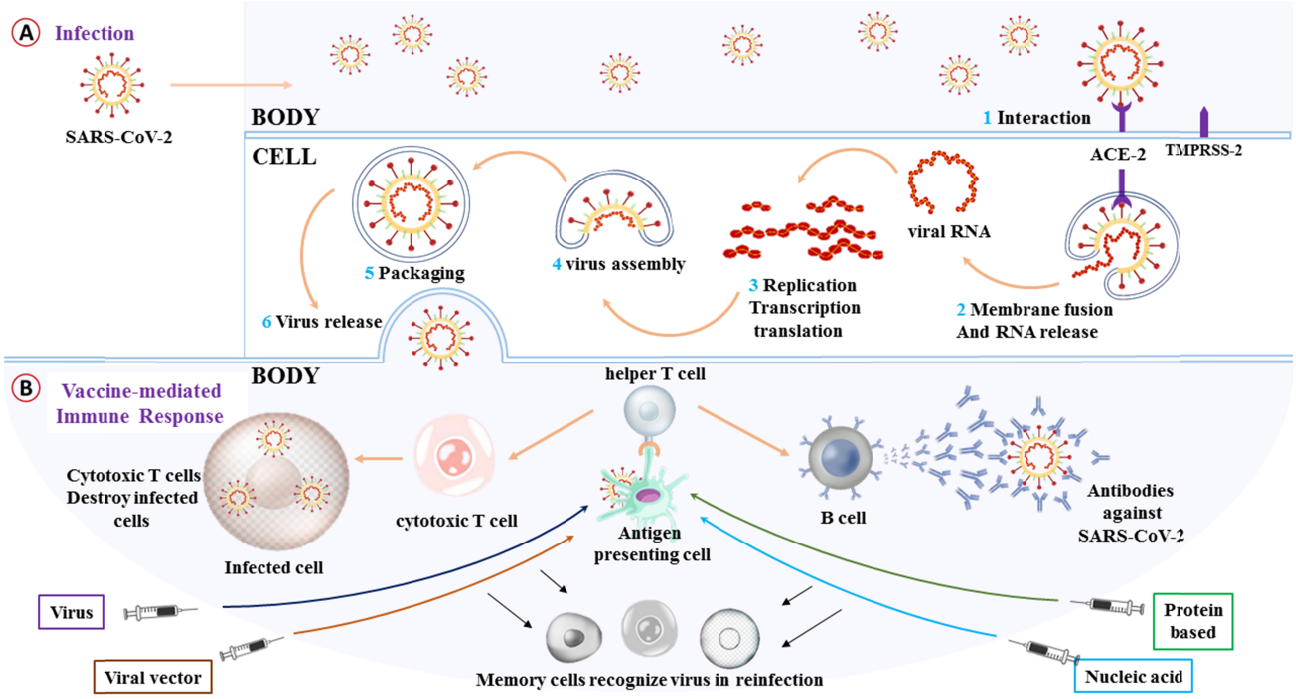

Fig. 2. COVID-19 and the vaccine. (A) A simple representation of the COVID-19 infection mechanism in the body. (B) Basic principles of vaccines in generalized form.

dation for the development of vaccine against infectious diseases, informed in September 2020 that the nine separate technological platforms are being used to make an effective vaccine against SARS-CoV-2 (Gopinathan *et al*., 2020). Scientist around the world using both the classical and next-generation platforms. The classical platforms are whole-inactivated virus, live-attenuated virus, protein subunit, and virus-like particles, and the next-generation platforms are nucleic acids (RNA and DNA), viral vectors (non-replicating and replicating), recombinant protein, and antigen-presenting cells (Le *et al*., 2020; van Riel and de Wit, 2020). However, as of September 2020 reported by CEPI, most of the frontrunner vaccines in clinical studies have emphasized on spike protein of coronavirus and its versions as the key antigen responsible for the infection of COVID-19. CEPI also pointed out that eleven candidate vaccine in clinical stage using adjuvant to improve the immunogenicity (Le *et al*., 2020).

Among the ongoing or planned clinical trial as of 11 November 2020, double-blind, single-blind, dose-confirmation, observer-blind randomized, and open-label non-randomized studies are designed for different types of the vaccine from the various technological platform, and of them, there are 18 nucleic acids, 8 Non-replicating viral vectors, 2 replicating viral vector, 9 inactivated virus, 1 virus-like particle, 11 protein subunit, and 3 other candidate vaccines. Moreover, on this clinical trial tally, China is on the top followed by the USA, Australia, Canada, UK, and others (Table 1).

THE CRITICAL QUESTIONS

The challenge for modern vaccinology is to be able to provoke all the requisite steps leading to immune system activation *in vivo*, and to provide a non-virulent, harmless type of a given agent capable of generating a strong and adequate immune response tailored against specific viral attack (Moser and Leo, 2010). Thus, some questions arise regarding the development of the vaccine (see Table 1 for current development state of COVID-19 vaccines) that will be administered to billions of people at risk of COVID-19 infection.

WILL VACCINE STIMULATE THE IMMUNE RESPONSE?

As mentioned earlier, ACE2 is the route of SARS-CoV-2 infection. However, this receptor plays a vital role in both innate and adaptive immune responses by modulating the antigen present antigen cells that interact with T cells to initiate defense initiatives (Bernstein *et al*., 2018). This receptor of transmembrane protease acts in the conversion of angiotensin 1-8 (Ang II) to angiotensin 1-7 (Ang 1-7), prompting diuresis/natriuresis, preserving renal function, and attenuating cardiac and vascular reformation (Vickers *et al*., 2002; Santos *et al*., 2008; Zhang *et al*., 2010). ACE2 also has an important role in the nervous system, and disruption of this receptor can trigger neurological disorders (Kabbani and Olds, 2020). However, a study reported that innate T cells, a heterogeneous class of T lymphocytes (MAIT, γδT and iNKT cells), are also altered by SARS-CoV-2 (Jouan *et al*., 2020). Besides, a study cohort of 38 patients found that a decline in T cells, B cells, and NK cells was linked to SARS due to coronavirus (Cui *et al*., 2003). On the other hand, a study conducted on bronchoalveolar lavage fluid of eight COVID-19 patients exhibited

Table 1. Ongoing or planned clinical trial for COVID-19 vaccine up to 11 November 2020

Candidate	Type	Phase	Study design	Volunteer	Country	Reference
Moderna mRNA-1273	RNA	3	Double-blind randomized	30000	USA	NCT04470427
WIBP vaccine	Inactivated	3	Double-blind randomized	45,000	Bahrain, Jordan, Egypt, UAE	NCT04510207
Sinovac CoronaVac	Inactivated	3	Double-blind randomized	13,060	Brazil	NCT04456595
Oxford ChAdOx1-S	Non-replicating viral vector	3	Double-blind randomized	40,051	USA, Chile, Peru	NCT04516746
Novavax NVX-CoV2373	Protein subunit	3	Double-blind randomized	30,000	USA, Mexico, Puerto Rico	NCT04611802
Novavax NVX-CoV2373	Protein subunit	3	Double-blind randomized	9,000	UK	NCT04583995
Moderna mRNA-1273	RNA	3	Double-blind randomized	30,000	USA	NCT04470427
Cansino Ad5-nCoV	Non-replicating viral vector	3	Double-blind randomized	40,000	Pakistan	NCT04526990
BIBP/ Sinopharm BBIBP-CorV	Inactivated	3	Double-blind randomized	3,000	Argentina	NCT04560881
Oxford ChAdOx1-S	Non-replicating viral vector	2/3	Single-blind randomized	12,390	UK	NCT04400838
BioNTech BNT162	RNA	2/3	Dose-finding, double-blind randomized	43,998	USA, Argentina, Brazil, others	NCT04368728
BioNTech BNT162	RNA	2/3	Dose-finding, open-label non-randomized	43,998	USA, Argentina, Brazil, others	NCT04380701
AZLB protein subunit vaccine	Protein subunit	2	Double-blind randomized	900	China	NCT04466085
Novavax NVX-CoV2373	Protein subunit	2	Single-blind randomized	4,400	South Africa	NCT04533399
Curevac CVnCoV	RNA	2	Dose-confirmation,double-blind, randomized	691	Peru	NCT04515147
Oxford ChAdOx1-S	Non-replicating viral vector	1/2	Double-blind randomized	2000	South Africa	NCT04444674
WIBP vaccine	Inactivated	1/2	Dose-finding, double-blind randomized	1,264	China	ChiCTR2000031809
Bharat Covaxin	Inactivated	1/2	Double-blind randomized	755	India	NCT04471519
Oxford ChAdOx1-S	Non-replicating viral vector	1/2	Single-blind randomized	1,090	UK	NCT04324606
Zydus Cadila ZyCoV-D	DNA	1/2	Double-blind randomized	1048	India	CTRI/2020/07/026352
CAMS vaccine	Inactivated	1/2	Dose-finding, double-blind randomized	942	China	NCT04412538
Sinovac CoronaVac	Inactivated	1/2	Dose-finding, double-blind randomized	744	China	NCT04352608
Cansino Ad5-nCoV	Non-replicating viral vector	1/2	Dose-finding, double-blind randomized	696	Canada	NCT04398147
CAMS vaccine	Inactivated	1/2	Double-blind randomized	471	China	NCT04470609
Sinovac CoronaVac	Inactivated	1/2	Dose-finding, double-blind randomized	422	China	NCT04383574
Genexine GX-19	DNA	1/2	Dose-finding, double-blind randomized	210	Republic of Korea	NCT04445389

Table 1. Continued

Candidate	Type	Phase	Study design	Volunteer	Country	Reference
Aivita AV-COVID-19	Other	1/2	Dose-finding, double-blind randomized	180	USA	NCT04386252
KBP-COVID-19	Protein subunit	1/2	Observer-blind, dose-finding randomized	180	Not Provided	NCT04473690
Inovio INO-4800	DNA	1/2	Dose-finding, Open-label (A), double-blind (B) randomized	160	Republic of Korea	NCT04447781
Arcturus ARCT-021	RNA	1/2	Double-blind randomized	92	Singapore	NCT04480957
AnGes AG0301-COVID19	DNA	1/2	Dose-finding, Open-label non-randomized	30	Japan	NCT04463472
Themis V591	Replicating viral vector	1/2	Dose-finding, double-blind randomized	260	USA, Austria, Belgium	NCT04498247
Inovio INO-4800	DNA	1/2	Dose-finding, open-label (A), double-blind (B) randomized	160	Republic of Korea	NCT04447781
Novavax NVX-CoV2373	Protein subunit	1/2	Dose-finding, observer-blind randomized	1,419	Australia, USA	NCT04368988
Imperial LNP-nCoVsaRNA	RNA	1	Dose-finding partially randomized	320	UK	ISRCTN17072692
Medicago CoVLP	Virus-like particle	1	Dose-finding, open-label randomized	180	Canada	NCT04450004
Curevac CVnCoV	RNA	1	Dose-finding, single-blind randomized	284	Belgium, Germany	NCT04449276
PLA-AMS ARCoV	RNA	1	Dose-finding randomized	168	China	ChiCTR2000034112
Moderna mRNA-1273	RNA	1	Dose-finding, open-label non-randomized	120	USA	NCT04283461
Clover SCB-2019	Protein subunit	1	Dose-finding, double-blind randomized	150	Australia	NCT04405908
BioNTech BNT162	RNA	1	Double-blind randomized	144	China	NCT04523571
Inovio INO-4800	DNA	1	Dose-finding, open-label non-randomized	120	USA	NCT04336410
University of Queensland vaccine	Protein subunit	1	Dose-finding, double-blind randomized	216	Australia	NCT04495933
Symvivo bacTRL-Spike	DNA	1	Dose-finding, observer-blind randomized	12	Australia	NCT04334980
Cansino Ad5-nCoV	Non-replicating viral vector	1	Dose-finding, open-label non-randomized	108	China	NCT04313127
SGMI aAPC	Other	1	Open-label non-randomized	100	China	NCT04299724
SGMI LV-SMENP-DC	Other	1	Open-label non-randomized	100	China	NCT04276896
Themis V591	Replicating viral vector	1	Dose-finding, double-blind randomized	90	Belgium, France	NCT04497298
Gamaleya Gam-COVID-Vac (Lyo)	Non-replicating viral vector	1	Open-label non-randomized	38	Russia	NCT04437875
AZLB protein subunit vaccine	Protein subunit	1	Double-blind randomized	50	China	NCT04445194
Medigen MVC-COV1901	Protein subunit	1	Dose finding, open-label non-randomized	45	Taiwan	NCT04487210
Vaxine protein subunit vaccine	Protein subunit	1	Double-blind randomized	40	Australia	NCT04453852

aAPC, artificial antigen presenting cell; AZLB, Anhui Zhifei Longcom Biopharmaceutical; BIBP, Beijing Institute of Biological Products; CAMS, Chinese Academy of Medical Sciences; KBP, Kentucky BioProcessing; LV-SMENP-DC, vaccine comprising dendritic cells (DCs) modified with lentivirus (LV) vectors expressing 'SMENP' minigene; PLA-AMS, People's Liberation Army Academy of Military Science; SGMI, Shenzhen Geno-Immune Medical Institute; WIBP, Wuhan Institute of Biological Products.

chemokine-dominant hypercytokinemia, often called a 'cytokine storm,' which robustly promotes expression of numerous IFN-stimulated genes that lead to multi-organ failure (Zhou *et al*., 2020). Therefore, SARS-CoV-2, directly and indirectly, triggers the impairment and hyper-stimulation of the immune system (Jamilloux *et al*., 2020; Yazdanpanah *et al*., 2020). But, cellular immunogenicity, humoral, and cell-mediated immune responses are crucial for vaccine-derived immunity and rapid cytotoxic response against viral infection (Morris *et al*., 2016; Ewer *et al*., 2017). Thus, should vaccines stimulate or suppress the immune response system of the host against COVID-19 infections?

WILL A VACCINE PROVIDE SUSTAINABLE IMMUNE ENDURANCE?

Another major concern about immunity against coronaviruses is the endurance of the immune response system. For effective immunization, vaccine-induced long-term regulation of the immune system, especially humoral and cell-mediated arms of the adaptive system, functions through producing the effector cells for the current infection and memory cells for future infections with the pathogenic agent (Clem, 2011). However, a number of studies showed that immune responses against COVID-19 do not last long-term. A study conducted on 285 SARS-CoV-2-infected persons reported that antiviral immunoglobulin-G (IgG) and IgM were increased during the first 3 weeks after symptom onset, and then began to decrease (Long *et al*., 2020a). A case report of 34 hospitalized patients (admitted from Feb 1 to Feb 29, 2020) with confirmed SARS-CoV-2 revealed that IgM levels reached their peak of after three weeks and then continued to decline up to the end of 7 weeks of observation, whereas IgG values remained more or less the same (Xiao *et al*., 2020). In another case report, both IgM and the IgG declined after the peak period; this study was conducted on 60 convalescent patients where the value of those two antibodies reached their summit 6-7 weeks after onset, and a decline was observed in the following week (Du *et al*., 2020). A report from the National COVID Scientific Advisory Panel of the UK mentioned that IgG titers increased within three weeks of the onset of symptoms and started to drop by eight weeks in plasma samples collected from 40 confirmed COVID-infected persons (Adams *et al*., 2020). Another study noted that the most plasma samples obtained from eight convalescent COVID-19 patients recovering from COVID-19 without hospitalization did not contain high neutralizing activity levels (Robbiani *et al*., 2020). In cases of asymptomatic infection, a study conducted on 37 individuals reported that they had a weaker immune response, i.e., a greater reduction of IgG and neutralizing antibody levels (Long *et al*., 2020b). These phenomena are not new to the scientific world. Exactly 30 years ago, in 1990, a study reported a similar result. From an investigation of circulating lymphocyte populations in 15 volunteers infected with a CoV 229-E strain, the researchers observed that the concentration of antibodies began to rise one week after inoculation and then reached their peak another week later. After that, titers of the antibody began to decline. They also claimed that despite the slightly high concentration after one year, this did not always prevent the volunteer from being reinfected with homologous virus (Callow *et al*., 1990). Thus, how long will a vaccine-mediated immune response be sustained and at what magnitude?

HOW WILL SARS-COV-2 MUTATE?

The genome of coronavirus is highly susceptible to mutations that result in genetic drift and evade immune recognition. Several studies have described this phenomenon. The genetic analysis of 86 complete or near-complete genomes of SARS-CoV-2 disclosed many mutations and deletions in coding and non-coding regions (Phan, 2020). High-resolution mapping of the SARS-CoV-2 transcriptome and epitranscriptome found at least 41 potential RNA modification sites with an AAGAA motif (Kim *et al*., 2020). A study of 95 complete genome sequences found 116 mutations including the three most common mutations, i.e., 8782C>T in ORF1ab, 28144T>C in ORF8, and 29095C>T in the N gene (Khailany *et al*., 2020). Mutations are also found in the S protein region, the crucial part for binding to human receptor ACE2. Another study reported that five of the six receptor binding domain residues of the S protein of SARS-CoV-2 differ from SARS-CoV (Andersen *et al*., 2020). However, this transformation does not stop there. A study identified 13 mutations in the S protein especially in spike D614G, which began to spread in Europe in early February 2020. This study also showed the evidence of recombination between the locally circulated strains indicating the multiple strain infections. (Korber *et al*., 2020). Twelve distinct variants were identified within the B-cell epitopes of the S protein, N protein, and M protein, and 21 distinct variants within T-cell epitopes. Of the 12 variants in the B-cell epitopes, 23403A>G Variant (p. D614 G) in an S-protein epitope has frequently been found in European countries such as the Netherlands, Switzerland and France, but rarely seen in China (Koyama *et al*., 2020). However, SARS-CoV-19 might not be evolving as rapidly as other RNA viruses, but we still need much more scientific evidence. Nevertheless, rapidly evolving viruses such as influenza need to be monitored to recommend new vaccine formulations twice each year (Gerdil, 2003). Similarly, no human immunodeficiency virus vaccines exist yet (Andrews and Rowland-Jones, 2017). In these circumstances, will the genetic stability of the SARS-CoV-19 remain such an extent that let the scientists develop a safe and effective vaccine?

ARE WE PREPARED FOR VACCINE BACKFIRES?

In this pressing time, perhaps some drug makers will rush through small-scale human tests that might not provide sufficient scrutiny of side effects or backfires. However, no vaccination is entirely free of any side effects or complications, and most are preventable illnesses (Kimmel, 2002). Recently, the phase 1/2 clinical trial of the ChAdOx1 nCoV-19 (NCT04324606) vaccine against COVID-19 also reported side effects such as fever, pain, muscle aches, chills, headache, and uneasiness. The research team claimed that these effects can be reduced by prophylactic paracetamol (Folegatti *et al*., 2020). Nevertheless, extreme caution must be taken to scrutinize backfire-effects i.e. the undesirable adverse effects (Table 2). One such dangerous backfire is vaccine-induced enhancement, which has been a major bottleneck in the development of certain corona-, flavi-, lenti-, and paramyxovirus vaccines. Here, antibody-dependent enhancement (ADE) per-

Table 2. Historical concerns about vaccine safety

Incident	Year	Consequence	Reference
Cutter Incident	1955	Started a polio epidemic. Two production pools accounting for 120,000 doses made by Cutter Laboratories caused 40,000 cases of polio; 51 were paralyzed, and five killed even though the vaccine had passed safety testing.	Offit, 2005
Simian Virus 40 (SV40)	1955 to 1963	From 1955 to 1963, an estimated 10-30% of polio vaccines administered in the US were contaminated with SV40, leading to the development of a certain type of cancer.	Stratton *et al.*, 2002
Respiratory Syncytial Virus (RSV)	1966	Of the 20 children who underwent the FI-RSV vaccine trial, 16 needed hospitalization, two died afterwards. On contrary, only one of the 21 control group participants was hospitalized. FDA promptly suspended all clinical trials.	Kim *et al.*, 1969
H1N1 Swine Flu Vaccine and Guillain-Barré Syndrome (GBS)	1976	Increased risk of GBS, a rare neurological disorder.	Schonberger *et al.*, 1979
Hepatitis B Vaccine (HBV) and Multiple Sclerosis (MS)	1998	A relationship between HBV vaccine and MS has been suggested but is disputed.	Ascherio *et al.*, 2001; Naismith and Cross, 2004; Le Houézec, 2014
Rotavirus Vaccine and Intussusception	1998 to 1999	Suspension after 15 cases of intussusception, a bowel obstruction in which one segment of bowel becomes enfolded within another segment.	Iskander *et al.*, 2004
H1N1 Influenza Vaccine and Narcolepsy	2009 to 2010	Concern raised after abrupt-onset childhood narcolepsy was seen in Finland in 2010, but not observed in other countries including in the USA.	Partinen *et al.*, 2012; Duffy *et al.*, 2014
Dengue Virus Vaccine-Dengvaxia	2017	Excess risk of severe dengue in seronegative vaccine recipients compared to seronegative non-vaccinated individuals. The Philippines stopped their immunization program after getting this warning.	Wilder-Smith, 2020

forms a key role (Huisman *et al*., 2009). One study reported that the recombinant vaccinia virus Ankara expressing the S protein of SARS-CoV increased hepatitis in ferrets (Weingartl *et al*., 2004). Anti-S protein IgG against SARS-CoV caused severe acute lung injury in macaques (Liu *et al*., 2019). New Zealand white rabbits displayed increased lung inflammation after re-infection with MERS-CoV due to the lack of non-neutralizing antibodies and complement proteins (Houser *et al*., 2017). Researchers assume that SARS-CoV-2 severity is a consequence of ADE (Tetro, 2020). However, a study opined that the ADE and immunopathology are linked to the inflammatory feedback of host Th17, and this can be overcome by using alum as an adjuvant (Hotez *et al*., 2020). Now, the question arises. Will it be possible to overcome the backfires in developing COVID-19 vaccine? In brief, researchers need to resolve these questions to develop effective and safe vaccines against COVID-19 infection. However, this is not a comprehensive list as COVID-19 infection is a dynamic phenomenon depending on a lot of factors.

EFFECTIVE DEVELOPMENT STRATEGIES

The design and development of an efficacious vaccine is always a complex work, particularly in the case of SARS-CoV-2 that already have been mentioned in the previous sections. On this hurdles race to reach that endpoint of efficacious vaccine, several initiatives can be taken. First, a detailed characterization of COVID-19 immunopathogenesis should be carried out continuously, so that we can have a substantial and scientifically endorsed dataset to make the SARS-CoV-2 more predictable and understandable. Scientists and researchers have already provided several appreciable insights about the novel coronavirus, and they are working relentlessly. As this a global issue and the research is going on a global scale, global collaboration is essential to compare and validate the outcomes of the studies in a wide range of contexts and health care systems. This collaboration and annotating data could break the obstacles and enhance the probability of picking the speed of discovery up as well. Second, utilization of new technologies could overcome those stumble blocks lying in the road of COVID-19 vaccine development. Besides, conventional inactivated or live attenuated virus-vectored, new developments for non-viral vaccines, such as viral particle-like and nanostructures vaccines, subunit vaccines, RNA/DNA vaccines, and the development of rational vaccines, could provide groundbreaking approaches to addressing current vaccine production problems (Brisse *et al*., 2020). The new technologies for vaccine development already showing silver lining for COVID-19 vaccine, and we have noted such vaccines in the types of vaccines section of this article (Table 1). Third, the continuous development of candidate vaccines by

the ongoing preclinical and clinical trials across the world. The studied population should be representative of the wide range of people based on ethnicity, habitat settings, geographic location, gender, age group, and underlying health conditions (Gaebler and Nussenzweig, 2020).

However, there may be no single winner of the vaccine; thus, it will be necessary to standardize different efficiency endpoints to permit reliable estimates and ensuring the deployment of the most successful candidates (Hodgson *et al*., 2020). Finally, artificial intelligence (AI) could play a significant and unprecedented role in solving problems to develop the COVID-19 vaccine. As all the probable ways discussed above need huge amounts of data to be evaluated, analyzed, and validated, AI could do the work with minimal cost, time, and effort compared to the existing setup. Besides, in silico method has already been used in developing drug and vaccine candidates. Therefore, the computational models may help us to find the candidate vaccines and therapeutics if it is feed with a sufficient amount of data (Keshavarzi Arshadi *et al*., 2020). In the end, in every hurdle race, sensibility, skill, and speed are indeed required to reach the finishing point successfully.

CONCLUSIONS

The number of morbidities and mortalities related to COVID-19 is increasing day by day. Global and local economies are on the verge of depression, which is exacerbating humanitarian crises across the globe. Most of the countries have imposed lockdown and stay-at-home-strategy to break the chain of the community transmission; however, these preventive methods are not sustainable for a long time. As such, there is a dire need for a vaccine against COVID-19. An efficient vaccine is the best option for controlling and prevention COVID-19 pandemic. Addressing the raised questions in this paper will improve the safety and efficacy of any COVID-19 vaccine.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

Adams, E. R., Ainsworth, M., Anand, R., Andersson, M. I., Auckland, K., Baillie, J. K., Barnes, E., Beer, S., Bell, J. I. and Berry, T. (2020) Antibody testing for COVID-19: a report from the national COVID scientific advisory panel. *Wellcome Open Res.* **5**, 139.

Andersen, K. G., Rambaut, A., Lipkin, W. I., Holmes, E. C. and Garry, R. F. (2020) The proximal origin of SARS-CoV-2. *Nat. Med.* **26**, 450-452.

Andrews, S. M. and Rowland-Jones, S. (2017) Recent advances in understanding HIV evolution. *F1000Res* **6**, 597.

Ascherio, A., Zhang, S. M., Hernán, M. A., Olek, M. J., Coplan, P. M., Brodovicz, K. and Walker, A. M. (2001) Hepatitis B vaccination and the risk of multiple sclerosis. *N. Engl. J. Med.* **344**, 327-332.

Bernstein, K. E., Khan, Z., Giani, J. F., Cao, D. Y., Bernstein, E. A. and Shen, X. Z. (2018) Angiotensin-converting enzyme in innate and adaptive immunity. *Nat. Rev. Nephrol.* **14**, 325-336.

Brisse, M., Vrba, S. M., Kirk, N., Liang, Y. and Ly, H. (2020) Emerging concepts and technologies in vaccine development. *Front. Immunol.* **11**, 583077.

Callow, K., Parry, H., Sergeant, M. and Tyrrell, D. (1990) The time course of the immune response to experimental coronavirus infection of man. *Epidemiol. Infect.* **105**, 435-446.

Clem, A. S. (2011) Fundamentals of vaccine immunology. *J. Glob. Infect. Dis.* **3**, 73-78.

Corman, V. M., Muth, D., Niemeyer, D. and Drosten, C. (2018). Hosts and sources of endemic human coronaviruses. In Advances in Virus Research, Vol. 100, pp. 163-188. Elsevier.

Cui, W., Fan, Y., Wu, W., Zhang, F., Wang, J. y. and Ni, A. p. (2003) Expression of lymphocytes and lymphocyte subsets in patients with severe acute respiratory syndrome. *Clin. Infect. Dis.* **37**, 857-859.

Du, Z., Zhu, F., Guo, F., Yang, B. and Wang, T. (2020) Detection of antibodies against SARS-CoV-2 in patients with COVID-19. *J. Med. Virol.* doi: 10.1002/jmv.25820 [Online ahead of print].

Duffy, J., Weintraub, E., Vellozzi, C. and DeStefano, F. (2014) Narcolepsy and influenza A (H1N1) pandemic 2009 vaccination in the United States. *Neurology* **83**, 1823-1830.

Ewer, K., Sebastian, S., Spencer, A. J., Gilbert, S., Hill, A. V. and Lambe, T. (2017) Chimpanzee adenoviral vectors as vaccines for outbreak pathogens. *Hum. Vaccin. Immunother.* **13**, 3020-3032.

Folegatti, P. M., Ewer, K. J., Aley, P. K., Angus, B., Becker, S., Belij-Rammerstorfer, S., Bellamy, D., Bibi, S., Bittaye, M., Clutterbuck, E. A., Dold, C., Faust, S. N., Finn, A., Flaxman, A. L., Hallis, B., Heath, P., Jenkin, D., Lazarus, R., Makinson, R., Minassian, A. M., Pollock, K. M., Ramasamy, M., Robinson, H., Snape, M., Tarrant, R., Voysey, M., Green, C., Douglas, A. D., Hill, A. V. S., Lambe, T., Gilbert, S. C. and Pollard, A. J.; Oxford COVID Vaccine Trial Group (2020) Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* **396**, 467-478.

Gaebler, C. and Nussenzweig, M. C. (2020) All eyes on a hurdle race for a SARS-CoV-2 vaccine. *Nature* **586**, 501-502.

Gerdil, C. (2003) The annual production cycle for influenza vaccine. *Vaccine* **21**, 1776-1779.

Gopinathan, U., Peacocke, E., Gouglas, D., Ottersen, T. and Røttingen, J. A. (2020) R&D for emerging infectious diseases of epidemic potential: sharing risks and benefits through a new coalition. In Infectious Diseases in the New Millennium, pp. 137-165. Springer.

Guo, Y. R., Cao, Q. D., Hong, Z. S., Tan, Y. Y., Chen, S. D., Jin, H. J., Tan, K. S., Wang, D. Y. and Yan, Y. (2020) The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. *Mil. Med. Res.* **7**, 11.

Hodgson, S. H., Mansatta, K., Mallett, G., Harris, V., Emary, K. R. and Pollard, A. J. (2020) What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. *Lancet Infect. Dis.* doi: 10.1016/S1473-3099(20)30773-8 [Online ahead of print].

Hotez, P. J., Corry, D. B. and Bottazzi, M. E. (2020) COVID-19 vaccine design: the Janus face of immune enhancement. *Nat. Rev. Immunol.* **20**, 347-348.

Houser, K. V., Broadbent, A. J., Gretebeck, L., Vogel, L., Lamirande, E. W., Sutton, T., Bock, K. W., Minai, M., Orandle, M., Moore, I. N. and Subbarao, K. (2017) Enhanced inflammation in New Zealand white rabbits when MERS-CoV reinfection occurs in the absence of neutralizing antibody. *PLoS Pathog.* **13**, e1006565.

Huisman, W., Martina, B., Rimmelzwaan, G., Gruters, R. and Osterhaus, A. (2009) Vaccine-induced enhancement of viral infections. *Vaccine* **27**, 505-512.

Institute of Medicine (US) Immunization Safety Review Committe (2002) Immunization Safety Review: SV40 Contamination of Polio Vaccine and Cancer (K. Stratton, D. A. Almario and M. C. McCormick Eds). National Academies Press (US), Washington DC.

Iskander, J., Haber, P. and Murphy, T. (2004) Suspension of rotavirus vaccine after reports of intussusception--United States, 1999. *MMWR Morb. Mortal. Wkly Rep.* **53**, 786-789.

Jamilloux, Y., Henry, T., Belot, A., Viel, S., Fauter, M., El Jammal, T., Walzer, T., François, B. and Sève, P. (2020) Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmun. Rev.* 102567.

Jouan, Y., Guillon, A., Gonzalez, L., Perez, Y., Ehrmann, S., Ferreira, M., Daix, T., Jeannet, R., Francois, B., Dequin, P. F., Si-Tahar, M., Baranek, T. and Paget, C. (2020) Functional alteration of innate T cells in critically ill Covid-19 patients. *medRxiv* doi: 10.1101/2020.05.03.20089300 [Online ahead of print].

Kabbani, N. and Olds, J. L. (2020) Does COVID19 infect the brain? If so, smokers might be at a higher risk. *Mol. Pharmacol.* **97**, 351-353.

Keshavarzi Arshadi, A., Webb, J., Salem, M., Cruz, E., Calad-Thomson, S., Ghadirian, N., Collins, J., Diez-Cecilia, E., Kelly, B., Goodarzi, H. and Yuan, J. S. (2020) Artificial intelligence for COVID-19 drug discovery and vaccine development. *Front. Artif. Intell.* **3**, 65.

Khailany, R. A., Safdar, M. and Ozaslan, M. (2020) Genomic characterization of a novel SARS-CoV-2. *Gene Rep.* **19**, 100682.

Kim, D., Lee, J. Y., Yang, J. S., Kim, J. W., Kim, V. N. and Chang, H. (2020) The architecture of SARS-CoV-2 transcriptome. *Cell* **181**, 914-921.e10.

Kim, H. W., Canchola, J. G., Brandt, C. D., Pyles, G., Chanock, R. M., Jensen, K. and Parrott, R. H. (1969) Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. *Am. J. Epidemiol.* **89**, 422-434.

Kimmel, S. R. (2002) Vaccine adverse events: separating myth from reality. *Am. Fam. Physician* **66**, 2113-2120.

Korber, B., Fischer, W., Gnanakaran, S. G., Yoon, H., Theiler, J., Abfalterer, W., Foley, B., Giorgi, E. E., Bhattacharya, T., Parker, M. D., Partridge, D. G., Evans, C. M., Freeman, T. M., de Silva, T. I.; on behalf of the Sheffield COVID-19 Genomics Group, LaBranche, C. C. and Montefiori, D. C. (2020) Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2. *bioRxiv* doi: 10.1016/j.cell.2020.06.043.

Koyama, T., Weeraratne, D., Snowdon, J. L. and Parida, L. (2020) Emergence of drift variants that may affect COVID-19 vaccine development and antibody treatment. *Pathogens* **9**, 324.

Le Houézec, D. (2014) Evolution of multiple sclerosis in France since the beginning of hepatitis B vaccination. *Immunol. Res.* **60**, 219-225.

Le, T. T., Cramer, J. P., Chen, R. and Mayhew, S. (2020) Evolution of the COVID-19 vaccine development landscape. *Nat. Rev. Drug Discov.* **19**, 667-668.

Liu, L., Wei, Q., Lin, Q., Fang, J., Wang, H., Kwok, H., Tang, H., Nishiura, K., Peng, J., Tan, Z., Wu, T., Cheung, K. W., Chan, K. H., Alvarez, X., Qin, C., Lackner, A., Perlman, S., Yuen, K. Y. and Chen, Z. (2019) Anti–spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight* **4**, e123158.

Long, Q. X., Liu, B. Z., Deng, H. J., Wu, G. C., Deng, K., Chen, Y. K., Liao, P., Qiu, J. F., Lin, Y., Cai, X. F., Wang, D. Q., Hu, Y., Ren, J. H., Tang, N., Xu, Y. Y., Yu, L. H., Mo, Z., Gong, F., Zhang, X. L., Tian, W. G., Hu, L., Zhang, X. X., Xiang, J. L., Du, H. X., Liu, H. W., Lang, C. H., Luo, X. H., Wu, S. B., Cui, X. P., Zhou, Z., Zhu, M. M., Wang, J., Xue, C. J., Li, X. F., Wang, L., Li, Z. J., Wang, K., Niu, C. C., Yang, Q. J., Tang, X. J., Zhang, Y., Liu, X. M., Li, J. J., Zhang, D. C., Zhang, F., Liu, P., Yuan, J., Li, Q., Hu, J. L., Chen, J. and Huang, A. L. (2020a) Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat. Med.* **26**, 845-848.

Long, Q. X., Tang, X. J., Shi, Q. L., Li, Q., Deng, H. J., Yuan, J., Hu, J. L., Xu, W., Zhang, Y., Lv, F. J., Su, K., Zhang, F., Gong, J., Wu, B., Liu, X. M., Li, J. J., Qiu, J. F., Chen, J. and Huang, A. L. (2020b) Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat. Med.* **26**, 1200-1204.

Morris, S. J., Sebastian, S., Spencer, A. J. and Gilbert, S. C. (2016) Simian adenoviruses as vaccine vectors. *Fut. Virol.* **11**, 649-659.

Moser, M. and Leo, O. (2010) Key concepts in immunology. *Vaccine* **28**, C2-C13.

Mullard, A. (2020) COVID-19 vaccine development pipeline gears up. *Lancet* **395**, 1751-1752.

Naismith, R. T. and Cross, A. H. (2004) Does the hepatitis B vaccine cause multiple sclerosis? *Neurology* **63**, 772-773.

Offit, P. A. (2005) The Cutter incident, 50 years later. *N. Engl. J. Med.* **352**, 1411-1412.

Partinen, M., Saarenpää-Heikkilä, O., Ilveskoski, I., Hublin, C., Linna, M., Olsén, P., Nokelainen, P., Alén, R., Wallden, T., Espo, M., Rusanen, H., Olme, J., Sätilä, H., Arikka, H., Kaipainen, P., Julkunen, I. and Kirjavainen, T. (2012) Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. *PLoS ONE* **7**, e33723.

Peeri, N. C., Shrestha, N., Rahman, M. S., Zaki, R., Tan, Z., Bibi, S., Baghbanzadeh, M., Aghamohammadi, N., Zhang, W. and Haque, U. (2020) The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *Int. J. Epidemiol.* **49**, 717-726.

Phan, T. (2020) Genetic diversity and evolution of SARS-CoV-2. *Infect. Genet. Evol.* **81**, 104260.

Ratan, Z. A., Hosseinzadeh, H., Runa, N. J., Uddin, B. M. M., Haidere, M. F., Sarker, S. K. and Zaman, S. B. (2020) Novel Coronavirus: a new challenge for medical scientist? *Bangladesh J. Infect. Dis.* **7**, S58-S60.

Robbiani, D. F., Gaebler, C., Muecksch, F., Lorenzi, J. C. C., Wang, Z., Cho, A., Agudelo, M., Barnes, C. O., Gazumyan, A., Finkin, S., Hagglof, T., Oliveira, T. Y., Viant, C., Hurley, A., Hoffmann, H. H., Millard, K. G., Kost, R. G., Cipolla, M., Gordon, K., Bianchini, F., Chen, S. T., Ramos, V., Patel, R., Dizon, J., Shimeliovich, I., Mendoza, P., Hartweger, H., Nogueira, L., Pack, M., Horowitz, J., Schmidt, F., Weisblum, Y., Michailidis, E., Ashbrook, A. W., Waltari, E., Pak, J. E., Huey-Tubman, K. E., Koranda, N., Hoffman, P. R., West, A. P., Jr., Rice, C. M., Hatziioannou, T., Bjorkman, P. J., Bieniasz, P. D., Caskey, M. and Nussenzweig, M. C. (2020) Convergent antibody responses to SARS-CoV-2 infection in convalescent individuals. *bioRxiv* doi: 10.1101/2020.05.13.092619.

Santos, R. A., Ferreira, A. J. and Simões E Silva, A. C. (2008) Recent advances in the angiotensin-converting enzyme 2-angiotensin(1-7)-Mas axis. *Exp. Physiol.* **93**, 519-527.

Schonberger, L. B., Bregman, D. J., Sullivan-Bolyai, J. Z., Keenlyside, R. A., Ziegler, D. W., Retailliau, H. F., Eddins, D. L. and Bryan, J. A. (1979) Guillain-Barré syndrome following vaccination in the national influenza immunization program, United States, 1976-1977. *Am. J. Epidemiol.* **110**, 105-123.

Shereen, M. A., Khan, S., Kazmi, A., Bashir, N. and Siddique, R. (2020) COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *J. Adv. Res.* **24**, 91-98.

Tetro, J. A. (2020) Is COVID-19 receiving ADE from other coronaviruses? *Microbes Inf.* **22**, 72-73.

van Riel, D. and de Wit, E. (2020) Next-generation vaccine platforms for COVID-19. *Nat. Mater.* **19**, 810-812.

Vickers, C., Hales, P., Kaushik, V., Dick, L., Gavin, J., Tang, J., Godbout, K., Parsons, T., Baronas, E., Hsieh, F., Acton, S., Patane, M., Nichols, A. and Tummino, P. (2002) Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. *J. Biol. Chem.* **277**, 14838-14843.

Weingartl, H., Czub, M., Czub, S., Neufeld, J., Marszal, P., Gren, J., Smith, G., Jones, S., Proulx, R, Deschambault, Y., Grudeski, E., Andonov, A., He, R., Li, Y., Copps, J., Grolla, A., Dick, D., Berry, J., Ganske, S., Manning, L. and Cao, J. (2004) Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets. *J. Virol.* **78**, 12672-12676.

Wilder-Smith, A. (2020) Dengue vaccine development: status and future. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* **63**, 40-44.

World Health Organization (2020) Coronavirus disease (COVID-19) weekly epidemiological update and weekly operational update. In Coronavirus Disease (COVID-19) Situation Reports, Vol. 2020. World Health Organization: WHO.

Xiao, A. T., Gao, C. and Zhang, S. (2020) Profile of specific antibodies to SARS-CoV-2: the first report. *J. Infect.* **81**, 147-178.

Yazdanpanah, F., Hamblin, M. R. and Rezaei, N. (2020) The immune system and COVID-19: friend or foe? *Life Sci.* **256**, 117900.

Zepp, F. (2010) Principles of vaccine design—lessons from nature. *Vaccine* **28**, C14-C24.

Zhang, C., Zhao, Y. X., Zhang, Y. H., Zhu, L., Deng, B. P., Zhou, Z. L.,

Li, S. Y., Lu, X. T., Song, L. L., Lei, X. M., Tang, W. B., Wang, N., Pan, C. M., Song, H. D., Liu, C. X., Dong, B., Zhang, Y. and Cao, Y. (2010) Angiotensin-converting enzyme 2 attenuates atherosclerotic lesions by targeting vascular cells. *Proc. Natil. Acad. Sci. U.S.A.* **107**, 15886-15891.

Zhou, Z., Ren, L., Zhang, L., Zhong, J., Xiao, Y., Jia, Z., Guo, L., Yang, J., Wang, C., Jiang, S., Yang, D., Zhang, G., Li, H., Chen, F., Xu, Y., Chen, M., Gao, Z., Yang, J., Dong, J., Liu, B., Zhang, X., Wang, W., He, K., Jin, Q., Li, M. and Wang, J. (2020) Heightened innate immune responses in the respiratory tract of COVID-19 patients. *Cell Host Microbe* **27**, 883-890.e2.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G. F. and Tan, W.; China Novel Coronavirus Investigating and Research Team (2020) A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.* **382**, 727-733.