

Review

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Review

Translational Virology—COVID-19, The Perfect Example

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Abstract

Translational virology, characterized as “from bench to bedside”, covers all issues from basic research through clinical evaluation and final registration and drug/vaccine approval. It covers the identification of the cause of disease, screening of potential prophylactic or therapeutic agents, evaluation in animal models, confirmation of activity in human clinical trials, registration and approval. The recent COVID-19 pandemic represents a perfect example of translational virology, which demonstrated an unprecedented cooperation from the identification of the SARS-CoV-2 to the rapid development of potential repurposed and novel drugs and vaccines for both prophylactic and therapeutic applications. After confirmation of therapeutic and prophylactic efficacy in animal models, clinical phase I-III evaluation was carried out in an overlapping strategy, reducing the development time significantly. To maximize the chances of success, vaccines based on whole viruses, protein and peptide subunits, viral vectors and nucleic acids were developed in parallel. Based on good safety profiles and robust immune responses, COVID-19 vaccine candidates were granted emergency use authorization worldwide allowing the start of mass vaccinations. More than 13.6 billion COVID-19 vaccine doses have been administered, and although severe adverse events have been registered millions of lives have been saved. Due to emerging SARS-CoV-2 variants vaccine re-engineering has been required as part of translational virology. Vaccine production, storage, transport and distribution have also been given attention.

Keywords: basic research; vaccines; drugs; COVID-19; clinical trials; SARS-CoV-2 variants; re-engineered vaccines; vaccine hesitancy; vaccine manufacturing

1. Introduction

Translational research has received more and more attention recently in the context of drug and vaccine development. It has become a platform connecting all development stages from basic research to the approved end product. It has commonly been defined as “from bench to bedside” implying the steps from basic research to find prophylactic and/or therapeutic compounds/molecules for clinical applications of treating patients. Moreover, it has been defined as translating laboratory findings into real-world applications enhancing patient care and public health. The whole process is complicated and lengthy, involving a number of timelines and milestones to be reached before moving forward to the next step. Despite major development in drug screening and evaluation methods, it is estimated that 90% of clinical drug development still fails [1].

Translational virology focuses on agents causing viral diseases, how antiviral drugs and vaccines can be developed and tested in animal models before subjected to clinical trials in humans. After confirmation of safety and efficacy in clinical settings, drug/vaccine approval can be granted by authorities. The main drawback is the long duration of the whole process and inefficient coordination of the different stages. The COVID-19 pandemic has elevated the whole field of translational virology to a totally new level. Therefore, COVID-19 and especially the unprecedented development of safe and effective vaccines in an impressively short time can be considered the perfect example of translational medicine. Here, is presented a review of what has been achieved, what has been learnt and what could have been done differently in hindsight.

2. Basic Research on SARS-CoV-2

2.1. Identification of Infectious Agent

The SARS-CoV-2 outbreak struck the world at the end of 2019 and quickly spread globally to reach pandemic proportions in March 2020 [2]. The first task was to determine the infectious agent causing the outbreak, the source of its origin, and its route of infection [3]. Relatively quickly, the genetic composition of SARS-CoV-2 was outlined [4]. SARS-CoV-2 was quickly identified as a novel human coronavirus and sequence data provided the necessary information for computational and modelling studies on potential antiviral drugs and vaccines against the virus. Structural studies on whole SARS-CoV-2 particles and individual proteins have also contributed to their identification as potential therapeutic targets [5].

2.2. Origin of SARS-CoV-2

The determination of the origin of SARS-CoV-2 has been important to better understand how it could so quickly spread all over the world [6]. Two contradictory theories have proposed that SARS-CoV-2 was accidentally released by spillover from a laboratory at the Wuhan Institute of Virology in China or alternatively spread through human contact with zoonotic diseases at a seafood market in Wuhan. Although arguments for both possibilities have been presented, no conclusive proofs for either theory has been accepted. In any case, the origin of SARS-CoV-2 is not the focus of this review.

3. Strategies for Drug and Vaccine Development

The extensive spread of COVID-19 to all corners of the world resulting in millions of deaths, social suffering and economic shortcomings demanded investment in all possible alternatives to develop prophylactic and therapeutic means for the global populations. In this context, enormous resources were dedicated to parallel development of antiviral drugs and vaccines.

3.1. COVID-19 Drugs

Concerning antiviral drug development, repurposing existing antivirals against other viral diseases has represented the first option for potential targets [7,8]. Drug repurposing presents concerns approved, investigational and discontinued drugs and presents several advantages such as previous knowledge of formulation, pharmacology, pharmacokinetics, toxicity, and manufacturing. Moreover, the drug approval process can be shortened and also can reduce costs. The two types of repurposed drugs for COVID-19 comprised virus-based and host-focused approaches [9]. Among virus-based repurposed drugs remdesivir, an RNA-dependent RNA polymerase inhibitor (RdRp), showed effectiveness among hospitalized adults according to a systematic review and meta-analysis [10]. Hospitalized COVID-19 patients who received remdesivir demonstrated a significant survival benefit independent of disease severity. Favipiravir, another RdRp inhibitor, showed shortened recovery time in surviving COVID-19 patients and significantly reduced 28-day mortality risk in patients with severe disease [11]. In the case of the RdRp inhibitor molnupiravir little to no difference in all-cause mortality, hospitalization rates and symptom resolution was demonstrated in outpatients with mild-to-moderate COVID-19 based on 11 studies with 31,272 participants [12]. Paxlovid, the combination of the 3C-protease inhibitor nirmatrelvir and the boosting agent ritonavir [13] showed in a systematic review and meta-analysis significant differences in hospitalization and all-cause mortality compared to the control group [14]. Moreover, Paxlovid reduced the hospital stay significantly.

Although initially considered as a potentially efficient repurposed drug due to proven clinical observations for various human diseases, hydroxychloroquine (HCQ) no data from cellular, animal model and clinical studies have supported any therapeutic efficacy against COVID-19 [15]. Similarly, despite numerous studies on ivermectin, a drug used against parasitic worms, there is low- to high-certainty evidence that it has no beneficial effect in COVID-19 patients [16]. Moreover, there is no evidence that ivermectin can prevent SARS-CoV-2 infections. Unfortunately, ivermectin has been

associated with two scandals [17]. In an experimental study, ivermectin was distributed to residents with COVID-19 in Mexico City without proper consent or appropriate ethical projections. In another experimental study in a jail in Arkansas, the US, for individuals who developed serious side effects after receiving high doses ivermectin without their knowledge.

3.2. Monoclonal Antibodies Against COVID-19

Monoclonal antibodies (mAbs) have proven useful for the treatment of COVID-19. Initially, mAbs against SARS-CoV such as CR3022, showed potent binding to SARS-CoV-2 [18]. The human 47D11 mAb elicited neutralizing antibodies against both SARS-CoV and SARS-CoV-2 S proteins and potent inhibition of Vero E6 cell growth after infection with pseudotyped vesicular stomatitis virus (VSV) expressing SARS-CoV-2 S protein [19]. Moreover, the S309 mAb from a SARS patient neutralized SARS-CoV-2 [20]. Interim results from a phase II/III trial with the VIR-7831 mAb (sotrovimab), a modified version of S309 with better half-life, showed reduced risk of progression of mild-to-moderate COVID-19 in high-risk patients [21]. Sotrovimab was granted emergency use authorization (EUA) in the US in May 2021 and full approval in the EU for adolescents and adults, who are at high-risk progression of severe COVID-19 [22].

In another approach, the fully humanized neutralizing IgG1 mAb LY-CoV555 (bamlanivimab) demonstrated good safety and tolerability in a phase I study in hospitalized COVID-19 patients [23]. Furthermore, LY-CoV555 has been subjected to monotherapy and in combination with LY-CoV016 (etesimivab) in phase II/III [24]. LY-CoV555 alone did not reduce viral load compared to placebo. In contrast, the combination of LY-CoV555 and LY-CoV018 significantly reduced the viral load. Although granted EUA by the FDA for treatment of adult and pediatric patients with mild-to-moderate COVID-19 [25], both LY-CoV555 and LY-CoV018 distribution were terminated because of providing no efficacy against COVID-19 variants [26].

The combination of the REGN10987 (imdevimab) and REGN10933 (casirivimab) mAbs targeting different epitopes of the SARS-CoV-2 S receptor binding domain (RBD) showed good safety and reduced viral load in COVID-19 patients in phase II/III [27]. The combination therapy was first granted EUA in the US followed by India, Canada, Switzerland, the EU, the UK and Australia [28].

3.3. Vaccines Against COVID-19

The development of COVID-19 vaccines has been the greatest contribution to save millions of lives and down-grade the pandemic to an epidemic status [29]. The global strategy was to develop COVID-19 vaccines based on whole viruses, protein subunits, viral vectors and nucleic acids in parallel [30]. Due to the urgent needs no resources were spared, and timelines were shortened by instead of finalizing preclinical studies before starting clinical trials, overlapping activities were conducted [31]. For example, after briefly confirming COVID-19 specific antibody responses and protection against SARS-CoV-2 challenges in animal models, clinical phase I safety studies were initiated in healthy volunteers. While the phase I trials were still in progress, phase II trials were started and similarly phase III studies commenced based on positive interim results from phase II. Production of large quantities of vaccine candidates took also place early to guarantee that sufficient ready-to-use vaccines were available once EUA was granted for mass vaccinations.

In the case of whole virus vaccines, 50.7% efficacy against symptomatic COVID-19 and 100% efficacy against hospitalization was achieved for the CoronaVac (Sinovac) vaccine in phase III [32]. CoronaVac was granted EUA in 54 countries in 2021 [33]. Another whole virus vaccine, BBiBP-CorV (Sinopharm) provided 78.1% vaccine efficacy in phase III [34]. BBiBP-CorV received EUA by the WHO in 2021 [35]. Protein subunit-based vaccines such as COVAX-19 have elicited robust immunogenicity in phase II [36]. Moreover, COVAX-19 reduced the severity and rates of COVID-19 in phase III [37]. Nanoparticle-encapsulated full-length SARS-CoV-2 S protein vaccine NVX-CoV2373 showed antibody and CD4⁺ T-cell responses, which were superior compared to those seen in convalescent COVID-19 patients on phase I/II [38]. The COVAX-19 vaccine gave 76.3% efficacy against symptomatic COVID-19 and 100% efficacy against severe disease in phase III [39].

Conditional marketing authorization (CMA) was given to NVX-CoV2373 in the EU in 2021 and in the UK in 2022 [40].

A number of different viral vectors have been applied for COVID-19 vaccine development as previously described [30]. For this reason, only a brief description of the most advanced vaccines developed for adenoviruses is presented here. In this context, the ChAdOx1 nCoV-19 vaccine based on the full-length chimpanzee virus vector ChAdOx1 expressing the full-length SARS-CoV-2 S protein provided 62-90% vaccine efficacy in phase III [41] and received EUA in the UK in 2020 [42]. The Ad5-nCoV vaccine based on the human adenovirus 5 (Ad5) serotype was granted EUA in China in 2021 [43]. Another strategy has been to apply a prime-boost regimen, where administration of the SARS-CoV-2 S expressed from an Ad26 is followed by another vaccination with an Ad5-based vector [44]. The Russian Ad26-S/Ad5-S vaccine (Sputnik V) showed a 91.6% vaccine efficacy in phase III [45]. Despite being tested in only 76 volunteers, it controversially received EUA in Russia in 2020 [46]. In contrast to the above-described adenovirus-based vaccines, the Ad26.COV2.S vaccine required only a single vaccination, which resulted in a 52.9% vaccine efficacy in phase III [47] and EUA by the FDA in 2021 [48].

Among nucleic acid-based vaccines, the synthetic INO-4800 DNA vaccine showed in phase II robust immune responses after a booster immunization with 1 or 2 mg DNA vaccines in persons previously vaccinated twice with INO-4800 [49]. Dose dependent superior immunogenicity was seen with the higher dose. The ZyCoV-D DNA vaccine expressing the SARS-CoV-2 S RBD showed good safety and strong immune responses in phase I/II [50] and a 66% vaccine efficacy in phase III [51]. ZyCoV-D received EUA in India in 2021 [52].

Much attention has been paid to RNA-based COVID-19 vaccines. For example. The liposome nanoparticle (LNP)-encapsulated prefusion-stabilized full-length SARS-CoV-2 S RNA (BNT162b2) vaccine demonstrated a 95% vaccine efficacy in phase III [53] and EUA was granted in 2020 in the EU and Switzerland [54]. Similarly, the mRNA-1273 vaccine provided a 94.1% vaccine efficacy in phase III [55] and EUA was granted by the FDA in 2020 [56]. An interesting approach for mRNA-based vaccines has been the utilization of the self-amplifying RNA (saRNA) technology, which has generated superior mRNA quantities with lower immunization doses compared to conventional synthetic mRNA [57]. Based on the Venezuelan equine encephalitis virus (VEE) RNA replicon, the LNP-nCoVsaRNA vaccine showed good safety and tolerability in phase I despite not reaching 100% seroconversion rates [58]. In phase II enhanced seroconversion was achieved by prolonged dose intervals and booster immunizations [59]. Another lipid organic nanoparticle (LION) formulation for VEE-SARS-CoV-2 S RNA demonstrated excellent safety and robust immunogenicity in phase II/III [60] and it received EUA in India in 2025 [61].

4. Drug and Vaccine Safety

Drug and vaccine safety is essential for any medical intervention and has become even more important in the context of the COVID-19 pandemic. The main concern has been any adverse events occurring especially after mass vaccinations of generally healthy individuals. Moreover, the effect on persons with pre-existing medical conditions and their reactions to drugs and vaccines need to be considered.

4.1. Drug Safety and Efficacy

Clinical trials have initially provided relevant information on safety and tolerability of novel COVID-19 drugs. Moreover, drug efficacy has been compared standard of care treatment to confirm whether drug candidates should move forward to additional clinical trials and further be considered for drugs registration and approval. Case reports also play an important role in the development process. The special case of COVID-19 with its wide spectrum of approaches and drug molecules has, however, caused some issues as effort has been wasted on small, underpowered studies for which it has been unclear whether certain drugs can be recommended or not [62]. It has been estimated that

more than 90% of COVID-19 drugs studies fall under this category [63]. Despite that, effective drugs are available for the treatment of COVID-19 as discussed earlier.

4.2. Vaccine Safety and Efficacy

In the case of vaccines against COVID-19, the question of safety has received even greater attention than for drugs. On one hand, vaccinations have always been associated with certain fears, suspicions, and risks, which has reached unprecedented levels with the application of mRNA-based vaccines. On the other hand, the mass vaccinations of more than 16 billion doses administered globally has certainly revealed a spectrum of adverse events, which most likely would go undetected in vaccination programs carried out at a smaller scale.

Generally, it can be concluded that all types of COVID-19 vaccines have demonstrated good safety profiles and tolerability. However, serious adverse events have been reported for several premature non-communicable diseases (NCDs) after vaccinations as reviewed in detail elsewhere [64]. Although pre-medical conditions and genetic predisposition have been linked to post-vaccination adverse events, serious attention and monitoring is required. In any case, vaccinations have saved millions of lives and benefits clearly outperform the risks associated with vaccinations. Unfortunately, massive misinformation and disinformation have discredited vaccine safety and increased vaccine hesitancy as discussed later in the text.

The different types of COVID-19 vaccines have also proven efficient for significantly reducing hospitalization and mortality and also in decreasing the number of cases of symptomatic COVID-19. However, the original COVID-19 vaccines did not protect individuals from SARS-CoV-2 transmission. Moreover, the vaccine potency has seen a decrease, which to some extent can be explained by the prolonged time since the last vaccine administration. Booster vaccinations have therefore indeed enhanced potency.

4.4. SARS-CoV-2 Variants and Vaccine Efficacy

Emerging variants of the original SARS-CoV-2 strain has significantly contributed to the reduced vaccine potency [65]. Although not considered as a virus with a high mutation frequency [66], a spectrum of mutations in the SARS-CoV-2 S protein and elsewhere in the genome have been identified. Many SARS-CoV-2 variants such as alpha, beta, gamma, delta and omicron and their many subvariants have shown significant reduction in vaccine efficacy [67]. This problem has been addressed by the re-engineering of existing COVID-19 vaccines. For example, the bivalent mRNA-1273.214 vaccine, which contains the original mRNA-1273 and the corresponding RNA for the omicron BA.1 variant, enhanced neutralizing antibody titers against omicron and induced binding activity against the alpha, beta, gamma, and delta variants in phase II/III compared to the mRNA-1273 vaccine [68]. Moreover, booster vaccinations with the re-engineered mRNA XBB.1.5 vaccine elicited 37-fold higher neutralizing antibody titers against the omicron XBB.1.5 and EG5.1 variants [69].

4.4. Vaccine Hesitancy

The success of vaccination relies not only on vaccine efficacy but the consistency and high frequency rates in populations. Although widespread childhood vaccination has eliminated or restricted many infectious diseases such smallpox, polio and measles, recent decline in vaccination rates has enhanced the risk of re-emergence of these diseases. Based on estimates from a modeling study in the US [70], declining childhood vaccination rates will most likely increase the frequency and size of outbreaks of such diseases as measles, rubella, poliomyelitis, and diphtheria making them endemic. Similarly, attacks against polio vaccine campaigns and healthcare workers have taken place in Pakistan and Afghanistan claiming that the vaccinations only serve Western propaganda and present a serious health risk to the local population [71].

Skepticism and hesitancy have reached new levels with the COVID-19 pandemic [72]. Especially, the application of mRNA-based vaccines has raised concerns with claims that the novel

mRNA technology has never been tested in animal models and human trials despite publications in 1990s of safe and successful mRNA delivery to mice [73] and numerous phase I-III trials conducted in humans [30] before EUA was granted. Another issue contributing to mistrust comprises the adverse events associated with vaccinations. There is no denial of even severe adverse events registered in vaccinated individuals with an estimated more than 13.6 billion COVID-19 vaccine doses administered globally [74]. However, in many cases only the temporal and not the causal association has been confirmed. Firm evidence-based science has through many clinical and epidemiological studies confirmed that the benefits of COVID-19 vaccinations outweigh the risks by a large margin. Unfortunately, much of this information is based on no reliable scientific studies and rather spread by individuals opposed to any vaccine development. Moreover, irresponsible misinformation and disinformation can be easily shared on social media platforms without any responsibility or consequences.

The hesitancy related to COVID-19 vaccines has been studied by conducting numerous surveys and systematic reviews. For example, vaccine hesitancy was strongly influenced by sex, age, education level and income status among Blacks/African Americans [75]. In a Chinese on-line survey, individuals with a higher educational level, married people, people in good health, non-smokers, and persons paying attention to hygiene such as hand washing, mask wearing, and social distancing showed a more positive attitude towards COVID-19 [76]. Individuals who were less confident about conspiracy theories, but who showed higher levels of trust in medical doctors were more favorable towards vaccinations. Interestingly, a study in 12-15-years-old children revealed that 42% showed no hesitancy at all to COVID-19 vaccinations, 22% "a little hesitancy", 21% "some hesitancy" and 15% "strong hesitancy" [77]. Moreover, a correlation between TV watching and hesitancy was established although factors such as age, gender, race and parental education were not statistically significant. Based on a meta-analysis of 35 studies, a remarkably large variation was seen among healthcare workers in different countries [78]. Very low vaccine hesitancy of 4.3% was observed in China, whereas 8-18% was reported in the US, 7-32.5% in Europe and 72% in Africa. Among male healthcare workers, elderly people and doctoral degree holders generally favored vaccines as did persons who had been infected by SARS-CoV-2, directly cared for patients, or had experience with influenza vaccinations. Vaccine hesitancy was higher among men, residents in rural areas and parents with children younger than 18 years, and in people preferring information from peers, social media, on-line forums and blogs in a Norwegian study [79]. Correlation between conspiracy theories and vaccine hesitancy could be demonstrated [80] among individuals who did not consider the COVID-19 pandemic dangerous and who denied the existence of SARS-CoV-2. Typically, individuals who considered COVID-19 vaccines unsafe had less knowledge about SARS-CoV-2/COVID-19, favored myths and conspiracy theories, had a lower level of education, earned less, and lived in rural areas based on a national survey in the US [81]. According to a recent study in Ireland, the concept of vaccine effectiveness and its waning with time are not well understood by the general public and these issues needs to be addressed [82]. Therefore, access to accurate and science-based information of COVID-19 and the safety and efficacy of existence vaccines is of utmost importance to be able to resist and counteract the massive misinformation and disinformation campaigns [80].

5. Drug and Vaccine Production and Distribution

Drug production has mainly followed conventional procedures established for drugs targeting infectious diseases. In the case of vaccines, methods for vaccines based on whole viruses, protein subunits, and viral vectors have already been developed and even utilized for years. However, in the case of RNA-based vaccines, the COVID-19 mRNA vaccines were the first produced in large quantities for mass vaccinations and despite its relatively simple manufacturing process a well-established platform is still needed to improve the production capacity [83]. Upstream processing comprises the enzymatic synthesis of mRNA and the downstream phase includes mRNA purification followed by LNP formulation and Fill-to-Finish steps [84]. In the context of in vitro transcription, the methods can be improved by continues processing, which can have a positive impact on reducing

costs and operation time and facilitate automation for higher productivity and better product quality [85,86]. Furthermore, minimizing expensive reagents can reduce the costs [87]. The quantity of the required mRNA dose and the production scale will have a strong impact on the costs of the upstream process. In this context, application of the saRNA platform where 100- to 1000-fold lower doses compared to conventional mRNA are needed to induce therapeutic immune responses [88] is an attractive alternative for cost-effective RNA production for vaccines.

The downstream processing still presents a bottleneck for cost-effective RNA production. Attention is required for mRNA purification to develop new chromatographic modes to avoid multiple mRNA purification steps. For example, application of multimodal chromatography has provided promising results in an integrated and intensified purification process [89].

Related to the mRNA production, optimization of the freeze-drying of lyophilized mRNA-LNPs by the selection of an optimal buffer and cryoprotectant [90]. This process maintained LNP characteristics and functionality of mRNA vaccines under refrigerated conditions for at least a year, thereby offering a viable solution for mRNA vaccine distribution.

As for other indications, the distribution of novel medications and vaccines is seriously biased for the rich and the developing countries. On one side, the costs play an important role, but also the logistics of delivery and the capacity of storage of thermosensitive drugs and vaccines under special conditions present real challenges. The development of appropriate cold chain storage, logistics and vaccine management was needed overcome the pandemic [91]. In another approach, product stability and half-life extension have been achieved by engineering thermostable vaccines, which allow transport and storage under less demanding conditions. For example, thermostable mRNA-based vaccines have successfully been developed [92,93]. In a novel approach, a lipid-free mRNA vaccine was engineered by spray-drying RNA embedded in glassy polysaccharide microparticles followed by atomic layer deposition (ALD) [93]. The alumina-coated mRNA vaccine could be stored for 6 months at temperatures of 40°C.

6. Conclusions

The milestone of six years since the onset of the COVID-19 has now been reached. In this review, the successful development of drugs and vaccines against COVID-19 has been summarized. Undoubtedly, major progress in this field has been achieved leading to approval of drugs and vaccines for global use. Particularly, mass vaccinations have substantially contributed to the downgrading of COVID-19 to an endemic status and allowing society to open to normal activities after the unprecedented lockdown experienced in many countries. The success can be especially attributed to the contribution of translational virology, which allowed exceptionally rapid development of drugs and vaccines, which prevented asymptomatic COVID-19 and particularly reduced hospitalization and mortality rates due to COVID-19. Unfortunately, unfounded and unscientific activities directed against researches, clinicians, authorities, and pharmaceutical and biotechnology companies tried to not only question the safety and efficacy of drugs and vaccines but also claimed that the COVID-19 pandemic was intentionally engineered and especially the vaccines were bioweapons [94]. Conspiracy theories went so far claiming that vaccines contained microchips to control individuals [95]. Fortunately, the reality based on sound scientific observations from large clinical trials and epidemiologic reports have confirmed the high efficacy and solid safety of COVID-19 drugs and vaccines. However, the continues emerging of SARS-CoV-2 variants, which have reduced the effectiveness of COVID-19 vaccines, has demanded acceleration of booster vaccinations and re-engineering of existing vaccines. It has also encouraged the development of novel drugs and vaccines targeting conserved regions of the SARS-CoV-2 genome less prone to mutational activity.

A comparison of the COVID-19 pandemic to the previous SARS epidemic demonstrated a major difference in the manifestation of the disease. Although SARS never reached pandemic proportions with total cases of 8422, 916 deaths, and a case fatality rate of 11% [96]. In contrast, more than 780 million cases have been reported for COVID-19 causing more than 7.1 million deaths and case fatality rates varying with age being 0.015% (0-17 years), 0.15% (18-49 years), 2.3% (50-74 years), 17% (75

years or over) [97]. A remarkable difference between SARS and COVID-19 is that while SARS surprisingly ended [98], COVID-19 continues its presence at an endemic state. The reason for this is unclear. In any case, with SARS-CoV-2 still very much present, emerging variants appearing, and potential novel epidemics/pandemics not ruled out, we need to stay alert and prepared to use the knowledge and experience from the perfect example of translational virology.

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Abbreviations

The following abbreviations are used in this manuscript:

ALD	Atomic Layer Deposition
CMA	Conditional Marketing Authorization
COVID-1	Coronavirus Infectious Disease-19
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HCQ	Hydroxychloroquine
mAb	Monoclonal Antibody
RBD	Receptor binding domain
RdRp	RNA-dependent RNA polymerase
saRNA	Self-amplifying RNA
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2
VEE	Venezuelan equine encephalitis virus
VSV	Vesicular stomatitis virus

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