



## Review

# Current global vaccine and drug efforts against COVID-19: Pros and cons of bypassing animal trials

BIJAYEETA DEB<sup>†</sup>, HEMAL SHAH<sup>†</sup> and SUCHI GOEL\*

Indian Institute of Science Education and Research (IISER) Tirupati, Tirupati 517 507, India

\*Corresponding author (Email, [suchi@iisertirupati.ac.in](mailto:suchi@iisertirupati.ac.in))

<sup>†</sup>These authors contributed equally to this work.

MS received 1 April 2020; accepted 23 May 2020

COVID-19 has become one of the biggest health concern, along with huge economic burden. With no clear remedies to treat the disease, doctors are repurposing drugs like chloroquine and remdesivir to treat COVID-19 patients. In parallel, research institutes in collaboration with biotech companies have identified strategies to use viral proteins as vaccine candidates for COVID-19. Although this looks promising, they still need to pass the test of challenge studies in animal models. As various models for SARS-CoV-2 are under testing phase, biotech companies have bypassed animal studies and moved to Phase I clinical trials. In view of the present outbreak, this looks a justified approach, but the problem is that in the absence of animal studies, we can never predict the outcomes in humans. Since animal models are critical for vaccine development and SARS-CoV-2 has different transmission dynamics, in this review we compare different animal models of SARS-CoV-2 with humans for their pathogenic, immune response and transmission dynamics that make them ideal models for vaccine testing for COVID-19. Another issue of using animal model is the ethics of using animals for research; thus, we also discuss the pros and cons of using animals for vaccine development studies.

**Keywords.** COVID-19; SARS-CoV-2; drugs; vaccines; animal models

**Abbreviations:** COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MERS, Middle East respiratory syndrome; ACE2, angiotensin-converting enzyme 2; HA, hemagglutinin; WHO, World Health Organization; VLP, virus-like particles; CQ, chloroquine; HCQ, hydroxychloroquine; FDA, Food And Drug Administration; NIAID, National Institute of Allergy and Infectious Disease; MCP1, monocyte chemoattractant protein 1; HIV, *Human immunodeficient virus*; AIDS, acquired immunodeficiency syndrome

## 1. Introduction

The recent pandemic of novel coronavirus has already affected thousands of people and is continuing to spread around the world. This virus is called ‘severe acute respiratory syndrome coronavirus 2’ (SARS-CoV-2) and the disease caused is called ‘coronavirus disease 2019’ (COVID-19). As of 5 May 2020, a total

of 3,517,345 confirmed clinical episodes of COVID-19 and 243,401 deaths have been reported worldwide (WHO 2020a). Most SARS-CoV-2-infected people experience mild to moderate respiratory distress and generally recover without requiring any special treatment. However, older people (generally >60 years of age), and those with underlying medical complications like diabetes, cardiovascular disease, chronic respiratory disease and cancer are more likely to develop serious symptoms like acute respiratory disease and multiorgan failure, ultimately leading to death (Lai *et al.* 2020).

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This article is part of the Topical Collection: COVID-19: Disease Biology & Intervention.

SARS-CoV-2 belongs to the same family as that of SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) viruses that were responsible for epidemics in 2003 and 2012 respectively (Lu *et al.* 2020). The genomes of SARS-CoV-2 is a single positive-strand RNA and codes for similar structural protein as of SARS, giving rise to a debate about whether it is a laboratory engineered SARS virus or a naturally evolved new virus. The sequence analysis of its RNA made available by China in the public database showed that it is a novel virus that originated possibly from bats through natural evolution (Andersen *et al.* 2020). However, how it got transmitted from bats to humans with such high transmission rates from humans to humans is still ambiguous.

For infection into human cells, the receptor-binding domain of spike protein (S) present on the envelope of the virus binds to ACE2 protein present on human cells, initiating the entry process. This binding induces large conformational change in S protein that leads to exposure of its proteolytic site. The proteolytic site is then cleaved by a protease, causing the fusion of the viral envelope to the host cell membrane, completing the entry of the virus into a human cell. Further, it is shown that the S protein of SARS-CoV-2 has a higher binding affinity with ACE2 as compared to SARS (Wrapp *et al.* 2020). Based on these results, it could be concluded that SARS-CoV-2 is a variant of SARS; however, the SARS-CoV-2 genome has additional features like the presence of a polybasic (RRAR) cleavage site at the junction of S1 and S2 subunits of the spike protein. The presence of a polybasic cleavage site helps in effective cleavage by furin and proteases and determines viral infectivity and host range (Andersen *et al.* 2020). Interestingly, in case of the avian influenza virus, the gain of this polybasic site in HA that performs a similar function of host receptor binding like Spike protein, can transform the virus from low virulent to high virulent forms. Along with this, the acquisition of cleavage site is positively selected for fast replication and transmission rates (Alexander and Brown 2009). To better understand the transmission rates, the growth rate  $r_0$  that defines the natural transmission of a pathogen needs to be calculated for SARS, MERS, and SARS-CoV-2. It is interesting to observe that although they belong to the same family, SARS-CoV-2 has twice the transmission rate when compared to SARS. Along with this, the multiplication cycles range is 5–10 days for SARS and MERS and 2–3 days for SARS-CoV-2 (Liang 2020). Probably this the reason why SARS and MERS were far more contained, whereas COVID-19 is highly widespread. The

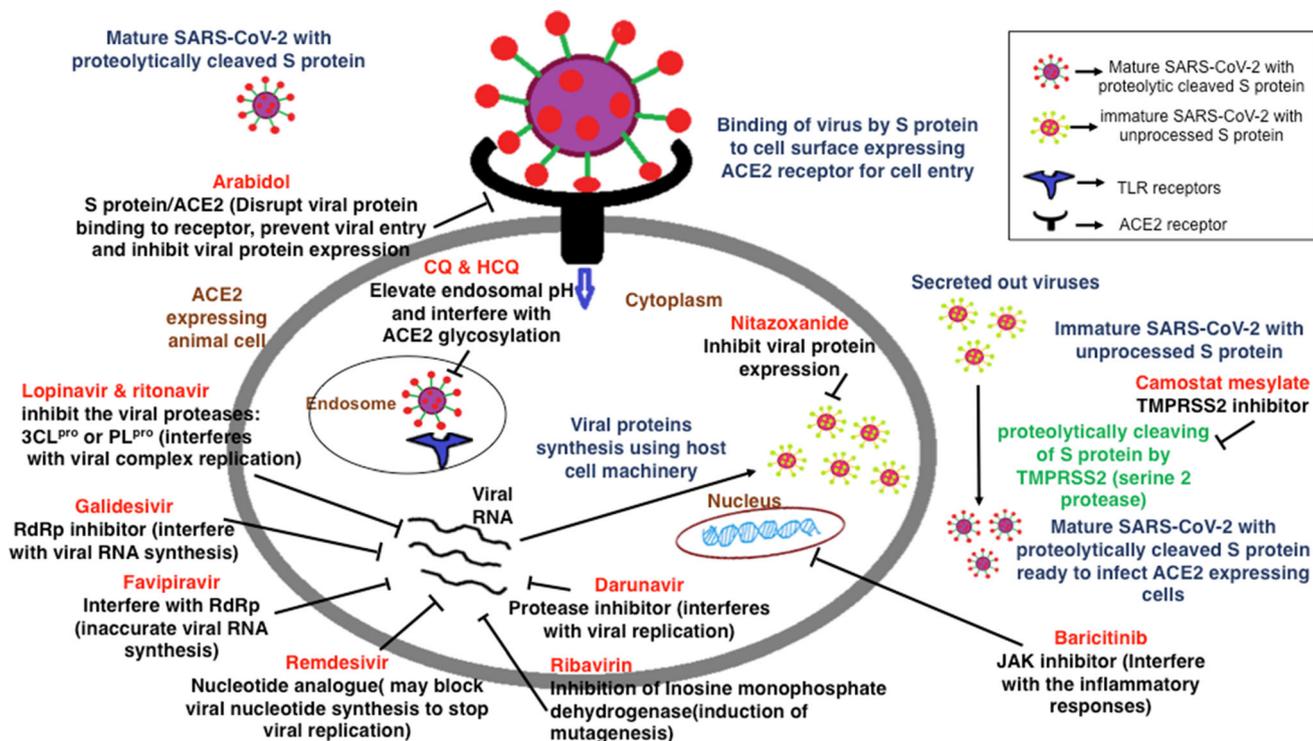
mortality rate of SARS-CoV-2 during the early outbreak in Wuhan, China, was calculated as 1.4% (Wu *et al.* 2020). However, in late February, WHO estimated this rate to increase to 5.8%. On the other hand, South Korea registered a death rate of 1% or less, while the death rate in Italy seems to be, for now, several folds higher (Rosenbaum 2020). The infection has advanced to more than 210 countries and territories with an average mortality rate of 3.4% according to recent reports (Rajgor *et al.* 2020). Therefore, therapeutic and vaccine initiatives in this direction are inevitable. Efforts have been made in drug therapy as well as vaccine development to combat COVID-19.

## 2. Current therapeutic options

Till date, the US Food and Drug Administration (FDA) has approved an antiviral drug, remdesivir, developed by Gilead Inc. USA, and an antimalarial drug, chloroquine (CQ)/hydroxychloroquine (HCQ), for the treatment of COVID-19. An array of drugs approved for other diseases are also considered potentially useful while several investigational drugs are under study in several clinical trials conducted across the globe (table 1A and B; figure 1). In order to clinically manage coronavirus, researchers from China, France, and a team of doctors from Rajasthan, India, have started using antiviral drugs in combination with chloroquine (Colson *et al.* 2020; Lai *et al.* 2020; Liu *et al.* 2020). Recently, WHO announced a global trial, called SOLIDARITY, to investigate whether this dangerous respiratory disease could be treated with the available therapeutic aids (<https://news.un.org/en/story/2020/03/1059722>). It is, however, an unprecedented effort that includes thousands of patients across many countries to volunteer for the clinical trials. The trials aim to test the effectiveness of the four potential candidates: (1) the antiviral drug remdesivir that is known to inhibit RNA dependent RNA polymerase, (2) a combination of two HIV drugs, lopinavir and ritonavir, (3) lopinavir and ritonavir plus interferon beta, and (4) the antimalarial drugs chloroquine or hydroxychloroquine (table 1B). Coronavirus being a RNA virus, retroviral drugs could possibly have an effect on treatment; however, CQ/HCQ, which was successful as an antimalarial, is currently being considered as a part of treatment strategy against COVID-19 (Colson *et al.* 2020). CQ has also been shown to possess anti-HIV activity through post-transcriptional inhibition of gp120 present on the viral envelope or inhibition of Tat-mediated transactivation (Jiang *et al.* 1996; Savarino *et al.* 2001). Moreover,

**Table 1.** (A) Repurposing drugs to treat COVID 19. (B) Combinations of drugs used in the SOLIDARITY project by WHO.

CAS/RN	Drug candidate	Target molecule	Mode of action	Drug originally used for
<b>A</b>				
1187594-09-7	Baricitinib	JAK kinase	A JAK inhibitor that may interfere with the inflammatory processes	Rheumatoid arthritis
206361-99-1	Darunavir	Aspartyl protease inhibitor	Interface with viral replication	Hepatitis C, Ebola virus, Marburg virus
36791-04-5	Ribavirin	Inosine monophosphate dehydrogenase	Inhibition of Inosine monophosphate dehydrogenase(induction of mutagenesis)	RSV infection, hepatitis C, some viral hemorrhagic fevers
259793-96-9	Favipiravir	RdRp	A purine nucleoside that acts as an alternative substrate leading to inaccurate viral RNA synthesis	Viral infections
131707-23-8	Arbidol	S protein/ACE2	An inhibitor that may disrupt that binding of viral envelope protein to host cells and prevent viral entry to the target cell	Influenza anti viral
55981-09-4	Nitazoxanide	Oxidative phosphorylation in mitochondria	A drug that may inhibit viral protein expression	Various helminthic, protozoal, and viral infection-caused diarrhoea
<b>B</b>				
54-05-7	Chloroquine	Endosome or ACE2	A drug that can elevate endosomal pH and interfere with ACE2 glycosylation	Material parasite infection
118-42-3	Hydroxychloroquine			
192725-17-0	Lopinavir	3CLpro & PLpro- viral proteases	Protease inhibitors that may inhibit the viral protease: 3CLpro or PLpro	Used in combination for HIV virus treatment
155213-67-3	Ritonavir			
1809249-37-3	Remdesivir	Act as nucleotide analogue	A nucleotide analogue that may block viral nucleotide synthesis to stop viral replication	Ebola virus infection
145258-61-3	Interferon beta-1a (used in combination with Lopinavir and Ritonavir)	Molecules of innate and adaptive immune system	Suppress T cell activation, activates macrophages that engulf antigens and NK cells, activates different immunomodulators and antiviral proteins	Multiple sclerosis



**Figure 1.** Effects of repurposed drugs on different pathways of SARS-CoV-2. Various drugs that were used to viral infections like Ebola and HIV or antimalarial drugs like chloroquine/hydroxychloroquine can also inhibit various processes of the virus and thus block the spread of the virus.

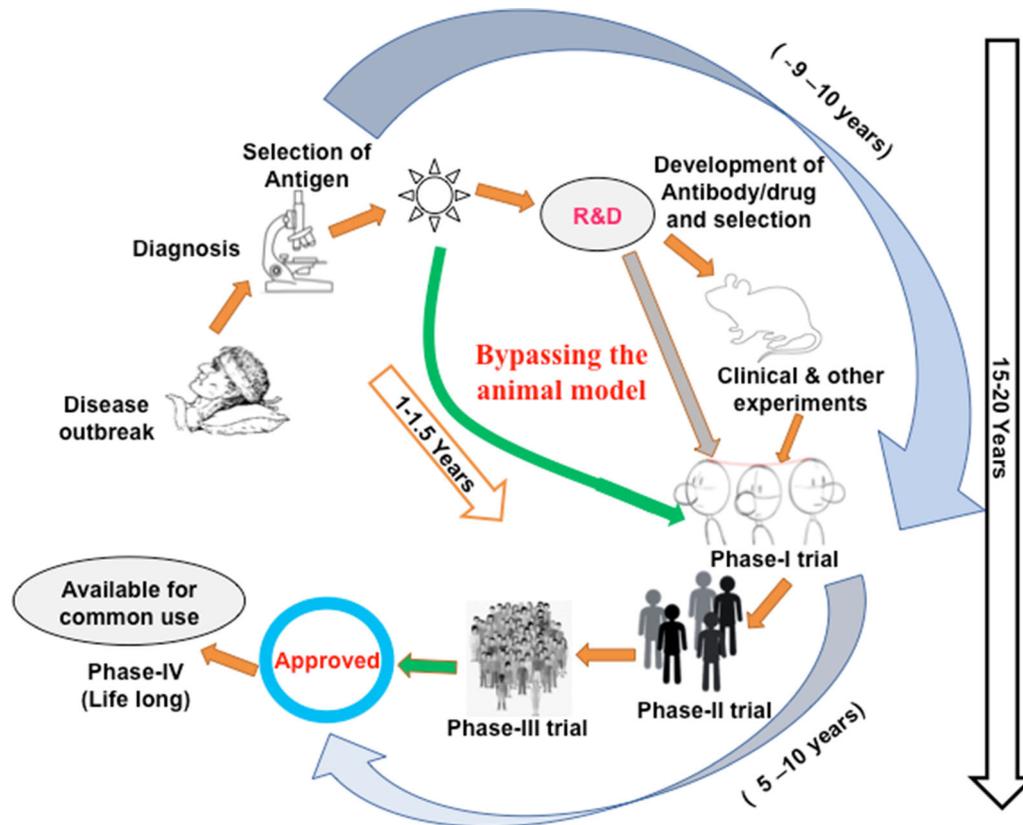
chloroquine can also increase the pH of endosomes (Mauthe *et al.* 2018). Since coronavirus do not encode for gp120 or Tat protein and low pH is essential for uncoating of the virus inside the host cell, it is more likely that chloroquine stops viral spread by blocking the process of uncoating and release of nucleic acid. However, the current data from various small and non-randomized trials show only limited effects of CQ/HCQ or HCQ-azithromycin combination on treatment for COVID-19. Since CQ/HCQ is known to cause toxic effects and unprescribed use has led to human deaths, large-scale randomized trials like the SOLIDARITY project will be able to convincingly prove the effectiveness of CQ/HCQ as a drug against COVID-19. Recently it has been shown that combination of lopinavir-ritonavir causes adverse effects on COVID-19-infected adults and no benefits are observed (Cao *et al.* 2020). Therefore, drugs should be used with caution until their mechanisms are well understood and their efficacy is well established. It is also known with viruses that mutate at high frequencies give rise to different strains, thereby easily gaining resistance to drugs. Thus, in-depth analysis in animal models is required to study their mechanism of action and the ability of the virus to gain resistance against these

drugs. Further animal testing will also be important to measure absorbance of the drug in the body, its dissociation chemistry, its metabolomics and the mechanism of drug clearance.

In principle, drugs only help in the treatment of humans once they contract the disease, but for long-term protection against the disease, vaccines have to be developed to avoid such a global pandemic. Vaccines will be able to mount an immune response against the virus by generating neutralizing antibodies that would protect humans when again infected with SARS-CoV-2 and thus avoid another outbreak of such a virulent virus.

### 3. Vaccine efforts and animal models

The development of a vaccine against a disease is a combined effort from academicians and industries. Under normal circumstances, the final product of the vaccine for use in humans takes at least 15–20 years passing through six phases of assessment (Bregu *et al.* 2011). In the first phase, the academician identifies a target that has the potential to be a vaccine candidate. Thereafter, this candidate is challenged for its vaccine potential by testing it in animal models for the disease



**Figure 2.** Timeline for vaccine development. The vaccine for common use takes 15–20 years to develop; however, if animal models are bypassed, the timeline can be hastened to 1–1.5 years.

where the safety as well as immune responses to the antigen is analyzed. This identification and development of the vaccine candidate is a bottleneck and takes majority of the time ( $\sim 9\text{--}10$  years) required for vaccine development. Once these steps are successful, only then is it taken to clinical trials in three phases where it is tested in humans for its safety in Phase I and efficacy to protect against the disease in Phases II and III, which take another 5–10 years (figure 2).

Different companies have already taken initiatives to develop a vaccine against COVID-19. It is important to note that the studies on SARS have provided important clues for vaccine against COVID-19 and has also fast-tracked the overall process of vaccine development. The vaccine initiatives by various companies against COVID-19 is broadly based on three strategies: (i) using DNA or RNA, (ii) weakened virus known as VLPs, and (iii) targeting viral proteins such as S protein (WHO 2020b). One of the important factors for an antigen to be considered as a vaccine candidate is its ability to mount a good immune response. However, in practicality one is always constrained in terms of the antigen that can be used as vaccine candidates. Thus, to enhance immune responses, Kim *et al.* developed a

microneedle delivery method that induces an antigen-specific antibody response as early as week 2 after immunization. Microneedle injection causes brief mechanical stress that induces the local innate immune response and thus avoids the use of adjuvant. Also, the skin possesses a high amount of immune cells involved in innate immune response, so even injecting a small amount of antigen can lead to significant activation of innate immune responses against the antigen (Kim *et al.* 2020), making it an effective strategy when antigens are not too immunogenic.

In order to establish an antigen as a vaccine candidate, animal models are of profound importance in various aspects of vaccinology, such as route and analyses of the mechanism, the transmission of the disease, duration of induced protection, the host immune response to infection and vaccination (Griffin 2002). Thus, testing in animals is considered to be an important and critical parameter to proceed with the clinical trials in humans. One of the major problems associated with vaccine efforts against COVID-19 is that the most of the animal disease models for SARS-CoV-2 are under testing and, in the absence of these models, it is difficult to predict the outcome of

challenge studies in humans (Gralinski and Menachery 2020). For an animal to be a model for a disease, the pathogen should be able to infect the animal using the same receptor on cells used in humans and then multiply inside the host successfully. Additionally, it should provide either similar clinical symptoms as humans; sometimes mild symptoms also work as this would help in studying immune responses against the pathogen. In the following sections, we discuss various animal models that are being tested based on their pathogenesis after infection with SARS-CoV-2.

### 3.1 Rhesus macaques

As the key 12 amino acid residues present in ACE2 of humans are conserved in ACE2 of macaques as well (Melin *et al.* 2020), macaques are a closer model system to humans, and hence the choice for animal studies for vaccine testing of COVID-19. The studies with macaques have shown that they do get infected with pulmonary infiltrates as observed in radiographs, with high viral loads in swabs of nose and throat and shedding in the upper and lower respiratory tract (Munster *et al.* 2020; Rockx *et al.* 2020). Taken together, the disease symptoms in rhesus macaques matches with the milder symptoms of SARS-CoV-2 infection in humans. Further, serum analysis demonstrate an increase in chemokine levels of IL1ra, IL10, IL15, MCP-1, IL6 and decrease in TGF $\alpha$  levels on days 1 and 3 post-infection but with no statistical significance (Munster *et al.* 2020). SARS-CoV-2 is known to affect older people as compared to young ones; similarly, it is also observed in macaques that older ones show higher viral loads in nose and throat along with prolonged viral shedding in the upper respiratory tract of old animals (Rockx *et al.* 2020). Thus, rhesus macaques can be a promising animal model for challenge studies and studying the efficacy of vaccines, as immune responses in monkeys are similar to humans. This will further allow us to understand how monkeys challenge coronavirus and protect themselves.

### 3.2 Ferrets

Ferrets are model organisms for influenza virus and have similar lung morphology as humans and can actually cough and sneeze, supporting their use as an animal model for SARS-CoV-2 (Cameron *et al.* 2012; Enkirch and von Messling 2015). A team of virologists led by SS Vasan from Australia has already shown that these animals are susceptible to coronavirus (Callaway

2020), but the virus only causes an increase in body temperature and other symptoms that are the hallmark for SARS-CoV-2 do not develop and the virus cannot replicate to high levels. But, interestingly, the infected ferrets can spread the virus with high transmission rates even to adjacent cages through direct contact or aerosols (Kim *et al.* 2020). Since most of the countries are now under community transmission stage, ferrets will act as a valuable animal model to study the transmission of the SARS-CoV-2.

### 3.3 Mice

Compared with the logistics, cost, and ethical regulations in using monkeys and ferrets, laboratory-bred mice always remain a convenient choice as a disease model. However, coronavirus do not infect mice and rats as 11 of the 29 amino acids in mice and 13 of 29 amino acids in rats differ in the binding region of ACE2 compared to humans (Chan *et al.* 2020). In order to solve this problem, Perlman Laboratory developed humanized mouse models for SARS where they incorporated human ACE2 in mice (McCray *et al.* 2007). The humanized ACE2 mice are successfully infected by SARS and develop lethal brain disease, making it an obvious choice to test infection with SARS-CoV-2 as well. However, due to lack of funding and high cost of maintenance of this mice colony, they discontinued breeding of mice in their facility and submitted the sperms of hACE2 mice to Jackson Laboratory. But these mice are now high in demand and Jackson Laboratory is facing a huge pressure to meet these demands. However, recent results from China have shown that hACE2 mice do support SARS-CoV-2 infection where they reduce weight by 20% and virus replication occur in lungs. Moreover, infected hACE2 mice also suffer from interstitial pneumonia where bronchioles are filled with periodic acid Schiff (PAS), positive exudation or detached bronchial epithelium, but are unable to transmit the disease. Also, the infiltrates are enriched in macrophages, T-lymphocytes, and B-lymphocytes. The authors also confirmed that the mice use hACE2 for entry and fulfill Koch's postulates, indicating that these mice are successful disease model for SARS-CoV-2 (Bao *et al.* 2020).

### 3.4 Syrian hamster

These animals support SARS infection and show maximum similarity to human ACE2, where only 4 amino acids out of 29 are different in the critical

binding region of ACE2, making them a testable model for SARS-CoV-2 infection. Upon infection of SARS-CoV-2, Syrian hamsters demonstrate weight loss by ~11% along with high viral load in nasal turbinate, lungs, and trachea. Further, the lethality rate in hamsters is 5% and exudative inflammation with hemorrhage and necrosis of alveolae damage is visible during the initial infection period. The inflammation of intestinal mucosal epithelium that is the causative agent of diarrhoea along with myocardial degeneration is consistent with the pathogenesis observed in humans. Importantly, Syrian hamsters show similar immune responses as that of humans where IFN- $\gamma$  and pro-inflammatory cytokines are induced at day 2 post-infection followed by the decrease of type II interferon and IL6 and increase of TGF- $\beta$  at day 7 post-infection. For an animal to be successful as a model system and perform challenge studies, is also dependent on its ability to transmit the pathogen. Consistent with this, Syrian hamsters are able to transmit the disease to naïve hamsters upon challenge with SARS-CoV-2 (Chan *et al.* 2020). Taken all the data together, as Syrian hamsters show pathogenesis, immune responses similar to humans, and are capable of transmission, this strengthens their use as one of the most testable models for vaccine studies.

Thus, there are many promising animal models for testing the vaccine candidates for SARS-CoV-2, but still extensive studies are required to confirm their efficiency as an appropriate model for COVID-19. In order to fight coronavirus infection and win the race against time, Moderna, a biotechnological company in collaboration with National Institute of Allergy and Infectious Disease (NIAID), USA, has already begun Phase I clinical trial with experimental vaccine mRNA-1273 ('RNA vaccine testing begins' 2020, WHO 2020b). Their argument for directly going for Phase I clinical trial is that the mRNA-1273 raised a good antibody response after immunization in mice and a lack of disease model for coronavirus. CanSino Biologics from China has also developed a replication-defective adenovirus expressing Spike protein of SARS-CoV-2 as a vaccine candidate for COVID-19 (WHO 2020b). Beijing Institute of Biological Products/Wuhan Institute of Biological Products and Sinovac are using inactivated method while Inovio Pharmaceuticals is using a DNA-based vaccine approach. Similarly, in order to fast-track vaccine development, all of them have skipped animal trials and are currently performing Phase I trials. The Phase I clinical trials will test the safety and toxicity of their vaccine target in humans and in a way help in

protecting humans from SARS-CoV-2. Although this looks promising for fast-tracking vaccine development, there is division among the scientific community about bypassing animal models before Phase I clinical trials. In addition, agencies like PETA are against using animals for research purposes. The question remains: Can vaccine research do without an animal model?

#### 4. Pros of bypassing animal models

In the history of mankind, it has been clear that viral pandemics have been common in affecting millions of people. The problem is due to its ability to multiply inside the host and produce high numbers by infecting a single cell accompanied by its stability in non-living surfaces which allows them to spread very fast. That is why virus pandemics are global with high transmission rates. Thus, to control viruses, extreme steps are often needed. Therefore, in the absence of disease model, backed by their antibody responses in mice, NIAID and CanSino Biologics moved ahead with Phase I clinical trials. After bypassing animal model studies for vaccines, different biotechnological companies are looking forward to come up with a vaccine in around a year to a year and a half.

Thus, the decision by the FDA to bypass animal trials is taken positively by entrepreneurs. According to them, flexibility of laws by the FDA could avoid delays in treating, as observed in the case of ganciclovir. Although ganciclovir is successful in treating patients with acquired immunodeficiency syndrome-related cytomegalovirus retinitis, due to lack of animal studies, it did not get approval by FDA and was delayed by 4 years (Van Norman 2019).

Besides overcoming the time frame in which a vaccine can enter the market, it is also important to note that results from animal studies may not translate to humans both in terms of toxicity and challenge studies. Isuprel, a treatment for asthma, was rendered safe in rats, guinea pigs, dogs, and monkeys, but still led to deaths in humans with far less dosages in Great Britain. In another instance, to treat human autoimmune disease, a monoclonal antibody TGN1412, after going through animal models, was processed for Phase I trials. The introduction of TGN1412 led to critical illness within minutes along with long-term complications in Phase I volunteers (Van Norman 2019). However, TGN1412 is now restored for rheumatoid arthritis after developing better assays for studying immune responses and lowering the dosage of this monoclonal

antibody (Brown 2018), further strengthening the fact that studies with animals may not always translate to use in humans.

In contrast, chemicals that are generally toxic in animal studies may be safe in humans. Penicillin, fatal to guinea pigs, would have failed animal studies but due to lack of regulations to perform animal studies at that time, it came into use and is presently a successful drug. Similarly, aspirin is toxic to rhesus monkeys and paracetamol is toxic to dogs and cats (Van Norman 2019).

Thus, these studies indicate that animal studies do not predict the outcomes to humans although they share a lot of genomic similarities; the final response to disease will also depend on the epigenome and environmental differences. Even with the transgenic humanized models that mimic the human system, we must remember that often genes do not work alone in such complex higher-order organisms.

## 5. Cons of bypassing animal model

Although bypassing animal models can save time, effort, and money, but, it is not possible to perform safety and challenge studies for a disease in humans. Also, animal studies provide the foundation to study disease. Further, it is difficult to study the progression of disease in humans but it is easy in an animal model as they can be sacrificed for histopathology in order to follow the course of infection. Although cell lines can also be used to study the infection process, animal models provide the advantage of studying the viral multiplication with respect to symptoms and physiology of an organism. Thus, it becomes really important for a newly originated coronavirus to be studied in an animal model. Further, studying animal models will also provide detailed information about the potential reservoirs of SARS-CoV-2 in an organism.

Another problem faced by vaccine efforts against viral diseases, especially viruses having RNA as the genetic material, is that repair mechanisms do not work on RNA and thus lot of mutations are accumulated in their RNA. This phenomenon is known as antigenic drift and is the reason that influenza shots are needed before every seasonal flu infection. Thus, SARS-CoV-2-possessing RNA genome is also prone to antigenic drift. Hence, animal models of coronavirus will help in understanding the selection pressure and antigenic drift and evolution of the virus once a vaccine is administered.

One of the major disadvantages of bypassing animal models is that it has been observed in case of viral

infections that sometimes the administration of vaccines enhances the susceptibility of the subject to the disease. This phenomenon is known as antibody-dependent enhancement or antigen sin and is common for vaccine candidates of HIV/AIDS virus and Dengue virus. Once the subject is immunized with the antigen, it mounts an immune response against the antigen. But, when the vaccinated individual is infected again with the virus having a different serotype, the pre-existing antibodies are not able to neutralize the virus. The formation of antibody–virus complex helps in attachment to Fc $\gamma$  receptor on circulating monocytes, resulting in the efficient infection of monocytes by the virus (Halstead 2002). Thus, instead of protecting the subject, it leads to higher complications and death of the subject in case of infection by the pathogen (Huisman *et al.* 2009). Therefore, the biotech companies that have bypassed animal models should note that antibody-dependent enhancement is also observed with feline coronavirus (FCov). The immunization of mice with spike (S) protein of this virus mounts an overall high antibody response but neutralizing antibody levels are low. However, challenge of these cats results in enhanced susceptibility to infection along with death of cats (Huisman *et al.* 2009). This phenomenon is especially relevant to proteins that are prone to antigenic drift such as the S protein and SARS and MERS, known to be capable of this phenomena (Liu *et al.* 2019; Houser *et al.* 2017). As S protein is the major vaccine target of SARS-CoV-2, studies in animal model are really required before establishing it as a vaccine candidate.

## 6. Conclusion

In this global emergency, the entire scientific community is attempting effective treatment and prevention of the disease. To shorten the time and for the larger interest of humanity, some routine yet essential processes like animal trials are bypassed in the process of development of vaccine and drug development. While options like drug repurposing are already adapted, with varying degrees of success, effective and targeted drugs and vaccines for the SARS-CoV-2 infection are still awaited. Moreover, agencies like WHO and FDA have already given a green signal for clinical trials of vaccines bypassing the regular process of animal trials. Hence, it is important to access the positive and negative effects of the same. Choosing a suitable animal model is one of the main concerns for animal testing as the animal should mimic the response and effects to be

generated after introduction of the drug/vaccine to humans. Importantly, some animal models such as the rhesus macaque, ferrets, mice, and Syrian hamster are proving to be successful for challenge by the SARS-CoV-2 with one or other similar symptoms as humans. However, a successful animal trial is not the only indicator of the success of any drug/vaccine due to physiological barriers; hence, the decision of bypassing the animal model needs to be taken with utmost caution. Further, saving time should not cost a large number of human lives as a failure of the drug/vaccine could have devastating consequences.

## Acknowledgements

The authors would like to thank IISER Tirupati, DST-SERB for funding. SG is supported by IISER Tirupati, DST-SERB (Grant no. ECR/2017/001703), BD by DST-INSPIRE fellowship, and HS by IISER Tirupati fellowship.

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Corresponding editor: DIPANKAR NANDI