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Vaccine for SARS-CoV-2- the facts that we know so far

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Abstract

The whole world is under the grip of a pandemic of COVID-19, a disease caused by a newly discovered strain of coronavirus and the name given is SARS-CoV-2. The term 'novel' is used for this virus because researches suggest that its origin is from an animal which was transmitted to a human and now is capable of having transmission from human to human. Symptoms of COVID-19 can be mild to severe. Mortality is high in severe cases. Also, this virus is a serious threat to the elderly and people with other systemic illness. There is no specific protocol provided for its treatment and the treatment primarily focuses on symptomatic relief. Human immune systems have never come across this particular type of strain of virus before. As a result, human body has not developed immunity for it moreover no effective vaccine is developed for it at this point of time. But there is an active strenuous work going on to understand more and more about the interaction of host-pathogen, how does host immunity responses to this virus moreover how this pathogen is able to invade the immune system which can be utilised for the development of a vaccine. As the disease is highly infectious, there is an urgent need for the development of a vaccine. Hence this review aims to summarize the undergoing scientific work and research in progress for the development of vaccine and all the advancement that has come in focus for its development.

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INTRODUCTION

In the year 2002, Coronavirus cracked wide open when it caused its first pandemic as"severe acute respiratory syndrome" or SARS primarily in Chinese and Hong Kong population which died off in a year (WHO, 2020c). The other outbreak caused by Coronavirus was in the year 2012 in Saudi Arabia and was responsible for "Middle East Respiratory Syndrome" or MERS which affected about 2,494 people since then (WHO, 2020b).

In the Hubei Province of Wuhan located in China, a cluster of cases reported on 31^{st} of December in the year 2019 (WHO, 2020) with symptoms of fever, coughing and tiredness, which "looked like flu or common pneumonia." But their CT scan images had features that were different from flu or common pneumonia. The blood test indicated viral infections and series of influenza-related tests were negative. The virus caused an outbreak of pneumo-

nia whose cause was unknown in the city which was later found out to be caused by a newly discovered strain of Coronavirus, i.e. SARS-CoV-2 (WHO, 2020) and COVID-19 referred to the clinical condition caused by SARS-CoV-2.

Novel Coronavirus has features of a family of viruses Coronaviridae further classified in bet acoronavirus 2b lineage (Wang *et al.*, 2020). When Full-genome sequencing, along with phylogenic analysis was done by researchers, It indicated that this virus is distinct from the beta coronaviruses that are associated with SARS and MERS (Zhu *et al.*, 2020). Symptoms of the disease can be mild to severe. Mortality rate is high in the elderly and people with other systemic illness. Manifestations of symptoms are usually 2-14 days after viral exposure and present as mild fever, sore throat, and cough in mild to moderate cases. In severe cases, breathlessness, symptoms similar to pneumonia, complications involving the respiratory system, digestive system and neurological system can happen which further lead to mortality.

Researchers reported that it spreads through human-to-human by direct contact with an infected person or by respiratory droplets (Li *et al.*, 2020) and has spread to 216 countries with 10,922,324 confirmed infected cases currently present globally with 523,011deaths in total were reported till 4th of July, 2020 (WHO, 2020d) and the numbers keep on increasing day after day.

The treatment is primarily symptomatic. This virus mostly targets lungs in the majority of cases and cause severe injury to them. Hence oxygen therapy comes up as the major treatment intervention for severe cases. In cases of respiratory failure, mechanical ventilation provides one of the major life support (Kumar *et al.*, 2019). Hemodynamic support is essential in cases with septic shock. Cause of the disease is viral, but still, there is no antiviral therapy or protocol have been permitted yet, numerous approaches with a combination of drugs have been proposed (lopinavir/ritonavir, chloroquine and hydroxychloroquine, alpha-interferon) (WHO, 2020).

Currently, no vaccine is available (WHO, 2020a). Preventive measure seems to be the most effective current strategy to limit the spread of cases and meanwhile, scientific research is taking place to develop a vaccine for it. Many countries have started in vivo and in vitro trials for the vaccine, but a clear success seems to be at a distance as there is no effective vaccine approved till date. This review aims to provide information regarding trial and error along with challenges that researchers are facing in the development of COVID-19 vaccine.

Structure of Coronavirus and its replication

The viral genome is about ~30000 nucleotides (Boopathi *et al.*, 2020). It encodes structural as well as non-structural proteins (Shanmugaraj *et al.*, 2020). Structural proteins of this virus are as follows:

1. Nucleocapsid (N): Protein that holds the viral genome (single positive-strand RNA),

2. Membrane (M) protein: It is believe to define the outline of the envelope of virus (Neuman *et al.*, 2011).

3. Spike (S) protein: It has its part in virus fusion to host cell membrane and facilitating virus entry into the host (Wu *et al.*, 2020).

4. Envelop (E) protein: It is the smallest of major structural protein constituting a minor component of a viral particle.Small portion of this protein is assimilated into the virus envelop and profusely expressed inside the host cell during replication and has a significant role in the assembly of virus, virus and permeability of host cell membrane (Venkatagopalan *et al.*, 2015).

The entry of virus to host cell occurs through binding with ACE2 receptor (angiotensin-converting enzyme 2) by its spike, i.e. S protein but to complete the entry to host cell, it requires cellular proteases for S protein priming, causing cleavage of S protein at the site- S1/S2 and the S2' which permits fusion of viral membrane with cellular membranes.In this case, the protease used is TMPRSS2 (Hoffmann *et al.*, 2020) which is succeeded by the release of its RNA particles into the cytoplasm where it further undergoes translation and subsequent transcription in the nucleus ultimately forming viral proteins. These viral proteins then further introduced into ER (endoplasmic reticulum) and from there they transfer to "Endoplasmic reticulum-Golgi intermediate compartment" (ERGIC) (Masters, 2006) where they are assembled and new viral particles are formed. Once the new viral particle formed, it is released into the circulation. Commonest affected site is the respiratory system because of the predominance of ACE-2 receptors in the epithelial cell.

Immunopathology of COVID-19

Severe cases of novel Coronavirus reported to reveal increased in serum levels of pro-inflammatory cytokines (IL-6, IL-2, IL-1β IL-17, G- CSF, IL-8 GM-CSF, MCP1, MIP1α IP10 and TNF alpha) which is characterized as cytokine storm (Cao, 2020). It can induce sepsis and severe lung injury due to uncontrolled inflammation. Initially host responses by

Innate Immunity which is non-specific and later it responses by Acquired immunity.The body also exhibits Human Leukocyte Antigen (a major part of the immune system, accountable for antigen presentation to T cell) (Mosaad, 2015). Variation in HLA and response of immunity is considered as one of the reasons why some patients have a serious infection.

When a virus enters the cell, endosomal RNA receptors (TLR3 and TLR7) and the cytosolic RNA sensor (RIG-I/MDA5) sense viral RNA or viral products which activates the signalling cascade, i.e. NF-κB and IRF3, escorted by type I Interferon (IFN-I). Some cytosolic receptor (MDA5 and RIG-1) can also detect viral replication and interact with mitochondrial protein FADD and TRAF-3 to produce caspases and NF-κB. IFN-I goes in circulation and reaches other cell and through JAK-STAT signalling pathway further interacts with a nucleus and reduces replication of viral products (Bagca and Avci, 2020).

Some virus can bypass this pathway predominantly by inhibiting IFN-I. It is suggested that deregulated response by innate immunity as seen in a patient with a systemic illness involving cardiovascular systems like (Bhinder and Kamble, 2018) hypertension, chronic kidney disease and coronary artery disease is one of the risk factors for the presentation of severe symptoms of the disease (Zheng *et al.*, 2020).

The later response is by Adaptive Immunity (Prompetchara *et al.*, 2020). When Type I INF and NF-κB enters into circulation, it predominantly helps T cells to produce cytokines and recruiting cell for cytotoxic activity. Helper T cell coordinate adaptive response as a whole, while cytotoxic T cells are required for killing of infected cells while humoral immunity requisite for the making of neutralizing antibody which not only limits the infection at later phase but also checks its re-infection.Both delayed response and feeble antibody action are linked with severe cases of COVID-19 (Li and Ma, 2020).

Patient with deregulated immune response delayed IFN response fails to limit the viral replication leading to more cells to get an infected and hence massive generation of cytokines, more recruitment of macrophages and neutrophils result in endothelial and epithelium damage, vascular damage followed by apoptosis and impaired virus clearance which is manifested as Acute lung injury and ARDS (Silva, 2020).

Approaches in development of vaccines

One of the hopes that have emerged in the handling of COVID-19 is Convalescent plasma (CP), also known as immune plasma used as post-exposure prophylaxis in COVID-19 infected patient. It is plasma collected from an infected patient with COVID-19. The science behind is that everyone who has infected from the disease carries neutralising antibodies in their blood which are capable of neutralizing a virus by preventing replication or through binding without causing any interfere with replication (Duan *et al.*, 2020).

According to a recent study done in severe COVID-19 cases, 200 ml of CP taken from newly recovered donors having neutralizing antibody in their blood of titres above 1:64 was transfused in the infected patients.It showed improvement in clinical outcomes and was well tolerated by the patients. But there is need of further investigation and clinical trials to get the optimal results (Anudeep *et al.*, 2020). CP therapy has already been used from a long period of time and has been proved beneficial for reducing infectious diseases (Harcourt *et al.*, 2004).

Various approaches to limit the replication of the virus in host cell targets RNA synthesis and the molecules which participate in the replication of virus are under research. papain-like proteinase (PLpro) cleavages N-terminus of the replicase polyprotein (Imbert *et al.*, 2008). As a result, Nsp1, Nsp2 and Nsp3 (non-structural RNA-binding protein) are formed which is essential for virus replication (Ivanov and Ziebuhr, 2004). It is a popular target for inhibiting replication of coronavirus.

Various other approaches which can be used as a target for inhibiting virus replication are "RNA-dependent RNA polymerase" (RdRp), Nsp12, Helicase (Nsp13) which is a multi-functional protein target inhibiting virus structural proteins (Wu *et al.*, 2020). Some anti-hypertensive drugs, anti-fungal drugs, anti-bacterial drugs and anticoagulant drugs (rescinnamine, iloprost and prazosin, posaconazole and itraconazole, sulfasalazine, azlocillin, penicillin and cefsulodin and dabigatranetexilate) has shown a high binding affinity towards S protein (Ge *et al.*, 2013). Virulence factor present in coronavirus is, Nsp1, Nsp3c and ORF7a which are known to interfere with innate immunity of host and helps this virus to escape the immune system. These virulence factors can be used as possible targets for the development of the vaccine. In Table 1, a list of various trials going on worldwide is summarized.

Current status in the development of Vaccine

Advanced technologies have been used for the development of a vaccine for novel coronavirus which is a challenge for the scientist as these new technologies have not been extensively tested and used for mass production so may takes up to years for

Table 1: Vaccines in Clinical Trials- Current scenario

Platform	Vaccines work with the same principle	Target	A biochemical aspect of Vaccine	Number of trials registered
Viral vector-based vaccine	CTII-nCoV, Covid-19 aAPC Vaccine, Covid-19 SyntheticMinigeneVaccine,CTCOVID	S protein Whole virion	Lentiviral vector system (NHP/TYF) is used and a minigenes (COVID-19) engineered which has the potential to alter artificial antigen-presenting cells and can activate T cells.	7
Convalescent Plasma (antibody)	Convalescent Plasma	Whole virion	Donor's blood contains neutralizing antibodies which have the potential of neutralizing a viral particle by preventing replication or by binding without interfering with replication	11
Inactivated vaccine	Inactivated SARS-CoV-2 vaccine	Whole virion	Vaccine constitutes of indigenous, inactivated virus developed by mutation of a different strain of viruses.	3
Plasma vaccine	Tableted COVID-19 TAngiotensin peptide (1-7), derived plasma herapeutic Vaccine,	Whole virion	Thermo stable vaccine, plasma is taken from COVID-19 patient and inactivated by heat (Supplementation of angiotensin peptide (1-7) as Hyper-inflammation can be due to deficiency of angiotensin peptide (1-7))	4
RNA vaccine	mRNA-1273, BNT162a1,BNT162b1 BNT162b2, BNT162c2	S protein	A vaccine based on novel lipid nanoparticle -encapsulated mRNA, encodes for S protein of SARS-CoV-2	4
Autologous DC (dendritic cells)laden with antigens	AV-COVID-19	Whole virion	Autologous DC incubated for one day(18 to 24 hours) with an antigen of novel Coronavirus	1
Nanoparticle vaccine	SARS-CoV-2 rS nanoparticle vaccine	Whole virion	Advanced nanoparticle vaccine. Trial with Matrix-M adjuvant and also without it.	1
Recombinant vaccine	bac-TRL-Spike	S protein	Advanced Vaccine engineered to deliver plasmids comprising synthetic DNA which encodes for spike protein (S protein) from n Coronavirus	1

its development.Many funds have been provided to aid in fast track development of a vaccine. Recently One of the vaccines in the race is mRNA-1273 developed by Moderna and the Vaccine Research Centre at the National Institutes of Health Moderna uses mRNA strand of the S protein of the virus, is under phase I clinical trial (NIAID, 2020). Another potential vaccine candidate is from Oxford University and AstraZeneca Plc. (University of Oxford, 2020). It is being developed by weak mutation of adenovirus. This virus then mixed with the genetic material of novel Coronavirus. It has begun standardized animal testing and is all ready to go in the second phase of clinical trials.

Another vaccine which is under research is Thailand's mRNA vaccine. It has shown positive results on mice and proceeded further to test on monkeys and claim to get the outcomes by September 2020. Pfizer-BNTECH vaccine another vaccine in pipeline, it has started the process of dosing patients and-Phase 1/2 clinical trial (Biontech, 2020).

Current status of development of vaccine in India

Covaxin is the first Indian COVID 19 vaccine candidate approved for human trials and allowed by Authorities of Central Drugs Standard Control Organisation to hold Phase I and II of human clinical trials, which is stated to hold in the month of July. It is being developed by Bharat Biotech India working in teamwork with the "Indian Council of Medical Research" and the "National Institute of Virology". It is indigenous, inactivated vaccine (Indian Counsel of Medical Research Press Release, 2020). Second vaccine candidate which got approval for human trial from Drug Controller General of India (DCGI) to run Phase I/II human trials is Zydus Cadila. It was able to induce a significant immune response in many species during its study on animals (Zydus Vaccine research programme, 2020).

Challenges faced in development of Vaccine

In an attempt to find a solution quickly which has encouraged some fast-track perspective for the development of a vaccine.There are few international programs which are very well funded and are trying to develop a vaccine using the above-mentioned technologies, but still, there are many challenges in the process.For in-vitro studies, there are several criteria which need to be fulfilled for an animal to be useful for testing purpose of a vaccine and of course they must be susceptible to infection, but not all animals are susceptible (Acqua, 2020). Another approach is by testing through cell culture model that if antisera are effective or not against it. The aspect of COVID-19 that makes it a serious threat to the world is that it's so contagious that the test should be able to detect it quickly and the vaccine should be able to establish high efficacy. But to test the efficacy of the vaccine in clinical trials, there should be enough people who catch the infection in the control group.

COVID-19 will probably have an impact on the future of vaccine design.The approaches being used to develop COVID-19 vaccines are different than the conventional method of preparation and can act as a prototype for future development.Moreover, if there will be vaccine developed in future, there's no sure shot assurance of mass-scale production and ready supply. Countries all around the world will be eager to secure stock for them.Also, the cost for the vaccine is also not clear which will further adding burden to the people financially (Swaminathan, 2020).

Impact of public health on spread of disease

Optimal public health intervention attempts are taking place to contain the outbreak of the disease as quickly as possible. Public health is using every measure to locate infected individuals, isolate and quarantine them. Furthermore, it is making every effort to provide widespread availability of testing, effective contact-tracing. Even after taking every possible effort, it is difficult to contain the virus as social distancing and frequent hand washing are currently the only measures to prevent the spreading of this virus. Due to limitations of treatment, more and more cases are getting hospitalised further increasing the burden on public health. One of the safest and faster ways to reduce this burden is herd immunity. It is attained when an adequate fraction of given community gets immune to an infectious disease by vaccination or attaining it naturally by a prior illness which makes the spread of the disease from person to another person unexpected or unlikely (Centres for Disease Control and Prevention, 2016). In case of SARS-CoV-2, herd immunity should be achieved by 70-90% of the population (Souza and Dowdy, 2020) and population can achieve it by either naturally or by vaccinations. The former method can take a long time, so the latter method seems to be needed the most at this moment to practice herd immunity.

CONCLUSION

"Prevention is better than cure" sounds very much real to covid-19 as no specific protocol for its treatment is currently available. The therapy is primarily based on symptomatic relief. It has a great impact on the whole world in every direction of development, be it health or economic or social domain. There is a need to limit the infection before it becomes "worst pandemic" in the history of the pandemic human race has ever faced.Impact of this emerging novel

coronavirus throws spotlight and major need for the development of a vaccine which can provide passive immunity.Recent clinical trials and studies have helped to understand the virus, but still, the development of a drug which can cure the disease is far from the success.Therefore there should be extensive work in the field of research to provide major success for vaccine development.

Conflict of Interest

The authors declare that they have no conflict of interest.

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REFERENCES

Acqua, D. J. 2020. Expediting Covid-19 Research. *The Jackson Laoratory*. Updated on: 29 June 2020.

Anudeep, T. C., Jeyaraman, M., Shetty, D. U. 2020. Convalescent Plasma as a plausible therapeutic option in nCOVID-19-A Review. *J Clin Trials*, 10(409):2167–0870.

Bagca, B. G., Avci, C. B. 2020. Overview of the COVID-19 and JAK/STAT Pathway Inhibition: Ruxolitinib Perspective. *Cytokine and Growth Factor Reviews*, 54:51–61.

Bhinder, H. S., Kamble, T. K. 2018. The study of carotid intima-media thickness in prediabetes and its correlation with cardiovascular risk factors. *Journal of Datta Meghe Institute of Medical Sciences University*, 13(2):79.

Biontech, S. E. 2020. Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults Clinical Trials.gov. Accessed on: 02 July 2020.

Boopathi, S., Poma, A. B., Kolandaivel, P. 2020. Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. *Journal of Biomolecular Structure and Dynamics*, pages 1–10.

Cao, X. 2020. COVID-19: immunopathology and its implications for therapy. *Nature reviews immunology*, 20(5):269–270.

Centres for Disease Control and Prevention 2016. Glossary for Medical Terms. Accessed on: 05 July 2020.

Duan, K., Liu, B., Li, C., *et al.* 2020. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proceedings of the National Academy of Sciences*, 117(17):9490–9496.

Ge, X. Y., Li, J. L., Yang, X. L., *et al.* 2013. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature*, 503(7477):535–538.

Harcourt, B. H., Jukneliene, D., Kanjanahaluethai, A., Bechill, J., Severson, K. M., Smith, C. M. 2004. Identification of Severe Acute Respiratory Syndrome Coronavirus Replicase Products and Characterization of Papain-Like Protease Activity. *Journal of Virology*, 78(24):13600–13612.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., *et al.* 2020. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 181(2):271–280.

Imbert, I., Snijder, E. J., Dimitrova, M., Guillemot, J.-C., Lécine, P., Canard, B. 2008. The SARS-Coronavirus PLnc domain of nsp3 as a replication/transcription scaffolding protein. *Virus Research*, 133(2):136–148.

Indian Counsel of Medical Research Press Release 2020. *ICMR process to develop a vaccine to fight Covid 19 pandemic as per globally accepted norms of fast-tracking safety and interest of people of India the topmost priority*. Indian Counsel of Medical Research.

Ivanov, K. A., Ziebuhr, J. 2004. Human Coronavirus 229E Nonstructural Protein 13: Characterization of Duplex-Unwinding, Nucleoside Triphosphatase, and RNA 5′-Triphosphatase Activities. *Journal of Virology*, 78(14):7833–7838.

Kumar, S., Bajaj, A., Inamdar, A., Agrawal, L. 2019. Noninvasive ventilation in acute hypoxic respiratory failure in medical intensive care unit: A study in rural medical college. *International Journal of Critical Illness and Injury Science*, 9(1):36.

Li, Q., Guan, X., Wu, P., *et al.* 2020. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *New England Journal of Medicine*, 382:1199–1207.

Li, X., Ma, X. 2020. Acute respiratory failure in COVID-19: is it "typical" ARDS? *Critical Care*, 24:1–5.

Masters, P. S. 2006. The molecular biology of coronaviruses. *Advances in virus research*, 66:193–292.

Mosaad, Y. M. 2015. Clinical Role of Human Leukocyte Antigen in Health and Disease. *Scandinavian Journal of Immunology*, 82(4):283–306.

Neuman, B. W., Kiss, G., Kunding, A. H., *et al.* 2011. Structural analysis of M protein in coronavirus assembly and morphology. *Journal of Structural Biology*, 174(1):11–22.

NIAID 2020. Safety and Immunogenicity Study of

2019-nCoV Vaccine (mRNA-1273) for Prophylaxis of SARS-CoV-2 Infection (COVID-19). Accessed on: 01 July 2020.

Prompetchara, E., Ketloy, C., Palaga, T. 2020. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol*, 38(1):1–9.

Shanmugaraj, B., Siriwattananon, K., Wangkanont, K., Phoolcharoen, W. 2020. Perspectives on monoclonal antibody therapy as a potential therapeutic intervention for Coronavirus disease-19 (COVID-19). *Asian Pac J Allergy Immunol*, 38(1):10–18.

Silva, D. 2020. Convalescent plasma: A possible treatment of COVID-19 in India. *The medical journal, Armed Forces India*, 76(2):236–237.

Souza, G. D., Dowdy, D. 2020. What is Herd Immunity and how can we achieve it with Covid-19. Accessed on: 10 June 2020.

Swaminathan, S. 2020. Covid-19 vaccines: a realistic look. Accessed on: 11 June 2020.

University of Oxford 2020. A Study of a Candidate COVID-19 Vaccine (COV001).

Venkatagopalan, P., Daskalova, S. M., Lopez, L. A., Dolezal, K. A., Hogue, B. G. 2015. Coronavirus envelope (E) protein remains at the site of assembly. *Virology*, 478:75–85.

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Zhao, Y. 2020. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *Jama*, 323(11):1061–1069.

WHO 2020. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance Coronavirus disease (COVID-19) Pandemic.

WHO 2020. Coronavirus. *World Health Organization*.

WHO 2020a. Coronavirus disease (COVID-19) Pandemic. Accessed on: 20 June 2020.

WHO 2020b. Middle East Respiratory Syndrome (MERS-CoV) Epidemic. Accessed on: 05 June 2020.

WHO 2020c. Severe Acute Respiratory Syndrome (SARS-CoV) epidemic. Accessed on: 05 June 2020.

WHO 2020d. WHO Coronavirus Disease (COVID-19) Dashboard. Accessed on: 04 July 2020.

WHO 2020. WHO Timeline - COVID-19. *World Health Organization*.

Wu, C., Liu, Y., Yang, Y., Zhang, P. 2020. Analysis of Therapeutic Targets for SARS-CoV-2 and Discovery of Potential Drugs By Computational Methods. *Acta Pharmaceutica Sinica. B*, 10(5):766–788.

Zheng, Z., Peng, F., Xu, B., *et al.* 2020. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *Journal of Infection*, 81(2):16–25.

Zhu, N., Zhang, D., Wang, W., *et al.* 2020. A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine*, 382:727–733.

Zydus Vaccine research programme 2020. Zydus vaccine for COVID-19 (ZyCoV-D) successfully completes preclinical development and receives permission to initiate human clinical trials vaccine for COVID-19. Accessed on: 03 July 2020.