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## The novel coronavirus and its possible treatment by vaccines, therapeutics and drug delivery systems: Current status and future perspectives

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### ABSTRACT

In the mid-end of December 2019, several cases of pneumonia outbreak of unknown cause and etiology were identified in Wuhan City of Hubei province in China, a city with a population of over 11 million. Till date (April 2020) around 1,051,635 confirmed cases of coronavirus disease 2019 (COVID-19) and 56,985 confirmed deaths have been reported according to COVID-19 Situation Report – 75 by WHO. On 7th January 2020, the causative agent was identified and named consequently as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the Chinese Centre for Disease Control and Prevention (CCDC) from throat swab samples. Later, on 12th January 2020, this coronavirus was named as 2019-novel coronavirus (2019-nCoV) by World Health Organization (WHO) and in 11th February 2020, it has been declared the epidemic disease caused by SARS-CoV-2 as Corona Virus Disease 2019 (COVID-19) as it is spreading rapidly from its origin in Wuhan City to the rest of the world. In this context, the current review provides a landscape of the novel Corona Virus including its origin, transmission, epidemiology, drugs and vaccines in clinical trials for better understanding to the reads and peoples the status and future perspectives of this pandemic disease.

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### THE ORIGIN AND TRANSMISSION

At the end of December 2019, people of Wuhan presenting to regional hospitals with severe pneumonia of unknown cause. Most of the primary cases

had a common exposure to the Huanan seafood market that traded live animals. On 31st December 2019, China reported the outbreak to the WHO followed by the closure of the Huanan seafood market on 1st January. On 7th January the virus was identified as a coronavirus that had 79.5% similarity with the SARS-CoV and 96.2% homology with the bat coronavirus RaTG13. SARS-CoV-2 belongs to  $\beta$ -coronavirus ( $\beta$ -CoV), which is an enclosed non-segmented positive-sense RNA virus (subgenus-sarbecovirus, and subfamily-Ortho coronavirus) (Wang *et al.*, 2020). CoVs are classified into 4 genera, which includes  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ -CoV. Mammals are infected by  $\alpha$ - and  $\beta$ -CoV, while birds tend to get infected by  $\gamma$ - and  $\delta$ -CoV. Earlier, 6 CoVs were recognized as a human-prone virus, amongst which  $\alpha$ -CoVs (HCoV-229E & HCoV-NL63), and  $\beta$ -

**Table 1: Approved drugs for emergency treatment of coronavirus**

Companies and organizations	Drug/Vaccine	Clinical trial details
Inovio (China) US FDA	COVID-19 vaccine  Chloroquine & hydroxychloro- quine /Plaquenil (emergency treatment)	Commence on April 2020  Ongoing Clinical Trails by Gov- ernment agencies and Academic institutions.

CoVs (HCoV-HKU1 & HCoV-OC43) are with weak pathogenicity, induce light respiratory symptoms alike to the common cold, respectively. The other two known  $\beta$ -CoVs (SARS-CoV & MERS-CoV) head to critical and potentially lethal infections of the respiratory tract. (Zhu *et al.*, 2019). SARS is a zoonosis caused by SARS-CoV, the first emergence of SARS-CoV was in 2002 in China before passing to around 29 regions through a global outbreak with 8,098 cases with 9.6% of fatality rate. The primary reservoir for SARS-CoV transmission was bats and civet cats were the intermediary source in wet markets and Nosocomial transmission was common (Yin and Wunderink, 2018) Bats have been suspected as the natural hosts for the SARS-CoV-2 origins based on the results of genomic sequencing and evolutionary analysis and maybe transferred from bats through anonymous intermediary hosts to infect humans. Now, it is obvious that SARS-CoV-2 uses the Angiotensin-converting enzyme 2 (ACE2) receptors which are abundantly expressed in the epithelial cells of the lungs to infect the human (Hui and Zumla, 2019; Zhou *et al.*, 2020).

### Structure

CoV contains 4 main structural proteins: 1) Spike (S)-(150 kDa), 2) Membrane (M)-(25-30 kDa), 3) Envelope (E)-(8-12 kDa), and 4) Nucleocapsid (N) proteins. All these are encoded within the 3' end of viral genome. The outstanding peculiarity of coronavirus is its club-shaped like spike projections originating of the virion's surface. The S protein uses an N-terminal signal sequence to get access to the Endoplasmic reticulum (ER) and it is N-linked glycosylated massively. These spikes are the defining peculiarity of the virion and provide an appearance of a solar corona, proposing the name, coronaviruses. The most abounding structural protein in the virion is M protein. It is a small protein with 3 transmembrane domains (Guo *et al.*, 2020) and is responsible for virion shape. The E protein is seen in small quantities within the virion. The E proteins of CoV are highly variant but have a common structure (Armstrong *et al.*, 1984). Though the E protein membrane topology is not completely resolved most data suggest that it is a transmem-

brane protein. A helically symmetrical nucleocapsid is present within the virion envelope which is not common with (+)sense RNA viruses still considerably common with (-)sense RNA viruses. The N protein is the only protein existing in the nucleocapsid, which is comprised of an N-terminal domain (NTD) and a C-terminal domain (CTD), 2 separate domains that are capable of in vitro binding of RNA, but uses distinct mechanisms for RNA binding. Another structural protein, the hemagglutinin-esterase (HE), also present in the  $\beta$ -CoVs subgroup. (Godet *et al.*, 1992). These actions enhance the entry of S protein-mediated and mucosal virus transmission (Klauegger *et al.*, 1999). Structurally, SARS-CoV has a distinct organization composing 14 binding residues that directly interact with human ACE2. Amongst certain amino acids, 8 have been maintained in SARS-CoV-2. (Cornelissen *et al.*, 1997)

### Epidemiology and symptoms

All ages are susceptible to SARS-CoV-2. The infection primarily transmitted through large droplets of saliva or from the nose discharge during cough and sneeze, respectively by symptomatic and asymptomatic people. (Fehr and Perlman, 2015). The infection can be acquired either by inhaling or touching these droplets or its contaminated surfaces followed by touching nose, mouth, and eyes. Pneumonia was the primary clinical sign of the SARS-CoV-2-related disease COVID-19 which supported case detection. Investigations so far suggest 5 days as a mean incubation period (Bastola *et al.*, 2020) and 3 days as the median incubation period of 3 days (range: 0-24 days) (Thompson, 2020). The clinical manifestations in symptomatic patients, the infection, usually begins in not more than a week, the primary symptoms include fever, cough, nasal congestion, fatigue and indications of upper respiratory tract infections. The infection advances to critical conditions like dyspnoea and critical chest symptoms resembling pneumonia in about 75% of cases, being detected by computed tomography on admittance (Thompson, 2020).

**Table 2: Pharmaceutical companies/ research organizations involved in developing coronavirus drugs/vaccines**

Pharmaceutical companies/ Research organizations	Drug/Vaccine	Clinical trial details
Gilead Sciences (UK)	Remdesivir	Started a pair of phase 3 trials
The National Medical Products Administration (China)	Favilavir	CT involving 70 patients. (Shenzhen, Guangdong province)
Entos Pharmaceuticals	Fusogenix DNA vaccine	Soon collaborate with health agencies/ pharmaceutical companies /government partners to advance to human CT
The Oxford University	ChAdOx1 nCoV-19	CT planned at Thames Valley Region (510 volunteers) Age-18 -55 years
Roivant Sciences	Gimsilumab (clinical-stage, human monoclonal antibody)	Completed Phase 1 study on march
Altimune & Alabama University (Birmingham)	AdCOVID (1 dose intranasal vaccine)	Preclinical and Phase I CT in between July to September of 2020
I-Mab Biopharma	TJM2 (a neutralising antibody)	Yet to receive IND approval from FDA
Airway Therapeutics	AT-100 (rhSP-D) novel human recombinant protein	AT-100 (efficient in preclinical studies)
Tiziana Life Sciences OyaGen	TZLS-501 (human anti- IL-6R) OYA1	- Needs further clinical research on drug to determine efficacy
BeyondSpring	BPI-002 (small molecule)	- Phase 2 CT
Altimune	Intranasal Covid-19 vaccine	Ongoing pre-clinical test
Inovio Pharmaceuticals & Beijing Advaccine Biotechnology Company	INO-4800	CT in April 2020 (US), followed by China, & South Korea (30 healthy volunteers)
Algernon Pharmaceuticals	NP-120 (Ifenprodil)	Phase 2 CT
APEIRON Biologics	APN01	Phase I pilot trial (China)
Moderna & NIAID	Vaccine (Unknown)	16 March -Phase I human CT with 45 males & females, Age-18-45.

*Continued on next page*

Table 2 continued

Pharmaceutical companies/ Research organizations	Drug/Vaccine	Clinical trial details
The MIGAL Research Institute (Israel)	Vaccine-Infectious Bronchitis Virus (IBV)	Pre-CT (Volcani Institute). Vaccine production in coming 8 to 10 weeks and gaining the safety approvals for in-vivo testing.
Tonix with Southern Research, a non-profit research organisation, Clover Biopharmaceuticals with GSK	TNX-1800 Vaccine based on S-Trimer of the SARS-CoV-2	- In 6 to 8 weeks Vaccine is expected to be available for pre-clinical studies.
Vaxart	Oral recombinant vaccine	Pre-clinical models (mucosal & systemic immune responses).
CytoDyn	Eronlimab (PRO 140), a CCR5 antagonist	Already investigated in phase 2 CT for HIV treatment
Applied DNA Sciences' subsidiary LineaRx & Takis Biotech	Linear DNA vaccine	4 DNA vaccine moieties-PCR for animal testing. Design 1-moiety based on entire spike protein of SARS-CoV-2, while others on protein antigenic portions.
Gilead Sciences	Remdesivir (GS-5734)	A randomised, placebo-controlled, double-blind study, (Wuhan hospitals) with 761 patients The trials results are expected in next few weeks.
Roche	Actemra	CT on 188 coronavirus patients. The CT in May 10 2020.
Biocryst Parma Regeneron with Sanofi	Galidesivir (BCX4430) REGN3048-3051 and Kevzara (antibodies)	Ongoing CT Human CT (NIAID). On 48 patients to study drug safety and tolerability.

Mostly Pneumonia transpires in the first 3 weeks of asymptomatic patients. Human transmission of coronavirus happens principally among family members, include relatives and friends that personally reached with sufferers or incubation transmitters. 33-42% of SARS cases are healthcare workers (Guan *et al.*, 2020). Personal contact with the intermediate host animals or wild animals consumption was assumed to be the main course of SARS-CoV-2 transmission. However, the rise and transmission of SARS-CoV-2 remain mysterious.

#### **Facts on Corona virus disease (COVID-19) Pandemic by WHO**

1. Pneumonia vaccines, like pneumococcal or Haemophilus influenza type B, not provide any protection against the SARS-CoV-2
2. Smokers are more likely vulnerable to SARS-CoV-2 due to their reduced lung capacity and as the means of smoking are fingers and lips which may increase the chance of virus transmission from hand to mouth.
3. Antibiotics don't act against COVID-19, they only control bacterial infections. COVID-19 is a viral infection.
4. Receiving a package from any reported COVID-19 area is safe as the package that has been transferred, traveled, and exposed to various conditions and low temperatures.
5. No reported evidence regarding an animal (dog, cat or any pet) that can transmit SARS-CoV-2 while, there has been only one instance yet that a dog being infected in Hong Kong.
6. COVID-19 is not airborne until unless you are within 1 meter of a COVID-19 person. As the primary mode of transmission is through the droplets of cough or sneeze of an infected person. These droplets are too heavy to hang in the air. They immediately fall on grounds or surfaces.
7. COVID-19 virus can be transmitted in all areas with hot and humid climates from the so far evidence.
8. Thermal scanners are efficient in recognizing people with developed fever; they cannot detect people infected with SARS-CoV-2. All ages of people can be infected by SARS-CoV-2. Elder people and people with pre-existing medical conditions like asthma, diabetes, heart disease are more vulnerable to become severely ill.

9. Alcohol consumption does not protect from COVID-19 and can be hazardous
10. Holding breath for 10 seconds/ more without coughing does not mean free from (COVID-19) or any other lung disease.
11. Exposing to the sun or higher temperature than 25 c does not prevent COVID-19.
12. The novel coronavirus cannot be transmitted through the mosquito bites.
13. Hot shower doesn't prevent the COVID-19.

#### **Current Drug/vaccines in clinical trials**

(Jin *et al.*, 2020; Coronavirus treatment: Vaccines, 2020) The ambiguous SARS-CoV-2 outbreak in the Wuhan (a China city), currently known as COVID-19, and its rapid roll out to several other countries, risk thousands of lives. This pandemic has catalyzed this advancement of novel SARS-CoV-2 vaccines over the biotech industries, and also pharmaceutical companies and research organizations Tables 1, 2, 3 and 4 shows,

#### **Challenges of coronavirus disease 2019**

COVID-19, presenting a global challenge, particularly in the rapid spread of infection, the raise in critically ill patients with pneumonia and the absence of definitive treatment therapy. Till 04/04/2020 around 1,051,635 confirmed COVID-19 cases and 56,985 confirmed deaths been reported according to COVID-19 Situation Report – 75 by WHO. One major concern is how well the health systems of the world are prepared and respond to this outbreak. To prepare for and respond to the outbreaks of infectious disease. The following challenges are being brought, which include political and institutional, social, environmental, technological, and pathogen-related, to the proximity by COVID-19 outbreak. Currently, there is no vaccine or specific antiviral drug moiety available to treat critically ill patients. Healthcare management mainly concentrates on the provision of supportive care like oxygenation, ventilation, and fluid management. However, no approved antiviral treatment for coronaviruses, and notwithstanding the two outbreaks of novel coronaviruses in the past two decades, the development of the vaccine is still in infancy. For critical management of COVID-19, several potential treatments are recommended, including baricitinib (a Janus kinase inhibitor), combination therapy of low systematic dose of corticosteroids with the antivirals and atomization inhalation of IF have been supported (Chowell *et al.*, 2015). Hence, there is an essential need to develop efficient diagnostics,

**Table 3: MERS CoV vaccines for coronavirus**

Pharmaceutical companies	Drug/Vaccine	Clinical trial details
Novavax	Modified MERS CoV vaccines for coronavirus	Commence of CT in few weeks
Inovio in partnership with GeneOne Life Science	INO-4700 (GLS-5300) for MERS-CoV	Efficacy against the 94% MERS-CoV patients in early-stage CT in July 2019.

**Table 4: Other companies developing coronavirus vaccines/drugs**

Companies	Vaccine/ Antiviral Drug	approaches
Enanta Pharmaceuticals	Antiviral drug	-
Predictive Oncology	Vaccine	-
Emergent BioSolutions	-	Plasma-derived therapy
CEL-SCI	Vaccine	Immunotherapy
AJ Vaccines	Vaccine	
Takeda Pharmaceutical	-	Plasma-derived therapy
Heat Biologics	Vaccine	-
Pfizer	Antiviral molecules	-
Vir Biotechnology	-	2 monoclonal antibodies
Serum Institute of India & Codagenix	Vaccine	-
Generex	Vaccine	-
Zydus Cadila	Vaccine	-

therapeutics, and vaccines. Unlike the previous outbreaks of infectious diseases, the complete genomic sequence of coronavirus had received and shared broadly by the middle of January, attainment not possible at such a short period. WHO has stated that the SARS-CoV-2 vaccine should be available within 18 months, but to achieve, this requires funding and attention of the public to be maintained even if the threat level drops. (Liu *et al.*, 2020; Lid The Challenges of coronavirus disease 2019, 2020)

#### Drug delivery systems for the delivery of vaccine/drugs

Currently, no vaccines are approved for the infection caused due to SARS-CoV-2. Trials are being executed for vaccines delivery by carriers in order to attain sustain release and reach the target site as they regulate the antigen's spatial and temporal offering to the immune system. Hence, weak immunogens of low doses can be delivered efficiently to excite the immune responses and eradicate the need for the frequency of administration like prime dose and booster doses as a replacement of the conventional vaccination regimen and provide long term therapy. Since Lungs are the most targeted organ for SARS-CoV-2, the drug administration through the oral route by the aerosol may produce an immediate therapeutic response. Immu-

nization through the Intranasal route is the only delivery mechanism to succeed both mucosal and systemic immune responses. Intranasal vaccines currently being used against influenza types group B meningococcal attenuated respiratory syncytial and parainfluenza 3 virus. Moreover, the inhalation of Nitric oxide gas given for the SARS-CoV-2 patient, which showed greater antiviral activity against the SARS-CoV in 2003 Cunningham *et al.* (2020). Hence the same treatment was suggested by the health professionals and the respective clinical trials were also in progress for the COVID 19 treatment according to (US National Library of Medicine). Crown proteins of the SARS CoV-2 possess a similar receptor-binding domain to the SARS CoV in the ACE 2 receptor. Now, it is obvious that SARS-CoV-2 uses the Angiotensin-converting enzyme 2 (ACE2) receptors which are abundantly expressed in the epithelial cells of the lungs to infect the human (Chen *et al.*, 2004; Xu *et al.*, 2020). Intranasal immunization would be the beneficial route of delivery to treat upper respiratory tract infections and also produce systemic immunity (Zhang *et al.*, 2020).

#### Feature perspectives

Researchers are working on safe, active and specific vaccine moieties and therapeutics for managing the inevitable COVID-19. To date, there are no spe-

cific vaccines or active antiviral drugs for COVID-19 available, where few are currently beneath the evaluation and development. Therefore, special attention and efforts are required to reduce the possible risk of transmission in susceptible peoples like children, elderly people, health care providers, and public services by implementing strict preventive control measures. (Pires *et al.*, 2009).

## CONCLUSIONS

Outcomes received from recent *in vitro* study against SARS-CoV-2 using Remdesivir and chloroquine are promising since these drugs are highly effective in infection control. Therefore, direct clinical trials can be performed on COVID-19 infected patients as these drugs are already being used for treating other disease conditions and also have well-established safety profiles which makes further drug evaluation much easier. Based on several preclinical studies, S protein is identified as a pivotal viral antigen for developing the vaccine. Though the researches are in progress to enhance prevention, treatment strategies, and control of transmission of COVID-19. Additional research should be focused on the study of SARS-CoV-2 in proper animal models for investigating the viral replication, transmission, and pathogenesis by understanding the mechanistic cause of COVID-19 by SARS-CoV-2 and immunopathological response in the host.

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