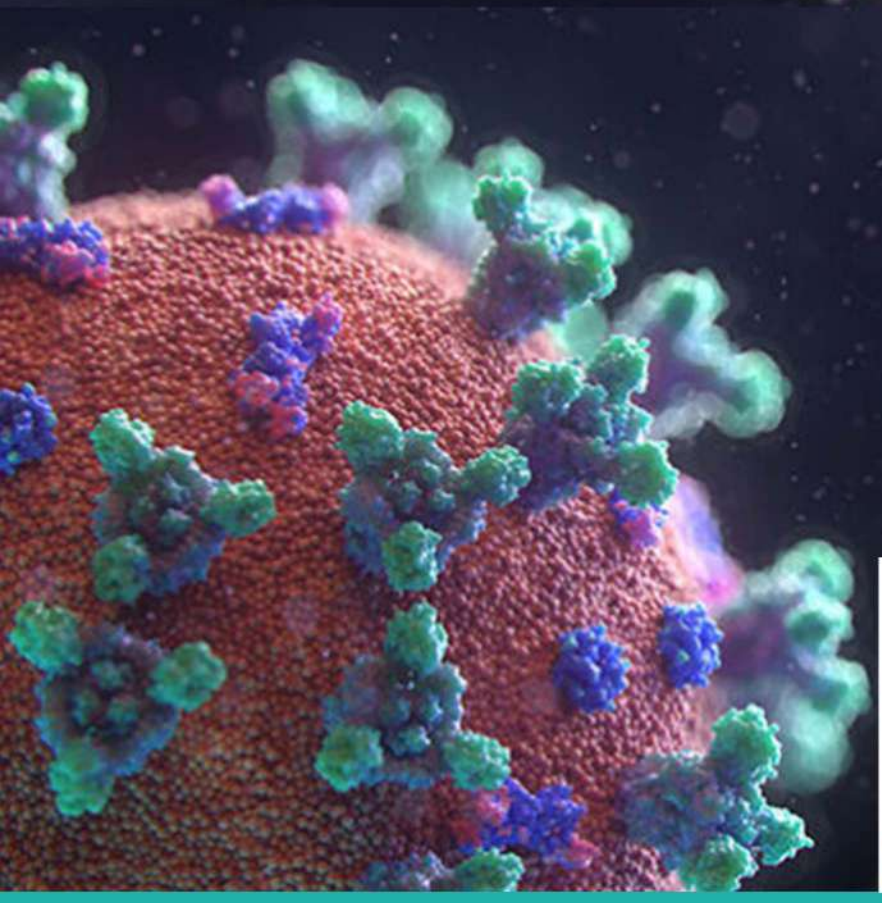
VOL.3/ISSUE 4/ April 2020
ISSN 2515-9534 (Print)
ISSN 2515-9542 (Online)

Scientific European

MONTHLY POPULAR SCIENCE MAGAZINE

Diagnostic tests for COVID-19: An Evaluation of Current Methods, Practices and Future



ISSN 2515-9542
9 772515 954000 04

WWW.SCIENTIFICEUROPEAN.CO.UK
WWW.SCIEU.COM

Published by UK Education Consultancy services Ltd, (Company Number 10459935 Registered in England);
Country of Publication: United Kingdom

Scientific European®

Contents

VOL. 3/ISSUE 04/ April 2020

Publisher's statement: Scientific European® is Both online and print science magazine published by UK EPC Lts, (Company Number 10459935 Registered in England); city: Alton, Hampshire; Country of Publication: United Kingdom., ISSN 2515-9534 (Print), ISSN 2515-9542 (Online)

Welsh Ambulance Service's Plea for Public's Honesty During Covid-19 Outbreak

The Welsh Ambulance Service is asking the public to be open and transparent about the nature of their call and their symptoms so it can signpost patients to the most appropriate care and safeguard its crews from contracting the virus.

THE Welsh Ambulance Service is urging the public to be honest about the nature of their illness when calling 111 or 999 for help.

It has become apparent that some members of the public have been withholding information about their illness during the Covid-19 outbreak for fear of not being sent an ambulance, according to feedback from Trust staff.

This means crews have been attending some incidents without the necessary protective equipment, exposing them to potential harm.

The service is asking the public to be open and transparent about the nature of their call and their symptoms so it can signpost patients to the most appropriate care and safeguard its crews from contracting the virus.

In a video message to the public shared on social media, Lee Brooks, the Trust's Director of Operations, said: "Right across our organisation, staff are working tirelessly to ensure we can continue to provide you the best possible care as we respond to Covid-19.

"This is unchartered territory for our generation but our plans continue to develop as we work with our partners to ensure that we deliver care as safely and effectively as possible.

Ymddiriedolaeth GIG
Gwasanaethau Ambiwlans Cymru
Welsh Ambulance Services
NHS Trust

"I have a plea for the wider public at this time. Our teams operating in your community are reporting that they arrive at the scene of an incident, possibly at your home, to discover that callers have withheld information about their symptoms.

"Some of you have told us that you were concerned that, had you been honest, an ambulance would not have been sent.

"We understand your concerns but I want to make a couple of things clear. Firstly, we will always send an ambulance where it is warranted, but this means relying on what our call handlers are told at the point that you call us.

"If you don't give us accurate information, you risk the welfare of the people whose job it is to care for us all. This is incredibly unfair on our staff, as it means that their right to enter your home prepared has been removed.

"Personal protective equipment is worn by our staff to protect them from contracting the disease.

"I must ask everyone who calls either 111 or 999 to be honest with us about what's wrong with you and allow us to signpost you to the right care.

"These are difficult times for us all, but please don't put our staff in harm's way when they just don't need to be."

Lee added: "Please heed the official advice from government and Stay At Home, Protect the NHS, Save Lives."

Use of Face Masks Could Reduce Spread of COVID-19 Virus

WHO doesn't recommend face masks generally to the healthy people. However, CDC has now laid down new guideline and say "people should wear cloth masks when they go outside". New evidence suggest that the usage of surgical face masks could prevent spread of human coronaviruses and influenza viruses from symptomatic individuals.

COVID-19 virus is present in exhaled breath and coughs of infected persons and spreads through airborne droplets from people coughing and sneezing.

There have been debate about efficacy of face masks in reducing spread of the virus. The international body WHO doesn't recommend them generally to the healthy people. However, CDC has now laid down new guideline and say "people should wear cloth masks when they go outside".

In the brief communication published in Nature Medicine on 03 April 2020, the researchers found that the usage of surgical face masks could prevent spread of human coronaviruses and influenza viruses from symptomatic individuals.

Respiratory virus infections spread between human beings through contact, respiratory droplets and fine-particle aerosols. However, there are uncertainties around modes of transmission of COVID-19.

In this study, the researchers quantified the amount of virus in exhaled breath of participants and determined the potential efficacy of surgical face masks in preventing the transmission. Of 3,363 screened individuals, 246 individuals provided exhaled breath samples The 50% participants were randomized to 'not wearing a face mask' during the exhaled breath collection and the rest were randomized to 'wearing a face mask'. They tested viral shedding in nasal swabs, throat swabs, respiratory droplet samples and aerosol samples and compared the latter two between samples collected with or without a face mask.

They found viral shedding to be higher in nasal swabs than in throat swabs. Further, they detected coronavirus in 30-40% samples collected from participants without face masks but no virus was detected in droplets and aerosols collected from patients wearing face masks.

This study demonstrated the efficacy of surgical masks in reducing coronavirus detection and viral copies in respiratory droplets and in aerosols suggesting that the surgical face masks could be used by ill people to reduce onward transmission of the virus.

Reference:
Leung, N.H.L., Chu, D.K.W., Shiu, E.Y.C. et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. Published on 03 April 2020. Nature Medicine (2020). DOI: https://doi.org/10.1038/s41591-020-0843-2 ■

COVID-19 Containment Plan: Social Distancing vs. Social Containment

The containment scheme based on 'quarantine' or 'social distancing' has emerged as the main tool in fight against COVID-19. But, there are concerns about economic and psychological costs. A researcher offers "social containment" as an alternative which seems to involve expanded 'social network' to include 'relatives, friends and other non-essential people' .But the expanded social network may put 'some' people at higher risk of mortality.

Some of the characteristics of COVID-19 that makes its containment difficult are the facts that the incubation period may be longer than 14 days (up to 28 days have been reported) and the people in the incubation period are contagious even though they have no symptoms. Therefore, with an aim to minimize contact among people within a reasonable time, a "two-stage containment scheme" was proposed by Chow and Chow in their paper published on 30 March 2020 (1).

Under this scheme, the first stage involves dividing the containment area into blocks, and the blocks into units. Smaller the size of units better the control of spreading. The contact is only permitted within the units; contact with outside unit prohibited for 14 days. Screen and test within the units to identify infected cases and quarantine of the people in the units with infected cases for 14 days from the confirmation date. In the second stage, contact between different units within a block is allowed but not among different blocks for another 14 days.

The scheme requires two stages of 14 days each to minimise spread and seems to strikes a balance between quarantine and freedom. In the first stage, it permits contacts only within the units and in the

the second stage within the blocks.

This model based on 'quarantine' or 'social distancing' has emerged as the main tool in fight against COVID-19 worldwide with reasonable results. For example, Wuhan is now limping towards normality and spread seems to be limited in India which is currently under total lockdown for a period of three weeks until mid-April. On the other hand, we see very high prevalence and mortality rates in countries like UK and USA who were late in enforcing restrictions on contacts with people. However, there have been concerns about economic and psychological costs associated with this model.

Social distancing could lead to heightened anxiety, depression and injury to self-worth because of its emphasis on 'essential contact' hence anthropologists, seem to offer "social containment" as an alternative. Nicholas Long, in his recent paper analyses conceptual problems with 'social distancing' and argues in favour of "social containment" which basically seems to involve 'social network' expanded from 'natural household' to 'relatives, friends and other people' as well despite being non-essential . This seems to offer a possibility of vibrant and varied social life with large amount of non-essential social contacts (2).

The "social containment" model can work well for those with right genetic make up endowing natural immunity against COVID (such people are more likely to be in the same household comprising biological relations) but can pose serious threat to life to those without right genes offering natural immunity by enhancing the probability of contacting the virus.

Hypothetically, assuming there were absolutely no understanding of epidemiology and no medical facilities in place to protect population against outbreak of COVID-19, would the entire human race been wiped out ? The answer is no. The natural selection would have worked in favour of those with just right genetic make up endowing natural immunity against COVID. The negative selection pressure would have worked against those without right gene and this pandemic would have possibly wiped out such people. This is what happened to human population in the past till advancement in medical sciences started saving those people as well against whom natural selection would have worked otherwise.

Compared to Ebola, COVID-19 has much higher survival rate meaning large number of people may have genes endowing natural immunity. 'Social distancing' model seems to offer higher probability of survival to the 'others' who would otherwise not survive (given there is no vaccine or drug to treat the infection at this time).

The question is should the probability of survival of those against whom natural selection may work otherwise be enhanced by social distancing or should the focus be on minimising economic and psychological costs to the rest.

Reference:

1.Chow, W.K. and Chow, C.L., 2020. A Short Note on Containment Scheme against Spreading of Novel Coronavirus COVID-19. Open Journal of Biophysics, 2020, 10, 84-87. Published on 30 March 30, 2020. DOI: https://doi.org/10.4236/ojbiphy.2020.102007 .

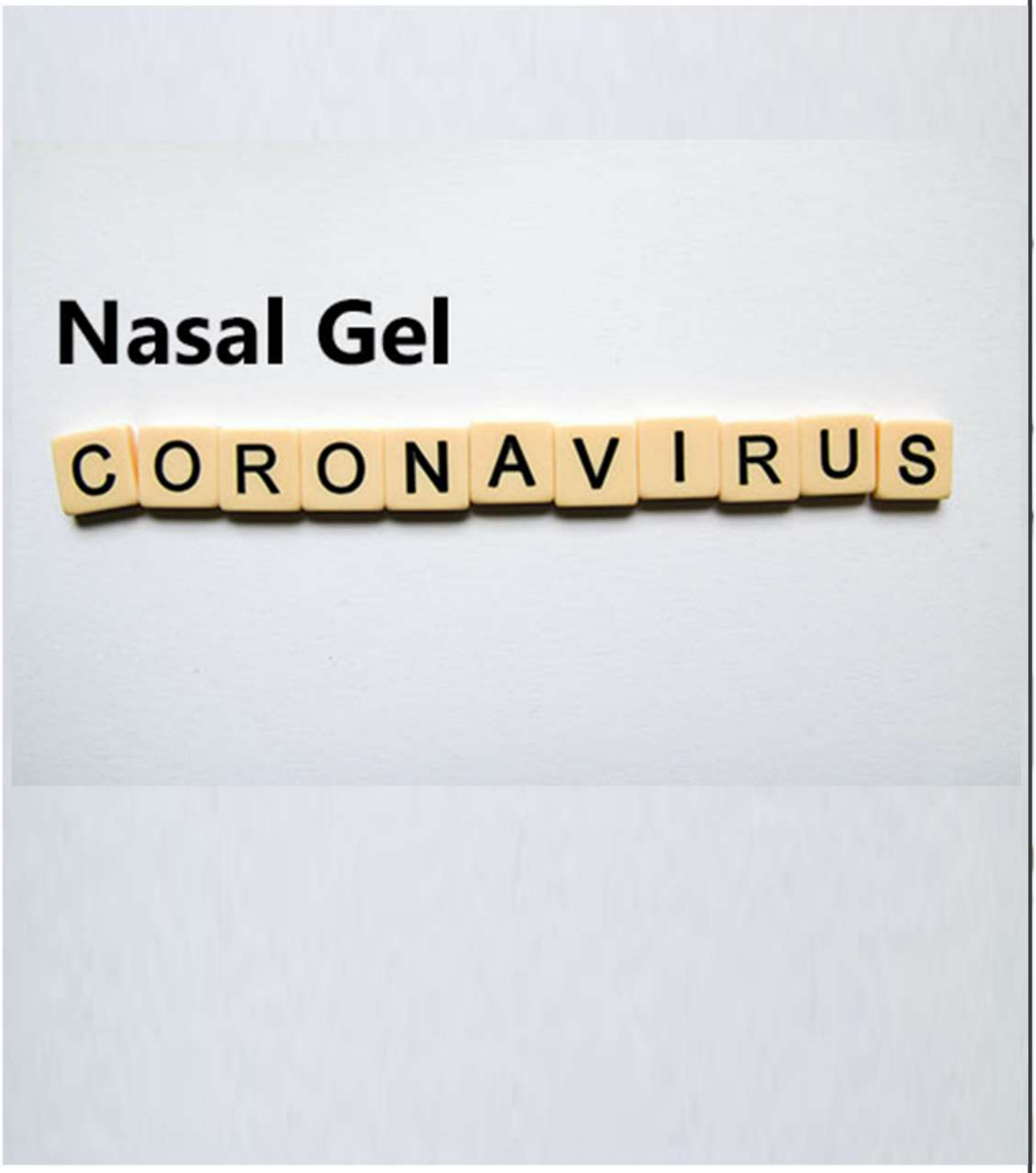
2.Long, Nicholas J. ORCID: 0000-0002-4088-1661 (2020) From social distancing to social containment: reimagining sociality for the coronavirus pandemic. Medicine Anthropology Theory. ISSN 2405-691X (Submitted). LSE Research Online URL for this paper: http://eprints.lse.ac.uk/103801/ ■

Nasal Gel: A Novel Means of Containing COVID-19

Use of nasal gel as a novel means to inactivate COVID-19 in a biological manner and prevent its entry into human body may help avert community transmission of this virus, thereby helping in disease control and management.

In an effort to contain COVID-19 pandemic, numerous ways have emerged over the past few months, wearing a face mask and maintaining social distancing among the top ones till now to prevent the spread of COVID-19 disease. Numerous labs around the world are frantically searching for ways to combat the virus that causes COVID-19, either by preventing it from infecting the human population by means of physical, social and biological barriers or by developing drugs that can cure the debilitating disease.

In this article, we discuss a novel and interesting biological means to inactivate the virus that causes COVID-19, before it physically enters the human body. We are all aware that the virus spreading COVID-19 enters the human body majorly through the nasal passage whenever the person comes in contact with the droplets containing virus in its surroundings. Scientists at IIT Mumbai in India have secured a grant from the Department of Science and Technology– Science and Engineering Board (DST-SERB) to work on the project,


Nasal Gel
CORONAVIRUS

"Antibody-based capture of 2019-nCoV and its inactivation using lipid-based in situ gel" (1).

The goal of the project is to develop antibodies against the receptor-binding domain of the spike glycoprotein of the disease causing COVID-19 virus involved in recognizing a host cell-surface receptor, namely, zinc peptidase angiotensin-converting enzyme 2. The antibodies developed would be incorporated in unsaturated free fatty acid-based emulsion loaded in-situ gels to inactivate the virus at the point of entry.

The gel to be developed above would be applied to the nasal passage, which is a major entry point of the COVID-19 virus. The virus on coming in contact with the gel would get inactivated and stuck inside the gel, thereby preventing its entry into the host. This solution can be suggested for protecting the safety of the health workers especially otolaryngologists (2, 3) who are at a greater risk due to close contact with mucus membranes of upper respiratory tract of infected people and people working for other essential services where they come in close contact with other fellow workers and public. This innovative method has the potential to safeguard doctors and healthcare workers, reduce community transmission, thereby helping in disease control and management.

However, as with all other measures, this particular innovation comes with its own challenges. Generation of specific antibodies against the surface glycoprotein of the virus in sufficient bulk quantities in a short time is the first one. The gel material used should be hypo-allergenic to humans and the quantity of gel administered to the nasal passage needs to be standardized as under-doing it may not help inactivate the virus properly and over-doing it may lead to blockage of the nasal passage, lead to potential breathing difficulties. It will be even more challenging to decide and administer the optimal gel quantity in patients with asthma and related disorders.

Nevertheless, the approach of using a nasal based gel for inactivating the virus by biological means seems to be an innovative one and worth pursuing to understand its effectiveness in controlling this pandemic.

References:

1. PIB, 2020. Government of India Pres Release ID 1612161. Available on https://pib.gov.in/PressReleseDetail.aspx?PRID=1612161

2. Vukkadala N,. et. al, 2020. COVID-19 and the otolaryngologist – preliminary evidence-based review. . Laryngoscope. 2020 Mar 26. DOI: https://-doi.org/10.1002/lary.28672 [Epub ahead of print].

3. Givi B., et al, 2020. Safety Recommendations for Evaluation and Surgery of the Head and Neck During the COVID-19 Pandemic. JAMA Otolaryngol Head Neck Surg. Published online March 31, 2020. DOI: http://doi.org/10.1001/jamaoto.2020.0780 ■

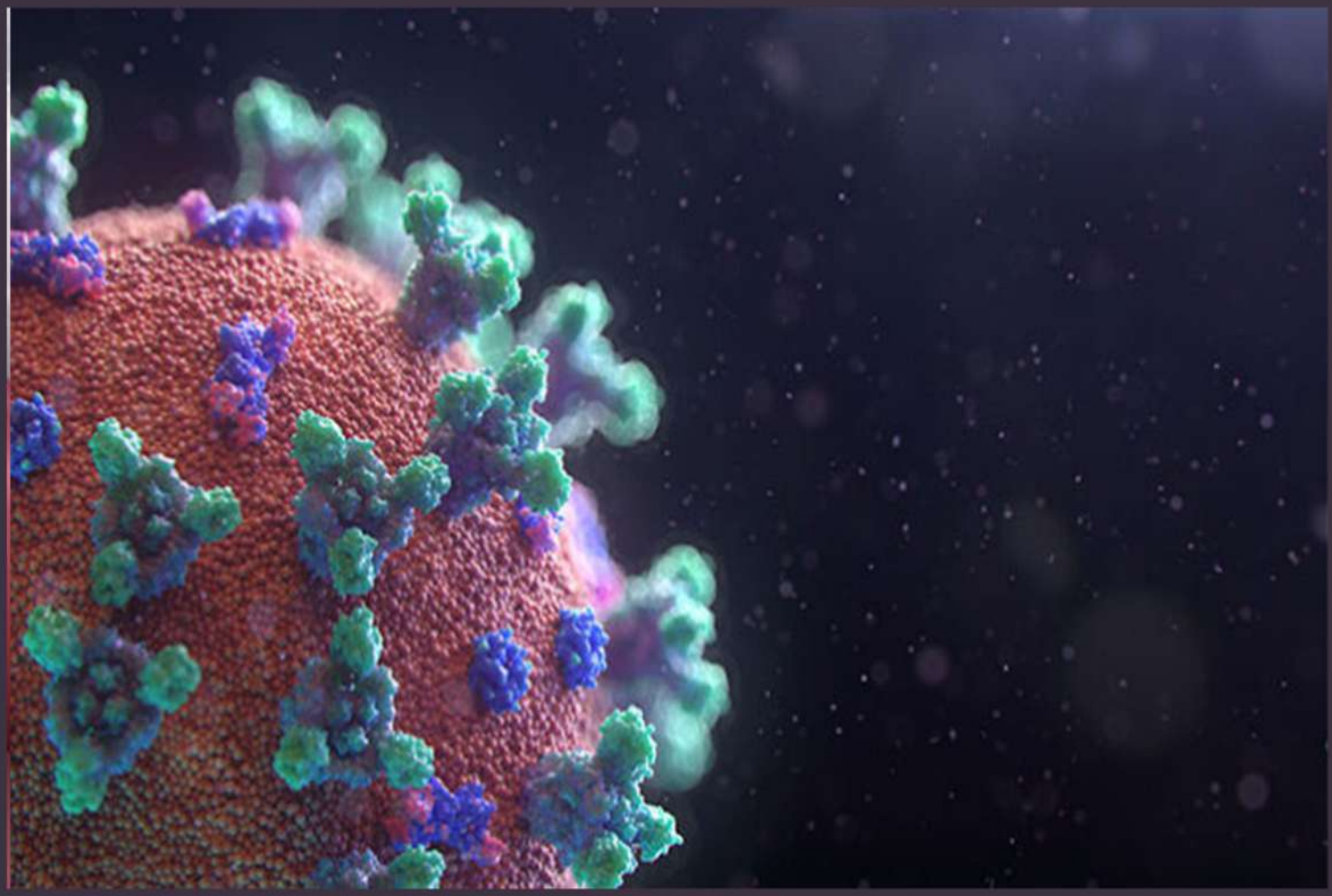
Diagnostic tests for COVID-19: An Evaluation of Current Methods, Practices and Future

Laboratory tests for diagnosis of COVID-19 currently in practice as advised by the international bodies of experts are reviewed and evaluated.

The COVID-19 disease, that originated in Wuhan China, has affected more than 208 countries till now. The scientific community in the entire world has been posed with a significant challenge in the past few months, to develop diagnostic tests for COVID-19 disease detection in order to screen patients and suspected individuals in order to effectively manage and control the pandemic.

Before we evaluate the current methods and practices used for detection of COVID-19, let us first understand what causes COVID-19 and how does one develop diagnostic tests to screen patients for this disease.COVID-19 disease is caused by a positively stranded RNA virus that are zoonotic, which means they can cross species barriers from animals to humans, and can cause, in humans, illness ranging from the common cold to more severe diseases such as MERS and SARS. The virus causing COVID-19 has now been named SARS-CoV-2 by the International Committee of Taxonomy of Viruses (ICTV), as it is very similar to the one that caused the SARS outbreak (SARS-CoVs). The diagnostic test for COVID-19 disease can be developed in number of ways.

The most popular and currently adopted method worldwide is to develop a diagnostic test that can detect the SARS-CoV-2 virus itself.



This test is based on the detection of the viral genome in the patient sample by RT-real time PCR (reverse transcriptase-real time Polymerase Chain Reaction). This entails conversion of viral RNA to DNA using an enzyme called reverse transcriptase and then amplifying the DNA using specific set of primers and a fluorescent probe, that bind to a specific region on the viral DNA, using a Taq polymerase and detecting the fluorescent signal. These tests are referred to as NAATs (Nucleic Acid Amplification Tests). This technique can be very useful for very early detection of the presence of nucleic acid in patient sample, even in asymptomatic patients that do not show COVID-19 disease symptoms (especially in the incubation period of 14-28 days) and in the later part as well when disease is full-blown

Various companies around the world have been working in a race against time during the past few months to develop NAAT based diagnostic test for the detection of SARS-CoV-2 based on CDC (Centre for Disease Control), Atlanta, USA and WHO guidelines (1, 2). The health authorities around the world have been approving these tests for emergency use for the detection of SARS-CoV-2. The viral genes targeted so far include the N, E, S and RdRP genes, along with appropriate positive and negative controls. The patient samples to be collected for such a test are from the upper respiratory tract (nasopharyngeal and oropharyngeal swab)

.

and/or lower respiratory tract (sputum and/or endotracheal aspirate or bronchoalveolar lavage).

However, it is also possible to detect virus in other samples, including stool and blood. The samples need to be collected rapidly in an appropriate manner taking all the necessary precautions and adhering to biosafety practices (as per guidelines laid down by WHO[1]), from patients meeting the suspected case definition for COVID-19, preserving and packaging it well if it requires to be transported to the diagnostic center and then processed (extracting RNA in a biosafety cabinet in a BSL-2 or equivalent facility) swiftly in a manner to ensure sample integrity. All this has to performed on a priority basis for better clinical management and outbreak control.

The detection time for various available NAAT based tests developed by major diagnostic companies around the world vary from 45 min to 3.5 hours. Various improvements are being made to these tests to convert them into point of care tests and achieve the desired results in as less time as possible without compromising the accuracy of result, to increase the number of tests that can be done in a day.

Other diagnostic test options are rapid diagnostic tests (RDTs) that either detect viral antigens/proteins that are expressed on the surface of the SARS-CoV-2 virus particles as they replicate in host cells and cause disease or host antibodies in response to infection; this test detects the presence of antibodies in the blood of people believed to have been infected with COVID-19 (3).

The accuracy and reproducibility of RDT to detect viral antigens depends on several factors including the time from onset of illness, the concentration of virus in the sample, the quality and processing of the sample, and the formulation of the reagents present in the test kits. Due to these variables, the sensitivity of these tests might vary from 34% to 80%. A major drawback of this option is that the virus needs to be in its replicative and infective stage in order to detect the viral proteins.

Similarly, tests detecting host antibodies are based on the strength of antibody response which depends on factors such as age, nutritional status, severity of disease, and certain medications or infections that suppress the immune system. A major drawback of this option is that antibodies are produced over days to weeks after infection with the SARS-CoV-2 virus and one has to wait that long to perform the test. This means that a diagnosis of COVID-19 infection based on host antibody response will often only be possible in the recovery phase, when many of the opportunities for clinical intervention or prevention of disease transmission have already passed.

Currently, the RDTs mentioned above have only been approved in a research setting and not for clinical diagnosis due to the lack of data (3, 4). As more and more epidemiological data becomes available for COVID-19, more RDTs will be developed and approved as point of care tests in a clinical setting as they can give results in 10-30 minutes as opposed to NAAT based tests that on an average takes few hours for detecting the disease.

References:

1. WHO, 2020. Laboratory Testing Strategy Recommendations for COVID-19. Interim Guidance. 21 March 2020. Available online at https://apps.who.int/iris/bitstream/handle/10665/331509/WHO-COVID-19-lab_testing-2020.1-eng.pdf Accessed on 09 April 2020

2. CDC 2020. Information for laboratories. Interim Guidance for Laboratories Available online at https://www.cdc.gov/coronavirus/2019-nCoV/lab/index.html Accessed on 09 April 2020.

3. WHO, 2020. Advice on the Use of Point of Care Tests. Scientific Brief. 08 April 2020. Available online at https://www.who.int/news-room/commentaries/detail/advice-on-the-use-of-point-of-care-immunodiagnostic-tests-for-covid-19 Accessed on 09 April 2020.

4. ECDC, 2020. An Overview of the Rapid Test Situation for COVID-19 Diagnosis in the EU/EEA. 01 April 2020. European Center for disease prevention and control.

■

Vaccines for COVID -19: Race Against Time

Development of vaccine for COVID-19 is a global priority. In this article, the author has reviewed and evaluated research and development and the present status of vaccine development.

COVID-19 disease, caused by SARS-CoV-2 virus, has been steadily increasing in the past few months around the world with no end in sight. Till date, there has been no vaccines approved for curing for this debilitating disease that has infected around 2 million people globally and causing death in about 120,000 of them (1), a figure of 6%. This 6% mortality rate is the worldwide average, with European Union having a mortality rate of around 10% while the rest of the world having a mortality rate of around 3%. There has also been a recovery of around 450,000 people, a figure of around 23%.

Pharma and biotechnology companies along with universities and research institutes around the world are working with great fervour to develop a vaccine against COVID-19 that could become the saviour of people and prevent them for getting the disease. This article will focus on the concept of vaccine development for viruses, the types (category) of vaccines being developed for COVID-19 by numerous companies, institutes and consortiums

around the world who are engaged in its research and development and its present status with emphasis on vaccine candidates that have already entered clinical trials.(1).

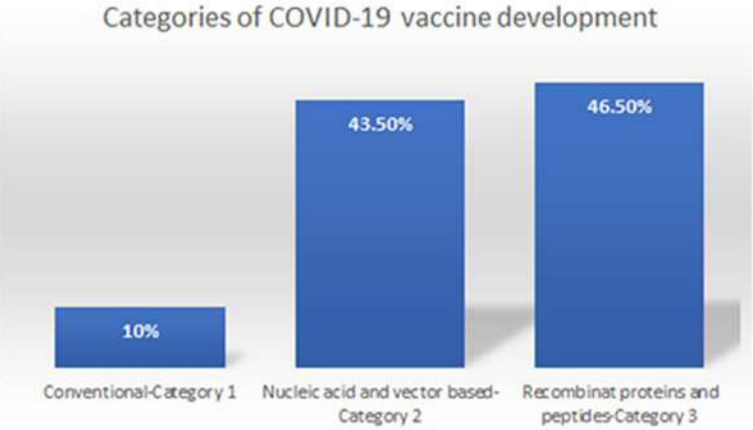
Vaccine development for viruses involves making a biological preparation of viral molecules consisting of live attenuated virus, inactivated virus, empty viral particles or viral peptides and protein(s) alone or in combination, which once injected into a healthy individual, triggers its immune system to produce antibodies against the viral molecules, thereby protecting the individual when actual infection happens. These viral molecules and proteins that act as antigens, can either be generated outside (in the laboratory) or produced (expressed) inside the individual (host) to generate the immune response. The technological advancements in the field of biotechnology in the past decade or so has played an important role in vaccine development as well, resulting in novel approaches for the production of viral antigens within or outside the host individual, that have contributed to the vaccine safety, stability and ease of large-scale manufacturing.

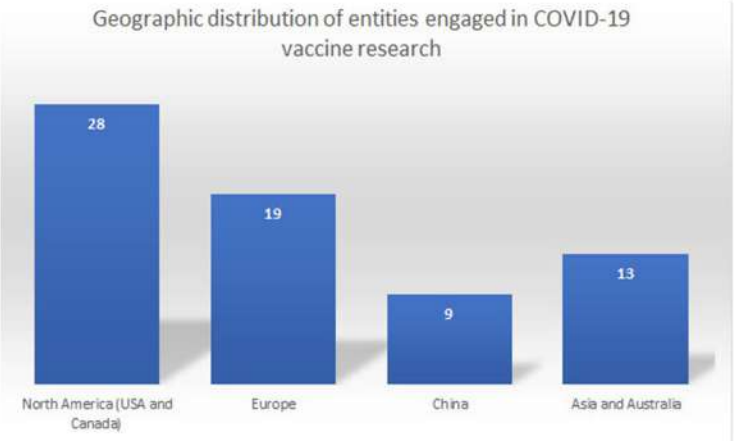
The types of vaccines under development for COVID-19 fall into three broad different categories based on the nature of technology platforms to generate viral antigens (2). The first category comprises of using the live attenuated vaccine

(that involves weakening the virulence of SARS-CoV-2 virus) or inactivated virus (in which the inactivation is performed using chemical means) and injecting it in the host to develop an immune response. This category represent the way in which vaccines were made conventionally. The second category in vogue focuses on the production (expression) of viral proteins inside the host (humans) by use of nucleic acids (plasmid DNA and mRNA) and viral vectors (replicating and non-replicating) containing viral genes. These nucleic acids and viral vectors use cellular machinery for the expression of viral proteins within the host upon injection, thereby triggering an immune response. The third category involves development of empty (without genome) viral like particles (VLPs) expressing viral proteins on their surface, use of synthetic peptides (selected parts of viral proteins) and recombinant production of viral proteins as antigens in various expression systems at a large scale outside the human host, and then using them as vaccine candidates alone, or in combination.

As of April 10th 2020, a total of 69 companies, research institutes, universities and/or a consortium of the above (3, 4) are actively engaged at an unparalleled speed in a race against time for the development of COVID-19 vaccine. These companies can be divided into either of the three categories mentioned above based on the technology they are using for COVID-19 vaccine development. Seven of these companies are exploiting the way vaccines are manufactured by the first category and the remaining 62 companies are almost equally divided (30 in the second category which uses plasmid DNA, RNA and replicating and non-replicating viral vectors while 32 in the third category which uses VLPs, peptides and recombinant viral proteins) in terms of the technologies used for vaccine manufacturing for COVID-19. Most of these companies are in exploratory or pre-clinical stages of research and development. However, six of these companies have advanced their candidate vaccines into clinical trials which are listed in Table I (information sourced from references 2-6). All these vaccines fall into the second category.

Vaccine development for COVID-19 based on the technology platforms used belong 10% to first category and 43.5% to category two and 46.5% to category three respectively (Figure 1). Based on the geographic location, North America (USA and Canada) leads COVID-19 vaccine development with highest percentage of companies (40.5%) followed by Europe (27.5%), Asia and Australia (19%) and China (13%). Refer to Figure 2.





S.No.	Vaccine Name And characteristics	Status	Clinical trial details	Companies/Institutes In collaboration	Country
1.	mRNA-1273: LNP (lipid nano particle)-encapsulated mRNA expressing S protein	Phase I (NCT04283461)	45 subjects, 18-55 years of age, will get administered an intramuscular injection of mRNA-1273 on Day 1 and 29 in the deltoid muscle and will be followed through 12 months post second vaccination (Day 364)	Moderna therapeutics and NIAID (National Institute of Allergy and Infectious Diseases)	USA
2.	Ad5-nCoV: Adenovirus type 5 vector expressing S protein	Phase I (NCT04313127)	108 subjects, 18-60, will receive an intramuscular injection of Ad5-nCoV (low, medium and high doses) in the deltoid muscle	CanSino Biologics	China
3.	ChAdOx1 nCoV-19: Chimpanzee adenovirus vector	Phase I	510 subjects, 18-60, will receive an intramuscular injection of ChAdOx1 nCoV-19, participate for 6 months with the option to come for an additional follow up visit at day 364	University of Oxford	UK
4.	INO-4800: Plasmid DNA encoding S protein	Phase I (NCT04336410)	40 subjects, 18-50, will receive two doses of INO-4800, each of 1.0 mg, four weeks apart administered through the skin	Inovio Pharmaceuticals Inc	USA
5.	LV-SMENP-DC: Dendritic cells modified with lentiviral vector expressing synthetic genes based on domains of selected viral proteins; administered with antigen-specific cytotoxic T lymphocytes	Phase I (NCT04276896)	100 subjects will receive approx. 5 million dendritic cells or 100 million Cytotoxic T Lymphocytes as a single infusion via sub-cutaneous route	Shenzhen Geno-Immune Medical Institute	China
6.	Pathogen-specific aAPC: artificial Antigen Presenting Cells expressing synthetic genes based on domains of selected viral proteins	Phase I (NCT04299724)	100 subjects will receive approx. 5 million aAPC cells each time via sub-cutaneous route at 0, 14 and 28 days	Shenzhen Geno-Immune Medical Institute	China

Figure 2. Geographic distribution of companies engaged in COVID-19 vaccine research and development.

The majority use of categories 2 and 3 in vaccine development for COVID-19 suggests the exploitation of modern state of the art technologies that have led to the ease of manufacturing and might contribute to the safety, stability and effectiveness of vaccine preparations. It is sincerely hoped that the current vaccines in clinical trials and the ones that follow would result in an effective vaccine candidate that can be fast tracked for approval by the regulatory authorities for vaccinating the human population, thereby preventing them from contracting the COVID-19 disease, and overcoming the misery that has been caused by this debilitating disease.

References:

1. Worldometer 2020. COVID-19 CORONAVIRUS PANDEMIC. Last updated: April 14, 2020, 08:02 GMT. Available online at https://www.worldometers.info/coronavirus/ Accessed on 13 April 2020.

2. Thanh Le T., Andreadakis, Z., et al 2020. The COVID-19 vaccine development landscape. Published 09 April 2020. Nature Reviews Drug Discovery DOI: http://-doi.org/10.1038/d41573-020-00073-5

3. Milken Institute, 2020. COVID-19 Treatment and Vaccine Tracker. Available online at https://milkeninstitute.org/sites/default/-files/2020-03/Covid19%20Tracker_WEB.pdf Accessed on 13 April 2020.

4. WHO, 2020. DRAFT landscape of COVID-19 candidate vaccines – 20 March 2020. Available online at https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus-landscape-ncov.pdf?ua=1 Accessed on 13 April 2020.

5. Regulatory Focus, 2020. COVID-19 Vaccine Tracker. Available online at https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker Accessed on 13 April 2020.

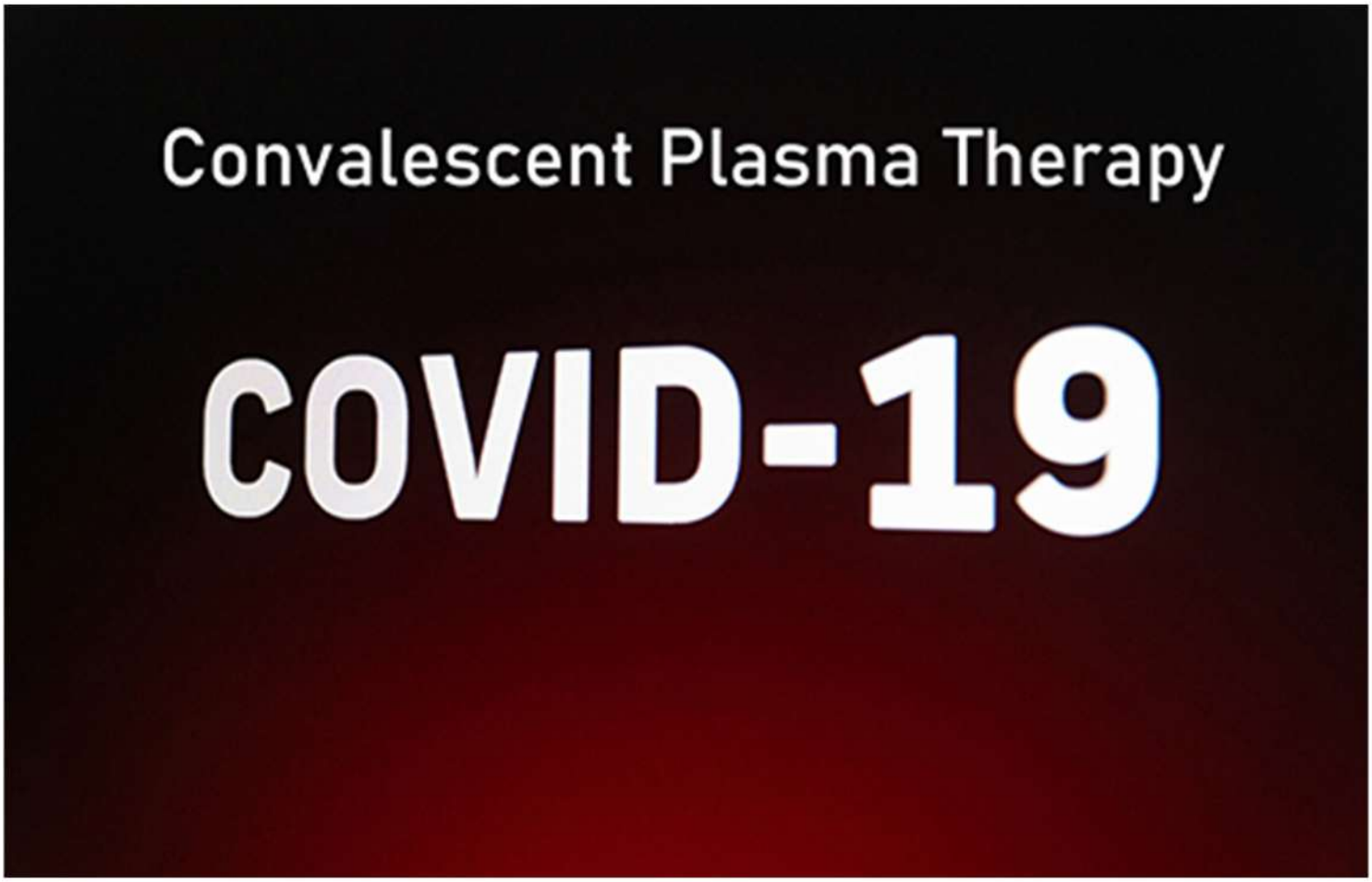
6. USNLM 2020. COVID-19 Clinical Trails Available online at https://www.clinicaltrials.gov-/ct2/results?cond=COVID-19 Accessed on 13 April 2020.

Convalescent Plasma Therapy: An Immediate Short-Term Treatment for COVID-19

Convalescent plasma therapy holds key for the immediate treatment of severely sick COVID-19 patients. This article discusses effectiveness of this therapy and its present status about its use in treating COVID-19

The COVID-19 disease has engulfed the entire world with varied effects in different countries with respect to infected individuals and mortality rates. Around 2 million people have contracted the disease globally and numbers are rising daily. Till date, there is no prescribed and approved treatment for this disease. The entire medical fraternity is eagerly waiting for a treatment that can not only provide cure for the infected people but also prevent the non-infected healthy individuals from this disease. Pharma and biotech companies and research institutes globally have already begun researching on several approaches to find a cure for COVID-19.

These approaches include use of small molecule drugs (1), vaccine development (2) and antibody therapy (3). However, all these approaches will lead to a treatment regimen that would take at least a year or a couple of years before a treatment is approved by the regulatory authorities, even as a fast track approval for emergency use. The need of the hour is to find an immediate treatment that can bring relief to the victims of COVID-19. Convalescent plasma therapy (CPT) is one such treatment that can be used to treat infected patients in the short term while waiting for the other therapies to develop. This article will discuss about the history and concept of convalescent plasma therapy, its relevance and effectiveness in treating COVID-19



patients and the approach taken by medical and regulatory authorities globally for its use.

The history of CPT dates back to 1890s, when a German physiologist, Emil von Behring, was successful in treating animals infected with diptheria using serum from animals that were immunized with attenuated forms of diptheria causing corynebacterium. The antibodies present in the serum from immunized animals prevented infected animals from getting the disease.

Convalescent plasma therapy involves isolating the plasma from infected individuals that have recovered from the disease and injecting it into the patients with disease, thereby providing passive immunity from the plasma containing antibodies generated against the pathogen in recovered individuals.

The process consists of drawing blood from donors that have recovered from the disease, separating the plasma and checking the antibody titre before administering it to the infected patients. This therapy has been successfully used previously for the Spanish flu pandemic of 1918, Ebola, SARS, MERS, and 2009 H1N1 pandemic (4-9). In case of Spanish flu, the mortality rates were reduced to 50% for infected patients that were given CPT in comparison to those who didn't (10), with the primitive technologies present at that time for separating plasma from blood. Due to the similarities of these disease causing viruses along with their clinical characteristics with the SARS-CoV-2 virus, convalescent plasma therapy may prove to be a good choice for treatment of infected patients

with COVID-19 (equivalent to ~ 523,000 people globally) have recovered (11) and plasma from these individuals can be used as an immediate and short term treatment of infected people, especially those showing severe symptoms.

Countries across the world have either already started or in the process of approving CPT for investigational use for the treatment of COVID-19. A limited small trial in China for CPT on 10 patients (six males and four females) with a median age of 52.5 years was conducted with primary outcome of safety and secondary outcome of improvement of clinical symptoms. The therapy was well tolerated without any adverse effects and there was a significant reduction in clinical symptoms within 3 days of administering the therapy (12), although the effect and time taken for patients to be SARS-CoV-2 negative, varied in different patients. This has provided enough relevance and hope for the CPT to be further used in clinical trials in other regions of the world affected by COVID-19.

The apex body of medical research in India, ICMR (Indian Council of Medical Research) has given permission to Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST) in Kerala for carrying out CPT in a clinical trial setting (13). The study would be conducted on a small number of patients who are severely infected with COVID-19 in partnership with five medical college hospitals. Severely infected patients represent those that are in intensive care experiencing shortness of breath, low blood oxygen saturation levels (less than 93%), septic shock and/or multiple organ impairment including ones that are about to be put on a ventilator. ICMR has also solicited cooperation from other medical researchers across the country to engage in clinical trials using CPT for COVID-19 patients with an aim to assess the safety and efficacy of this procedure (14).

European Union has also endorsed the use of CPT as a promising treatment for COVID-19 and is seeking help from member States for collecting blood from recovered donors for carrying out CPT (15). It is also building a database in partnership with European Blood Alliance (EBA), for blood collection and the outcome of clinical trials, that will be shared with member States.

National Health Services (NHS) in UK is also soliciting patients who have recovered from COVID-19 to donate their blood through various centres across the UK in order to start clinical trials of CPT for the severely ill COVID-19 patients (16).

US FDA on April 13th 2020, issued guidance to use CPT as an investigational procedure in a clinical trial under the traditional IND regulatory pathway (21 CFR Part 312) for patients affected severely by COVID-19 (17). The responsibility of reviewing requests from sponsors would be undertaken by the office of Blood Research and Review, a unit of CBER (Center for Biologics Evaluation and Research).

As with all other therapies, CPT also comes with its own challenges. The first and foremost is to get access to the recovered patients and convincing them to donate their plasma. The recovered individuals should be free of any other disease condition, which is a real issue in case of COVID-19 where majority of victims are aged people who might have a history of other medical complications such as heart disease, diabetes, blood pressure etc. Plasma obtained should be in sufficient quantities and have a high antibody titer so that enough people can benefit from the same. Blood from plasma donors would have to undergo testing for infectious agents and blood group compatibility with the recipient. All this would require a massive coordination between the medical personnel, agreed donors that have recovered from the disease and the patients receiving CPT, for the entire procedure to yield a successful outcome.

Nonetheless, notwithstanding the shortcomings, CPT still holds promise, with safety and efficacy being prime attributes, for the short-term treatment of COVID-19 patients. If CPT for Spanish flu can reduce the mortality rate to 50%, it is surmised that the reduction in mortality rate using CPT for COVID-19 should be greater than 80%, keeping in mind the present state-of-the-art technologies for plasma separation, storage and administration accompanied with modern patient care facilities. The medical fraternity should leave no stone unturned to exploit CPT for the treatment of COVID-19 patients until a small molecule, vaccine or antibody therapy is approved which would take its own course of time with the hope of vaccine being developed the fastest (one to two years), followed by novel small molecule(s) and/or repurposing of existing small molecular drugs and antibody therapy.

References:

1. Gordon CJ, Tchesnokov EP, et al 2020. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem. 2020. First Published on April 13, 2020. DOI: http://doi.org/10.1074/-jbc.RA120.013679

2. Soni R., 2020. Vaccines for COVID-19: Race Against Time. Scientific European. Published on 14 April 2020. Available online at https://www.scientificeuropean.co.uk/vaccines-for-covid-19-race-against-time Accessed on 16 April 2020.

3. Temple University 2020. Temple Treats First Patient in the U.S. in Clinical Trial of Gimsilumab for Patients with COVID-19 and Acute Respiratory Distress Syndrome. Lewis Katz School of Medicine News Room Posted on 15 April 2020. Available online at https://medicine.temple.edu/news/-temple-treats-first-patient-us-clinical-trial-gimsilumab-patients-covid-19-and-acute Accessed on 16 April 2020.

4. Mupapa K, Massamba M, et al 1999. Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. The Journal of Infectious Diseases, Volume 179, Issue Supplement_1, February 1999, Pages S18–S23. DOI: https://doi.org/10.1086/514298

5. Garraudab O, F.Heshmati F. et al 2016. Plasma therapy against infectious pathogens, as of yesterday, today and tomorrow. Transfus Clin Biol. 2016 Feb;23(1):39-44. DOI: https://doi.org/10.1016/j.tracli.2015.12.003

6. Cheng Y, Wong R, et al 2005. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur. J. Clin. Microbiol. Infect. Dis. 24, 44–46 (2005). DOI: http://doi.org/10.1007/s10096-004-1271-9

7. Zhou B, Zhong N, and Guan Y. 2007. Treatment with convalescent plasma for influenza A (H5N1) infection. N Engl J Med. 2007 Oct 4;357(14):1450-1. DOI: http://doi.org/10.1056/NEJMc070359

8. Hung IF, To KK, et al 2011. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis. 2011 Feb 15;52(4):447-56. DOI: http://doi.org/10.1093/cid/ciq106

9. Ko JH, Seok H et al 2018. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: A single centre experience. Antivir. Ther. 23, 617–622 (2018). DOI: http://doi.org/10.3851/IMP3243

10. Dave R 2020. Before Vaccines, Doctors 'Borrowed' Antibodies from Recovered Patients to Save Lives. Available online at https://www.history.com/news/blood-plasma-covid-19-measles-spanish-flu Accessed on 16 April 2020.

11. Worldometer 2020. COVID-19 CORONAVIRUS PANDEMIC. Last updated: April 16, 2020, 12:24 GMT. Available online at https://worldometers.info/coronavirus/https://worldometers.info/coronavirus/ Accessed on 16 April 2020. ■

Why 'Matter' Dominates the Universe and not 'Antimatter'? In Quest of Why Universe Exists

In the very early universe, soon after the Big Bang, the 'matter' and the 'antimatter' both existed in equal amount. However, for the reasons unknown so far, the 'matter' dominates the present universe. The T2K researchers have recently shown occurrence of a possible Charge-Parity violation in neutrino and the corresponding anti-neutrino oscillations. This is a step forward in understanding why matter dominates the universe.

The Big Bang (which occurred about 13.8 billion years ago) and other related theories of physics suggest that the early universe was radiation 'dominant' and the 'matter' and the 'antimatter' existed in equal amount.

But the universe that we know today is 'matter' dominant. Why? This is one of the most intriguing mysteries of universe. (1).

The universe that we know today started with equal amounts of 'matter' and 'antimatter', both were created in pairs as the law of nature would require and then got annihilated repeatedly producing radiation known as the 'cosmic background radiation'. Within about 100 micro seconds of the Big

Bang the matter (particles) somehow started outnumbering antiparticle by say one in every billion and within seconds all the antimatter was destroyed, leaving behind only matter.

What is the process or mechanism that would create this kind of difference or asymmetry between the matter and antimatter?

In 1967, the Russian theoretical physicist Andrei Sakharov postulated three conditions necessary for an imbalance (or production of matter and antimatter at different rates) to occur in the universe. First Sakharov condition is the baryon number (a quantum number that remains conserved in an interaction) violation. It means that protons decayed extremely slowly into lighter subatomic particles like a neutral pion and a positron. Similarly, an antiproton decayed into a pion and an electron.

Second condition is the violation of charge conjugation symmetry, C, and charge conjugation-parity symmetry, CP also called Charge-Parity violation. Third condition is that the process that generates baryon-asymmetry must not be in thermal equilibrium due to rapid expansion decreasing the occurrence of pair-annihilation.

It is the Sakharov's second criterion of CP violation, which is an example of a kind of asymmetry between particles and their antiparticles that describes the way they decay. By comparing the way particles and antiparticles behave, i.e., the way they move, interact, and decay, scientists can find evidence of that asymmetry. The CP violation provides an evidence that some unknown physical processes is responsible for the differential production of matter and antimatter.

The electromagnetic and 'strong interactions' are known to be symmetric under C and P, and consequently they are also symmetric under the product CP (3). "However, this is not necessarily the case for the 'weak interaction', which violates both C and P symmetries" says Prof. B.A. Robson. He further says that "the violation of CP in weak interactions implies that such physical processes could lead to indirect violation of baryon number so that matter creation would be preferred over antimatter creation". Non-quark particles do not show any CP violations whereas the CP violation in quarks are too small and are insignificant to have a difference in matter and antimatter creation. So, the CP violation in leptons (neutrinos) become important and if it is proved then it would answer why the universe is matter dominant.

Although CP symmetry violation is yet to be proved conclusively (1) but the findings reported by the T2K team recently shows that scientists are really close to it. It has been demonstrated for the first time that the transition from particle to electron and neutrino is favoured over the transition from antiparticle to electron and antineutrino, through highly sophisticated experiments at T2K (Tokai to Kamioka) (2). T2K refers to a pair of laboratories, the Japanese Proton Accelerator Research Complex (J-Parc) in Tokai and the Super-Kamiokande underground neutrino observatory in the Kamioka, Japan, separated by about 300 km. The proton accelerator at Tokai generated the particles and antiparticles from high energy collisions and detectors at Kamioka observed the neutrinos and their antimatter counterparts, antineutrinos by making very precise measurements.

After the analysis of several years of data at T2K, scientists were able to measure the parameter called delta-CP, which governs the CP symmetry breaking in neutrino oscillation and found the mismatch or a preference for enhancement of the neutrino rate which can eventually lead to the confirmation of CP violation in the way neutrinos and antineutrinos oscillated. The results found by the T2K team are significant at statistical significance of 3-sigma or 99.7% confidence level. It's a milestone achievement as confirmation of CP violation involving neutrinos is linked with the dominance of matter in the universe. Further experiments with larger database will test whether this leptonic CP symmetry violation is larger than CP violation in quarks. If it is so then we will finally have the answer to the question Why the universe is matter dominant.

Though the T2K experiment does not clearly establish that CP symmetry violation has occurred but it is a milestone in the sense that it conclusively shows a strong preference for enhanced electron neutron rate and takes us closer to prove the occurrence of CP symmetry violation and eventually to the answer 'why the universe is matter dominant'.

References:

1. Tokyo University, 2020. "T2K Results Restrict Possible Values of Neutrino CP Phase -….." Press Release Published 16 April 2020. Available online at http://www.icrr.u-tokyo.ac.jp/en/news/8799/ Accessed on 17 April 2020.

2. The T2K Collaboration, 2020. Constraint on the matter–antimatter symmetry-violating phase in neutrino oscillations. Nature volume 580, pages339–344(2020). Published: 15 April 2020. DOI: https://doi.org/10.1038/s41586-020-2177-0

3. Robson, B.A., 2018. The Matter-Antimatter Asymmetry Problem. Journal of High Energy Physics, Gravitation and Cosmology, 4, 166-178. https://doi.org/10.4236/jhepgc.2018.41015 ■

How Compensating Innovators Could Help Lift Lockdown due to COVID-19

For quicker lifting of lockdown, the innovators or entrepreneurs holding IP rights over novel technologies with potential to improve diagnostics and therapeutics for COVID-19, who may otherwise be unable to launch the products at scaled up level due to financial and operational constraints should be suitably compensated for the value of their IP rights by the public bodies and/or pharma/biotech giants which would in turn enable the novel technologies to see the day of mass production to fight the infection effectively thus helping lift the economic lockdown sooner.

Coronavirus pandemic caused by COVID-19 has taken the entire world by storm and COVID-19 cases are rising daily with the figure crossing 2.3 million globally on 19th April (1). Presently, the only way of prevention from COVID-19 is social distancing, i.e. staying away from each other, till a cure is developed in terms of small molecule drugs (2), vaccines (3) and/or antibody therapy (4). In order to maintain social distancing, various governments across the world have imposed mandatory lockdowns to ensure people stay at home to halt the spread of the virus. In countries where lockdowns have not been enforced by authorities, people are trying to learn from others across geographical boundaries and maintaining social distancing themselves by avoiding social gatherings and also staying indoors to prevent themselves from contracting COVID-19.

Although lockdown is imperative to avoid further spread of COVID-19, it has brought the world economy to tatters (5) due to huge losses by virtue of businesses and establishments being closed

indefinitely till lockdown continues.

In addition, there is a huge social cost with impact on people's relationships and mental health of individuals due to confinement indoors and being unable to interact face to face with each other, leading to problems such as depression, mood swings etc. Medical fraternity, general public and government experts are battling with disease with the following questions in mind. How long should the lockdown continue? What could be the lockdown lifting strategy? Complete or in phases. How can we mitigate the consequences of lockdown? Unfortunately, there is no easy and straightforward answers to all these questions and each person or entity has his/her own perception of what the future is going to be, both short-term and long-term.

However, one thing which is certain is that huge investments have been and are being made not only to contain the COVID-19 disease but also to develop diagnostic and therapeutic interventions that can help in managing the COVID-19 pandemic. The consequences of lockdown can be minimised and its lifting can be eased depending on how quickly diagnostics and therapeutics can be developed. In the wake of this crisis, the world is looking at the entire global scientific community, particularly smaller organisations to bring out innovative technological solutions, in the area of COVID-19 diagnostics and treatment, by being more flexible and agile compared to the bigger giants. While these innovators can provide path breaking technologies, they may not possess the manufacturing capability and distribution reach to bring their product to the masses. In this regard, the bigger companies, philanthropic foundations and other high

net worth individuals need to provide the financial muscle required for large scale production and marketing of the product. This can be done by rewarding the innovator either through outrightly purchasing the IP rights owned by the innovator or by entering into an exclusive/non-exclusive licensing agreement to use innovator's technology for manufacturing and distribution on a bigger scale. The financial stimulus can also be provided by the various governments as well in order to make these technologies available at an affordable cost to the people. This view has been expressed in an article by Prof. Elias Mossialos (6). He emphasized that various governments and philanthropic organisations should come forward and intervene in this crisis situation to fund and/or purchase the technologies from the innovators and then translating them in a manner that it becomes available to general public at an affordable price.

The concept of in licensing technologies from innovators by other companies and then translating them into a realisable product is nothing new and has been in vogue. Small innovator companies either outrightly sell their intellectual property rights of the technology for a one-time fee or enter into a licensing agreement with a bigger company with more financial power, in which the smaller innovator companies get an upfront payment followed by royalty on sales and milestone payments depending on the terms and conditions of the agreement. The concept of utilisation of patents by in licensing for a fee has been elegantly captured and referred by Prof. Elias Mossialos in his book titled "Policies and incentives for promoting innovation in antibiotic research", where he analysed the opportunities and incentives to stimulate R&D for antibiotics, and proposed of having a 'Patent Pool (PP)' as "a coordinating mechanism that enables the collective acquisition and management of IP for use by third parties for a fee" and 'Product Development Partnerships (PDP's) as a vehicle to provide greater collaboration among different entities.

The concept of 'PP' is that it can be populated by patents coming either from public or the private sector. Any entity that wishes to utilise the patent to develop the novel product can in licence the patent from the pool by paying an upfront fee and/or royalties on the sale of the product later. This can help reduce transaction costs and barriers to market entry resulting from IP protection. Prof. Mossialos also discusses examples in his book where patent pooling was helpful, pertaining to antibiotic research.

In case of PDP's, entities can enter into a greater collaboration by aiming at product development from the end of clinical phase all the way upto clinical trials. This would result in completion of the product development with various entities sharing the risk and the reward.

Development of a similar concept of 'Patent Pool' and 'Product Development Partnerships' is the need of the hour today as the world is grappling with the COVID-19 pandemic. The 'Patent Pool' will provide a mechanism wherein different entities can contribute by providing their patents, which can then be picked up by interesting and capable companies/research institutes to further develop COVID-19 diagnostic and/or therapeutic products quickly so as to help lift the lockdown soon. Once developed, the 'Product Development Partnerships' concept comes in where different/same companies pick up the developed product and enter into clinical development and validation.

Another option of 'Marketing and Commercial Partnerships (MCP's)' following PDPs is proposed once the product is developed and manufactured and ready for commercialisation. This involves companies entering into marketing agreements with the developer of the product for marketing and commercial rights in various geographies across the world in order for the product to reach the entire global population without any major issues. The skills required of companies participating in MCPs are very different than that of companies/institutes involved in PDPs. MCPs can even involve different state governments and public health institutions if there is a need to supply a product at an affordable rate to the population of a particular country to lower the disease burden

The amount of finances involved in developing the concepts of PPs, PDPs and MCPs for COVID-19 is far less than the amount of money the individual countries are losing due to lockdown and other consequences related to the pandemic.

The point that needs to be taken home here is that, in this pandemic situation which the entire world is experiencing regarding COVID-19, the concepts pertaining to PPs, PDPs and MCPs if developed can lead to a swift development of a diagnostic and/or therapeutic regimen concomitantly with compensating the relevant discoverers and developers of the product.

The resulting new and affordable diagnostic procedures and therapeutic interventions for COVID-19, would ease lockdown possibilities moving forward, perhaps much earlier than anticipated and save economic losses that the world is suffering from.

References:

1. Worldometer 2020. COVID-19 CORONAVIRUS PANDEMIC. Last updated: April 19, 2020, 14:41 GMT. Available online at https://worldometers.info/coronavirus/ Accessed on 19 April 2020.

2. Gordon CJ, Tchesnokov EP, et al 2020. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem. 2020. First Published on April 13, 2020. DOI: http://doi.org/10.1074/jbc.RA120.013679

3. Soni R., 2020. Vaccines for COVID-19: Race Against Time. Scientific European. Published on 14 April 2020. Available online at https://www.scientificeuropean.co.uk/vaccines-for-covid-19-race-against-time Accessed on 19 April 2020.

4. Temple University 2020. Temple Treats First Patient in the U.S. in Clinical Trial of Gimsilumab for Patients with COVID-19 and Acute Respiratory Distress Syndrome. Lewis Katz School of Medicine News Room Posted on 15 April 2020. Available online at https://medicine.temple.edu/news/temple-treats-first-patient-us-clinical-trial-gimsilumab-patients-covid-19-and-acute Accessed on 19 April 2020.

5. Maital S and Barzani E 2020. The Global Economic Impact of COVID-19: A Summary of Research. Samuel Neaman Institute. Published March 2020. Available online at https://www.neaman.org.il/-Files/Global%20Economic%20Impact%20of%20COVID-19.pdf Accessed on 19 April 2020.

6. Mossialos E., 2020. Paying innovators is the way out of lockdown. The Times. Published 15 April 2020. Available online at https://www.thetimes.co.uk/article/paying-innovators-is-the-way-out-of-lockdown-b3jb6b727. Accessed on 19 April 2020.

7. Mossialos E, Morel CM, et al, 2010. Policies and incentives for promoting innovation in antibiotic research. European Observatory on Health Systems and Policies WHO. Available online http://www.euro.who.int/__data/assets/pdf_file/0011/120143/E94241.pdf Accessed on 16 April 2020. ■