# Clinical Trials Final Semester Examination PGDSMA 2019-2020

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# Name- Dristanta Nirola

# Roll No- DST-19/20-010

# The Origin, Spread and Clinical Trials on Coronavirus Disease-19

The pandemic of 2019-ncov, which causes serious respiratory illness such as pneumonia and lung failure is believed to have first originated from a live animal market selling exotic animals for meat in Wuhan, the capital city of the Hubei province of China in December 2019 and from there the virus took less than three months to spread around the world. “The coronavirus disease 19 (COVID-19) is a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Genomic analysis has found that SARS-CoV-2 is phylogenetically related to severe acute respiratory syndrome-like (SARS-like) bat viruses.”[1] Therefore, the researchers have claimed that bats might be the attainable primary reservoir. However, the intermediate source of origin and transfer to humans isn’t known. The primary instances of COVID-19 were enlisted in the city emergency clinic of china toward the end of December. On 31 December 2019, the WHO China Country Office was reported regarding instances of pneumonia of obscure aetiology identified in Wuhan City, Hubei Province of China. Starting at 3 January 2020, an aggregate of 44 patients with pneumonia of obscure aetiology have been accounted for to WHO by the national experts in China. Of the 44 cases revealed, 11 are seriously sick, while the staying 33 patients are in stable condition. As per media reports, the concerned market in Wuhan was shut on 1 January 2020 for natural sanitation and sterilization.

The rapid transmittable characteristic of the virus among the human has been the major cause of the widespread of the virus out from the city of the metropolis, China. Even before the human to human transmission was confirmed, WHO reported the first case outside of China in Thailand on January 13, in a woman who had arrived from Wuhan. Meanwhile, on 20th of January China revealed the third demise and in excess of 200 contaminations. New cases were also reported outside Hubei including in Beijing, Shanghai and Shenzhen. Following this, a Chinese expert on infectious diseases [**confirmed human-to-human transmission**](https://www.aljazeera.com/news/2020/01/china-confirms-human-human-transmission-coronavirus-200120162507948.html) of the virus to state broadcaster CCTV. The cities of Wuhan, Xiantao and Chibi in Hubei province were placed under effective quarantine on **January 23** as all the air, rail departures to and from the city were suspended. Raising fears of a major outbreak as millions travelled for the Lunar New Year holiday, by the end of the week, more province of China was put under lockdown affecting a total of 56 million people in China. But WHO, on the other hand, had said that the outbreak did not yet constitute a public emergency of international concern and there was "no evidence" of the virus spreading between humans outside of China. Until on January 30 WHO could confirm the spread and declare it as a global emergency the virus had already reached major countries like Russia ,India, Philippines, Spain, Sweden and the United Kingdom, Canada, Australia, Germany, Singapore, Japan, the US, the UAE and Vietnam where the first cases were reported within few days. The first death due to virus outside china was reported by the Philippines on 2nd Feb 2020. On February 6, experts in Malaysia announced the nation's initially known human-to-human transmission while the contaminated in Europe reached at 30. On February 7, Li Wenliang, a specialist who was among the first to sound the caution over the coronavirus in China, passed away due to the virus. On February 9, the loss of life in China outperformed that of the 2002-03 SARS outbreak, with 811 deaths recorded and 37,198 contaminations. An insightful group drove by specialists from the WHO left for China and on February 11, the WHO declared that the disease caused by new coronavirus would be known as the "COVID-19” and guideline was issued in order to contain the virus. The screening was done in airports and public places. International flights were suspended by most of the countries. Finally, in a long-anticipated move, the WHO on March 11 declared the coronavirus outbreak a pandemic. Meanwhile, as the number of cases worldwide surpassed 600,000, with more than 27,000 deaths on March 27, India and South Africa joined the countries to impose nationwide lockdown and announced the suspension of all schools and universities across the country until further notice. People who were stranded abroad were brought back to their respective country and put to 14 days observations at different quarantined facilities. Contact trashing was done to find all the possible links to the persons those who were tested positive to the virus. Special isolation wards were arranged to isolate the patient who were confirmed to be infected by the virus. Many leaders from around the world have questioned China and the WHO over its handling of the outbreak and have claimed that the attempt made by the Chinese government trying to hide the virus was the main cause of the widespread of the virus around the globe. Some even claim the virus is a biological weapon designed by china at its laboratory in the Wuhan Institute of virology which is well known for conducting research on world's most dangerous diseases. “Had the CCP gov. taken appropriate steps to contain the virus at the early stage, the scenario would have been different” claims US president Mr Donal Trump. Currently as of **19th July** there are 5,299,894 active cases of Covid-19. Out of them, 99% of them are mild patients and only 1% are critical patients. Since its emergence till this day, there have been a total of around 14,646,707 cases, out of which 606,978 resulted in death and 8,373,835 of them have recovered from the disease. By current data, the USA has been the worst hit nation in the world in terms of number of cases followed by Brazil and India in 2nd and 3rd positions. Initially, WHO had declared that the Infection Fatality Rate (IFR) was around 3.4%. As time went on, with the improvement in the treatment and as more cure was introduced everyday this rate has become even lower. The Centres for Disease Control and Prevention reported later that it is about 0.65%. But Current estimates lie anywhere between 0.2% and 1%, and these estimates will keep changing from time to time also the rate varies from region to region. It was found that people with a mild case of Covid-19 can take from one to two weeks to recover with medical assistance. For severe patients, the recovery time can be around six weeks or more. The recovery time depends on how good the immune system is.

As COVID-19 has triggered massive human casualties and severe economic recession posing a serious global threat, an understanding of the ongoing situation and the development of strategies to contain and mitigate the virus from the spread are urgently needed. There is no clinically approved antiviral drug or vaccine to be used against COVID-19. However, few broad-spectrum old antiviral drugs have been repurposed and were being evaluated in clinical trials and now used against COVID-19. Some of them are discussed below. Also, developing effective vaccines to stop the virus spread are undergoing clinical trials. However, before talking about the vaccine and the clinical trials associated with them, let us find out how our immune system works and how does a virus, in particular, the COVID-19 kill us. The scientist has still not understood the virus, but they have found out how this virus kills. “Virus kills by getting one’s body to kill itself” but how does this happen? This happens because this virus is a strange new virus; it makes our immune system particularly when it goes to T-cells react in funny ways. The immune system, initiate our body to produce antibodies, and then our T-cells will also get activated against the host, they will fight, and sometimes they get very confused and aggressive toward the unknown host, and they start malfunctioning and ending us killing their own. Thus, there are two kinds of drugs that seem to be working at this point in time are **immunosuppressants** and **immunomodulators**. The immunosuppressants like **Dexamethasone** suppresses the immune responses of the body by giving time to fight back; these are all repurposed old drugs, and it seems logical to use them. Another kind of drugs is like **Tocilizumab**; it is the first immunomodulator to be cleared for emergency use and is trending a lot. Tocilizumab worked on our cells which release the cytokines to prevent them from doing so. What they do is, T-cells also has a receptor called CD-6s thus a Tocilizumab goes and inhabits CD-6s on our T-cell which means it doesn’t allow the body to release cytokines, again this is only used in the early stage of the treatment before the patient goes into the ventilators. This drug is designed to treat an autoimmune condition like Chikungunya, Diabetics. Thus, it must work well with the COVID also as COVID is also a kind of autoimmune disease; this was the simple science behind the use of this drug like Hydroxy and others. Even there was a lot of politics in the use of hydroxychloroquine in treating the COVID patient. The drug that was talked about by Donald Trump and was supplied by the government of India to more than 150 countries. But later this drug was proven that it was not effective for the treatment of the COVID and WHO had issued a guideline not recommending the use of the medicine on COVID patient. Still, this is still being used by some countries like India and Brazil. Some of the trials of this were conducted in India later and found that the drug worked well if used at an early stage of the treatment. The research found that the trial performed had 13% fatality rate for a patient with HCQ and almost 26% for non HCQ patient. The sample was large and had a patient range from 18 to 78 also the doses used during the trial were ten times more than the usual dose provided to the patient shows that the tablets have no such side effects.

One of the most awaited events today around the world is the development of the vaccine. Some also called it a race to develop a vaccine, as the race has actually begun to find the vaccine that can stop the spread of the COVID-19. Countries around the world are researching on different technology that might make the process of vaccine development much faster. This has happened for the first time in the history of vaccine development that the phases of clinical trials of the vaccine are being completed in such a short period. Of the 163-candidate vaccine that the researchers are working on 23 of them are now already being approved for human trials. Among them the University of Oxford/AstraZeneca’s ChAdOx1-S and Sinovac’s Inactivatedalum are leading the race. Another US firm Moderna/NIAID has a claim to complete its Phase 1/Phase II human trials, and claims that the results shown are promising.

The trails for the new drug and vaccines development are conducted in 4 different phases which includes:

**Preclinical trials:** The clinical trials are only conducted when there is enough evidence to believe that the new drug/treatments have some promising result. Preclinical trials are not performed in human.  Investigators conduct preclinical research using human cell cultures or animal models.

**Phase 1** trials aim to ensure treatment is safe and help determine an effective dose.

**Phase 2** trials test a treatment in a larger group and get an early read on effectiveness.

**Phase 3** trials are conducted in a large group of individuals to confirm the efficacy and identify the rare side.

“The University of Oxford/AstraZeneca’s named ChAdOx1 nCoV-19, is based on a weakened version of the common cold that causes infections in chimpanzees. It also contains the genetic material of the spike protein of SARS-CoV-2 – the strain of coronavirus that causes the COVID-19 illness.”[5] “The vaccine has already completed its Phase 1/Phase II human trials and In a study published on Monday 20th of July 2020, Oxford and AstraZeneca's coronavirus vaccine trial showed "potent" cellular and humoral immunogenicity in all 1,077 participants in a Phase 1/Phase II study”[6] claims the source. "I can tell you that we now know the Oxford vaccine covers both bases – it produces both a T cell and an antibody response. It’s the combination of these two that will hopefully keep people safe. So far, so good. It’s an important moment. But we still have a long way to go," says Sarah Gilbert, professor of vaccinology at the university’s Jenner Institute who is leading the research. “A phase III randomized controlled trial to determine safety, efficacy, and immunogenicity of the non-replicating ChAdOx1 nCoV-19 vaccine is underway. Participants for the trail are randomly allocated to receive the investigational vaccine or a well-established meningitis vaccine. Volunteers will be followed for years, and they will be tested for COVID-19 to find if they develop any symptoms representing the COVID-19 disease in this event. In addition, blood samples will be collected from this volunteer at a regular interval during the study to look at how the volunteers' immune systems have responded to the virus. At the end of the study, the researchers will look at how many people had developed the antibody against the COVID-19 disease in each group and this will help them to decide if the vaccine has worked.” [7]

The US firm Morderna has also claimed that all 48 volunteers attained the trail has developed cover from the virus and with this Moderna is all set to start its phase 3 trail from 27th July 2020.

Indian firm Bharat Biotech with the ICMR has also shown promising results in their pre-clinical trial and has been approved for the human trails across India. The phase II results are expected in 2 months claims the researchers.

**Conclusion:**

If we talk about the absolute value then the number of cases is really horrifying but at the same time if we look at the percentages, in those terms India probably in not doing so badly compared to other nation. For example, Brazil, which is about 1/7 times the size of the Indian population has 3 times as many deaths. Us has 6 times as many deaths. We say that the situation is better in India because India is testing a lot now and also India has entered into this peak quite late compare to other such that the situation is prepared and new treatments are coming in. I know many people are actually worried and are blaming the government for the mismanagement, but I believe it's not true, and everything is not in the hand of the government. The percentage shows that more people are recovering, the fatality rate is also going down, from about 3.3% about 3 weeks back; it's now 2.6%. In a study done by Dr Faheem Younus form University of Maryland hospital, there is a scientific claim that the risk of dying due to COVID in the ICU has reduced by >30%. According to some studies India should have about 1.5 crore cases which are unidentified but, even if that is the case the fatality rate will further reduce to below 15% which is another good news for the people that only 3 out of 2000 are dying due to the virus. So, what I believe is we should not go with the absolute value; instead, we should now more focus on the fatality rate, not the number of daily cases. At the same time, I am very much disappointed by COVID being political tools for many. Some are denying the impact od a Novel virus, refusing facemask touting the low death rate, on the other hand, some are exaggerating fears of brain damage and severe long-term effects but what I believe is we COVID is BAD but its neither as dangerous as Polio nor as simple as a flu. We should not fear, but at the same time, we should be cautious. There are many myths around as one brought by Dr Faheem Younus in his recent tweet

Myth: COVID damages the lungs, so you’re prone to future pneumonia

Facts: Currently, there is no evidence or likelihood of non-ICU COVID patient being porn to future pneumonia.

Nearly 55 Million people recovered and are doing well so far he added.

Thus, with the passes of time, we have to be smarter and smarter and less political about this pandemic and continuously keep educating ourselves from the more relevant source.

**References:**

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[2] Guo, Y., Cao, Q., Hong, Z. et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Military Med Res 7, 11 (2020). <https://doi.org/10.1186/s40779-020-00240-0>

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