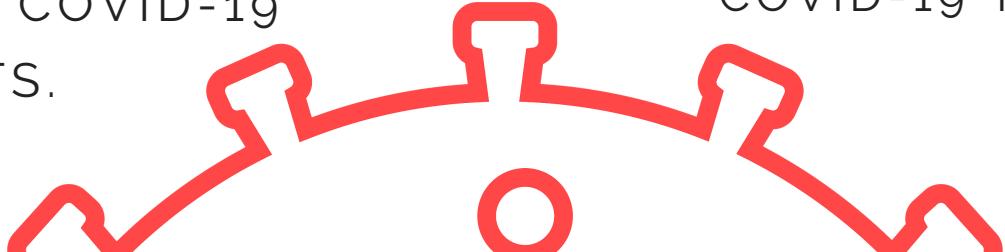


SCICATALYST

**CORONAVIRUS
VACCINE**

REPURPOSING DRUGS
TO TREAT BLOOD
CLOT IN COVID-19
PATIENTS.

IIT-DELHI RESEARCHERS
DEVELOP CHEAPEST
COVID-19 TESTING
KITS.



Vol 02

01 **mRNA-1237
VACCINE**

– Mandira,
University of Hyderabad.

02 **REPURPOSING
DRUGS TO
TREAT **BLOOD**
CLOT IN COVID-19 PATIENTS.**

– Meera,
University of Hyderabad.

03 **IIT-Delhi
Researchers
Develop cheapest
**COVID-19 Testing
Kits.****

– Krishna Chaitanya,
University of Hyderabad.

04 ****HANTA VIRUS**
NEXT PANDEMIC
OR DAMP SQUIB?**

– Roshan Samuel,
University of Hyderabad.

mRNA- 1273 VACCINE

42 days after the genome sequence of the SARS-CoV-2 virus was released, a company called **Moderna Therapeutics** began to produce the first batches of mRNA-1273, a modified mRNA vaccine for the disease COVID-19. The vaccine is already undergoing clinical trials to test its safety and efficacy. Let us explore how mRNA vaccines work, why they are more versatile, and what challenges they may present:

Firstly, how does a vaccine work?

Vaccines make use of artificially introduced inactivated pathogens or antigens to stimulate the immune system. The host immune system then produces antibodies against the antigens, thus creating “memory” of the specific pathogen so that it may mount a response and prevent infection the next time the pathogen attacks.

What types of vaccines have been developed so far?

Live Attenuated Vaccines (LAVs) introduce a weaker form of the pathogen that are asymptomatic. Though they elicit a stronger immune response compared to the other types of vaccines, they are still unsuitable for immunocompromised individuals due to the possibility of the pathogen reverting to its virulent form. Inactivated Vaccines, on the other hand, introduce pathogens that have been inactivated by heat or chemical means. The immune response they trigger is not as long-lasting as that of LAVs, but are suitable for immunocompromised individuals.

“ **RNA vaccines are faster and cheaper to produce than traditional vaccines, and are not produced using infectious elements.** ”

- University of Cambridge

614217

Infected

28238

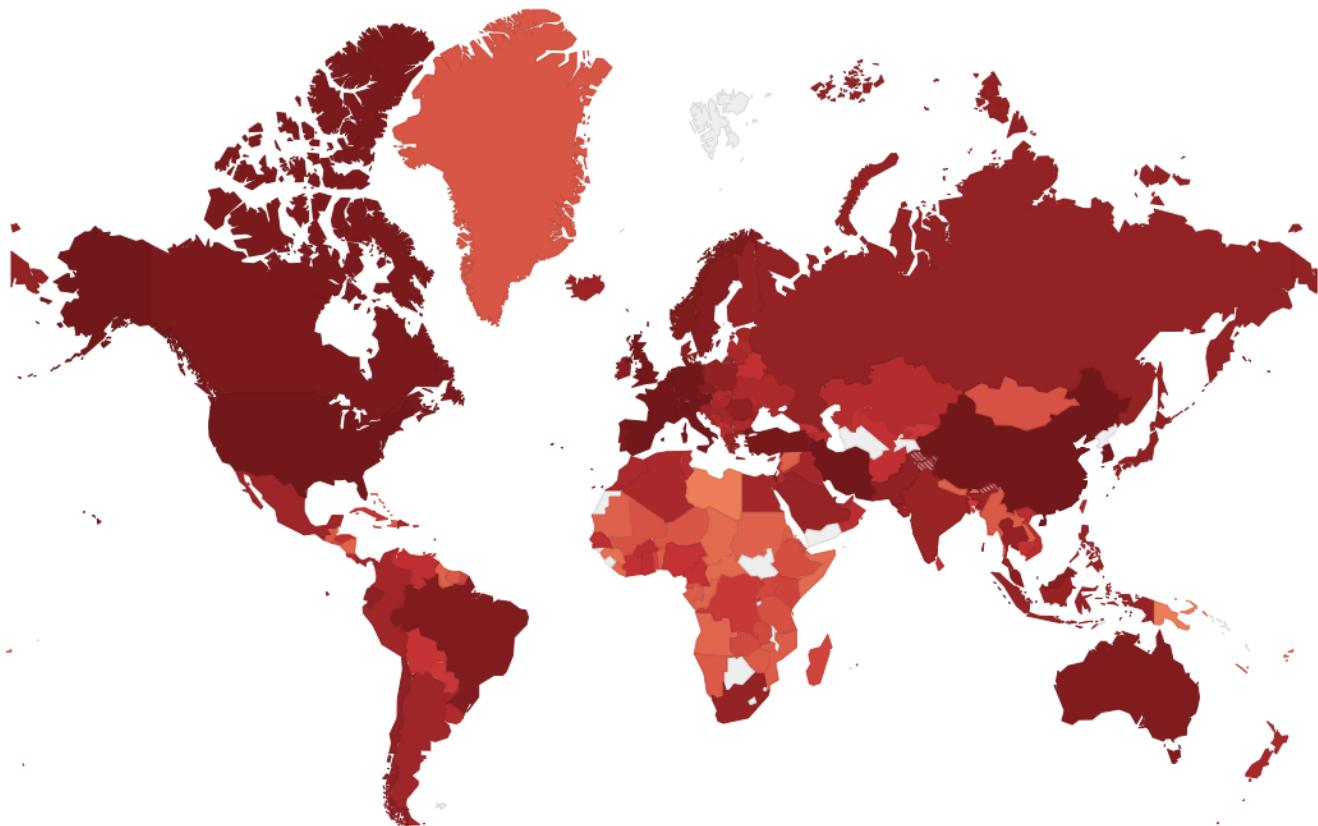
Deaths

137271

Recovered

202

Countries affected



Picture Credits: THE BASE LAB (Corona virus Statistics as of 7.00 PM, 28th MARCH, 2020).

Subunit and Peptide vaccines introduce only a particular antigen such as a carbohydrate or a protein that can be recognized by the immune system and still elicit a response. Nucleic-Acid Based Vaccines introduce DNA or RNA that encode a specific antigen. Once produced, the antigen on the surface of the particular host cell(s) is recognized by the cells of the immune system.

Why was an mRNA vaccine chosen as the candidate for COVID-19?

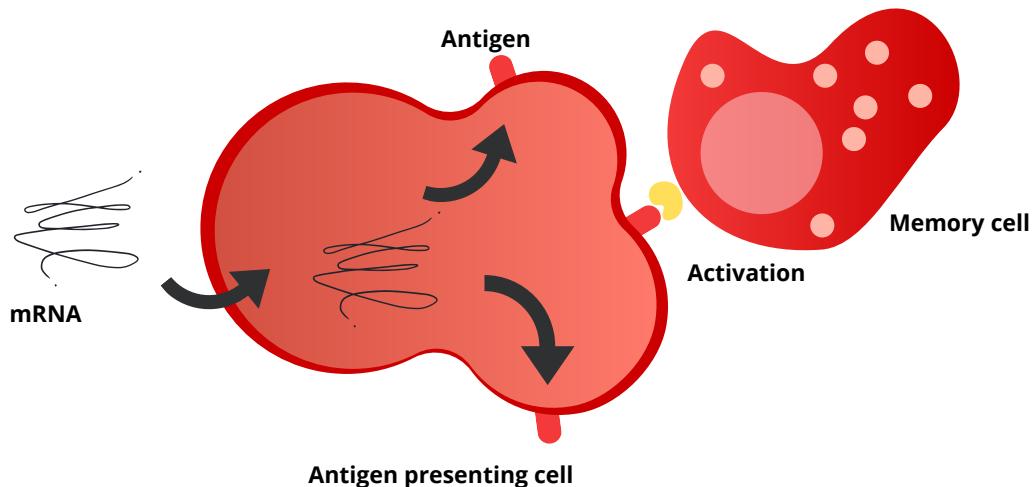
COVID-19 is a disease caused by a novel virus; one that has never infected humans before. Therefore it is unwise to administer Live Attenuated Vaccines, or even Inactivated vaccines, as we cannot afford to take the risk of how it may affect those it is administered to. Nucleic acid vaccines are much faster to develop than Sub-unit vaccines, as the nucleic acid can be easily synthesized in vitro. mRNA vaccines, in particular, are more potent and immunogenic than DNA vaccines and do not pose the potential risk of integration into the host genome.

mRNA-1273 vaccine candidate for SARS-CoV-2 , synthesized by Moderna Inc., USA, have successfully completed phase 1 trial with 45 healthy patients, by helping immune system to produce antibodies. However its unlikely to be ready before one year.

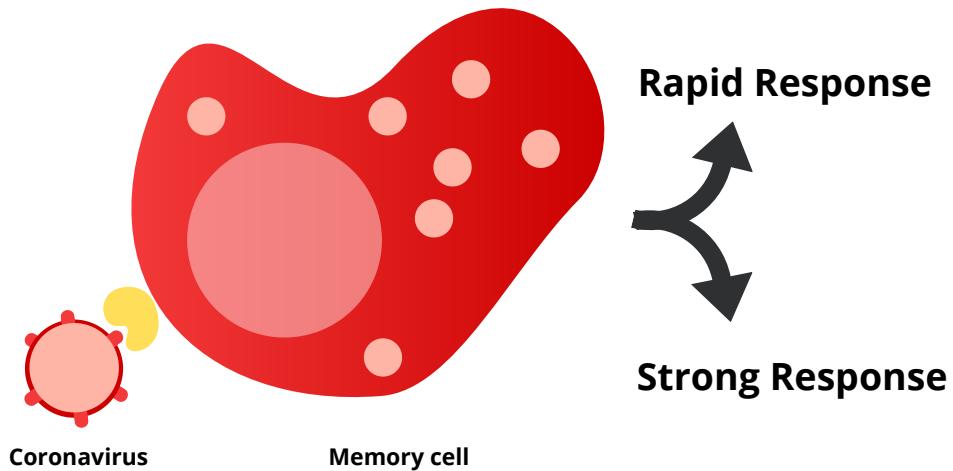
How does the mRNA vaccine work?

For the COVID-19 vaccine, the mRNA encodes a version of the SARS-CoV-2 spike (S) protein that is usually present on the surface of the virus. Once injected into the body, the mRNA enters the antigen-presenting cells. Once inside, it is translated by the cells' ribosomes, and the protein (antigen) is produced. The antigen is then presented on the outer surface of the host cell, and is recognized by immune cells, thus triggering the activation of immune cells and the production of antibodies, just like any vaccine does. Furthermore, the mRNA cannot produce active viral particles, as it lacks the genes coding for the viral structural proteins.

1. Creation of Immunological Memory (Primary Response)



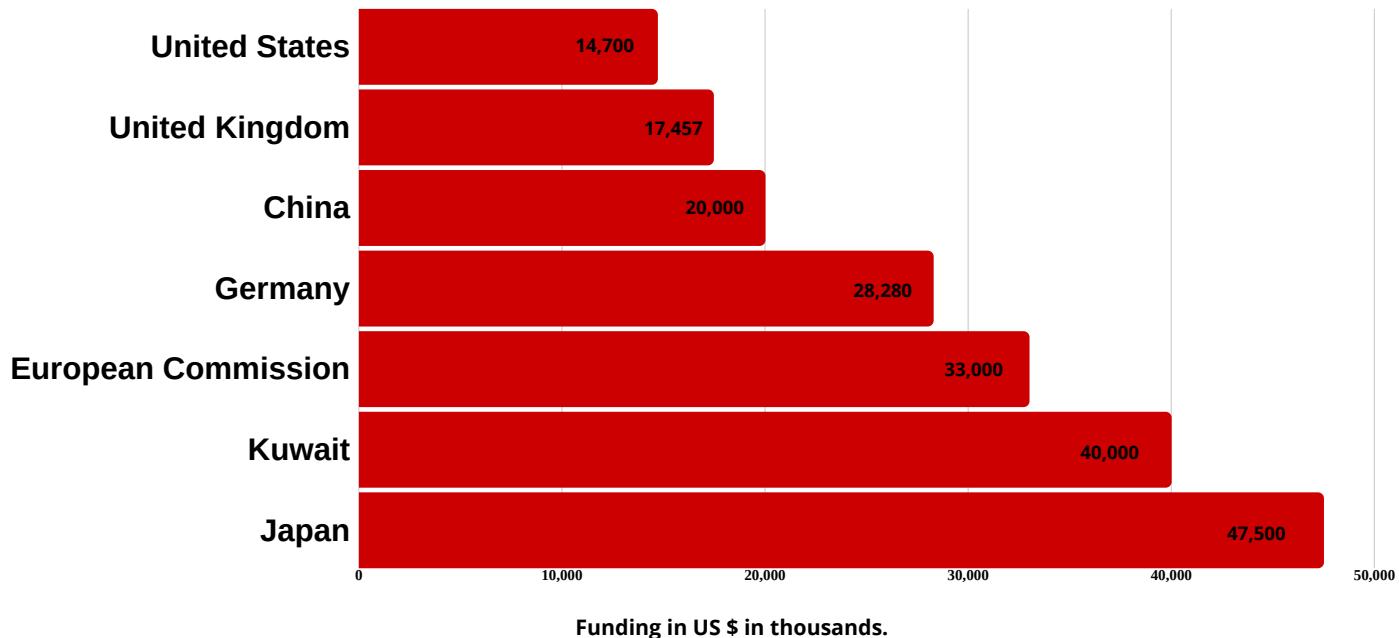
2. Secondary Response to real Pathogen.



Picture Credits: **Scicatalyst**

How is the mRNA protected from host RNases and innate immune receptors?

Incorporating modified nucleosides (such as pseudouridine) and cap structures prevent the formation of secondary structures that are recognized by translation-preventing innate immune receptors. The mRNA molecules are further encapsulated in Cationic Liposomes or are bound by Cell-Penetrating Peptides (CPPs), which prevent degradation by ribonucleases and enhance the delivery of the mRNA into the cell.



Graph: **Funding received by World Health Organization.**

Source : **WHO**

What are the challenges of mRNA vaccines?

- RNA, being of a particularly unstable nature, is highly prone to degradation and must, therefore, be stored and transported in a continuous cold-chain process. This may not be feasible in many regions across the world, thus greatly reducing its accessibility.
- The process of delivery of mRNA to the cell is still being optimized, as are the methods to improve the stability of the RNA molecules.
- The results of various human clinical trials, mRNA vaccines still present certain safety concerns, such as inflammation, auto-reactive antibodies, the persistence of the expressed antigen, and the potential toxicity of delivery components. Therefore, mRNA vaccines are all still in various clinical trial stages and none have been approved for the public as of yet.

Keeping in mind the challenges associated with such vaccines, or unprecedented roadblocks during clinical trials, it is possible that the vaccine may take much longer to be made available, or may not be approved at all. However, if the clinical trials for the mRNA-1273 vaccine are successful, we may see a COVID-19 vaccine in use by as early as 2021.

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REPURPOSING DRUGS TO TREAT **BLOOD CLOT IN** COVID-19 PATIENTS.

-MEERA KRISHNAN
UNIVERSITY OF HYDERABAD.

A very recent news from the researchers at MIT and the University of Colorado at Denver have proposed the usage of a protein now used for treating blood clots- tissue plasminogen activator- to treat the acute respiratory distress in COVID-19 patients which may help them from the risk of respiratory failure. In the current scenario, this innovation might prove useful when ventilator is not working or if a ventilator is not available. The approach is based on emerging data from China and Italy that Covid-19 patients have a profound disorder of blood clotting that is contributing to their respiratory failure.



Image Credits: Uniprot (Tissue Plasminogen Activator Protein - P00750 (TPA_HUMAN))

The drug, a protein called **tissue plasminogen activator (tPA)**, is commonly given to heart attack and stroke victims. A natural protein found in our bodies, tPA converts plasminogen to an enzyme called plasmin, which breaks down clots. If the approach works, it could potentially be scaled up very quickly. As on March 24th 2020, three hospitals in Massachusetts and Colorado are developing plans to test this approach in severely ill COVID-19 patients.

Reports are there that 5 percent of COVID-19 patients required intensive care and 2.3 percent required a ventilator in Wuhan, China. Many doctors and public health officials in the United States worry that there may not be enough ventilators for all COVID-19 patients who will need them. In China and Italy, a significant number of the patients who required a ventilator went on to die of respiratory failure, despite maximal support, indicating that there is a need for additional treatment approaches.

Animal experiments, and one human trial, have shown potential benefits of this approach in treating respiratory distress. In the human trial, all of the patients in the trial had respiratory distress so severe that they were not expected to survive, but 30 percent of them survived following treatment which is the only study using plasminogen activators to treat respiratory failure in humans to date, largely because improved ventilator strategies have been working well. This appears not to be the case for many patients with COVID-19.

COVID-19 patients suffer from inflammation-linked tissue damage, which has been seen in autopsy results from those patients and may contribute to clot formation. Colorado and MIT research team has spent the last several years studying the inflammation and abnormal bleeding that can occur in the lungs following traumatic injuries and that is why this approach is important.

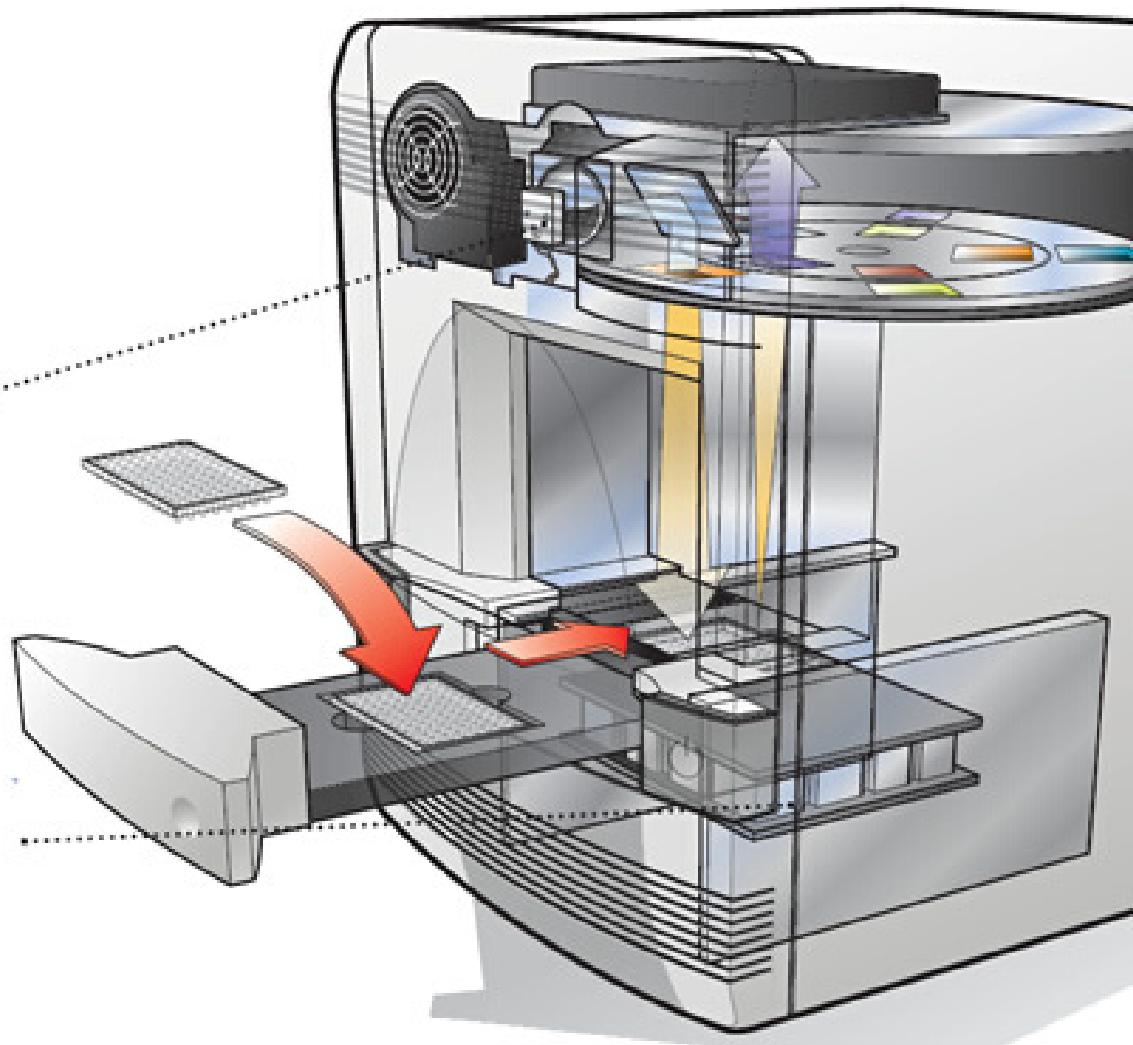
If the approach works, the next step will be to deliver the drug both intravenously and/or instill it directly into the airways. The intravenous route is currently used for stroke and heart attack patients. Their idea is to give one dose rapidly, over a two-hour period, followed by an equivalent dose given more slowly over 22 hours. Applied BioMath, a company spun out by former MIT researchers, is now working on computational models that may help to refine the dosing schedule.

Hopefully, we might get people off ventilators quicker, and we could potentially prevent people from needing to go on a ventilator if the whole innovation proves plausible.



IIT-Delhi Researchers Develops cheapest **COVID-19 Testing Kits.**

-KRISHNA CHAITANYA,
UNIVERSITY OF HYDERABAD.



At present, the SARS-CoV2 is being detected by a technique called real-time PCR. In this method, the RNA is first converted to cDNA molecules. Later, these cDNA molecules are amplified using specific primers and detected by fluorescent reporter molecules (SYBR green/probes). The kits that are now being imported from Germany follow the reporter probe-based method.

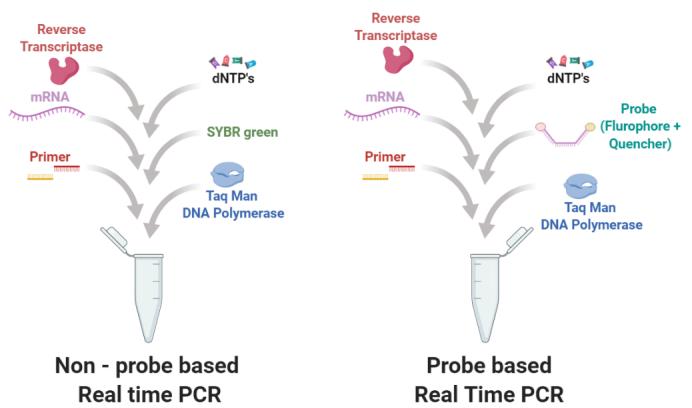


Image Credits: **Scicatalyst**

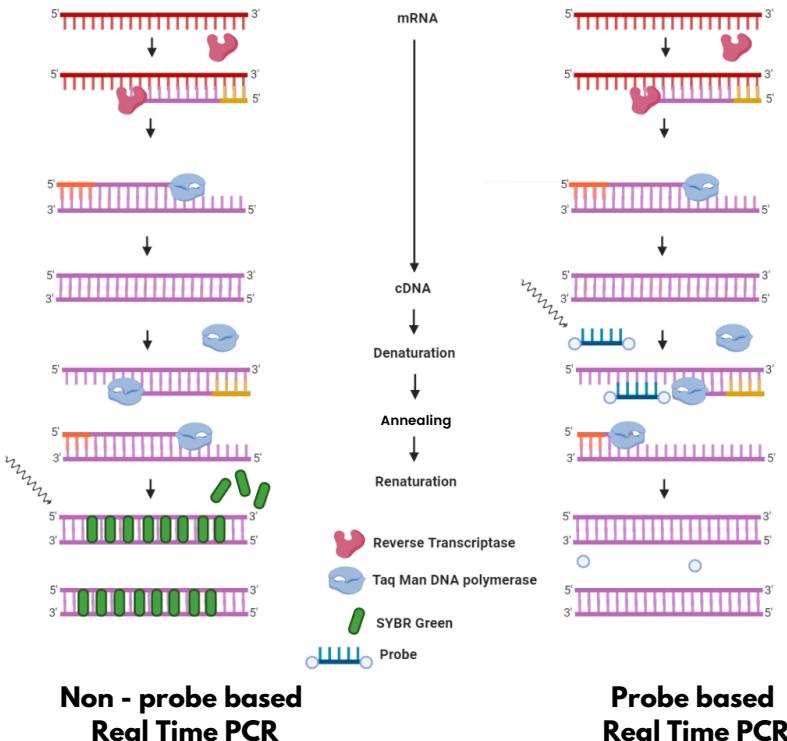


Image Credits: **Scicatalyst**

Probes are fluorescently labeled oligonucleotide molecules that bind to the targeted regions of the cDNA downstream to the primers. These reporter probes have a fluorescent molecule called fluorophore at one end and a quencher at the other. Until both the molecules are free, the probe remains non-fluorescent.

When Polymerase tries to amplify cDNA it digests probe in the process and this digestion makes the probe active and fluorescent.

The amount of fluorescence is directly proportional to the amount of cDNA in the reaction, which in turn depends upon the viral RNA in the sample. This process can also be performed without a probe. In a non-probe based method, SYBR green serves as a signaling molecule. SYBR green, a Double-stranded DNA binding dye fluoresces upon binding to the dsDNA. Therefore, the intensity of fluorescence is directly proportional to the amount of dsDNA in the reaction. Although the SYBR green method is relatively cheap it has a drawback of being nonspecific when compared to the probe-based method. To avoid this non-specificity, researchers at IIT Delhi have found a unique sequence that can only be found in the SARS-CoV2 virus. Using this unique sequence the primers have been designed accordingly. By doing this, they have not compromised the accuracy but have definitely reduced the cost per reaction in the detection process of the novel coronavirus.

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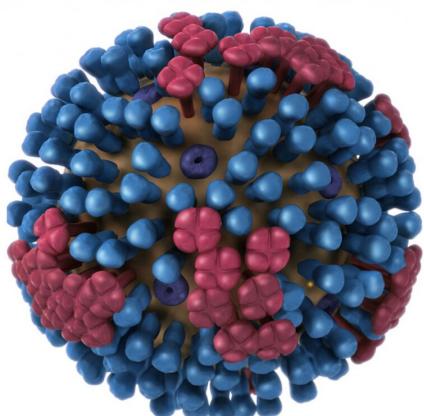
HANTAVIRUS- NEXT PANDEMIC OR DAMP SQUIB?

-ROSHAN SAMUEL,
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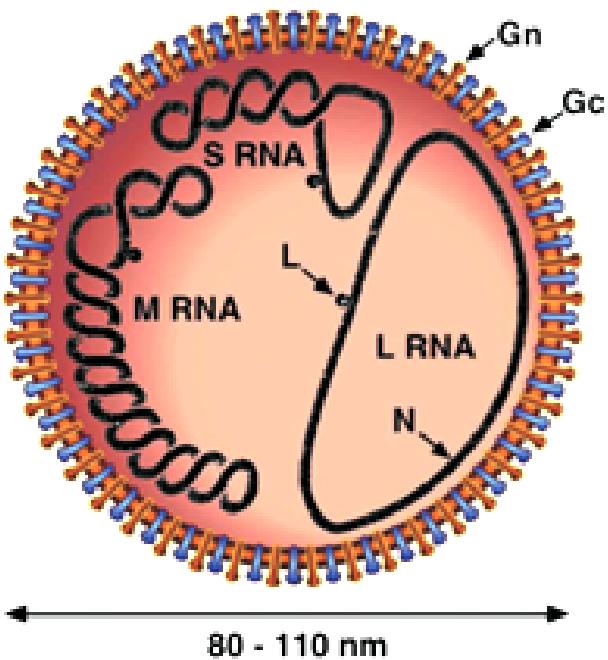
A man in China reportedly died in on his way to work on a bus, on the 23rd of March 2020. He later tested positive for Hantavirus. Reports of this led to widespread panic, with it being one of the top trends on Twitter the next day (1). However, Hantaviruses shouldn't be a cause for alarm, and the following article will give some brief information about it.

Introduction:

Hantaviruses are not new, and have been infecting humans since the 1950s. An outbreak of haemorrhagic fever with renal syndrome (HFRS) among UN troops, during the Korean war (1950-1953) led to the first Hantavirus being isolated by Lee et al. (2)



They are primarily transmitted by rodents, and are classified as 'emerging' viruses. They result in two broad disease manifestations, Nephrological- haemorrhagic fever with renal syndrome(HFRS), and pulmonary-Hantavirus pulmonary syndrome. (3) A milder form of the nephrological manifestation called nephropathia epidemica has also been reported (4).



General Characteristics (5):

- Family: Bunyaviridae
- Enveloped virus.
- 80-110 nm size.
- Negative stranded RNA virus.
- Segmented-Tripartite virus: small (S), medium (M) and large (L) segments.
- S, M, and L segments encode viral nucleoprotein (N), envelope glycoprotein, and viral RNA dependent RNA polymerase respectively.
- Reservoir hosts- Murinae rodents (includes rats, field mice, voles)

Hantavirus hemorrhagic fever with renal syndrome

The symptoms of HFRS include fever, chills nausea, followed by low blood pressure and kidney failure. HFRS has a fatality ranging from 1-15 percent.

Hantavirus pulmonary syndrome

The symptoms of HPS include fever, chills, dizziness, shortness of blood, and gradual filling of the lungs with fluid. In severe cases it is followed by respiratory failure. HPS has a fatality rate of 38 per cent.

Necrotic enteritis

The symptoms of NE include fever, chills, nausea, intense headaches and blurred vision.

Epidemiology

As seen from the map, HFRS and HPS are found in the Old World and New World respectively. The viruses that cause them are called Old World Hantaviruses and New World Hantaviruses respectively. They are caused by different strains of the virus. More than half of the reported HFRS cases come from China. Moreover, most cases in Europe are of the NE type, while cases in China and Russia are of the more lethal HFRS type. Till date, India has not reported any cases of HFRS. However, seropositive samples of clinical isolates with Hantavirus have been reported (9). The first reported outbreak of HPS in the US occurred in 1993, in the Four Corners region. While only 24 were infected, it had a mortality rate of 50 percent. Since then, localised outbreaks have been reported in many of the South American countries, including Brazil, Argentina, Uruguay and Panama. A 1993 outbreak in Brazil had a mortality of 66 percent (5).

Transmission

According to the CDC, it is primarily spread by aerosolized viruses shed in rodent faeces and urine, or by a bite from an infected rodent. Any person who comes into contact with an infected rodent is at risk of contracting the virus. Till now, there have been no cases of human to human transmission of the virus (6).

Replication of Virus

Diagnosis

Primary method of diagnosis of Hantavirus infections are primarily serological, including ELISA, neutralisation assays and immunoblotting. However, the most common test are ELISAs that detect IgG and IgM antibodies in the patient serum. Real time PCR is also a highly sensitive method used for diagnosis (3).

Treatments

There are currently no FDA approved drugs or vaccines for the treatment of Hantavirus infections. Primary treatment options are supportive in nature. However, there are several vaccine studies with some candidate vaccines in various phases of clinical trials (3). Additionally, a randomised, double blinded clinical trial in China, revealed that Ribavirin (broad spectrum antiviral) was able to significantly improve HFRS patient recovery (10).

Prevention

The best way to prevent it is to minimize or eliminate all potential contact with rodents. Recent research results show that many people who became ill with Hantavirus developed the disease after having been in frequent contact with rodents and/or their droppings around a home or a workplace. On the other hand, many people who became ill reported that they had not seen rodents or rodent droppings at all. Therefore, if you live in an area where the carrier rodents are known to live, try to keep your home or workplace clean. (6)

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