Research Diary

KID: 20200105

Repurposing of anti-malarial Nanoformulation targeting lung tissues to tackle virus-mediated inflammation/ fibrosis and acute respiratory distress

The COVID-19 outbreak has drawn the attention of researchers around the world. Currently, there aren't any clinically approved medications for the treatment of COVID-19 infection. Although chloroquine, remdesivir, etc, have exhibited a significant inhibitory effect of the viral infection, their clinical efficacy is yet to be established. The cardiotoxic effect and hepatic damage of these drugs limit their usage. Our group intends to develop an injectable hydrogel depot embedded with nanoparticles entrapping repurposed drugs. The drug entrapped nanoparticles get released from the gel matrix into the bloodstream and localize in the inflamed lungs region. The main advantage of the hydrogel is to enable sustained drug release, that eliminates the need for repeated drug administration thereby minimizing the dosage. This would significantly reduce the adverse effect, and improve the therapeutic output.

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India must prepare for the manufacture of millions of low-cost ventilators

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The following article has been submitted to Govt. of India to initiate immediate action to identify the best designs to manufacture low cost portable ventilators. We are happy that Indian Govt. has immediately formed a committee chaired by Dr. Satish Reddy, Chairman, DRDO, to come up with specifications for such ventilators, which was immediately done. This committee has called for designs that satisfy these specifications and identified the best ones, which were connected to industry for their speedy manufacturing.

There are two ways to defeat the current coronavirus India is currently in the second stage of the COVID-19 crisis. The cases till now have been mostly related to travel abroad and transmission between family members and close contacts. But if the virus spreads into the general population, which is called "community transmission" and is labelled Stage-3 of the pandemic, there will be a very rapid increase in COVID-19 cases. Experts believe that it is an eventuality that must very rigorously be prepared for even while we are in this 21-day lock-down period to prevent the virus from spreading. Apart from India, the whole world faces the same threat and many countries will inevitably be unable to control the virus in the second stage and it will progress into the general population. The 3rd stage is a period in which the number of infected people increases exponentially - their number doubling every few days until, if not stopped by some means, 60% to 80% of the population is infected - which would mean millions would be infected in any country where this happens, and in India, it would mean hundreds of millions. While it is fervently to be hoped that our prompt actions would prevent that from happening, we must prepare for that possibility. Even if we are providentially spared, we must be prepared to help others in the world who may not be so fortunate.

The COVID-19 virus has a strangely varied effect on different people it infects. Some barely show symptoms and may not even realize that they are infected, while they still pass on the virus to others who may be more seriously affected. Others show symptoms after a few days even while in the interim they are passing on the infection to others. Of those infected, it is estimated that up to 85% will have mostly mild symptoms and will recover within two weeks. Of the remaining 15% who may need hospitalization, around one-third, i.e., 5% of the total infected persons, would pose the greatest challenge. They would develop respiratory difficulties for which ventilators for assisted breathing will become necessary. It is concerning these ventilators that the rest of this article will focus.

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A Ventilator is a device designed to force breathable air into the lungs of patients who are unable to breathe for themselves. Modern ventilators are very expensive and sophisticated devices, which are generally found only in the ICUs of large hospitals. The most sophisticated ventilators, with computer controls, etc., cost around Rs. 40 lakhs, more modest foreign-made ones cost around Rs. 15 lakhs, Indian-made ones around Rs. 6 lakhs. There are around 40,000 ventilators in India right now, mostly in private hospitals.

The Indian industry has a manufacturing capacity of at most 6000 such units per month, but even the Indian-made devices use a lot of foreign-made parts whose availability would now be uncertain when every country would be maximizing their own ventilator production.

Let us now consider the requirements in the case the Covid-19 crisis reaches Stage-3 in India. Assuming a low 6% infection rate in the Indian population of 1.3 Billion, that would mean that around 80 million people would get affected. (Please note we are avoiding the more alarming 60-80% infection rate proposed by most models of a general Stage-3 epidemic. To get those figures just multiply our figures by ten). Of these 80 million, at least 5% would require ventilators, i.e., 4 million. Each of these 4 million patients would need the ventilators for around 21 days, thereby blocking that machine for at least that amount of time. Further, the machines are not portable and are found only in high-end hospitals in large cities, so patients from villages would need to be transported to these cities, which would be a logistics problem of unimaginable complexity. It is quite clear that even a mild 6% Stage-3 would overwhelm the country's capacity to a devastating degree. Even if the Indian Industry was at peak production it could manufacture only another 60,000 machines in the next 10 months, at a cost of 3600 Crores. Therefore, the total number of ventilators would barely be 1 lakh devices - at a time when millions of machines may be needed. It is clear that we cannot depend on conventional ventilators for a solution to this crisis.

Yet, even with these grim figures, there is hope. While the conventional ventilators are expensive, hard to produce, and not portable, there are small devices which are used to deliver breathing support in emergency situations that are inexpensive, easy to produce, and portable - which therefore have every quality that is required in this crisis. The most common of these devices is the bag valve mask, often called by the propriety name of Ambu Bag, that is used for resuscitation in emergency situations. Such devices are hand-powered and therefore not suitable for continuous use as a ventilator.

However, it would be easy to design a similar device powered by an electrical source, which could be a car battery, say, apart from the conventional power supply. It could be made portable, and therefore could be used in villages and areas without a power supply, and be inexpensive enough to manufacture in bulk. Our estimate of the cost is that it can be manufactured for less than Rs 5000, i.e., one-hundredth the cost of a conventional machine. The cost of manufacturing 6 million of these devices will be probably less than that of the inadequate number of 60,000 conventional machines mentioned above. The cost is so low that it can be considered a single-use device that will be given over to a single patient and never used again. It needs to be manufactured, however, on an industrial scale, in millions, within a short time of a few months.

It must be mentioned that this idea is not new. In the past few weeks, many countries have come up with this idea of manufacture of low-cost ventilators, and have even started competitions where the winning design would be declared open-source, i.e., not patented, and given free for anyone to copy if so inclined. Several designs are already available for 3-D printing, and so can be manufactured on a small scale on a 3-D printer. There have been several designs

proposed within India itself, with IIT Hyderabad having at least one proposed design. While this is reassuring, we mention that there are some caveats involved - these designs are untested and uncertified. Even if inexpensive, the designed devices should be capable of continuous and faultless 24x7 operation for at least one month - which requires very high performance both of the design and the manufactured components. Also, while 3-D printing could be part of the manufacturing solution, conventional manufacturing may be much more effective for making the millions of devices most rapidly and cost-effectively. It is on the steps required for this manufacture we will now focus.

We are proposing that the Government of India (through the DST/DRDO, or some other nodal organization) constitute a highly empowered task force, directly answerable to the highest levels of Government, which will carry out tasks mentioned in the accompanying Table-1 (which should be taken merely an indicative guide, as all the details will need to be worked out by the task-force).

Table-1: Tasks at hand and proposed timeline

S.No.	Task	Time line (weeks)
1	**a)** Create an expert committee to lay out the design parameters for low-cost ventilators, designed for inexpensive manufacturability and easy transportation that can run on alternative power supplies in addition to regular power supply. **b)** Announce these parameters and ask for design submissions with prototypes within 1 week. These may include international open-source designs, whose prototypes should be given over to specific IITs for making.	1
2	Waiting period (which should be used for publicity and soliciting design/prototypes from Indian Institutes and Industry).	2
3	**a)** Evaluate the submitted designs based on actual prototypes. (The evaluations should also continue beyond this period for durability, etc.). **b)** Choose the best few designs (allowing for a diversity in applications and manufacturing process, etc., so that our industrial capacity is fully engaged, with the different designs). **c)** The chosen designs should be simultaneously medically certified for use on human patients.	2
4	**a)** Assign manufacture of the several designs to different Public and Private industries and ask them to immediately prepare for production. The number of devices being produced will finally have to be several lakhs per week, so the manufacturing effort involved will need to be on a war-footing. **b)** Set up testing facilities for product testing and quality control and plan for their distribution. **c)** Set up training facilities all over the country for training volunteers	2
5	Total time till production starts (items 1-4 above)	**7 Weeks**
6	Start the manufacture of the devices	**Continuous**
7	Train the tens of thousands of volunteers (from all regions, cities, towns and villages) in the use of these devices. They will be needed to deliver the devices to the patients' home and train the patient's care-takers in its use.	**Continuous**

We believe that this plan is completely within the reach of our nation, but should be conducted with the utmost speed and efficiency to be useful at the time of the direst need. In the happy circumstance that the millions of devices so manufactured are not needed, i.e., if the virus is contained in Stage-2, say, India could then give these devices to other nations who may not be so fortunate. Even otherwise, due to the low costs involved, India can manufacture them beyond its own requirements for distribution to other nations. It is the least we can do for humanity in such dire circumstances.

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