

Emerging outbreaks and epidemic threats: The practicality and limitations in the development and manufacturing of treatments for Coronavirus (COVID-19)



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INTRODUCTION

The disease, named COVID-19¹⁻³ has put immense pressure on the global emergency preparedness and response. The extent of the spread and the speed of the spread of this virus in global populations, which continues to cause severe pneumonia-like symptoms in many of those infected, keeps soaring by the hour and is creating widespread fear and uncertainty in global populations and economy. Coronaviruses, named for their “crown-like” appearance due to the surface spike glycoprotein, are a large family of viruses that spread from animals to humans and include diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) in addition to COVID-19. While information (structural, genetic) regarding the coronavirus seems to be evolving, it is known that the virus can spread via human-to-human transmission before any symptoms appear.

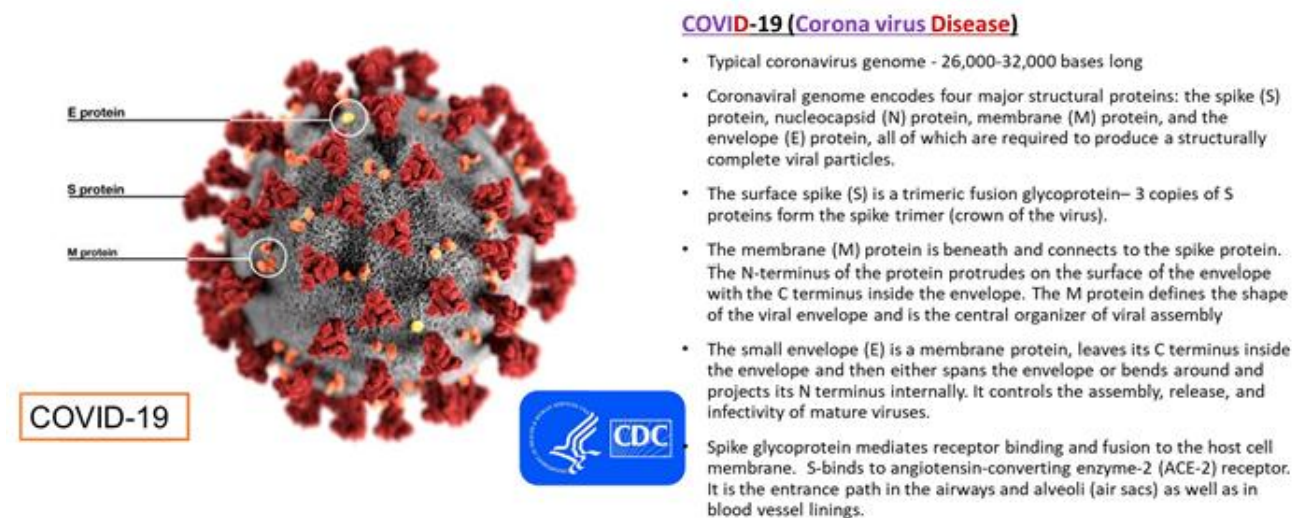
The goal of this article is not to comment on the approach or route to treat the coronavirus. While a lot of articles, blogs and posts have been published on the virology, epidemiology, the biology of disease, potential diagnosis, evaluation, and management; the perspective that is missing is the production/manufacturing and supporting studies and analysis that will be critical for meeting the demands of potential treatment for this coronavirus. While many companies have jumped into the fray with the promise of delivering an effective treatment (prevention or cure) and diagnosis, what is unclear is the timeline, resources and effort required in the production and development of a COVID-19 vaccine and the time by which a released vial, licensed product will become accessible to the global community. Most importantly, aspects related to the GMP manufacturing for different phases, fill/finish and release, the product analytics, consistency and critical quality attributes including the potency/functionality of the product,

formulation and product presentation, non-clinical evaluations, and long-term stability are big unknowns. These aspects gain significance from a stockpiling point of view, as the stability window (product expiry) and analytics over a period of time become extremely critical factors in supply availability and which will dictate how soon new batches of product doses will have to be manufactured and restocked in order to alleviate the drug shortage or the severity of a shortage.

Treatment modalities, development challenges for COVID-19^{4,5}

As Coronavirus threat continues, biopharma and academia are gearing up to test and develop vaccines and therapies. While DNA vaccines may provide a robust platform in terms of ease of manufacturing, characterization and product stability, however, its immunological and neutralization efficacy and end points will need to be established. Further, the question related with the delivery, administration and uptake of DNA vaccines using various devices and electroporation methods needs further understanding from patient compliance point of view and the fabrication scale at which these devices will have to be manufactured to meet the global challenges.

The challenges with an mRNA vaccine for COVID-19 are unique and will require understanding of the lipid nanoparticle (LNP)/delivery system, formulation, scalability, manufacturing, and batch to batch consistency of this product presentation. Most importantly, the safety profile, reactogenicity/toxicity, storage and short/long-term stability of the LNP-mRNA product and establishing regulations will have to be evaluated prior to its translation to clinic (and subsequently as a licensed product).



COVID-19 (Corona virus Disease)

- Typical coronavirus genome - 26,000-32,000 bases long
- Coronaviral genome encodes four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein, all of which are required to produce a structurally complete viral particles.
- The surface spike (S) is a trimeric fusion glycoprotein— 3 copies of S proteins form the spike trimer (crown of the virus).
- The membrane (M) protein is beneath and connects to the spike protein. The N-terminus of the protein protrudes on the surface of the envelope with the C terminus inside the envelope. The M protein defines the shape of the viral envelope and is the central organizer of viral assembly
- The small envelope (E) is a membrane protein, leaves its C terminus inside the envelope and then either spans the envelope or bends around and projects its N terminus internally. It controls the assembly, release, and infectivity of mature viruses.
- Spike glycoprotein mediates receptor binding and fusion to the host cell membrane. S-binds to angiotensin-converting enzyme-2 (ACE-2) receptor. It is the entrance path in the airways and alveoli (air sacs) as well as in blood vessel linings.

Figure 1: Snapshot of the coronavirus, COVID-19 (published from the Center for Disease Control website).

At this stage it is unclear if the product will be a one-vial vs two-vial presentation. Significantly, the logistics around the optimal vaccine dose, dosing regimen, will the final marketed vaccine be a multivalent multi-strain vaccine, what is the degree/level and quality of expression of the encoded antigen in vivo (in animals and humans) and what are the levers or metrics to indicate that the product is efficacious (efficient intracellular delivery of mRNA to the cytosol continues to pose a major hurdle, especially for mRNA administered systemically), will require consideration and are big unknowns. Currently, there are no DNA or RNA vaccines licensed for human use. Further, targeting COVID-19 can be challenging exercise because efforts to develop a vaccine against its relative, the SARS coronavirus (SARS-CoV) elicited only partial responses. The learnings obtained from this endeavor however will serve as a starting point for biotech/pharma.

Also, are there other potential approaches or disruptive technologies or platforms that

merit attention that can challenge these paradigms and which can significantly accelerate the production? The development of recombinant or subunit protein-based vaccine candidates eliciting surface spike protein specific humoral and cellular immune responses may need investigation (longer product development path compared to DNA/RNA vaccines) if sub-optimal results are obtained from DNA/RNA approaches. The longer path also indicates development of cGMP compliant cell lines and cell banks and upstream and downstream processes which usually is a laborious and time-consuming process. This can very easily get complicated by the use of adjuvants (and access to it) which will need significant formulation development and titration studies in non-clinical animal studies for induction of optimal immune response and understand the early correlates of protection and safety profile. Most importantly, are these vaccination strategies ready for prime time, mass scale production and broad-based deployment to meet the requirements of

emergency preparedness, response and health security concerns?

- Post the publication of the article, an experimental mRNA vaccine encoding the prefusion stabilized form of the Spike (S) protein which is encapsulated by a lipid nanoparticle has been developed by Moderna (mRNA-1273) and will be tested in Phase I clinical trial starting April 2020 in collaboration with US National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC).⁶ The manufacturing batch was funded by Coalition for Epidemic Preparedness Innovations (CEPI).
- Sanofi Pasteur is collaborating on a vaccine with the Biomedical Advanced Research and Development Authority (BARDA), investigating an advanced preclinical SARS vaccine candidate that it had worked on during the 2002-2003 severe acute respiratory syndrome (SARS outbreak) which is caused by a coronavirus that has some structural similarities to the COVID-19 virus.
- Novavax had developed a vaccine for MERS in 2013. The COVID-19 causing virus has similarities to MERS and SARS. Novavax is using its proprietary recombinant protein nanoparticle technology platform to generate antigens derived from the coronavirus spike (S) protein. The vaccine formulation will utilize its proprietary saponin-based Matrix-M™ adjuvant with its COVID-19 vaccine candidate to enhance immune responses.
- Inovio and Wistar Institute, funded by CEPI, and in collaboration with Beijing Advaccine Biotechnology is developing a plasmid DNA based vaccine (INO-4800) expressing the viral protein. It is currently

bein tested in early preclinical animal studies (mice).

- The German biotech CureVac, again under the funding of CEPI, is developing an LNP formulated/encapsulated mRNA vaccine currently being tested preclinically.

Examining the pressures upon the current contract manufacturing model

Significant Federal and non-profit investments have been made in the USA (Biomedical Advanced Research and Development Authority (BARDA), National Institutes of Health (NIH), Coalition for Emergency Preparedness Initiative (CEPI), Bill and Melinda Gates Foundation (BMGF)) at various levels with multiple international biotech/pharma players (Moderna, Janssen, Inovio, Sanofi) to accelerate and fund priority research. FDA may also be able to grant fast track clinical evaluation and emergency use authorizations for some of these product candidates. While there is consensus that flexibility and scalability are key in rapid response to an emerging infectious disease threat, however, at a minimum, the FDA will still require a detailed understanding of the primary endpoints in healthy volunteers (Phase I trial comprising of testing different investigational therapies against a placebo) related to adverse events (AEs), safety, quality and some basic immunogenicity and neutralization parameters (secondary endpoints) even before moving into the next phase of development and clinical testing in infected volunteers/populations. Most significantly, the uncertainty related to the unpredictability and fatality of the virus (more information seems to be forthcoming at a rapid pace) and the subsequent market size, will weigh heavily on big pharma decision

prior to foraying into this space. As such, I anticipate Governments and non-governmental organizations will be the key (or only) investors and likely buyers in medical countermeasure (drugs, vaccines, antibodies etc.) and pandemic preparedness. At some point, given the investments made, it will be prudent for the healthcare agencies to push for a head to head comparison between the different investigational treatments (vaccines/therapeutic candidates) to understand the effectiveness and safety of the treatments and technologies.

The pressures of the current contract manufacturing outsourcing model, their surge capacities and phase-appropriate readiness (and viability) will have to be examined carefully by funders and policy makers. For example, (i) The burden of impact of this outbreak on GMP manufacturing facilities, fill/finish sites/capacities and readiness for the different vaccine types/classes, short term production bottle necks and capacities across the globe which are already committed to their clientele, especially in recent times to high demand for cell and gene therapy products, on raw material and reagent availability, and the appropriate process and manufacturing expertise at these sites, have not received much attention and will need critical consideration. (ii) Product manufacturers may not have the necessary plans to assess and address vulnerabilities in their manufacturing supply chain. (iii) Currently, majority of the biotech players, possibly with the exception of big pharma, do not have the production facilities to make mass amounts of commercial product in bulk. Majority of the contract manufacturing

organizations (CMOs) operate at full capacity and depending on their size may not have the prerequisite surge capacities to tackle emergency preparedness and onsite fill-finish capabilities/operations triggering a bottleneck in clinical development due to the limited number of appropriate sites and the volume of vials required for Phase 2 and 3 trials. (iv) Critical to any biologics development program is the oversight and due diligence required for production Technology Transfer including methods, processes and unit operations, assays and appropriate documentation to develop a viable, scalable, reproducible and consistent process and that product quality is consistent and in compliance with the regulatory bodies. Given the global scale of this virus spread, public-private-international partnerships may have to be incentivized for local production capacities and policies may have to be put in place for production technology transfer. Most importantly, as one plans to transfer these activities to new production sites, are the proposed sites a good manufacturing fit for the activities to be conducted will require careful verification.

One approach that has potential to reduce the time and cost is screening of existing drugs or compounds, also known as drug repurposing or repositioning,⁷ consisting of therapeutic nucleoside anti-viral inhibitors/drug analogues targeting the RNA-dependent RNA polymerase. This could be an attractive option for the development of coronavirus treatment and could allow for a faster regulatory approval pathway through the 505(b)(2) application. As per WHO, an existing antiviral drug, remdesivir, is showing signs of helping to treat this new coronavirus.

However, Remdesivir is an experimental drug that was tested in humans to treat the Ebola virus, though studies found it was ineffective for that. Remdesivir (200 mcg and 100 mcg dose) is currently being evaluated in a clinical trial in the USA. Another experimental antiviral called galidesivir developed by BioCryst Pharmaceuticals for treating Ebola is active against coronaviruses. It has already passed safety tests in people with manufacturing unit operations already in place and can offer a quick route to antiviral treatment for COVID-19. Combination or cocktail of such antivirals can offer an alternative approach if they can improve bioavailability of the targeted antivirals and manage the side effects triggered by these antivirals. AI based strategies, molecular data bases and data mining can facilitate development of new strategies for high throughput screening (in vitro and in vivo) and drug repositioning to treat SARS-CoV-2 infections

(On Feb 27, the FDA released a statement indicating that the FDA is closely monitoring the supply chain with the expectation that the COVID-19 outbreak would likely impact the medical product supply chain, including potential disruptions to supply or shortages of critical medical products in the U.S. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-supply-chain-update>)

Realistic development timelines and opportunities

I agree that speed is crucial to saving lives and reducing further spread of the virus and while there could be learnings and technologies utilized or adapted from prior such outbreaks (SARS/MERS/Ebola), in my

personal opinion, just to manage expectations, the challenges of the GMP manufacturing, the scale and capacities, analytics, product quality and stability will need to be addressed, are still open ended and will define how quickly authorities and different stakeholders can pivot in addressing this global threat. Importantly, the nonclinical and clinical development timelines will also influence the development activities and timelines. Not considered in the article here is the downstream distribution and supply chain vulnerabilities that will impact the deployment. Additionally, continued and iterative research will be required to better understand the correlates of protection, appropriate animal models and, of course, the discovery of new antigens that can protect against these emerging pathogens. I believe that such information discussed in this article should be presented in order to avoid public misperceptions (actual readiness vs. the possibility of technologies and products to tackle the challenge). The following comparison should provide a realistic perspective:

- Ebola outbreak 2013-14, approved vaccine genetically engineered rVSV-ZEBOV in 2019. 2 experimental anti-viral treatments REGN-EB3 and mAb-114 are available.
- Zika outbreak 2014. As of April 2019, no vaccines have been approved for clinical use, however a number of vaccines are currently in clinical trials. No specific antiviral treatment for the Zika virus exists.

While prevention of the infection remains an ultimate goal, very little seems to be known about the disease and the development of vaccine that will be tested in large clinical trials and subsequently be licensed for use in large population in the near future is

therefore remote. Just going by these trends and timelines, it may well be plausible that a coronavirus treatment (in particularly preventative vaccine) may very well follow a similar timeline and therefore public expectations should be managed and tempered.

More information seems to be evolving. The recent identification of 2 mAbs (Vir Bio) for antibody-based treatments that might potentially neutralize coronaviruses and the experimental antiviral drug (remdesivir) treatment from Gilead may throw some new light on the potential routes for treatments and management of the disease. The small molecule, Chloroquine phosphate, an antimalarial drug, with curative effects has also shown strong in vitro and in vivo antiviral activities against human coronavirus associated pneumonia (apparent efficacy & acceptable safety as per Chinese officials). It is currently being evaluated in the new treatment guidelines in China and will be used in wider clinical trials against COVID-19/SARS-CoV2.

From India's perspective, as per the reports, though no severe cases have been detected so far, nearly 450 people are currently under observation, most of them in Kerala. However, this situation can change quickly. In absence of suitable drugs and vaccines, strict monitoring and preventive measures, screening, testing, quarantining and surveillance is a norm. Further managing the pain by pain killers, body salts and treatment with antibiotics remains the first line of defense for intervention, patient management and for mitigating the risks. However, India's biotech and vaccine manufacturers could play a more proactive

role in the development efforts. Serum Institute of India has partnered with Codagenix (American Biotech company), seems to be the only Indian vaccine manufacturer which has committed to tackle this global outbreak. As today's supply chains become more global in their outreach and more complex than they were even a decade ago, India's manufacturers/developers and innovators cannot be bystanders while the rest of the world develops vaccines, therapeutic solutions and processes/platforms/technologies to tackle the COVID-19 and other outbreaks. I believe there is an opportunity to be seized and to leverage production infrastructure and capacities with Indian manufacturers and to tap into the knowledge base and resources to tackle this outbreak for global good. The Indian government and policy makers (DBT, CSIR and others) together with the vaccine and biotech industry should proactively show some initiative, vision and courage to actively participate, partner and join forces with the global community and vaccine/therapeutic developers in innovating and developing real world solutions and processes for such epidemics and outbreaks (or be left aside). While India has been slow to react on the discovery and development front, contributing in areas of biomanufacturing, drug/therapeutic discovery, capacity-building and creation of global supply chains remains a significant opportunity to showcase its biotechnology merit and bio-manufacturing hubs and create goodwill.

Infectious diseases will continue to emerge/re-emerge and will reshape emergency preparedness response and countermeasures in the coming years, the

key points discussed in this article will remain critical for defining the global development strategies (with a realistic timeframe in mind) targeting COVID-19/SARS-CoV2 for enhancing national and global health security.

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- 3 Coronavirus Disease 2019 (COVID-19) | Food and Drug Administration <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/coronavirus-disease-2019-covid-19>
- 4 <https://www.biocentury.com/article/304456> | Listed in this link are the companies and academic groups that have announced programs to develop new vaccines for COVID-19 (2019-nCoV) acute respiratory disease as of Feb 14. The majority of the vaccine programs are being developed by China-based groups. Ongoing programs include live attenuated, inactivated, protein-based, viral vector and DNA and RNA vaccines. Source: China Association for Vaccines, group websites
- 5 <https://blog.bisresearch.com/coronavirus-outbreak-what-type-of-developments-in-drugs-and-technologies-are-being-carried-out> | The following link provides insights on the different development modalities being developed in the market in terms of diagnostics, drugs and technologies.
- 6 Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) to Treat Novel Coronavirus" (NCT04283461), was disclosed by NIAID today on ClinicalTrials.gov. The open-label, dose-ranging trial is designed to assess the safety, reactogenicity and immunogenicity of Moderna's mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated mRNA vaccine against the novel coronavirus encoding for a prefusion stabilized form of the Spike (S) protein, which was designed by Moderna in collaboration with investigators at the NIAID Vaccine Research Center (VRC).
- 7 Therapeutic option for repurposing | https://www.nature.com/articles/d41573-020-00016-0?utm_source=facebook&utm_medium=social&utm_content=organic&utm_campaign=NGMT_USG_JC01_GL_NRJournals