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Vaccine development series

Virus mutations and time: the race for a vaccine

Part two

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Vaccine development before CV-19

Under normal circumstances, vaccine development takes about as long as therapeutic development (10 -15 years); the one caveat to that is if the vaccine platform has been used before and/or the disease has some similarities to another infection, which may shorten the timeline. However in some cases, despite decades of work, no vaccine exists for certain diseases, as is the case for Respiratory Syncytial Virus, RSV.

Back in 2017, in the aftermath of the Ebola epidemic in West Africa (2014-15), an organisation was set up to tackle the lack of scientific progress in managing epidemics. The coalition for epidemic preparedness innovation **(CEPI)** was established with the mission to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines for people during outbreaks. CEPI is working to raise the estimated $2 billion it will take to develop a vaccine for CV-19 in the next 12-18 months and this money is being put towards funding vaccine development.

Planning for the unknown – Disease X

One of the biggest issues facing vaccine research is planning for infectious disease – developing a vaccine for something that does not exist (a situation that we now face with CV-19) or something that mutates (seasonal flu virus). It is clear that we need a better system for developing vaccines at a quicker pace. The Jenner Institute vaccination team has planned for Disease X, a placeholder name that represents a hypothetical, unknown pathogen. By doing so, the hope is they can now move more quickly towards a viable vaccine but we don't yet know what the impact is from Disease X planning.

The following link is the latest update on the progress of the vaccine development from Disease X planning.

Oxford University's Covid-19 vaccine shows promise in animal study

The scale and time problem with CV-19

Assume that a vaccine gets through initial human trials with positive effects, the next challenge is scale up of manufacture. Even the most prescribed or consumer-used medicine is not needed at the scale and urgency that a CV-19 vaccine is needed. No doubt any vaccine will go to those on the frontline first, then to our most vulnerable (which in the case of a global pandemic is millions of people worldwide), before the rest of us are vaccinated.

In addition, CV-19 may have already mutated into 2 strains; one is more aggressive than the other and it is possible to be infected by both. This is quite common in RNA viruses as they adapt to their new host – they become better at replication and enabling human-to-human infection. Vaccines will have to accommodate this.

CV-19 – a beta coronavirus

Coronaviruses are common human pathogens; two types of alpha and two types of betacoronaviruses circulate in humans and cause the common cold. Other more pathogenic coronaviruses (all of the beta variety) for humans include SARS-CoV-1, the middle eastern respiratory syndrome coronavirus (MERS-CoV) and now SARS-CoV-2.

As CV-19 emerged in Wuhan, China, it was quickly identified as a betacoronavirus with a genomic sequence closely linked to severe acute respiratory syndrome (SARS). Hence its official name SARS-CoV-2. This virus uses Angiotensin-converting enzyme 2 (ACE2) as a receptor in a number of species including humans (more on that later).

Therapeutic options

There are a handful of therapeutics undergoing clinical trials. Remdesivir* works against coronaviruses similar to CV-19 in animal models and was also tested for treatment of ebola virus infections in humans. This provides us with useful safety data for this potential treatment, which should speed up the clinical testing. In addition, a combination of HIV inhibitors, lopinavir and ritonavir are also being tested in clinical trials.

* Remdesivir was granted an emergency use authorisation on 1st May by the FDA **https://www.fda.gov/media/137564/download**

Phase IIb trial to study hydroxychloroquine and azithromycin as COVID-19 treatment launched

In clinical practice, many drugs that are already licensed are being used as potential treatments for CV-19. This is all experimental (there is only anecdotal evidence of therapeutic benefit); there are also questions about drug interactions – something that would routinely be explored in a longer approach to clinical development on new therapies, but is now being accelerated under current circumstances.

There are therapies in play that treat the result of the infection, one of the most serious being a cytokine storm. CV-19 seems to trigger this; the immune system is overstimulated and the inflammatory response gets out of control, which can result in death. Treatments focus on blocking Interleukin-6 and are usually used in autoimmune diseases such as Rheumatoid Arthritis.

There are a number of other therapeutic options including convalescent serum (plasma therapy), as mentioned in the previous **post**.

If any of these treatments show promise in CV-19, they could be widely used within a short time frame. Compassionate use of these drugs has already been reported.

A note on ACE2: these receptors are found on many cell types and usually regulate blood pressure. Its presence marks cells as vulnerable. The virus uses this receptor to enter a cell and cause havoc (replicate, damage etc). If the first line of defence fails to keep the virus at bay, it heads deep into the lungs where there is a mix of cells expressing ACE2. Many organs in our body become vulnerable to CV-19 due to their expression of ACE2: the heart, blood vessels, the kidneys and the brain. Pre-existing conditions that may already impact the function of key physiology lay us open to more severe infections.

Betacoronavirus vaccine design

The genomic sequence of SARS-CoV-2 was made swiftly available by Chinese researchers providing a starting point for vaccine development. From work on SARS-CoV-1 and MERS-CoV, scientists also know the ideal target for a vaccine – an antigen that can be used in advanced vaccine platforms.

As with other viruses, infection with a human coronavirus does not always induce long-lived antibody responses; re-infection of an individual with the same virus is possible after an extended period of time. An effective vaccine will need to overcome these issues to protect the general population in a scenario where the virus may cause recurrent seasonal epidemics.

Since there are currently no coronavirus vaccines on the market and no large-scale manufacturing capacity for these vaccines exists, we are starting from scratch. The technologies (production platforms, vectors etc.) are also new and need to be tested thoroughly for safety. This is unlike seasonal flu where the platforms are in place and a relatively quick process of changing strains without changing process and release criteria can be followed.

A vaccine may come too late for the first wave of the pandemic, but should be available for subsequent waves or in a post-pandemic scenario where CV-19 circulates as a seasonal virus (we don't know for sure that it will yet).

If nothing else, lessons will be learned – from population containment to therapeutic options to vaccine development, we have to be more responsive to something that will undoubtedly happen again.

For now, take comfort from the evidence that the pharma world has been galvanised, funding has been released and some really clever people are working night and day to find a solution so we can get back to each other in whatever form that takes.

Stay safe.

Sources

Pharmaceutical Technology —

Gilead's remdesivir prevents Covid-19 progression in preclinical study

Live Science —

Drug used to treat Ebola may help COVID-19 patients, preliminary results suggest

Symphony Health —

COVID-19 Weekly Trend Insights

Report

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