HAS THE COVID-19 PANDEMIC CHANGED VACCINE DEVELOPMENT FOREVER?

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Since 2020, the impact of the COVID-19 pandemic reverberated around the globe and has been felt throughout our populations, professions, industries and markets. In the face of spiralling case numbers and widespread disruption, international organisations and domestic governments worked in close collaboration to formulate a response intended to curb the spread of the disease, ease pressure on national healthcare systems and limit fatalities. Viewed as an essential component of any global strategy, the hunt for an effective vaccine was soon underway – never before has the combined attention of science been so acutely focused.

You may have seen articles discussing the progress of clinical trials and the efficacy of approved COVID-19 vaccines within the media, often comparing the merits and drawbacks of multiple vaccines. Here, we aim to provide an overview of the expectations of vaccines against COVID-19, how they are being assessed in abbreviated clinical trials and how the availability of multiple, efficacious vaccines will be crucial in bringing the pandemic to an end.

What is expected of a vaccine?

The expectation of a prophylactic vaccine is long-term disease prevention, or even eradication: through vaccination, the occurrence of a potentially life-threatening infectious disease can be avoided by providing immunity to specific foreign pathogens. As a result of universal mass immunisation programmes, cases of some diseases, such as polio, are now non-existent or, indeed, are rare in many countries.[1] As the worldwide immunisation programme against smallpox has shown, widespread immunity through vaccination can lead to the global eradication of a disease.[2] The expectations placed upon vaccines are huge.

How long does it take to approve a vaccine?

In addition to the 12–36 months required to design and manufacture a vaccine,[3] it can take between 10 and 15 years to fully assess a candidate vaccine within clinical trials and acquire authorisation.[4] Such a long period of testing is necessary to determine whether the vaccine can induce an immune response within individuals in a safe and tolerable manner. This is assessed during a series of lengthy (and essential) clinical trials: Phase I trials, which are conducted with 10–20 healthy participants who are used to assess safety, determine optimal dosing strategies and investigate how a vaccine may interact with, and be absorbed by, the body; Phase II trials, which are carried out with a larger number of participants (tens to hundreds of individuals) to investigate efficacy and safety; Phase III trials, which involve even greater numbers of participants (hundreds to thousands of individuals) who are used to deduce the therapeutic efficacy and safety of a vaccine; and, finally, Phase IV trials, which take place post-authorisation, to monitor long-term effectiveness and safety.[5]

The majority of vaccines in development fail to reach the market for a number of reasons, but principally, it is due to a lack of therapeutic efficacy, the emergence of a severe side effect or the withdrawal of funding – clinical trials are very expensive, with costs of up to US$2 billion.[6]

How has a COVID-19 vaccine been developed so quickly?

The very nature of the COVID-19 pandemic – a life-threatening disease that spread rapidly across the globe – called for an accelerated vaccination strategy that aimed to achieve widespread protection for populations in the shortest possible time. The volume of bureaucracy and red tape usually associated with clinical trials (often due to the strictness of regulations, guidelines and approval systems) risked causing a major delay and, as such, needed to be streamlined to ensure the expedited development and approval of much-needed COVID-19 vaccines.[7]

Nevertheless, it was absolutely imperative to achieve this while still maintaining high standards of assessments in terms of efficacy, safety and tolerability of candidate vaccines. With multiple governments and other organisations collectively pledging billions in funding to support research into COVID-19, vaccine manufacturers have been emboldened to take risks they previously wouldn't have considered,[8] such as the accelerated development of mRNA vaccines for use in humans[9] and the rapid adaption of the pre-existing ChAdOx1 vaccine template for use within the Oxford/AstraZeneca vaccine.[10]

Efficacy and effectiveness – similar, but not the same

While a large portion of a clinical trial is spent establishing whether the candidate vaccine acts against the disease (i.e. determining its **efficacy**), it remains unclear how **effective** it will be in preventing widespread disease until it is used in the real world.

Vaccine efficacy determines whether inoculation with a vaccine, under optimal care settings, reduces the incidence of disease across a small number of individuals within a clinical trial (compared with a group of unvaccinated individuals). Efficacy is measured by the number of individuals demonstrating an immune response, often presented as a percentage value.

Vaccine effectiveness assesses whether a vaccine is capable of preventing disease within the general population, in real-world settings – unfortunately, vaccine uptake is never 100%, and optimal care settings are not always possible.

Thanks to unprecedented global cooperation in research, and the granting of multiple 'emergency-use' approvals, long-established 10- to 15-year timelines for clinical trials have been shattered, with trials for COVID-19 vaccines taking less than 12 months.[11] As a result, at the time of writing, nine COVID-19 vaccines have received regulatory approval in different markets, while a further 58 vaccines are currently in development.[12]

While this is good news, the brevity of the clinical trials for multiple COVID-19 vaccines has raised several questions regarding the efficacy, safety, tolerability and long-term effects of these products. Typically, participants in a vaccine clinical trial are 'blinded' as to whether they receive a candidate vaccine or a placebo – let's call them 'Group V' and 'Group P', respectively. Once the efficacy, safety and tolerability of the vaccine have been demonstrated, those in Group P may be offered the vaccine; in the case of COVID-19 vaccines, those in Group P are highly likely to accept this offer.[11] However, this can make the deduction of long-term effects extremely challenging, as Group P provide the most suitable comparison against Group V. By receiving the vaccine, the strength of this comparison is weakened.[11]

Another question relates to effectiveness within individuals with underlying health conditions (one of the most vulnerable populations to suffer complications from COVID-19) – are the current trials of COVID-19 vaccines adequately assessing the efficacy, safety and tolerability in these vulnerable populations? Ultimately, it is imperative that the findings from ongoing clinical trials, and subsequent real-world use, are disseminated widely and appropriately to instil confidence within the general public that these vaccines are effective in preventing disease and do so without causing any unexpected adverse events.

Will the COVID-19 pandemic change clinical trials forever?

The international response to the COVID-19 pandemic, and the development and approval of vaccines in such a short time frame, raises another major question – what about other diseases, such as dengue fever, malaria or HIV? Has the speedy development and approval of COVID-19 vaccines sufficiently demonstrated that vaccine clinical trials could be fundamentally changed to expedite the process without compromising the end product?

Standard clinical trials were established to investigate new treatments in a controlled, stepwise manner. As outlined above, Phase I–IV trials investigate how well a candidate treatment works, how it interacts with the body and whether it has an acceptable safety and tolerability profile. Trials are often sculpted by multiple practicalities, including, but not limited to, the availability of volunteers, funding and practical costs, and the availability of other pre-existing and already approved treatments.

The development of COVID-19 vaccines reveal how future clinical trials may be optimised – a reduction in bureaucratic burden, optimisation of study protocols, increased use of digital technology to collect data, streamlining of mandatory clinic visits and the identification of clinically relevant endpoints that can easily be reported by the patient (facilitating decentralisation of trials) – all without jeopardising safety.[13] A joint statement from multiple European medical societies and patient advocacy groups has already highlighted how the rewriting of clinical trial guidance is necessary to pave the way for more rapid, affordable, less bureaucratic, patient-centred clinical trials.[7]

Interestingly, this is not the first time we have seen accelerated vaccine development and approval. During 2014/2015, thanks to a major collaboration between the World Health Organization (WHO), Doctors Without Borders and the pharmaceutical industry, the rVSV-ZEBOV Ebola vaccine successfully completed Phase I–III clinical trials in just 12 months.[14] In November 2020, the WHO provided emergency approval for a vaccine against a circulating vaccine-derived poliovirus (cVDPV) present in the Southern Hemisphere, in spite of the fact that the vaccine had not yet entered Phase III trials. Similar to the COVID-19 pandemic response, albeit on a smaller scale, this achievement was driven by an urgent need to respond to an epidemic in Western Africa. However, unlike COVID-19 vaccines, the cVDPV vaccine had been in development for 10 years prior to its emergency approval.[11]

> *"Waiting for the 'very best' vaccine, which may not come for some time, bearing in mind some future vaccines in development may yet fail, will cost lives."*[15]
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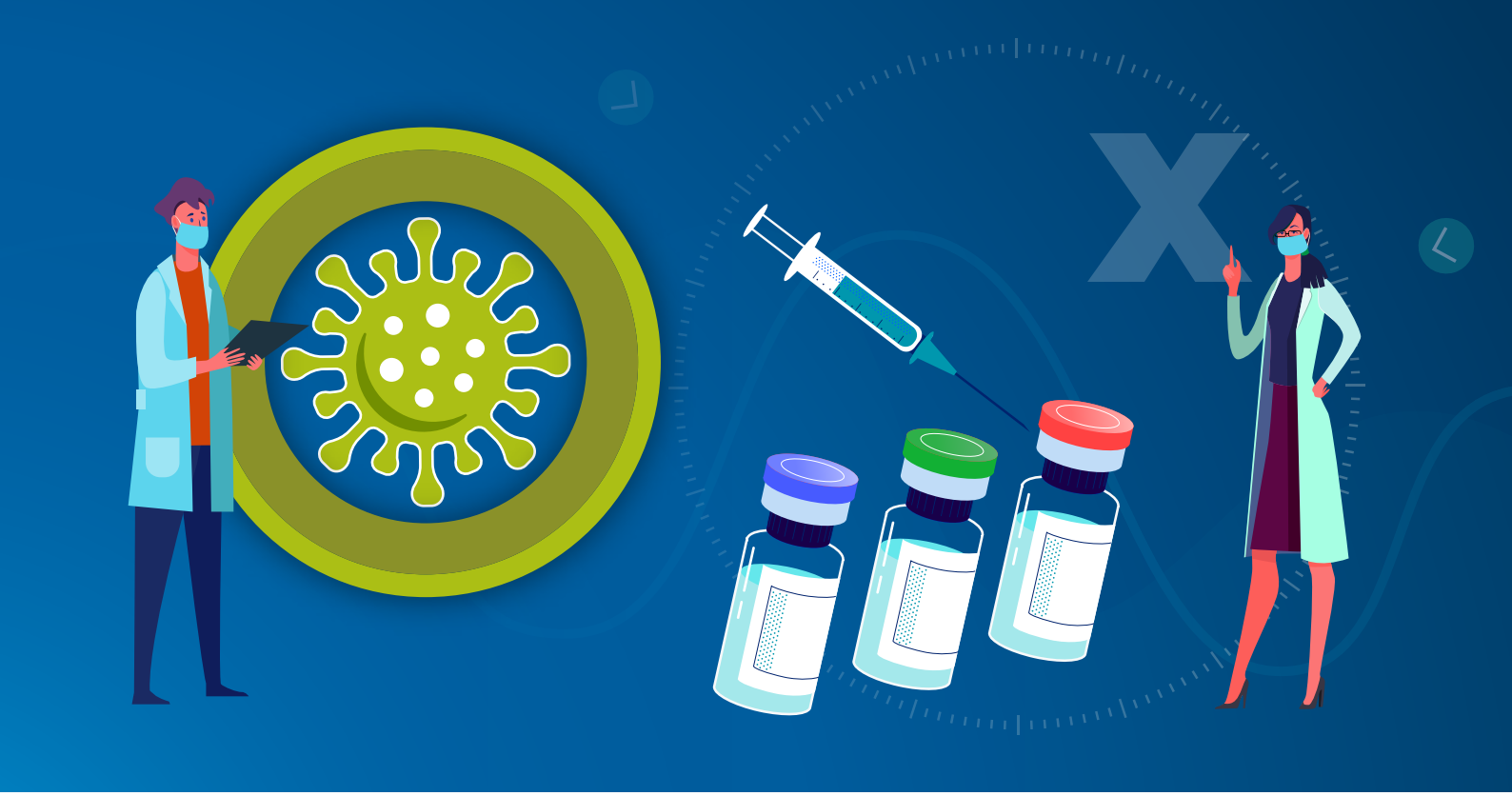
> *Professor Jonathan Van-Tam, The Guardian, 18 November 2020*

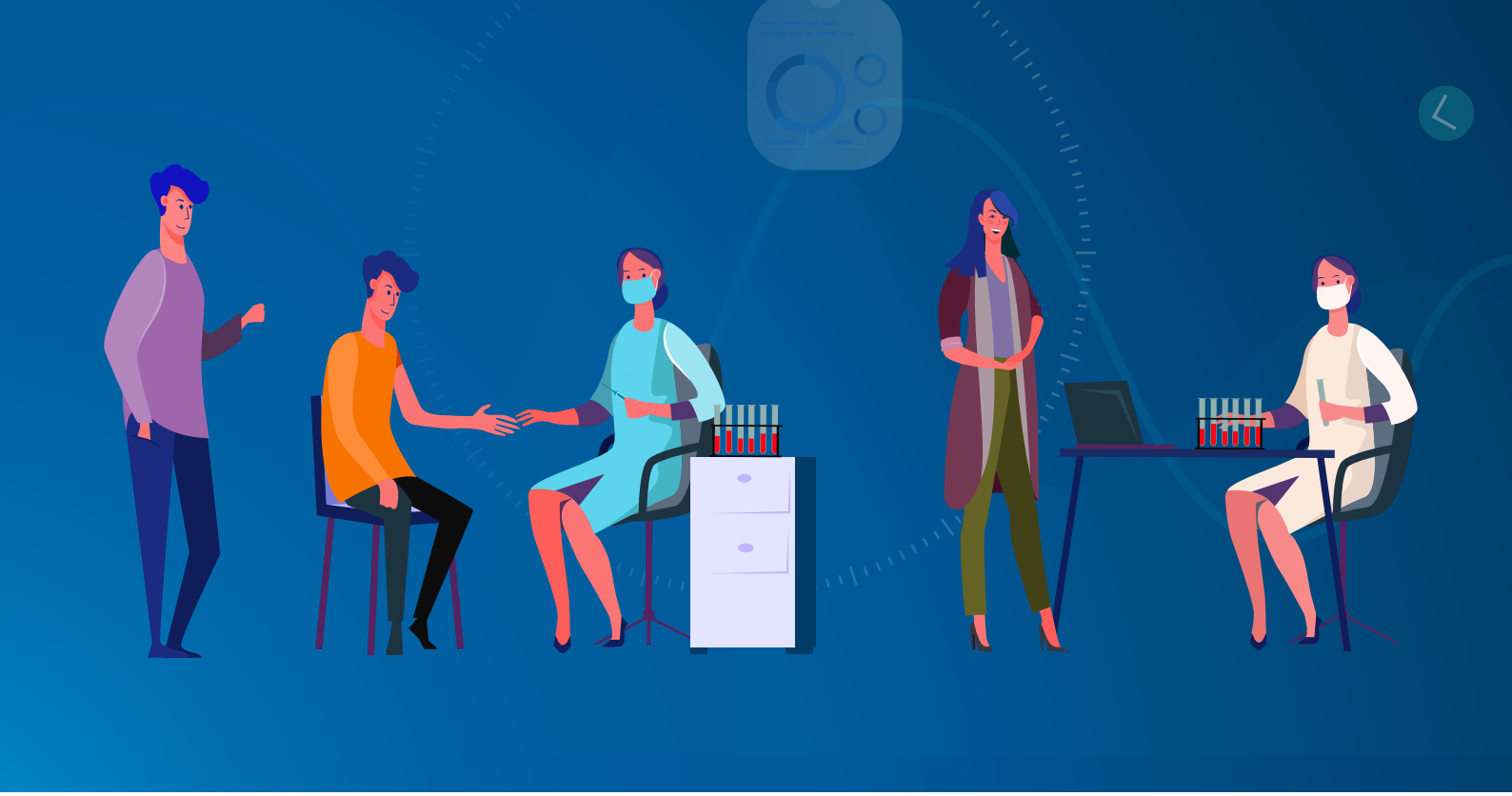


Multiple COVID-19 vaccines are a good thing

In a recent letter to *The Guardian*, Professor Jonathan Van-Tam, Deputy Chief Medical Officer for England, highlighted that we must not wait for a single optimised vaccine to provide widespread protection.[15] He also stated that the vaccines should be administered as they become ready for use, even if they are not available in the quantities necessary to vaccinate the entire general population in a short time frame. Professor Van-Tam proposed that it is imperative that we do not delay immunisation to wait for the optimal vaccine.[15]

These statements make clear the need to act as soon as possible, immunising populations immediately when vaccines are authorised and become available – a message that has been acknowledged by multiple nations. After all, although several vaccines have demonstrated efficacy during clinical trials, their true effectiveness within the real world will only become apparent over time. In application, some vaccines may be more effective in preventing disease (in the long-term) than others; some may prove more effective in certain populations; some may have different safety and tolerability profiles, and so on. The discovery of SARS-CoV-2 variants[16] raises questions about the effectiveness of vaccines developed against a single target in treating COVID-19 caused by different variants. Interestingly, Pfizer-BioNTech and Moderna have announced that the efficacy of their approved vaccines does not appear to be affected when treating COVID-19 caused by two new, currently circulating variants.[17,18] Parallels can be made with vaccinations against seasonal influenza – multiple types of vaccines are produced each year, based not only on geographical distribution of subtypes, but also different preparations and routes of administration for different types of patients.[1] This is achieved through tri- and quadrivalent influenza vaccines, which provide protection against three or four different subtypes of influenza, respectively. As a result, different formulations of influenza vaccines are produced each year for use in the Northern and Southern Hemispheres.[20] Could a similar approach be employed for global immunisation against COVID-19?

Multiple different types of COVID-19 vaccines are in development, some of which require specific conditions for storage and transportation, which may limit their widespread distribution and availability.[21] The manufacturing of sufficient quantities of each vaccine is proving to be a major logistical challenge, often due to shortages in raw materials,[22] delays in approvals of vaccine batches[23] and interruptions in supply chains caused by manufacturing optimisation.[24]



By incorporating more than one vaccine into a national immunisation plan, such limitations in the supply chain can be largely negated.

Could multiple, rapidly developed vaccines be used for other diseases?

Based on the principal that vaccinating as many people as possible, using multiple COVID-19 vaccines, is more likely to provide protection throughout the population in a timely manner *versus* using a single vaccine (which could be susceptible to interruptions in the supply chain), does this approach set a precedent for vaccination against other diseases?

It is possible to draw an analogy between the development of vaccines and modern-day video games. In years gone by, video games were bug tested prior to release as it was not possible to update or improve a game sold on a cartridge or CD. The finished game was the ultimate finished product, even if any faults were discovered post-launch. However, many modern video games are released digitally, available for instant download on the day of release.

This strategy allows publishers to develop post-launch 'patches' – small add-ons that can be downloaded free of charge or purchased by the user – to improve stability and playability or provide additional game content.

Let's apply the analogy to vaccination: should multiple, rapidly developed vaccines that prevent the spread of other viral diseases be authorised and made available as soon as possible (while maintaining acceptable safety and tolerability profiles)? In cases where widespread protection may not be possible via a single vaccine (due to geographical strain variance, lack of efficacy in certain subpopulations or manufacturing bottlenecks, for example), it may be more effective to produce multiple vaccines against a single disease. Although each of these vaccines may only provide protection to certain subpopulations or against certain viral subtypes, the cumulative effect would be greater protection throughout the general population compared with the use of a single vaccine. Furthermore, rapid vaccine development and approval could provide swift protection against viral evolution, which would not be possible with a single vaccine developed through a traditional, lengthy clinical trial.[21]

The future is bright

Has the COVID-19 pandemic changed vaccine development forever? The initial signs are positive. While the development and approval of multiple vaccines against COVID-19 via accelerated clinical trials has been driven by an immediate necessity, the framework for expedited vaccine development may be beginning to solidify for future epidemics or pandemics.[10] It remains to be seen whether a similar approach could be applicable (or even possible) for the development of vaccines against other diseases, including those at the centre of future pandemics. The likelihood of adopting a similar approach may be determined by multiple virological and epidemiological factors, including viral mutation rate, global epidemiological variance or geographic strain variation, drawing parallels with influenza vaccines. Pragmatic factors will have an impact: manufacturing capabilities, vaccine storage and delivery, and – in what may be one of the sharpest of all double-edged swords – financial incentive. Why invest in the development of a single vaccine when you can invest in multiple vaccines?

Could an incremental approach to vaccination provide the best solution in both the short and long term? With regard to the COVID-19 vaccine, the effectiveness and tolerability of any vaccine developed and investigated within abbreviated trials will only become known over time.

Ultimately, the success of any vaccine depends on the level of uptake within a population – vaccines against any disease need to be accepted by the general public. To ensure the greatest level of uptake, and a success story, a strong, clear, educational narrative must be developed to assuage any concerns, highlighting that approved vaccines are able to greatly reduce the chances of contracting a particular disease, while demonstrating acceptable safety and tolerability profiles. After all, a vaccine is only effective if the wider population is willing to receive it.

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