Accelerated regulatory pathway for pandemic vaccines

Vaccines form an important part of the combat against the current COVID-19 health crisis. Getting a range of effective vaccines to the market quickly will be essential if we are ever to "return to normal". Following the landmark moment of a first COVID-19 vaccine approval in December 2020, this article explores how an accelerated regulatory pathway using challenge studies could speed up time to market for further COVID-19 vaccines

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The current SARS-CoV-2 pandemic creates an unprecedented health crisis on a global scale. Pandemic diseases – epidemic diseases that spread over a wide region – are not new and have swept through human populations for millennia. Well known examples include the bubonic plague, also known as the Black Death, that killed between 25 and 75 million people in Europe in the 1300s and the "Spanish flu" 1918–19 influenza pandemic that killed an estimated 40–70 million people worldwide.

Other less severe pandemic influenzas emerged in 1957–58, 1968, and 2009. In the latter three cases, researchers developed influenza vaccines targeted specifically to the circulating virus, although experts disagree about how effectively the vaccines curtailed disease spread. More recently the 2014–2016 Ebola outbreak in west Africa caused more than 28,000 cases and 11,000 deaths.

Vaccines play a critical role in overcoming a pandemic. Developing vaccines for pandemics – in particular for the current SARS-CoV-2 global outbreak – is, however, a challenging task.

Even in normal times, vaccine development is a lengthy, expensive process as attrition is high.[1] Usually multiple candidates and several years of development are required to produce a licensed vaccine. Because of the cost and high failure rates, pharma companies typically follow a sequential development, with multiple pauses for data analysis or manufacturing updates.

The current global pandemic needed a shift in thinking from the normal vaccine paradigm to a pandemic vaccine paradigm as it has required accelerated development on one side and the need to manufacture several billion doses

of vaccines within months on the other, while performing development steps that are normally performed sequentially in parallel. To add to the complication, this all has to be done against a background where the scientific knowledge on SARS-CoV-2 changes almost daily. This has created unprecedented strain on the global pharma industry and required innovative regulatory approaches in order to get a safe and efficacious vaccine to market as quickly as possible.

COVID-19 vaccine development

A number of SARS-CoV-2 vaccines platforms are currently under development in different stages of development, as highlighted in Table 1.

At the time this article was written, the Pfizer/BioNTech vaccine was granted marketing authorisation in the UK by the Medicines and Healthcare products Regulatory Agency. Several vaccines are potentially close to the market and currently under (rolling) review with both the European Medicines Agency (EMA) and the US FDA, namely the AstraZeneca/Oxford, Pfizer/BioNTech and Moderna vaccines. In the case of the Pfizer/BioNTech and Moderna vaccines, if successful, these would be the first approvals of an mRNA vaccine by the EMA and FDA.

Developing a COVID-19 vaccine has several challenges on the nonclinical, clinical, and chemistry, manufacturing and controls front, as seen by the multiple steps that need to be taken simultaneously and the need to accelerate the development. In Figure 1, a traditional vaccine development is compared with an accelerated pandemic development. In an accelerated development it is critical to balance the need for speed, while maintaining the adequate and required quality, and regulatory requirements.

The need for the ability to produce hundreds of millions of vaccines rapidly has led to the start of manufacturing commercial grade batches early in the development process in parallel with the early stage clinical trials. This means that the commercial grade manufacturing has to start at risk. Use of next-generation sequencing to support or partially replace adventitious agent testing is a possibility to speed up development. However, in that case, one has to ensure the provisions of ICH Q5A are met.

The nonclinical experience with vaccine candidates for severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) have raised concerns about potential for exacerbating lung disease, either directly or as a result of antibody-dependent enhancement. Such an adverse effect may be associated with a type 2 helper T-cell (Th_2) response. Hence, rigorous testing in a suitable animal model is essential and regulators might not be keen in approving accelerated approaches.

In a classic vaccine development, vaccine efficacy is confirmed in one or more Phase III efficacy field trials. These trials are large, contain several thousands of subjects and are conducted globally. Conducting Phase III trials for a pandemic vaccine can prove difficult for different reasons:

- Such Phase III trials can take very long to recruit and to complete, requiring a global footprint
- Conventional field trials require subjects to be exposed to virus in the community to be able to test the vaccine. In countries with successful COVID-19 containment measures and now have very low infection rates, vaccine trials are near impossible as it will be hard to have sufficient virus circulation to be able to see a statistically relevant outcome and could lead to massively under-powered trials
- As the pandemic is likely to proceed in waves, it is difficult to predict where and when new outbreaks will occur, and how high the infection rates will be. This therefore makes it very hard to prepare trial sites to coincide with these outbreaks and to have trial supplies deployed at the right location at the right time
- Performing field studies in regions where the disease is not present will not give any meaningful result, as it will give the same outcome in both the placebo and the active treatment group
- Finally, a large number of candidate vaccines is currently being developed, but it will be extremely difficult, if not impossible, to test all of these for efficacy due to the ethical issue of including people in a placebo group when other vaccines have already shown efficacy. It will be important not to crowd sites or burden countries and their ethics and regulatory authorities with multiple trials, as happened with Ebola therapeutics during the 2013–2016 outbreak.

TABLE 1

Overview attributes COVID-19 vaccine platform

Type of vaccine	Dose	Licensed platform
DNA	Multiple	No
RNA	Multiple	Yes
Inactivated	Multiple	Yes
Live-attenuated	Single	Yes
Protein sub-unit	Multiple	Yes
Replicating viral vector	Single	Yes
Non-replicating viral vector	Single	No

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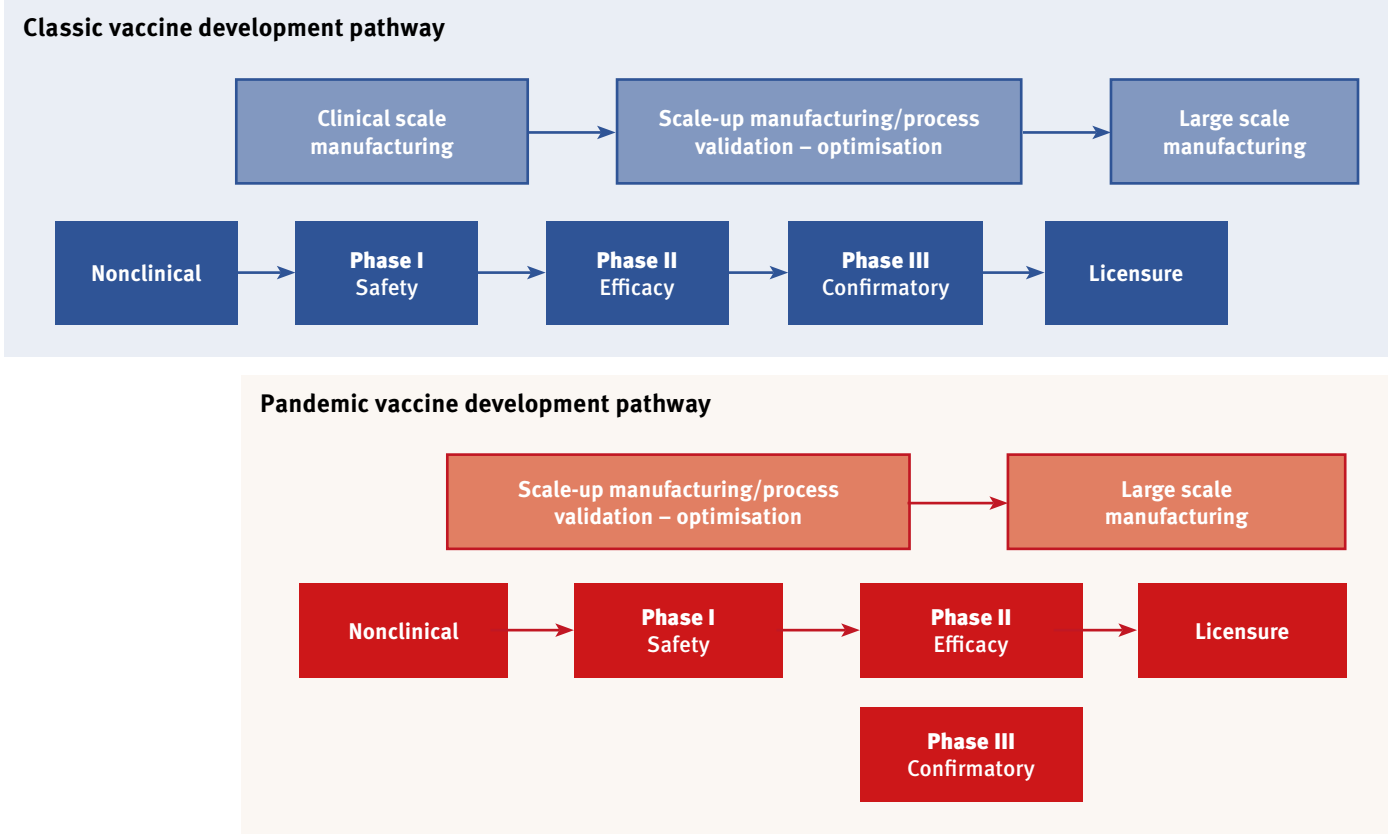
CHIM model

Performing large Phase III trials might therefore potentially be expensive and – in the absence of being conducted in a region where there is a COVID-19 outbreak – not provide any meaningful efficacy data. In this case one could also argue if it is ethical to expose trial participants to investigational products if the trial they are participating in is not expected to yield any conclusive result – positive or negative.

A potential solution to have early efficacy data and to detect any disease exacerbation would be the use of a COVID-19 controlled human infection model (CHIM) model. In a CHIM study, a well-characterised strain of an infectious agent is given to carefully selected adult volunteers after they have been vaccinated. They follow a traditional double-blind

FIGURE 1
Classic vs pandemic vaccine development pathway



design with an active treatment group and a placebo group. These trials are performed in specialised quarantine units, where the inoculated volunteers are under 24/7 medical supervision.

These studies play a vital role in helping to develop vaccines for infectious diseases and have become widely accepted as an alternative to traditional early stage field trials to show the efficacy of antiviral and vaccine therapeutics in respiratory syncytial virus (RSV), influenza and other diseases. Conducting challenge studies in a controlled quarantine environment allows for a superior study design and allows for establishment of an early efficacy profile. This critically accelerates the selection of a safe and effective dose and dosing regimen for a new vaccine, and could, for a pandemic vaccine, provide efficacy data that would be otherwise difficult to obtain.

Since the 1990s, these types of studies have been used to provide early performance data through proof-of-concept (PoC) and mode of action (MoA) studies to accelerate the clinical development of vaccines. Governmental and commercial organisations are developing challenge models to accelerate vaccine development programmes, eg, for small interfering RNA (siRNA) and monoclonal antibody (mAB) trials in respiratory tract infections (influenza and RSV), and to gain a better understanding of the underlying pathological processes that drive immune responses. Such exploratory models started gaining favour in regulated clinical trials in the early 1990s and were first mentioned in regulatory guidance in 2010.

Regulatory-wise, CHIM trials have been accepted by regulators as supportive for the following:

- As PoC studies for influenza and other upper respiratory tract infections In such early phase studies, protective (vaccine) or curative (vaccine/drug) efficacy is being assessed. There are currently no specific guidelines regarding efficacy markers (correlates of protection) for PoC in CHIM studies, although the US FDA guideline on influenza studies mentions haemagglutination and tissue culture infective dose 50% (TCID50)
- As a method for determining optimal dosage (to identify the correct individual dose, dose range, or schedule for field studies).

Human challenge trials may help to resolve at least some of the issues faced in the development of a COVID-19 vaccine. First of all, fewer subjects are needed for a CHIM than for a classic clinical trial, between 80 and 120, and the inclusion criteria for the study group can be limited to subjects at the lowest possible risk, ie, 18 to 25-year-olds. Secondly, challenge trials can be used to determine the infectious dose of SARS-CoV-2, starting from a very low dose and uptitrating. Additionally, CHIMs can be used to compare vaccines side by side, limiting the need for placebo controls, and therefore reducing potential ethical burden. Challenge studies could determine correlates of protection, which could be used in Phase III studies. Finally, if the CHIM results are favourable, such a trial can help in obtaining emergency use authorisation for a vaccine to be used, for example, in high-risk populations.

Although challenge studies have not been used as pivotal efficacy trials for pandemic vaccines before, there is a precedent of an approved vaccine where a CHIM trial formed the pivotal efficacy part of the marketing authorisation application. The Vaxchora vaccine – aimed at preventing cholera – received marketing authorisation approval based on a pivotal efficacy part (see Case Study). The challenge trial was supported by a large safety immunogenicity trial. The main reason for both the FDA and the EMA to have agreed with a CHIM trial as a pivotal efficacy trial is that it would have been extremely difficult to perform a meaningful Phase III trial that would give conclusive results in this indication.

A similar approach could be considered for a COVID-19 vaccine. As discussed, performing large Phase III trials in SARS-CoV-2 could prove challenging and not be able to provide conclusive data. A development pathway where a human challenge trial would form the efficacy part of the dossier could be able to fulfil the requirements on efficacy data.

In 2016 the World Health Organization (WHO) published a guidance document, "Human challenge trials for vaccine development: regulatory considerations",[2] where it says: "whether the purpose of the study or studies is to provide supportive evidence for licensure or to help inform and design traditional efficacy studies or vaccine design, human challenge trials may contribute to the preponderance of evidence upon which regulators could take a clinical trial or licensure decision."

In its "Guidelines on clinical evaluation of vaccines: regulatory expectations"[3] guidance document, the WHO describes that if it is not feasible to perform vaccine efficacy trials and if there is no immunological correlate of protection, it may be possible to obtain evidence in support of vaccine efficacy and/or to derive an immunological marker from a human challenge trial. The guidance also specifies that if they are performed, human challenge trials may be of particular use:

- When there is no appropriate nonclinical model (eg, when a candidate vaccine is intended to protect against an infectious disease that is confined to humans)
- When there is no known immune correlate of protection (ICP)
- When vaccine efficacy trials are not feasible.

As we do not have an ICP for COVID-19 and as for the reasons already described, human challenge trials could indeed be an excellent tool to obtain efficacy data that could not otherwise be obtained.

Things to consider for CHIM trials

The WHO recently published a paper, "Key criteria for the ethical acceptability of COVID-19 human challenge studies"[4] and the research and development blueprint "Feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental COVID-19 infection and illness in healthy young adult volunteers"[5] to discuss the ethical considerations of a COVID-19 CHIM trial, and under which conditions this type of trial could be conducted. Several discussion points, however, remain

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and should be discussed with the applicable regulators. These include the choice of COVID-19 strain (wild-type versus attenuated), current lack of rescue medication to be administered to the subject, etc. The International Alliance for Biological Standardization (IABS) organised a COVID-19 webinar on 23 June, bringing together a broad range of international stakeholders, including academia, regulators, funders and industry, to discuss the use of CHIMs to accelerate development and market authorisation assessment of a vaccines against SARS-CoV-2.[6]

Despite all these benefits of CHIM, it is important to remember they are a potential risk to the participants, especially with a disease which is not completely understood and for which no rescue therapy is currently available. Thus, even if such trials can provide sufficient information for efficacy testing, the small size means they will not be sufficient to create a sizeable safety database to allow for a proper safety assessment, so Phase III studies will still be needed to investigate safety in appropriate numbers of participants to determine infrequent adverse events following immunisation.

Discussions with regulators in an early stage of development are paramount in order to speed up development to ensure the accelerated pathway taken is in line with their expectations.

CASE STUDY: Vaxchora

Vaxchora is a live oral cholera vaccine intended to prevent cholera disease in adults and children aged from 6 years (18 years in the US).[7,8] The vaccine is aimed at travellers travelling to cholera-endemic regions. It contains a weakened form of the cholera bacterium Vibrio cholerae (serogroup O1). Vaxchora received marketing authorisation valid throughout the EU in April 2020 and was approved by the FDA in June 2016. In the US the marketing authorisation holder is PaXVax; in Europe it is Emergent BioSolutions.

Developing a vaccine for cholera – in particular one aimed at travellers – has a major challenge as performing a Phase III field trial in this population would be difficult, as both placebo and active group would need to be meaningfully exposed to cholera – in the same order of magnitude – in order to achieve a conclusive result on efficacy.

To be able to demonstrate efficacy, a CHIM trial was included in the development pathway as the pivotal efficacy study, replacing a Phase III efficacy field trial.

In this CHIM study 197 healthy adults aged 18 to 45 years received a single dose of either Vaxchora (95 volunteers) or placebo (102 volunteers) and were then given infectious cholera bacteria (O1 strain). Moderate to severe diarrhoea (a symptom of cholera) occurred in about 6% of those given the cholera bacteria 10 days after Vaxchora and 12% of those given the bacteria three months after receiving Vaxchora. By comparison, moderate to severe diarrhoea occurred in 59% of adults who had received placebo. The trial showed that Vaxchora can prevent symptoms of cholera in people coming into contact with the bacteria and provided the pivotal part of the efficacy data.

In order to have a sufficiently large safety database, a main safety immunogenicity study involving 3,022 healthy adults aged 18 to 45 years was performed. This trial found that antibodies against cholera bacteria were present after 11 days in 94% of adults who had received Vaxchora compared with 4% in those who received placebo.

Two further studies in special populations confirmed that giving Vaxchora to adults aged 46 to 64 years or to children and adolescents aged 6 to 18 years was effective at producing antibodies against cholera bacteria.

Supporting development of a vaccine

Regulators have been scrambling to support companies in the development of their vaccines. The EMA, for example, issued a guidance (EMA/213341/2020 EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines to support development and regulatory approval for treatments and vaccines for COVID-19) with the involvement of the dedicated EMA Pandemic Task Force (COVID-ETF). It sets out the available regulatory pathways to fast-track assessment of both new or repurposed methods of treating or preventing COVID-19.

The US FDA issued similar guidance, as did several national competent authorities in Europe. Among the measures taken by the EMA is an accelerated scientific advice procedure, taking as little as 20 days. The EMA will also accelerate the marketing authorisation procedure whereby, depending on the quality of the submitted data, the minimum duration of the procedure could be as short as 80 days or even fewer.

The current pandemic creates an unprecedented situation, whereby vaccines are developed at a scale previously unseen, and at speeds that where considered unimaginable. The main issue in getting a vaccine to the market quickly is the collection of sufficient efficacy data, and the difficulty and time required in the execution of Phase III efficacy field trials. Human challenge trials could form an alternative and be the basis of a regulatory pathway for accelerated approval. There have been recent examples of challenge studies being part of an accelerated regulatory approval pathway. A similar approach could be considered for COVID-19 vaccine development. A challenge trial could be an ideal tool for efficacy head-to-head comparisons of COVID-19 vaccines in development with vaccines already on the market, without the need for extensive field trials. In the meantime, the search continues for a range of vaccines that will, hopefully, put an end to the pandemic that has claimed many lives and caused unspeakable disruption and damage globally. ■

KEYWORDS
Pandemic; COVID-19; Vaccines; Accelerated pathways; Accelerated access; Global health.

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