



How the Global COVID-19 Pandemic Brought Drug and Vaccine Development into the Public Mainstream

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Abstract

Pharmaceutical development was at the forefront of efforts to prevent infection with the SARS-CoV-2 virus as well as to treat its often-devastating effects. Drug development, and its multifaceted and multi-disciplined activity toward effective vaccines and drugs, became part of everyday news. I review several key areas of vaccine and drug development that were brought into the public mainstream over the evolution of the pandemic. These include the unprecedented speed of vaccine discovery and development, issues uncovered from early clinical studies, and regulatory concepts that were highlighted throughout the development process. Among these was the importance of pharmacovigilance as each new agent was rapidly deployed to a mostly eager public. Critical challenges around production, packaging, and procurement of product for patient use were often centre stage. Finally, the ever-important need to transition not only from scientific concept to vaccine and drug, but from their authorized and approved use to their implementation in health systems to insure the intended effects both in individuals and populations.

Key Points

The COVID-19 global pandemic put drug development, vaccines, and pharmaceutical medicine in the public forefront.

Issues such as discovery and development, pharmacovigilance, supply chain, and implementation science were mainstream.

The journey from scientific concept to drug approval was followed by the multifaceted challenges of vaccine implementation into health systems.

state of alert. One can sense a palpable urgency to thwart its devastating medical, social, and economic effects. The frontline fundamental measures of hand washing, physical distancing, personal protection, and crowd avoidance laid the foundation of the battle. These measures were in parallel to efforts focused on development of pharmaceutical products that could prevent infection (i.e., vaccines) as well as therapeutics that could help minimise the manifestations and impact of infection.

The media reported every milestone which, in normal times, would be of limited interest and confined mostly to the pharmaceutical sector. They performed an important service by using their platform to educate on drug development. Conversely, and unfortunately, the spread of false and misleading information by some drowned out credible sources [1]. Table 1 lists some drug development concepts that suddenly appeared in the mainstream.

The primary areas of pharmaceutical development related to development of new therapeutics [2], repurposing existing drugs approved for other indications against COVID-19 infection [3] and development of vaccines [4]. While new therapies and vaccines introduced us to the phased drug approach, repurposing old drugs quickly taught us that efficacy and safety needs to be established in the condition for which it is being used. Given the desperation for interventions, the Emergency Use Authorization (EUA) programme

1 Introduction

As the global COVID-19 pandemic unfolded, its rapid spread and often severe manifestations put both the public health profession and general population at an unprecedented

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Table 1 Drug development terms and concepts that emerged to mainstream media during the COVID-19 pandemic

Term	Definition
Compassionate use	This is a treatment option that allows the use of an unauthorised medicine. Under strict conditions, products in this development can be made available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter clinical trials
Cold chain	Involves a series of procedures and equipment utilised to maintain specified temperature of vaccine from filling to arrival and storage at clinic for administration
Drug repositioning	Examining existing drugs for a new therapeutic indication. Development may be somewhat “de-risked” due to existing data on safety and mechanism of efficacy. Overall development costs and timelines are often reduced
Drug Safety Monitoring Board (DSMB)	Purpose is to oversee and monitor clinical trials to ensure participant safety and the validity and integrity of the data. One must have a DSMB if one is conducting a multi-site clinical trial involving interventions that pose more than a minimal risk to the participants
Emergency Use Authorisation (EUA)	An Emergency Use Authorisation (EUA) is a mechanism to facilitate the availability and use of medical counter-measures, including vaccines, during public health emergencies, such as the current COVID-19 pandemic
Interim analysis	An analysis that is used to evaluate efficacy or safety issues between treatment arms prior to a clinical trial’s formal completion. Planning of such analysis is done in advance and is detailed in the trial protocol. An example can be found in the Pfizer protocol [45]
Life cycle management	Involves strategies in between patent granting and expiration to improve product utility, often through evaluation of new indications or improved formulation of a product. The development of a powder formulation of the vaccine being manufactured by Pfizer was the early recognition of the need for a second-generation product to simplify supply chain of first-generation product
Pharmaceutical supply chain	The means by which drugs, vaccines and devices are manufactured and ultimately delivered to caregivers and their patients. In addition to manufacturing, it involves the transportation and storage details between manufacturers and distributors and end-user portals such as pharmacies and/or clinics
Primary endpoint	A typical efficacy measure in a clinical study that addresses the main research question. It should be a direct measure of improved survival, an improvement in symptoms and/or functional capacity or decreased chance in developing a disease. The primary endpoint in the Pfizer-sponsored vaccine trial was stated as: “Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group”
Viral vectors	Viral vector vaccines consist of a recombinant virus (that is, the viral vector), often attenuated to reduce its pathogenicity, in which gene-encoding viral antigen(s) have been cloned using recombinant DNA techniques
Viral variant	A viral variant is the deviation of a virus’ genetic profile from its standard form. Mutations arise as a natural by-product of viral replication. These viral variants can be formed by the introduction of errors to the virus during its replication life cycle
Herd immunity	Herd immunity occurs when the majority of the population is immune to an infectious disease, which extends the protection to individuals who are not immune. This phenomenon is important for protecting vulnerable individuals who are unable to be vaccinated due to certain vaccine contraindications or medical circumstances
Scale-up	The process of increasing in size, quantity, activity, or productivity. For vaccines, the annual production of some 5 billion doses required nearly a doubling scale-up capacity for COVID-19 vaccines to nearly 10 billion doses

was utilised at a pace never seen previously. Importantly, the complexity of drug development was exemplified as new data led some EUAs to be modified and some even revoked (e.g., hydroxychloroquine).

The global COVID-19 pandemic provided a unique platform for the public and non-research practitioners to learn

and appreciate drug development. I will use the discovery, development, and implementation of COVID-19 vaccines over the first 18 months of the global pandemic to highlight those key elements of drug development that became part of our daily lives.

2 Vaccines Science and Development Hits the Mainstream

2.1 Vaccines Seen as the Most Viable Weapon

Vaccines remain an integral part of preventative public health despite controversies in some quarters [5]. Considering the average vaccine development time is about 10 years [6], and the fastest development to date to prevent mumps, took 4 years [7], the public soon had no choice but to accept a hopeful reality for a vaccine while reinforcing the basic public health measures in the interim. The positivity of the journey was nevertheless fostered by many groups, taking many approaches, and regulators willing to fast track any appropriate steps.

The various methods of vaccine development quickly became associated with curiosities about probability of success, effects in various types of patients, and the speed to a realistic availability. With respect to the latter, formulation, packaging, and distribution, which are often behind the scenes, became the leading topic of prime-time news. Discussions ensued on basic factors such as age, gender, race, and pre-existing conditions of the trial cohort that will ultimately determine its value and effectiveness in widespread use. Finally, the ability of the vaccine to prevent infection, reduce or eliminate transmissibility, prevent symptoms, and/or reduce severity of an infection and requirements for hospitalisation and mechanical ventilation are all possible outcomes, each representing a potential question of how the vaccine may work in the real-world setting.

2.2 Vaccine Platforms and Their Development

While the pre-clinical proof of concept studies is different with drugs and vaccines, the choosing of a platform for the vaccine was a critical first step with many scientific teams in industry and academia taking different approaches. Interestingly, the two main approaches of a viral vector or a messenger RNA platform were in some regard repurposing of the platform for a COVID-19 vaccine. For example, the Pfizer/BioNTech mRNA platform capitalised on years of research on its potential utility where mRNA would instruct cells to produce proteins. This was being considered for a potential HIV vaccine but also for other conditions associated with diabetes. When the sequence of the SARS-CoV-2 virus was reported in January of 2020, teams of scientists went to work and the spike protein on the surface of the virus was the target. The second mRNA vaccine that was approved from Moderna also utilizes this platform after years of study for utility in other diseases.

The viral vector platform had been used with other vaccines in the past and was the basis for the third vaccine approved. The Johnson and Johnson vaccine was the first approved in the USA with a viral platform and utilised adenovirus 26 (Ad26). In the recent past, Johnson & Johnson used Ad26 to develop vaccines for Ebola and other diseases. Thus, they had experience in engineering AD26 and could initiate a programme rapidly.

The AstraZeneca vaccine, approved in several countries outside the USA, also uses a viral platform; specifically, one consisting of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene.

3 Initial Clinical Studies Fuel Optimism and Faith in Science

3.1 Vaccine Concepts Rapidly Proved in Man

The development timeline of the first approved vaccine illustrates the remarkable achievements conveyed to an eager public and scientific community. Early studies, that were conducted combining Phase 1 and Phase 2 objectives of initial safety and proof of concept, demonstrated that an mRNA approach to immunity was possible as evidenced by development of antibodies to the viral spike protein as well as an immune T-cell response [8, 9]. There were no side effects that precluded advancing development rapidly.

Rapid development proceeded with the launched a Phase 2/3 trial with 30,000 volunteers, which was further expanded to 44,000 participants. This expansion reinforced both safety observations but also potential efficacy in a wider age group as well as those with pre-existing condition.

In addition to the large Pfizer/BioNTech trial, several other sponsors similarly proceeded to Phase 3 in rapid succession [10], giving further hope to thwarting the pandemic.

3.2 Phase 3 Milestones Achieved

In mid-November of 2020, nearly 1 year since the pandemic virus was first identified, preliminary reports of the Pfizer/BioNTech Phase 3 study showed a 95% effect rates with no obvious safety issues [11, 12]. This news came at a time when infection rates in most jurisdictions were at an all-time high with growing concern of overwhelming surge capacity of acute and critical care [13]. With the possibility of a harvestable pharmaceutical in sight, the Phase 3 results of the Moderna vaccine [14] were reported soon after with similar efficacy results.

Positive Phase 3 data from the Johnson and Johnson [15] vaccine gave further hope as did the viral vector approach of AstraZeneca/ Oxford University [16, 17], although these

later data were subjected to a call for further evaluations [18, 19].

3.3 All Hurdles in the Limelight

Potential safety signals in both viral vector programmes led to trial pauses while they were evaluated. A Phase 3 trial initiated in August was halted in September 2020 to evaluate a case of symptoms of transverse myelitis [20]. Another Phase 3 trial in 60,000 volunteers started in September 2020 was paused in October to evaluate a patient incident before resuming shortly thereafter [21]. These events highlighted the fact that clinical trials are to establish both safety and efficacy and that halting trials, allowing an independent Data Safety Monitoring Board (DSMB) to review adverse event cases, is a careful and established procedure [22, 23].

Atypical regulatory principles were also illustrated by the announcement that a Russian-developed vaccine would be available for administration prior to the ultimate publication of the Phase 2 trial [24] and absence of Phase 3 data [25, 26]. This approval was relabelled a “conditional registration certificate,” with the Phase 3 report ultimately showing an efficacy rate of 92% [27].

As all of these Phase 3 trials were approaching completion, the media were constantly balancing promises from politicians and realities from the developers. In order to reinforce faith in proper drug development, several chief executives of the research-based pharmaceutical industry issued a pledge not to submit their respective firm’s vaccine for licensing until safety and efficacy is established in Phase 3 trials [28]. While this did not preclude justifiable fast tracking of regulatory procedures, it did reinforce that the established drug development process is rooted in improving and protecting public health. This was then followed by a self-defence statement by Food and Drug Administration (FDA)

regulators promising to uphold the scientific integrity and independence of their work [29].

4 Regulatory Use Authorisations: Concepts of Safety and Efficacy

The decision-making process for authorisation, even during the pandemic, followed a thorough data review by FDA scientists after unblinding, analysis and reporting of studies by the sponsoring firm. The FDA also utilises an independent advisory committee who also review the data carefully, discuss it openly in a public forum, and vote on questions posed to them by the FDA.

4.1 Emergency Use Authorisations with High Efficacy Vaccines

By the 1-year anniversary of the global pandemic declaration, there were three vaccines authorised for emergency use by FDA with others, including the AstraZeneca vaccine, also available for use in other jurisdictions. The importance of multiple product authorisations giving implementation flexibility proved extraordinarily valuable given the need for rapid global immunisation as well as subsequent hurdles driven by careful pharmacovigilance [30]. This science brought hope to the public as well as the medical profession. For industry scientists, it confirmed their vocational commitment that the answer to the pandemic was in science.

Given that the FDA published guidelines that required at least 50% efficacy for vaccine approval [31], the initial reports of Phase 3 data demonstrating 90–95% effectiveness were remarkable (Table 2). The efficacy rates of the mRNA vaccines against infection somewhat dampened the efficacy reports of 66% with the first approved viral vector agent; however, these data instructed the public on the important

Table 2 Key methodologic features and results from 3 major vaccine trials

Sponsors	Pfizer/BioNTech		Moderna		Johnson & Johnson	
	Placebo	Intervention	Placebo	Intervention	Placebo	Intervention
Sample size	21,728	21,720	15,210	15,210	19,691	19,630
Number infected	162	8	185	11	351	117
Infection risk	162/21,728 = 0.007456	8/21,720 = 0.000368	185/15,210 = 0.012163	11/15,210 = 0.000723	351/19,691 = 0.017825	117/19,630 = 0.005960
Vaccine efficacy	(0.007456–0.000368)/0.007456 = 95%		(0.012163–0.000723)/0.012163 = 94%		(0.017825–0.005960)/0.017825 = 67%	
Start and end date	July 27, 2020–November 14, 2020		July 27, 2020–November 21, 2020		September 21, 2020–January 21, 2021	
Location (country)	USA, Argentina, Brazil, South Africa, Germany, Turkey		USA		Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, USA	
References	[46]		[47]		[48]	

aspects of trial comparisons, including the concept of endpoints and period of conduct. Specifically, Johnson and Johnson trial highlighted the importance of endpoints beyond infectivity, choosing to focus on severity of illness, hospitalisation, mortality and death. These were of particular importance given the ever-stressed acute-care hospitals and their 'head-to-head' studies. In the Johnson & Johnson pivotal study, for example, the trial was conducted at later dates when infectivity was peaking (September–December 2020) and in USA, Latin America, and South Africa. FDA analysis [32] showed an overall efficacy rate of 72% in the USA and 64% in South Africa, where a concerning variant was emerging. Furthermore, 86% efficacy was observed against severe forms of COVID-19 in the USA, and 82% against severe disease in South Africa. This lower risk of vaccinated persons in contracting severe disease or dying was particularly welcome in those jurisdictions where 'flattening the curve' of serious infections would reduce burden on the healthcare system (e.g., intensive care unit [ICU] beds).

4.2 Efficacy and Effectiveness

As vaccine trials were being reported, a great deal of attention was given to the concepts of efficacy and effectiveness.

The vaccine efficacy rate is calculated from observations in a clinical trial by subtracting the placebo infection risk by the intervention infection risk, and subsequently dividing the difference by the placebo infection risk. Multiplying this number by 100 will provide us with the efficacy rate in percentage form. In other words, the percentage change of infection risk between the placebo group and intervention group is calculated. After a vaccine is authorised for emergency use or ultimately has an approved New Drug Application (NDA), clinical epidemiologists continue to assess vaccine effectiveness—i.e., how a vaccine works in real-world conditions. The goal is to understand how a vaccine protects people outside of strict clinical trial settings with a variety of study designs employed [33].

5 The Vaccine to Vaccination Implementation is Complex

5.1 Translational Science Illustrated

The landmark of established vaccine efficacy in the COVID-19 pandemic confirmed the unique skills of the pharmaceutical industry in translational science, i.e., bridging scientific knowledge to a tangible therapy, device or diagnostic

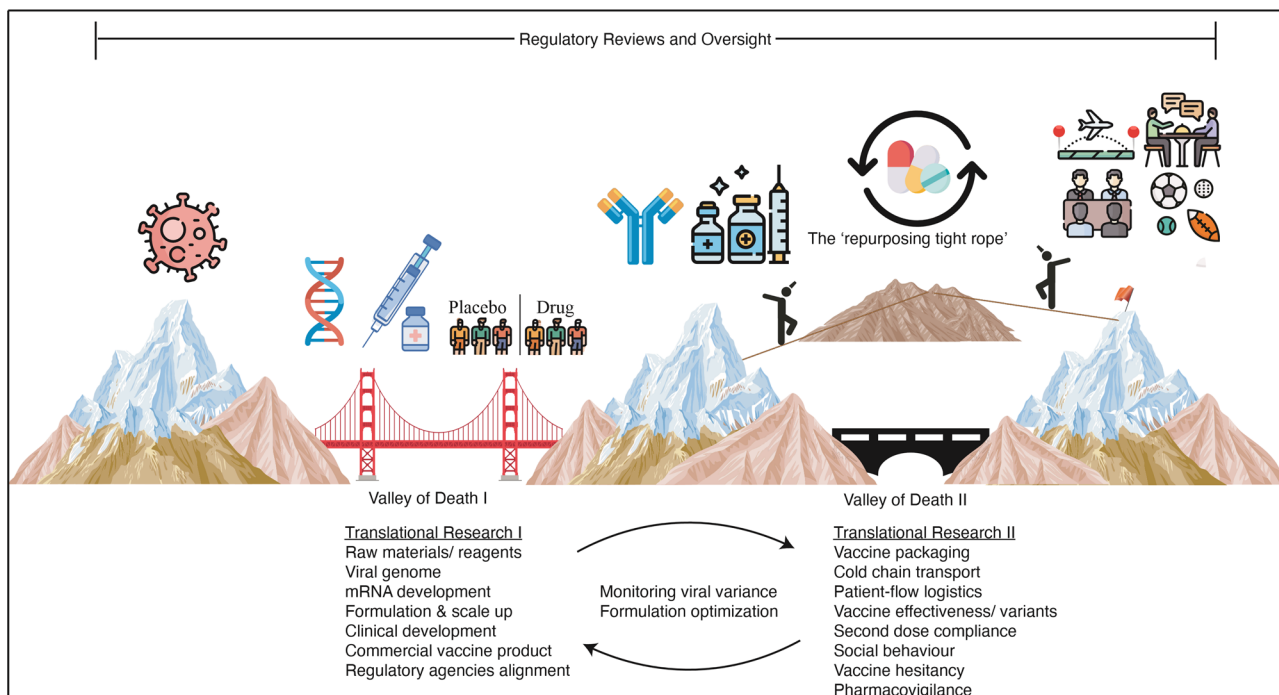


Fig. 1 Drug development for COVID-19 infection involves bridging the “First Valley of Death” from scientific concept (Viral Identification) to a tangible drug or vaccine. This was achieved with Emergency Use Approval of an effective vaccine in record time. Bridging the “Second Valley of Death” with a COVID-19 vaccine was com-

plicated by supply chain logistics and vaccine access hurdles, including hesitancy. Repurposing an approved drug for COVID-19 infection was partially successful, but seriously tarnished by lack of leadership and misinformation. Illustrations in this figure were created with Flaticon.com

(Fig. 1). Often referred to as “the valley of death” based on the difficulty of such translational goals, the pharmaceutical industry not only triumphed, but did so in record time with the team of clinical investigators and clinical trial volunteers.

The public often heard ‘it is vaccination, not vaccines which are needed to thwart the pandemic’. This journey from approved drug to patient health and happiness has also been termed “the second valley of death” as sometimes useful therapies are not integrated into health systems to have their intended effects. In the case of COVID-19 vaccines, this second translation involves packaging, distribution, acceptance and optimal delivery of care, e.g., decisions on vaccination sequence to various cohorts. This is a crucial aspect of the public health objective of herd immunity, which occurs when most of the population is immune to the viral infection, thus providing protection to those who are not immune. Herd immunity could be achieved if, for example, 8 out of 10 individuals developed immunity. In this case, 4 out of 5 people (80%) who contact someone with infection will not get ill nor will they spread the disease to others. Thus, spread is controlled.

5.2 Production, Packaging, and Procurement

As approvals of vaccine were imminent, modelling experts noted that their trial efficacy rates were important, but perhaps not as important as factors related to implementation effectiveness and background epidemic severity [34]. Implementation issues related to manufacturing and deployment delays, vaccine hesitancy or greater epidemic severity. Thus, the general public was exposed to other complexities of the process that are both unnoticed, and frankly, taken for granted.

Formulation of drugs, along with their packaging and preservation along the distribution pathway is complex and can present enormous challenges. First, vaccines being produced with new gene-based mRNA technology requires the solution to be stored at sub-zero temperatures including deep freezing during transport. This presented unique challenges considering millions of glass vials needed to be produced for transportation thousands of miles between logistic hubs – all while being kept at up to -80 degrees Celsius. Many logistics companies were preparing for such challenges in parallel with Phase 3 trials with assembly of “freezer farms” to assist with an unprecedented global scale logistics challenge [35, 36].

While freezers were one challenge, a global shortage of dry ice due to lower production of ethanol (its by-product carbon dioxide) during the pandemic presented another. Additionally, conventional glass commonly contains boron, which can lead to content contamination. Therefore, the need for pharmaceutical grade glass to withstand cracking in frozen conditions and maintain purity must be secured in

parallel with clinical development to avoid delays in distribution once approved for distribution.

The cold-chain challenges were being addressed in parallel by the industry in cooperation with established logistics specialists in the public and private sectors as well as with major airlines. In parallel came the development of global positioning system (GPS) tracked temperature-controlled containers to allow for real-time monitoring [37].

Toward the end of this value chain comes ultimate administration protocols, most often complicated by the need for a second dose. While this passing of the baton to government authorities represents a clear milestone, the industry continued to scale-up procedures for continuity of supply and conduct life-cycle management (e.g., development of a powder formulation to simplify transport and storage) [38]. The reality of supply hurdles was illustrated by the quality control issues at one manufacturing facility [39] and seriousness of proper logistic planning was illustrated by alterations in EUA-approved dosing regimens [40] that were admittedly driven by procurement problems causing debatable public health trade-offs [41]. These dosing adjustments away from the authorised label uncouple real-world observations from clinical trial learnings.

5.3 Pharmacovigilance

Perhaps the most important aspect following emergency use is pharmacovigilance. Despite trial observations in tens of thousands of volunteers in clinical trials, real-world dosing in millions of individuals will uncover more rare events. This was illustrated with the rare, but potentially serious, observations of a vaccine-related variant of heparin-induced immune thrombotic thrombocytopenia [42, 43] (termed VITT), which resulted in a temporary pause in authorisation. This vigilance led to a temporary pause of the EUA while the FDA and Centers for Disease Control and Prevention (CDC) evaluated 13 cases among over 8 million doses of vaccine administered to that point. Following this in-depth review, administration was resumed [44].

6 Conclusions

The drug-development process is complex. The development of therapies to prevent and/or treat COVID-19 infection became a vital need during our global pandemic. While we relied on frontline measures of hand washing, facemasks, physical distancing, and crowd avoidance, the daily media was focused on drugs and vaccines with late-breaking news highlighting areas of drug development not commonplace in prime-time broadcasts. We have reviewed the steps along

this journey, reinforcing the value of the research-based pharmaceutical industry and associated regulatory bodies. The months ahead will undoubtedly witness important new information from pharmacovigilance and real-world effectiveness studies along with new vaccines and therapeutics as our knowledge of the SARS-CoV-2 virus and its variants evolves.

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