

Development of the COVID-19 (SARS-CoV-2) mRNA Vaccines: Translational Medicine at its Best

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Introduction

The interdisciplinary approach of translational medicine brings research discoveries to the bedside and eventually to the whole community. These discoveries usually help orchestrate the diagnosis and/or therapy of disease [1].

Bringing discoveries from the lab bench to the people is often a daunting process that involves leaps rather than steps. The path from discovery to therapy is usually crooked instead of straight, multifaceted instead of simple. The development of the mRNA vaccines designed to help prevent the onset and spread of COVID-19 were no exception.

The miracle of the development of these vaccines is found in the speed of translation, as much as it is in their effectiveness. It took only about one year from the time of COVID-19 discovery to the beginning of vaccine distribution, a process that has often taken decades with other vaccines (Table 1).

Name of Pandemic	Death Toll	Timeframe for Vaccine Development	Duration
Spanish flu	40-50 million	1917-1942	25 years
SARS	774 (ongoing)	2003-present	17 years (ongoing)
Ebola	11,300	1976-2019	43 years
AIDS	25-35 million (ongoing)	1981-present	39 years (ongoing)
MERS	858 (ongoing)	2012-present	8 years (ongoing)
COVID-19	5.7 million (ongoing)	Dec 2019-Nov 2020	11 months

This astonishing speed of development can be explained in part because many facets of the basic discovery of mRNA vaccine technology had been stewing for more than a decade. In retrospect, the basic research stage (T0, in the translational research classification system – See Figure 1) probably started more than a decade ago when scientists developed an efficient and reproducible method for RNA transfection, using a protective liposome [2,3], which then stimulated translation of the appropriate protein [4]. The liposomes were designed to package and protect the delicate mRNA and then the mRNA, inside a ball of lipid fused with the host cell membrane to release the RNA. Once inside, the mRNA, along with the genetic material of the host cell, orchestrates the production of viral protein [5].

These experiments were built on years of work with liposomes and mRNA. The challenges that impeded the successful translation of transplanted mRNA into proteins, relative to other molecules, included the fact that mRNA is very large. It also tends to be unstable and is susceptible to degradation by nucleases. It may also activate the immune system in the host [6].

However, mRNA vaccines have advantages when compared to vaccines based on other types of nucleic acids (DNA, particularly plasmid DNA). It is particularly difficult to deliver DNA into the cell nucleus, where transcription of viral antigens take place. There is also the risk of integration of DNA into the host genome, potentially causing mutagenesis. In contrast, mRNA vaccines are only targeted for cytoplasmic delivery, circumventing the risk of genomic integration [7]. mRNA vaccines can induce both cellular and humoral immunity while not being subject to MHC haplotype restriction [8]. Also, mRNA can be produced in a cell-free environment by in vitro transcription (IVT), avoiding associated quality and safety issues. This permits simple downstream purification, and rapid, safe and cost-effective manufacturing [9].

The successful use of mRNA-liposome vaccines took many years of research after its invention. As an example, the vaccines that Pfizer and Moderna created were modified to stop immune reactivity by replacing the mRNA nucleotide uridine with pseudouridine. Also, the mRNA sequence was tweaked to ultimately stabilize the translated spike protein so it would deliver the best immune response in the host [10].

This paper will summarize the research associated with the development and testing of the Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines, as it relates to the phases of translational medicine.

Phases of Translation for Development of mRNA COVID-19 vaccines

Translational research has often been described in phases of translation, or “T-phases”, which is a model of 5 phases (T₀-T₄) [11] (Figure 1).

Development of the COVID-19 mRNA Vaccines: T0 phase of translation

T0 phase of translation is characterized by the identification of opportunities and approaches to health problems. For the current pandemic, this phase began when COVID-19 was identified as the causative agent. Since much of the research establishing mRNA

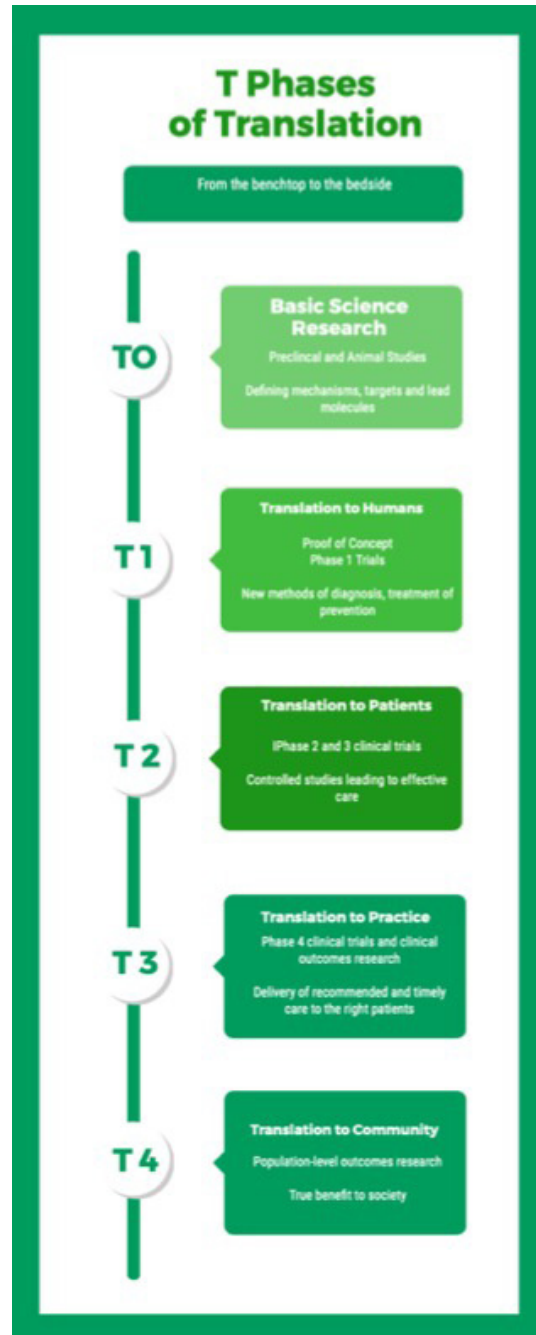


Figure 1: Translational Phases (© AJ Russo).

as a good choice for vaccine development was already well established, once the decision to develop a RNA-lipid nanoparticle (LNP) of nucleoside-modified mRNA vaccine was made, non-human animal studies proceeded.

Pfizer-BioNTech COVID-19 vaccines, BNT162b1 and BNT162b2

The Pfizer-BioNTech COVID-19 vaccines, named BNT162b1 and BNT162b2, encode a P2 mutant spike protein (PS 2) and was formulated as an RNA-lipid nanoparticle (LNP) of nucleoside-modified mRNA (modRNA). It is a highly purified single-stranded, 5'-capped mRNA that has been generated through in vitro transcription in cell-free conditions from the corresponding DNA.

In Pre-clinical Studies when mice were immunized with this vaccine, they produced high neutralizing antibody titers after a single injection. There was also high T helper 1 (TH1), T follicular helper (TFH) type CD4, IFN, IL-2 and CD8 T-cell cellular responses, suggesting little chance of causing hypersensitivity, or allergic-like responses [12].

Antibody response to this vaccine in rhesus macaques was similar to the response in mice [13].

Moderna mRNA-1273 SARS-CoV-2 Vaccine

Preclinical data with Moderna's mRNA vaccine also produced promising results in animal models. Mouse experiments demonstrated that a low dose of the vaccine induced a high level of neutralizing antibody and a high-level of protection against SARS-CoV-2. Also, vaccination of nonhuman primates with this mRNA vaccine induced high levels of neutralizing activity, particularly, rapid protection in the upper and lower airways.

Specifically the mRNA-1273 vaccine candidate induced antibody levels exceeding those in human convalescent-phase serum, in non-human primates. Vaccination induced type 1 helper T-cell (Th1)-biased CD4 T-cell responses and low or undetectable Th2 or CD8 T-cell responses. Viral replication was not detectable in Broncho alveolar-lavage fluid by day 2 after challenge in seven of eight animals in both 10-µg and 100-µg dose vaccinated groups. No viral replication was detectable in the nose of any of the eight animals in the 100-µg dose group by day 2 after challenge, and limited inflammation or detectable viral genome or antigen was noted in lungs of animals in either vaccine group.

In summary, mRNA-1273 induced robust SARS-CoV-2 neutralizing activity, rapid protection in the upper and lower airways, and no pathologic changes in the lung [14].

By 2020, Moderna had nine mRNA vaccines that were being tested in human subjects, including one vaccine engineered for a different form of coronavirus [15], and in mid-January 2020, only one month after Chinese authorities shared the genetic sequence of the novel coronavirus, COVID-19, Moderna completed the first clinical batch of mRNA-1273 for COVID-19 [16]. Approximately one month after that, the FDA completed its review

of the investigational new drug (IND) application filed by the NIH for mRNA-1273 and allowed the study to proceed to clinical trials.

Development of the COVID-19 mRNA Vaccines: The T1 phase of translation

The T1 phase of translation is the phase to human application. It is the phase of proof of concept and first clinical trials when new methods of diagnosis and treatment are tested.

Pfizer-BioNTech COVID-19 vaccines, BNT162b1 and BNT162b2

Based on four BNT162 RNA candidates, two emerged as strong candidates for Pfizer-BioNTech COVID-19 vaccines. The BNT162b2 candidate generated a strong anti-viral protective effect and T-cell responses in mice and rhesus macaques, and fully protected the lungs of immunized rhesus macaques from infectious SARS-CoV-2 challenge [17].

In a placebo-controlled, observer-blinded, dose-escalation, phase I trial conducted in the United States, healthy adults 18 to 55 years of age and those 65 to 85 years of age were randomly assigned to receive either placebo or one of two lipid nanoparticle-formulated, nucleoside-modified RNA vaccine candidates: BNT162b1, which encodes a secreted trimerized SARS-CoV-2 receptor-binding domain; or BNT162b2, which encodes a membrane-anchored SARS-CoV-2 full-length spike, stabilized in the prefusion conformation. The primary outcome was safety (e.g., local and systemic reactions and adverse events); immunogenicity was a secondary outcome.

In this study, trial groups were defined according to vaccine candidate, age of the participants, and vaccine dose level (10 µg, 20 µg, 30 µg, and 100 µg). In all of the groups but one, participants received two doses, with a 21-day interval between doses; in one group (100 µg of BNT162b1), participants received one dose.

195 participants underwent randomization. In each of 13 groups of 15 participants, 12 participants received vaccines and 3 received placebo. BNT162b2 was associated with a lower incidence and severity of systemic reactions than BNT162b1, particularly in older adults. In both younger and older adults, the two vaccine candidates elicited similar dose-dependent SARS-CoV-2-neutralizing antibodies [18].

Moderna mRNA-1273 SARS-CoV-2 Vaccine

In a preliminary study, Moderna also conducted a phase 1, dose-escalation, open-label trial including 45 healthy adults, 18 to 55 years of age, who received two vaccinations, 28 days apart, with mRNA-1273 in a dose of 25 µg, 100 µg, or 250 µg. There were 15 participants in each dose group.

The first vaccination showed a dose dependent antibody response, the second (21 days after dose 1) showed exponentially higher titers in each group. The vaccine elicited no serious adverse events, passing all safety concerns [19].

Another phase I trial specifically looked at dosage levels of the vaccine in 40 older adults, ages 56 and older. The vaccine was most effective at the 100- μ g dose in comparison to a 25- μ g dose for adults 56 and older. This matched the results of the earlier trial with younger participants. [20].

Development of the COVID-19 mRNA Vaccines: T2 Phase - translation to patients - Phase 2 and 3 clinical trials are performed leading to effective care.

Moderna mRNA-1273 SARS-CoV-2 Vaccine

A phase 3 randomized, observer-blinded, placebo-controlled trial was conducted at 99 centers across the United States. Persons at high risk for SARS-CoV-2 infection or its complications were randomly assigned in a 1:1 ratio to receive two intramuscular injections of mRNA-1273 (100 μ g) or placebo 28 days apart.

The trial enrolled 30,420 volunteers. The average age of volunteers was 51 years. Approximately 47% female, 25% were 65 years or older and 17% were under the age of 65 with medical conditions placing them at higher risk for severe COVID-19. Approximately 79% of participants were white, 10% were Black or African American, 5% were Asian, 0.8% were American Indian or Alaska Native, 0.2% were Native Hawaiian or Other Pacific Islander, 2% were multiracial, and 21% were Hispanic or Latino. More than 96% of participants received both injections, and 2.2% had evidence (serologic, virologic, or both) of SARS-CoV-2 infection at baseline.

Symptomatic COVID-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; $P < 0.001$). The vaccine also demonstrated efficacy in preventing severe COVID-19. Investigators identified no safety concerns and there was no evidence of vaccine-associated enhanced respiratory disease [16].

Pfizer-BioNTech COVID-19 vaccines, BNT162b1 and BNT162b2

In a multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, assigned persons 16 years of age or older were randomized in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μ g per dose).

43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of COVID-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing COVID-19 (95% credible interval, 90.3 to 97.6).

The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache.

The incidence of serious adverse events was low and was similar in the vaccine and placebo groups [21].

Data from Israel's largest health care organization were used to evaluate the effectiveness of the BNT162b2 mRNA vaccine. All persons were matched to unvaccinated controls in a 1:1 ratio according to demographic and clinical characteristics.

Each study group included 596,618 persons. Estimated vaccine effectiveness for the study outcomes at days 14 through 20 after the first dose and at 7 or more days after the second dose was as follows: for documented infection, 46% (95% confidence interval [CI], 40 to 51) and 92% (95% CI, 88 to 95); for symptomatic COVID-19, 57% (95% CI, 50 to 63) and 94% (95% CI, 87 to 98); for hospitalization, 74% (95% CI, 56 to 86) and 87% (95% CI, 55 to 100); and for severe disease, 62% (95% CI, 39 to 80) and 92% (95% CI, 75 to 100), respectively. Estimated effectiveness in preventing death from COVID-19 was 72% (95% CI, 19 to 100) for days 14 through 20 after the first dose. This study suggested that the BNT162b2 mRNA vaccine was effective for a wide range of COVID-19 related outcomes [22].

Development of the COVID-19 mRNA Vaccines: T3 Translation to Practice – Phase 4 clinical trials to test population level outcomes, which are a true benefit to society.

There are several phase 4 clinical trials ongoing using both the Moderna and Pfizer mRNA vaccines [23].

A National cohort of over 10,000 participants were elected to study the effectiveness and safety of the SARS-CoV-2 mRNA vaccines. The primary outcome will be the minimal protective neutralizing antibody titre (the minimum level of neutralizing antibodies sufficient to protect the person from becoming infected). Completion date is set at December 31, 2024.

SARS-CoV-2 Immune Responses after COVID-19 Therapy and Subsequent Vaccine Study of the Moderna mRNA vaccine. Primary outcomes will measure neutralizing antibodies, T4, and T8 responses. Completion date is set at June 2023.

Another ongoing phase 4 trial involves optimal third dose strategy for SARS-CoV-2 vaccination in kidney transplant patients. The primary outcome is the positive SARS-CoV-2 seroresponse (antibodies and cellular). Completion date is set at January 2023.

Another ongoing phase 4 trial - Factors Influencing the COVID-19 Vaccine Immune Response (Reactogenicity and Immunogenicity) According to Age and Presence or Not of a Past History of COVID-19. Primary outcomes will measure anti-S neutralizing antibody titer. Completion date is set at March 2023.

Development of the COVID-19 mRNA Vaccines: T4 Transition to community - Population level outcomes research studying benefits to society.

Despite the speed development of the mRNA COVID-19 vaccines, all steps have been taken to ensure their safety and

Phases of Translation for Development of mRNA COVID-19 Vaccine

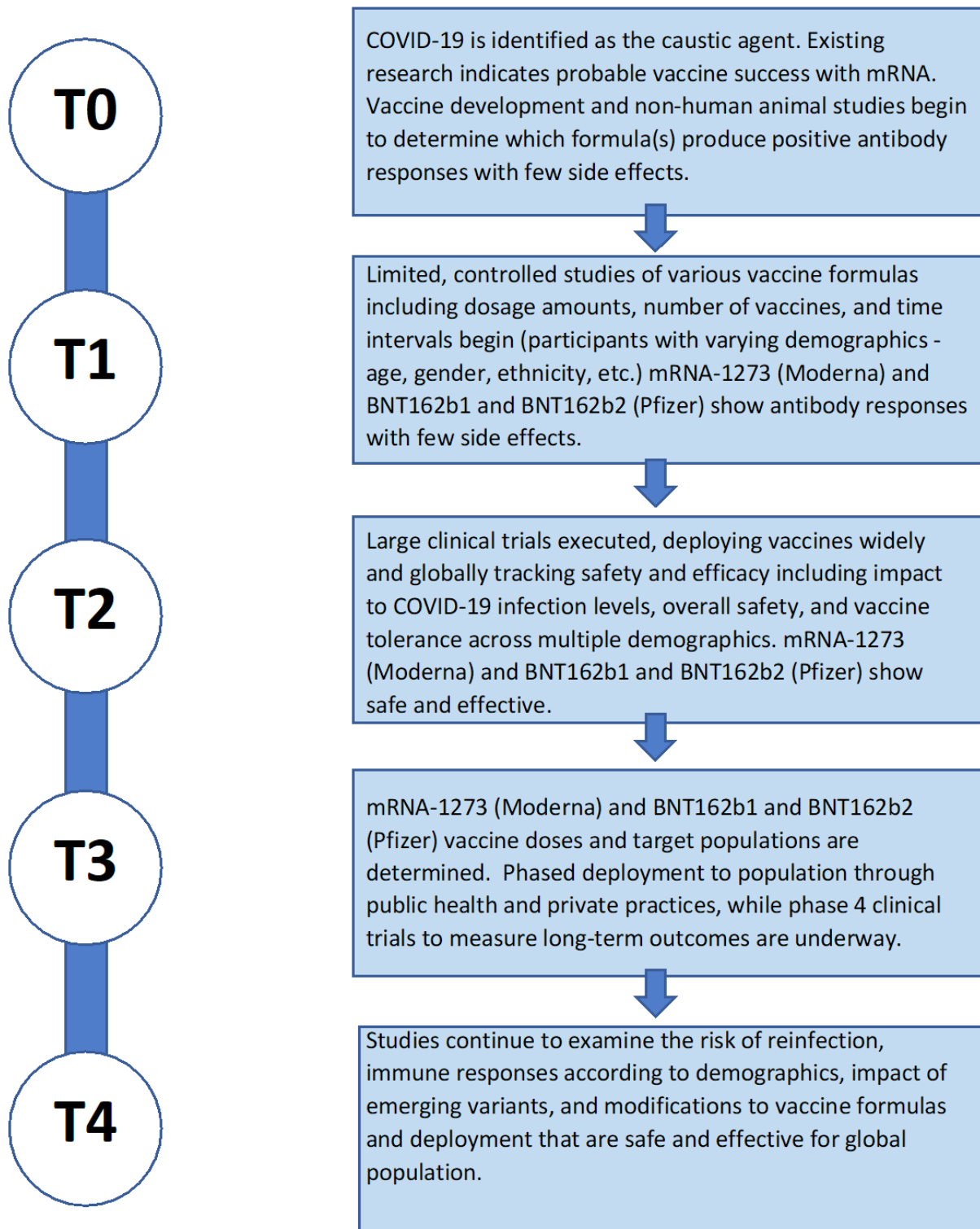


Figure 2. Phases of Translation as they relate to mRNA vaccine development

effectiveness (see results of clinical trials above). As of the writing of this paper, the Pfizer-BioNTech COVID-19 vaccine (now called COMIRNATY) has been granted full approval by the Food and Drug Administration (FDA), meeting the government's highest standards for safety, effectiveness, and manufacturing quality. The Moderna COVID-19 vaccine is soon to follow.

The results of the vaccine studies (above) show that getting vaccinated against COVID-19 can greatly lower your risk of becoming infected with and spreading the virus that causes COVID-19 [24,25]. These vaccines can also help prevent serious illness and death, which may occur by being infected and unvaccinated (see clinical studies above).

In studies directly comparing risk of reinfection among previously infected individuals who were never vaccinated versus individuals who were vaccinated after infection, previously infected persons who were unvaccinated had 2.3 times greater odds of reinfection [26] and vaccinating previously infected individuals significantly enhances their immune response and effectively reduces the risk of subsequent infection. This includes the setting of increased circulation of more infectious variants, suggesting that regardless of pre-infection, getting the mRNA vaccine will greatly reduce chances of developing serious disease [27].

There are many studies in progress assessing the benefits and potential health risks of these mRNA vaccines, but all indications are that medical research, like with most vaccines, has hit another home run.

In summary, there are many clinical trials still ongoing, which are designed to continue to assess the effectiveness and safety of the mRNA vaccines. The translation of COVID-19 vaccine development from lab bench to bedside is a great example of scientific ingenuity at its best (see Figure 2 for summary of the phases of translation as they relate to this development).

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