COVID-19 Vaccine Evolution and Beyond

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ABSTRACT: In December 2019, a new severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) was first reported in China. It would quickly spread and emerge as a COVID-19 pandemic. The illness caused by SARS CoV-2 would fall on a clinical spectrum ranging from asymptomatic, mild to severe respiratory symptoms, ARDS, and death. This led to significant morbidity and mortality further impacting at-risk populations with severe complications. Thus, a concerted worldwide effort to meet the challenges of diagnosing, treating, and preventing COVID-19 led to rapid advances in medicine. Some mitigating methods of masking, social distancing, and frequent handwashing, helped to slow the spread of SARS-CoV-2. Effective therapeutics consisting of antivirals and monoclonal antibodies, plus their use for prophylaxis, contributed to the management of COVID-19. The vaccines from various platforms (mRNA, viral vectors, protein base, and inactivated) contributed to decreased incidence, severity, and overall decreased hospitalizations and mortality. This article aims to review the novel mRNA vaccines (Moderna + Pfizer/BioNTech), viral vector (Janssen& Johnson), and protein base (Novavax), their side effects, and their use as boosters.

KEYWORDS: COVID-19 vaccines, COVID-19 mortality, and morbidity, COVID-19 post-vaccination, infection prevention

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Introduction

In March 2020 the World Health Organization (WHO) announced the COVID-19 pandemic. As of October 2022, there have been greater than 621 million cases and 6.5 million deaths globally.[1] COVID-19 disease is caused by SARS-CoV-2 a single positive-strand RNA virus belonging to a subset of beta-coronaviruses that are known to infect mammals.[2,3] It is most commonly spread in 3 ways (1) through respiratory droplets from an infected person through inhalation, (2) exhaled droplets settling on mucosal membranes of the uninfected person (eyes, mouth, nose), and (3) touching inanimate surfaces with high viral inoculum and inadvertently touching ones mucosa. The incubation period for SARS-CoV-2 is between 1 and 14 days. Symptoms generally consist of fever, cough, fatigue, and sore throat, but most people are asymptomatic. In the early stages of the pandemic, the *R*-naught (R0) was thought to be between 2 and 3, however, that number has increased with different variants. Infection and prevention strategies consist of social distancing (6ft), wearing masks, avoiding areas with poor ventilation, and quarantining those who are infected or exposed.

Unfortunately, the elderly and certain ethnic groups (Blacks, Latinos) and those with certain health conditions (Cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, obesity, and the immunocompromised) were more likely to have severe presentations and associated mortality.[4,5] The urgency for prevention put vaccine development, a process that historically took 10 to 15 years, on a fast track. In 2020 Operation Warp Speed, a multi-agency collaboration within the United States government later changed to White House COVID-19 response team in 2021, supported 6 vaccine candidates. The novel mRNA platform by Pfizer/BioNtech & Moderna, viral vector platforms Johnson& Johnson /Janssen & AstraZeneca/Oxford Univ, and protein platforms Novavax & Sanofi/GSK.[6,7]

SARS CoV-2 has 4 structural proteins: the Envelope (*E*), Spike protein (*S*) Membrane proteins (*M*), and Nucleocapsid protein(*N*). Together these 4 structures are necessary for viral entry into the host cell.[2,3] The spike protein has an affinity for ACE2 receptors in human cells causing conformational changes that fuse the host membrane to the viral membrane. As a result, COVID-19 vaccines have specifically targeted the surface spike protein of SARS-CoV-2.

Pfizer/BioNtech BNT162b2 (Comirnaty) was the first mRNA vaccine approved under emergency use by the US on 12/11/20 and later granted full approval from FDA on 8/23/21. It demonstrated a 95% protection against moderate-to-severe complications of COVID-19 when given as a 2-dose regimen 21 days apart.[8,9] Moderna mRNA-1273 (Spikevax) was the second mRNA vaccine approved for emergency use on 12/17/20 and later granted full approval on 1/31/22. It demonstrated a 94% vaccine efficacy against severe complications of COVID-19. It was given as a 2-dose primary series 28 days apart.[10] Common side effects of both vaccines consist of pain at the injection site, fever, headache, and lymphadenopathy. These side effects are more prominent after the second dose.

Johnson/Janssen was first approved on 2/27/21 by FDA for emergency use but early reports of thrombotic events temporarily held distribution in April 2021 and resumed use in May

2021. It demonstrated a vaccine efficacy of 66.9% as a 1-time dose across all groups. More recently Novavax was approved 7/13/22 under emergency use. It demonstrated a 90% efficacy with 2-dose primary series 21 days apart.[11] The side effects are similar to those found in the mRNA vaccines. Whether vaccinated or previously infected with SARS-CoV-2, people experience waning neutralizing antibodies. Both Moderna and Pfizer have been approved for boosters. The development of these vaccines has contributed to better control and decreased transmission of SARS-CoV-2 globally.

Evolution and Approval of Vaccine

Pfizer BioNTech identified BNT162b1 and BNT162b2 as strong COVID-19 vaccine candidates.[9] BNT162b1 and BNT162b2 are lipid nanoparticle-formulated mRNA vaccines that encodes SARS-CoV-2 spike protein. Once inoculated, the lipid nanoparticle facilitates delivery of RNA within host cells thus promoting expression of SARS-CoV-2 S antigens which protects against COVID-19. Preclinical trials on mice and rhesus macaques using both vaccine candidates induced strong antibody responses protective against SARS-CoV-2.[12] Robust CD4+ and CD8+ *T*-cell responses were elicited upon administration of the BNT162b1 or BNT162b2 vaccines, but a more potent IFNy-producing CD8+ response was seen among mice that received BNT162b2. On April 23, 2020, phase 1 to 2 clinical trials were started. Participants were separated into dose groups (1, 10, 30, and 50 µg). Participants received either a single-dose or 2-dose schedule of BNT162b1 or BNT162b2.[9] Vaccination with either candidate elicited a strong antigen-specific immune response and antibody production which increased exponentially after the second dose. BNT162b2 was selected over BNT162b1 to progress in clinical trials due to its better tolerability (specifically the 30 µg dose) and MHC diversity of *T*-cell epitopes. In phases 3 to 4 clinical trials, BNT162b2 demonstrated 95% efficacy in the prevention of COVID-19, and a good safety profile.[8] By December 11, 2020, Pfizer BioNTech's BNT162b2 became the first candidate to receive Food and Drug Administration (FDA) Emergency Use Authorization (EUA) approval for a 2-dose (30 µg, 0.3 mL each) schedule administered intramuscularly, 21 days apart in people ages 16, and above.[13] On May 10, 2021, FDA issued EUA to include adolescents aged 12 to 15 years[14,15] after clinical trials demonstrated 100% efficacy, and an acceptable safety profile.[16] October 29, 2021, the FDA again released an EUA for Pfizer-BioNTech in children aged 5 to 11 years, after clinical trials demonstrated 90.9% efficacy, and good safety profile.[17]

The Moderna COVID-19 vaccine candidate (mRNA-1273) is a lipid nanoparticle formulated mRNA vaccine that contains prefusion stabilized full-length spike protein of the SARS-CoV-2 virus which induces COVID-19.[10] mRNA-1273 showed a robust and protective dose-dependent antibody production in primates during preclinical trials.[18] Phase 1 clinical trial involved 3 dose groups (25, 100, or 250 µg), and participants received two-dose vaccines 28 days apart. A dose-dependent antibody response was observed with moderate adverse reactions after the second dose, especially among the 250 µg dose group.[19] The trial was expanded to include 2 cohorts of older adults (56-70 years and 71 and older) in 2 dose groups (25 or 100 µg). The mRNA-1273 vaccine provoked a strong antigen-specific type 1 *T*- helper cell response and the adverse effects were mild.[20] In phase 3 clinical trials, mRNA-1273 had a favorable safety profile and 94.1% efficacy in preventing COVID-19 infection and critical disease.[10] By December 20, 2020, FDA issued an EUA for mRNA-1273 in individuals 18 years and older. Two doses of mRNA-1273 (100 µg, 0.5 mL each) were administered intramuscularly, 4 weeks apart.

Preclinical trials show that Johnson and Johnson's (Ad26.COV2.S) COVID-19 vaccine candidate stimulates strong protective immune responses in primates.[21] Ad26.COV2.S is a recombinant, replication-incompetent adenovirus serotype 26 (Ad 26) vector-based vaccine expressing full-length stabilized SARS-Cov-2 spike protein.[22] Upon inoculation, Ad 26 delivers SARS-Cov-2 spike protein into host cells where it stimulates immune response. Ad26.COV2.S was found to induce a robust neutralizing antibody response after single-dose administration. The study also showed full protection in 5 of 6 vaccinated animals exposed to SARS-CoV-2. In July 2020, the phase 1 to 2 clinical trial of Ad26.COV2.S was initiated. Participants received either a low (5×10^{10}) or high dose ($1 \times 10^{\wedge 11}$) vaccine intramuscularly in a single-dose or two-dose schedule. By post-vaccination day 57 antibody titers rose to 96% and remained stable at follow-up (day 71).[21] Adverse effects were rare among participants who received low doses. In Phase 3 to 4 clinical trials, the single low dose Ad26.COV2-S protected against COVID-19 infection and was potent against severe-critical disease. Vaccine efficacy 14 days post-vaccination was ⩾63% irrespective of race, sex, and age. On February 27, 2021, a EUA was issued for the single dose ($5 \times 10^{\wedge 10}$ virus particles per 0.5-mL dose) Ad26.COV2.S vaccine in people aged 18 years and above for the prevention of COVID-19.[23] On April 13, 2021, both CDC and FDA recommended the discontinuation of Ad26.COV2.S due to the risk of cerebral venous sinus thrombosis (CVST). On April 23, 2021, Ad26.COV2.S was again approved for use among persons ages 18 years and older with warnings about the rare but potential adverse event of thrombosis among women of reproductive age (18-49 years).[24] The vaccine benefits were found to outweigh the risk of thrombosis among all populations.

On July 13, 2022, the FDA issued an EUA for the Novavax COVID-19 vaccine (NVX-CoV2373), adjuvanted in people aged 18 years and older.[25] It was approved following a phase 3 clinical trial conducted in the United States and Mexico in individuals aged 18 years and older. NVX-CoV2373 was found to have 90.4% efficacy in preventing COVID-19 infection and 100% efficacy in moderate to severe cases.[11] On

August 19, 2022, the EUA was expanded to include individuals aged 12 years and older.

Complications of Vaccine

COVID-19 vaccinations have been utilized as a prophylactic measure against the worst effects of the virus, but unwanted side effects such as anaphylaxis and thrombotic events still occur. Anaphylaxis is an allergic reaction that is severe, prompting systemic hypersensitivity, rapid onset of breathing, airway, and circulatory issues. Acute onset is characterized by pruritus, GI disturbances, and swelling of the lips, tongue, and uvula. The WHO reported in March 2021 after the first day of mass vaccination that there was a 0.0005% incidence rate of anaphylaxis for the Pfizer-BioNTech vaccine in both the US and the UK.[26] The CDC also reported that between December 2020 and January 2021 that the incidence of anaphylaxis was 0.37 per 100 000.[27] Though these events are relatively rare, there are certain steps that can be taken for risk evaluation. Risk analysis should include consultation with an allergist in a shared decision-making process (1) when to get the vaccine (2) which 1 to get, and measures of mitigation. The CDC also recommends that individuals with a proven allergy to polyethylene glycol (PEG) should avoid mRNA COVID-19 vaccines for both doses. Premedication with antihistamines is also not recommended.[28] .

Skin tests, and basophil activation tests are recommended by multiple immunological authorities, to confirm allergic reactions. The skin test involves using a lancet to puncture the skin, then exposing it to saline and histamine to test for allergies. The basophil activation test involves incubating a blood sample with a specific allergen to see if basophils populate, which indicates an allergy exists. Another strategy used to address allergic reactions to vaccines is to utilize vaccines with different components than the first dose but this also comes with the risk of cross-reactivity. One example is having the ChadOx1 nCoV-19 boosted with BNT162b2.[28] Further studies need to be done to determine the impact of associated risks and benefits.

Another serious adverse effect of COVID-19 vaccines includes thrombotic events. The phenomenon is known as vaccine-induced thrombotic thrombocytopenia (VITT). In a systematic review, after vaccination, platelet levels drop significantly in Pfizer, Moderna, and AstraZeneca.[29] In one exploratory study, there were thrombotic events found across all 3 vaccines the authors analyzed. The individuals within the Moderna and Pfizer studies had low platelet levels. For treatment, 2 of these 3 received corticosteroid therapy, platelet transfusion, and intravenous immunoglobulin. One of these 2 also received a thrombopoietin receptor agonist and the final patient did not receive treatment. Within the Astra-Zeneca cohort, there was an indication that many individuals had low platelet levels.

Further review revealed that across this cohort, the most common location for thrombotic events was basivertebral veins. There were also other studies found in this review where 1 patient had a case of carotid artery thrombosis and another had a multi-locational thrombosis event that was in the cerebral venous sinus (CVS), intracerebral, and pulmonary. A few other studies within this review said thrombosis events manifested mostly in the CVS. The common treatments to address thrombotic events include antifibrinolytic treatment, corticosteroid therapy, and heparin.

The mechanism of VITT is not well understood because there are many possible pathways that can lead to these thrombotic events. The current understanding is that the VITT mechanism is similar to heparin-induced thrombocytopenia as it is an immune-mediated response. Another explanation involves antibody cross-reactivity between spike proteins and PF4 epitopes, but this needs to be further explored in research. Inflammation also stimulates neutrophils and even after getting the vaccine, this could trigger a coagulopathy cascade pathway parallel to fibrin deposition. The vaccine has components that trigger the neutrophils and also activate *T* and *B* cells.[29] For both anaphylaxis and thrombosis events, these events are relatively rare as indicated by the incidence rate. Further research is needed to better determine both prophylactic and mitigating measures to vaccine serious/life-threatening reactions.

Booster

Following the first major surge in US and worldwide cases of the alpha variant, emergency use authorization (EUA) was provided for the 3 primary vaccines directed against SARS-CoV2 involving Pfizer/BioNtech, Moderna, and Johnson & Johnson on December 11, 2020, December 18th, 2020, and February 27th, 2021 respectively.[8,10,30,31] Unfortunately, the reprieve from severe illness, hospitalization, and death was short-lived and it became clear that re-infection from a combination of waning immunity both by prior infection and vaccination, as well as the emergence of new variants, threatened our newfound protection. On August 18th, 2021 the CDC released a memorandum concluding that booster vaccinations would be necessary to maintain appropriate titers of neutralizing antibodies.[31] On October 21, 2021, Pfizer/BioNtech and Moderna received EUA for booster shots for high-risk groups, and boosters were recommended for everyone over 18 years and those that had received the Johnson & Johnson initial vaccination.[31] This guidance was quickly expanded to everyone 18 and older on November 19th, 2021.[31] On January 3rd, 2022 EUA was provided for booster shots for 12 to 15 yo with Pfizer/BioNtech with further data released on February 11th, 2022 demonstrating the safety and efficacy of both Pfizer/BioNtech and Moderna booster shots for those 5 yo and up[31] On March 9th,2022 guidance was provided recommending a booster for all versions of vaccine to those immunocompromised or older than 50 yo and that anyone having received the J&J vaccine also receive a dose of either Pfizer/BioNtech or Moderna.[8] Second

Boosters were then recommended on May 9th, 2022 for those 12 to 18 yo who are immunocompromised and primary boosters for those 5 to 11 yo with Pfizer/BioNtech.[31] As of the time of writing this article, the most updated recommendation is for everyone 12 yo and older to receive an updated bivalent booster directed at Omicron subvariants BA.4 and BA.5.[32]

Discussion

In summary, the COVID-19 pandemic has changed the landscape of vaccine development, production, and rollout. This involved different international partnerships to track, study and release relevant information that allowed medical societies to stay on top of how the virus was changing. This intense monitoring and release of information allowed for better prediction and protection for populations worldwide. Many mitigating measures were taken like social distancing, wearing masks, and PPE, and following other hygienic practices, however, the vaccines contributed significantly to slowing the spread of COVID-19 disease and its deadly grip. Not only were the vaccines developed with many novel platforms but highly effective in protecting against and minimizing severe complications from COVID-19 disease. The mRNA vaccines as a primary series have greater than 90% efficacy but their boosters have been just as effective. The rollout and uptake of the vaccine were not without resistance and controversy. There were many concerns due to the pace at which the vaccines were studied, produced, and distributed.

Equity of vaccine distribution became apparent with rich countries buying a disproportionate number of vaccines in comparison to their populations. The side effects of the vaccines were a great concern due to the shorter length of time to elucidate potential adverse reactions compared to prior vaccines. The unknown side effects would not be known until distributed in a much larger population. This played out the J&J vaccine, with a subsequent higher association of developing thrombotic events when compared to the regular population. As a result, J&J became a secondary option for COVID-19 primary vaccination in the US. The anti-vaccine sentiment spurred many false claims and led to initial lag uptake of the vaccine in the US. A considerable effort was undertaken to combat disinformation through many organized scientific organizations on the local, national, and international levels. The vaccines produced as a result of this pandemic have spurred new research and more are being developed in order to meet the next pandemic. It has laid a rough but evolving blueprint of what worked, potential barriers, and setting services or institutions to deal with unexpected problems. More importantly, gauging the public understanding of the vaccine and implementing strategies that build trust is crucial to public engagement and the use of therapeutics. This pandemic revealed that a consistent message to the public in regard to the threat, and transparency about all stages of vaccine development, effectiveness, and safety will likely lead to better reception and uptake of the vaccine for the next major health crisis.

Author Contributions

All authors contributed equally to the revisions, research, and development of this publication.

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