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Efficacy, effectiveness and safety of Comirnaty vaccine in the prevention of symptomatic and asymptomatic SARS-CoV-2 infections

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ABSTRACT

The high infectiousness and contagiousness of the SARS-CoV-2, as well as the alarmingly severe course of COVID-19, inspired research teams from around the world to begin an urgent search for effective methods to neutralize the new pathogen. The mRNA vaccine Comirnaty was the first conditionally licensed vaccine against SARS-CoV-2. Its key ingredient is a fragment of matrix RNA obtained by *in vitro* transcription that corresponds to the sequence that encodes the spike protein (S protein) of the SARS-CoV-2. Today, it is well established that in the face of the continued evolution of the SARS-CoV-2, the effectiveness of the vaccination in the core regimen is not sufficient to prevent infection. However, the sustained high level of vaccine protection against severe forms of COVID-19 can significantly reduce hospitalizations and deaths. In addition, the documented risk of serious adverse events following each dose of the vaccine appears relatively small compared to the potential health consequences of COVID-19 infection. This article presents scientific studies describing the role of the Comirnaty vaccine in the prevention of COVID-19 infection and severity.

Keywords: SARS-CoV-2; COVID-19; Comirnaty; Pfizer/BioNTech; mRNA vaccine; vaccine efficacy; vaccine effectiveness; vaccine safety.

INTRODUCTION

When a new infectious viral disease was announced in the city of Wuhan in central China in December 2019, it was impossible to predict the scale of the problem that the world would face just a few months later [1]. The SARS-CoV-2 was rapidly expanding in scope, and the COVID-19 it caused was titled a pandemic by WHO in March 2020. The high infectiousness and contagiousness of the virus, as well as the alarmingly severe course of COVID-19, inspired research teams from around the world to begin an urgent search for effective methods to neutralize the new pathogen [2]. The lack of adequate treatment with antivirals had led the scientific community to develop standards for prophylaxis, and as a result of the intensive work by pharmaceutical companies, protective vaccines against SARS-CoV-2 appeared on the market [3]. Currently, the most widespread are: Comirnaty – the result of cooperation between BioNTech and Pfizer [4], Spikevax – Moderna [5], Vaxzevria – AstraZeneca [6] and Ad26.COV2.S – Janssen/Johnson&Johnson [7]. The widespread campaign promoting vaccination as a fundamental form of combating the SARS-CoV-2 has been met with controversy and mistrust regarding the actual effectiveness and safety of the conditionally approved vaccine preparations. This article presents scientific studies describing the role of the Comirnaty vaccine in the prevention of COVID-19 infection and severity.

COMPOSITION AND MECHANISM OF ACTION OF THE COMIRNATY VACCINE

The mRNA vaccine Comirnaty was the first conditionally licensed vaccine against SARS-CoV-2. The decision to make it available to countries in the European Union in the phase 3 of clinical trials was made by the European Commission on December 21, 2020.

The Comirnaty formulation is a genetic vaccine. Its key ingredient is a fragment of matrix RNA obtained by *in vitro* transcription that corresponds to the sequence that encodes the spike protein (S protein) of the SARS-CoV-2 [8]. The composition of the vaccine is completed by lipids, salts and sucrose, which ensure the stability and viability of the preparation. The addition of polyethylene glycol ensures that the active substance of the vaccine is not neutralized before reaching the target cells [9].

The mechanism of action of the vaccine involves the introduction of mRNA, among others, into antigen-presenting cells, where translation of the finished matrix into the desired polypeptide occurs. The penetration of mRNA into cells takes place by endocytosis and is made possible by dedicated carriers – lipid nanoparticles [10]. Efficient translation of delivered mRNA is enabled by modifications introduced at the *in vitro* transcription stage, such as the selection of optimal codons [11] and the addition of 1-methyl-pseudouridine nucleoside [12]. An additional advantage of the presence of the uridine analog is its inhibitory effect on the mechanisms of innate immunity and, as a result, minimization of the inflammatory reaction

following introduction of the vaccine into the system [13]. It is worth mentioning that the vaccine mRNA presents features of mature cellular mRNA due to the presence of a guanylyl cap at the 5' end and a poly A sequence at the 3' end. In this form, the mRNA is unable to reach the cell nucleus, and its reading and degradation occur exclusively in the cytoplasmic environment [14]. The polypeptide chain obtained by translation undergoes post translational modification. The inclusion of triplets encoding 2 adjacent prolyl moieties into the sequence of the matrix RNA allows the formation of the S protein in a pre-fusion conformation, which contributes to maximizing the immunogenic effect of the antigen [15]. The production of the S protein is time-limited and continues until the vaccine mRNA is fully degraded by cytoplasmic nucleases [14].

EFFICACY AND EFFECTIVENESS OF THE COMIRNATY VACCINE AGAINST DIFFERENT VARIANTS OF THE SARS-COV-2

One of the first reports of the high efficacy of the Comirnaty vaccine was made by Polack et al. who conducted a randomized cohort study on a group of 43448 volunteers over the age of 16 years [4]. Half of the subjects formed the study group that received 2 doses of the vaccine 21 days apart. The remaining participants received a placebo, thus constituting the control group. After 7 days of the 2nd dose, the authors described 8 cases of COVID-19 in the vaccinated group and 162 cases of infection in the control group. The results provided a preliminary estimate of clinical efficacy of 95%. The safety profile at 2 months after receiving the full vaccination schedule presented similarly to that observed after administration of other antiviral vaccines. That study was conducted during the clinical trials of the vaccine and served as a reference for subsequent analyses.

The promotion of SARS-CoV-2 vaccination in Israel gave data on the effectiveness of Comirnaty. In a cohort study conducted from 20 December 2020 to 1 February 2021, Dagan et al. examined a population of more than 1 million individuals over the age of 16 years with no prior diagnosis of COVID-19 [16]. The study group comprised 596618 participants vaccinated with at least 1 dose of the product. An equal number of unvaccinated subjects formed the control group. The purposes of the study included assessing the frequency of different clinical forms of COVID-19. A total of 10561 infections were diagnosed, comprising 5996 cases of symptomatic disease, 369 cases requiring hospitalization, 229 cases of severe COVID-19 infection, and 41 deaths. The authors evaluated the effectiveness of a single dose within 14–20 days of vaccination. The risk of SARS-CoV-2 infection was reduced by 46%, onset of symptomatic illness by 57%, hospitalization by 74%, and severe illness by 62%. Analogous data were collected in subjects vaccinated with 2 doses. After 7 days of receiving the full vaccination schedule, the estimated effectiveness was 92%, 94%, 87% and 92%, respectively.

A satisfactory effectiveness of the Comirnaty vaccine was demonstrated by Amit et al. in their study on the employees of Sheba Medical Centre in Israel [17]. The study included 9109 medical personnel without a documented history of COVID-19; 7214 participants received a 1st dose of vaccination and 6037 of these subsequently received a 2nd dose. The control group consisted of 1895 unvaccinated workers. Between 19 December 2020 and 24 January 2021, 170 cases of SARS-CoV-2 infection were reported in the study population; 89 in the control group, 78 in the single-dose vaccinated group, and 3 in the full-dose vaccinated group. The authors analyzed the risk of developing asymptomatic and symptomatic COVID-19 at 1–14 days and 15–28 days after the 1st dose of vaccine. The estimated risk reduction for asymptomatic disease was 30% in the first 2 weeks and 75% in the following 2 weeks, while the risk reduction for symptomatic disease was estimated at 47% and 85%, respectively.

A study by Abu-Raddad et al. provided data on the effectiveness of the Comirnaty vaccine during expansion of the B.1.1.7 and B.1.351 variants of SARS-CoV-2 in Qatar [18]. The study population underwent RT-PCR testing, after which participants were classified into 2 groups of 40473 individuals each. The study group consisted of infected individuals, while negatively diagnosed volunteers served as controls. A risk assessment of COVID-19 incidence was performed using vaccination rates in both groups. The authors documented 89.5% effectiveness 14 or more days after 2 doses of Comirnaty in preventing infection with variant B.1.1.7 and 75% effectiveness for variant B.1.351. Focusing solely on the risk of contracting severe, critically severe, and fatal forms of COVID-19, vaccine effectiveness for the full schedule was estimated to be 100% against both variants tested and 97.4% against all SARS-CoV-2 variants discovered to date.

Another need to verify the effectiveness of vaccines arose during the period of increased expansion of the B.1.617.2 variant (also known as Delta) in the United Kingdom. Lopez Bernal et al. conducted a test-negative case-control study assessing the risk of developing symptomatic COVID-19 caused by the Delta variant, among others, in subjects vaccinated with a single or double dose of Comirnaty vaccine [19]. At 21 days after the 1st dose, vaccine effectiveness was estimated at 35.6%, and at 14 days after the full vaccination schedule, effectiveness was 88%. The results were compared with analogous effectiveness data against the earlier variant B.1.1.7 The authors noted a slight decrease in the protection of Comirnaty vaccine against symptomatic COVID-19 caused by the variant B.1.617.2.

A cohort study with retrospective data collection by Tartof et al. focused on the effectiveness of the Comirnaty vaccine in preventing hospitalizations due to the Delta variant infection [20]. The population analyzed consisted of 3436957 members of Kaiser Permanente Southern California medical centers vaccinated with a single or 2 doses of the product. The authors demonstrated 93% effectiveness in preventing hospitalizations associated with the Delta variant infection after receiving the full vaccination schedule, which was slightly lower than the estimated effectiveness against other SARS-CoV-2 variants (95%). The same study also evaluated the degree of protection against the Delta variant infection and other

viral variants as the months following receipt of the full vaccination progressed. It was noted that actual effectiveness at 4 months (compared with the 1st month after full vaccination) decreased from 93% to 53% in Delta variant infections and from 97% to 67% for other variants.

The alarming decline in vaccine effectiveness during the period of Delta variant dominance has resulted in studies on the impact of the 3rd dose in the months following administration. Data collected from Clait Health Services in Israel allowed Barda et al. to assess the degree of protection against hospitalization, severe course and death from COVID-19 infection [21]. A study group of 728321 individuals was vaccinated with a 3rd (booster) dose. An equally large control group consisted of volunteers who had received a 2nd dose of Comirnaty at least 5 months earlier. The effectiveness of the 3rd dose was estimated to be 93% in preventing hospitalizations, 92% in preventing severe forms of infection, and 81% in preventing deaths. A similar analysis, also in Israel, was conducted by Bar-On et al. focusing on severe forms of COVID-19 and hospitalizations in individuals over 60 years of age [22]. The study enrolled 1137804 volunteers who had received the Comirnaty core vaccination schedule at least 5 months previously. The study population focused on the portion of the population that had been vaccinated with a booster dose at least 12 days earlier. The authors found that receiving a 3rd dose of the vaccine reduced the risk of SARS-CoV-2 infection 11.3 times and the risk of hospitalization for infection 19.5 times.

SAFETY AND SIDE EFFECTS OF COMIRNATY VACCINE

Concerns about the potential side effects of SARS-CoV-2 vaccination keep many people from receiving even a single dose of any of the available preparations. The Comirnaty vaccine showed a promising safety profile in late-stage clinical trials. Polack et al. looked at the most common adverse events within 7 days of receiving the 1st and 2nd doses of Comirnaty vaccine in the 16–55 and over 55 age groups [4]. The results were compared with a control group that received placebo. Overall, more cases of both local and generalized vaccine reactions were described among members of the study group. The most common reports from vaccinated subjects were mild to moderate pain at the injection site (66–83%). Severe pain occurred in less than 1% of all study participants. Other rare local reactions included redness (5–7%) and swelling (6–7%). Generalized symptoms were more common in young patients, mostly in the form of headache (25–52%) and fatigue (34–59%). Fever was observed more often after the 2nd dose, in young patients (16%). Most adverse post vaccination reactions resolved after 1–2 days. A randomized cohort study conducted by Thomas et al. was a follow-up of clinical safety testing of the vaccine [23]. The follow-up period was 1 month after the 1st dose and 6 months after the full vaccination schedule. The incidence and severity of individual vaccine reactions presented similarly to the results obtained in the baseline study. Some new adverse events potentially related to the vaccination were reported, such as a lack of appetite, excessive sleepiness, chronic fatigue, decreased mood, night sweats, and increased sweating.

The Comirnaty vaccine required verification of its safety profile for serious adverse events, a task undertaken by Barda et al. by conducting a dedicated cohort study at facilities owned by Clait Health Services in Israel [24]. A total of 1769656 volunteers over the age of 16 years with no documented history of COVID-19 infection were eligible. Half of the analyzed population was vaccinated with Comirnaty; the other half was not vaccinated. The essence of the study was to compare the risk of specific adverse events in both groups within 42 days of receiving the vaccine. Among those vaccinated, there was an increased risk of developing myocarditis (3.24 times greater than for the unvaccinated ones), lymphadenopathy (2.43 times), appendicitis (1.4 times) and secondary chickenpox virus infection (1.43 times). In the next part of the study, the authors collected data on the risk of adverse events in the course of COVID-19 infection. Infected patients showed an increased risk of myocarditis (18.28 times), acute renal failure (14.83 times), pulmonary embolism (12.14 times), intracranial hemorrhage (6.89 times), pericarditis (5.39 times), myocardial infarction (4.47 times) and deep vein thrombosis (3.78 times).

The data obtained by Barda et al. provided an argument for further analysis of the issue of post-vaccination adverse events [24]. Mevorach et al. decided to look more closely at myocarditis incidents in vaccinated and unvaccinated individuals [25]. A cohort study with retrospective data collection conducted in Israel comprised 5442696 individuals vaccinated with at least 1 dose of Comirnaty. It was assumed that an adverse event could be correlated with vaccination if it occurred within a defined exposure period i.e. up to 21 days after the 1st dose or up to 30 days after receiving the 2nd dose. Of the 283 reported cases of myocarditis, 142 occurred within the exposure period in vaccinated subjects, 40 occurred outside the exposure period in vaccinated subjects, and 101 occurred in unvaccinated subjects. The established relative risk value up to 30 days after receiving a full vaccination averaged 2.35 relative to the unvaccinated individuals. The relative risk was highest among 16–19 year old males up to 7 days after the 2nd dose, at an estimated 31.9. The authors noted that incidents of vaccine-associated myocarditis were largely mild and with total recovery (95%), but with one fatality.

In the United Kingdom, researchers set out to evaluate the effect of vaccination on the incidence of thrombocytopenia and thromboembolic events. Hippisley-Cox et al. included 30879728 people vaccinated with Vaxzevria by Astra Zeneca or Comirnaty, among whom 9513625 participants received the genetic vaccine [26]. Adverse events were recorded in the analyzed population within the defined exposure period (up to 28 days after vaccination) or outside it. The authors showed a slight increase in the risk of arterial thrombosis (1.06 times), cerebral venous sinus thrombosis (3.58 times), and cerebral ischemic stroke (1.12 times) between 15–21 days after receiving the Comirnaty vaccine. Further considerations focused on that portion of the baseline population diagnosed with SARS-CoV-2 infection and similarly assessed the risk of adverse events, also

considering the 28-day exposure period. An increase in the risk of developing arterial thrombosis (4.52 times), cerebral venous sinus thrombosis (13.43 times), cerebral ischemic stroke (3.25 times), and other conditions such as thrombocytopenia, venous thrombosis, and myocardial infarction was observed between 8–14 days after confirmation of infection.

The era of rapidly advancing mutations of the SARS-CoV-2 is associated with the need to verify the safety of booster doses of vaccine preparations. In the United States, Hause et al. verified the types and incidence of adverse events after the 3rd dose of Comirnaty using data collected in the V-safe and VAERS systems [27]. It was found that subjects vaccinated 3 times with Comirnaty were less likely to report local and generalized adverse reactions compared to the exposure period after the 2nd dose. Medical attention was reported more frequently. An interesting finding was that those previously vaccinated with Moderna were less likely to report complaints after receiving a booster dose of Comirnaty vaccine than after receiving another dose of the same formulation. The most commonly reported adverse events were headache, fever, and pain in the injection area. Incidents of myocarditis were rare. A study conducted in the United Kingdom evaluated the safety of 7 different booster variants in the context of prior receipt of various available vaccines at baseline. Munro et al. demonstrated a favorable safety profile when a homologous booster was received with Comirnaty [28].

Undoubtedly, one of the features characterizing the safety profile of a vaccine is its effect on overall mortality in the population. Xu et al. conducted a cohort study with a retrospective data registry including 3452126 Comirnaty vaccinated subjects and 4600000 unvaccinated subjects as a control group. The overall mortality rate was estimated using data collected from both groups. The adjusted relative risk after vaccination with a single dose was 0.41 and decreased to 0.34 after receiving 2 doses [29].

CONCLUSION

The development of mRNA vaccine technology has allowed the world to enter a new era of infectious disease prophylaxis, making it possible to achieve results comparable to, and often superior to, previously used methods of active immunization. Expansion of the SARS-CoV-2 for the first time on such a large scale verified the efficacy, effectiveness and safety of the new forms of vaccine preparations.

The Pfizer/BioNTech vaccine showed promise in clinical trials [4, 23], thanks to which it was the first in its class to be approved for mass distribution. Today, it is well established that in the face of the continued evolution of the SARS-CoV-2, the effectiveness of the vaccination in the core regimen is not sufficient to prevent infection. However, the sustained high level of vaccine protection against severe forms of COVID-19, hospitalizations and deaths is important [16, 18, 20]. The validity of a booster dose to maintain the protective effect of the product has been demonstrated [21, 22].

Studies have also shown that there is some risk of serious adverse events following each dose of the vaccine, but this risk appears relatively small compared to the potential health consequences of COVID-19 infection [24, 26]. The most common vaccine reactions usually resolve quickly or are successfully treated [4, 23, 25, 27]. The analyses provided not only demonstrate the consistently favorable safety profile of the product but even suggest a protective effect of the vaccine on health [29].

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