Efficacy and Effectiveness of SARS-CoV-2 Vaccines

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The major determinants of vaccine acceptance are vaccine safety and efficacy. Most COVID-19 vaccines have mild side effects, such as pain at the site of injection, tiredness, headache, fever, or shivering for 1–2 days after vaccination. Very rare side effects include allergic reactions and blood clotting problems, the latter affecting a small number of people who had the Oxford/AstraZeneca vaccine. Vaccine efficacy is defined as the degree to which a vaccine prevents disease, and possibly, also its transmission under ideal and controlled circumstances; this is determined by comparing a vaccinated group with a placebo group in a randomized controlled trial (RCT). Vaccine effectiveness also refers to how well the vaccine performs in the real world based on observational studies.

Keywords: SARS-CoV-2 ; efficacy ; effectiveness ; COVID-19 vaccine ; systematic review ; meta-anlysis ; mortality

1. Introduction

Three novel coronaviruses have been discovered until the writing of this review. The first virus, named severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), was discovered in China in 2002 and caused severe acute respiratory syndrome. That same year, it led to more than 8000 infections and a 10% case fatality ratio (CFR) [1]. The second virus emerged in Saudi Arabia in 2012 and was called Middle East respiratory syndrome (MERS-CoV), with more than 2500 cases and a CFR of about 33% [2][3]. Following the appearance of SARS-CoV-1 and MERS-CoV, many vaccines were developed with live-attenuated, DNA-based, and recombinant viral vectors vaccines [4][5][6]. However, the development of clinical trials to test these postulated vaccines was abandoned when the outbreaks subsided due to the limited number of infections [7][8].

Late in 2019, a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan city, China [9]. The emerging virus causes a disease called coronavirus disease 2019 (COVID-19). Even though the great majority of SARS-CoV-2 infected patients have mild to moderate symptoms, the illness killed a considerable number of patients [10]. A hyperinflammatory process is known as “cytokine storm” is thought to be the cause of much of the serious disease associated with SARS-CoV-2 infection [11]. On 11 February 2022, 407.6 million got SARS-CoV-2 infection with 5.8 million deaths [12]. The CFR varied across countries from less than 0.1% to more than 25% [13].

The world is engaged in a fierce war against COVID-19; The United States Food and Drug Administration (FDA) [14] has granted Paxlovid from Pfizer an emergency use license for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (≥12 years of age) who are at high risk of progressing to severe COVID-19. Paxlovid is only accessible by prescription and should be started as soon as possible following a COVID-19 diagnosis and within five days of the onset of symptoms.

The World Health Organization (WHO) has approved nine vaccines for emergency use up to December 2021. These include two RNA vaccines, Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2); three non-replicating viral vectors, Janssen (Johnson & Johnson) (Ad26.COV2.S), Oxford/AstraZeneca (AZD1222), and Serum Institute of India Covishield (Oxford/AstraZeneca formulation); two protein subunits (NVX-CoV2373 and NovaVax); and inactivated virus techniques, Sinopharm (Beijing) BBIBP-CorV (Vero Cells) and Sinovac (CoronaVac) [15]. The vaccination process against COVID-19 started in December 2020 with the Pfizer-BioNTech, Moderna mRNA vaccines, and the Astra Zeneca/Oxford Chad Ox vaccines, as well as the Chinese Sinovac, inactivated SARS-CoV-2 and Russian Sputnik V adenovirus vaccines, and hundreds of vaccines at different stages of development and different mechanisms, including protein subunits with adjuvant, non-replicating viral vectors, RNA, virus-like-particles (VLP), DNA, inactivated, and live-attenuated virus [16][17]. On 23 August 2021, the FDA has approved the Pfizer-BioNTech vaccine to protect from COVID-19 for people above 16 years old. The vaccine’s previous emergency use authorization will continue for 12- to 15-year-olds [18]. Recently, Pfizer-BioNTech was approved for use among children aged 5–11 years [19]. In total, 61.7% of the population in the world has got at least one dose of COVID-19 vaccine. About 10.32 billion doses have been provided worldwide, and about 26.74 million are now administered each day [19]; however, only 10.6% of people living in low-income countries have received at

least one dose. Until February 2022, less than 12% of Africans were fully vaccinated [20], while more than 62% of the population in Asia [21], 62% in South America, 63% in North America [22], and 70% in Europe were fully vaccinated [23].

The characteristics of an ideal vaccine are that it can be produced at a large scale with the lowest possible cost, that it is safe, easy to store and distribute, induces strong protection, has long-lasting neutralizing of antibody and T cell responses, and is equally suitable for any age and sex. Moreover, with the emergence of many variants of the COVID-19 virus, the vaccine also needs to be technically modifiable to deal with these emerging variants [24].

2. Current Insights

The aim of vaccine development is to provide a weapon that protects people from getting infected or becoming a source of transmission. By the end of 2020, several COVID-19 vaccines had become available for use across the world, with over 40 different vaccines in human trials, and over 150 in preclinical trials. An updated list of vaccine candidates under evaluation is maintained by the WHO [25]. Although some of the vaccines were approved for emergency use by the FDA in the USA and the respective health departments of other countries across the world, the efficacy and effectiveness should be periodically assessed due to the ongoing antigenic drift. It is worth noting that while vaccinations are still being administered worldwide, the vaccinated population (received at least one dose of vaccine) represents around three-fifth of the entire population [26], with safety and effectiveness representing the main concern and points of hesitation for many people [27]. Another main concern affecting vaccination coverage is COVID-19 vaccine inequity; vaccine supply will have a long-term and severe impact on socioeconomic recovery in low-and lower-middle-income countries (LMIC) unless immediate action is taken to increase supply and provide equal access for all countries. If LMIC had similar vaccination rates as high-income countries (HIC), an acceleration in scaling up manufacturing and providing adequate vaccine doses might have added costs. A high price per COVID-19 vaccine dose in comparison to other vaccines, as well as delivery costs, including those for the health workforce surge, could put a huge strain on fragile health systems, undermining vaccination programs and essential health services, and causing alarming spikes in measles, pneumonia, and diarrhea [28].

2.1. Mortality and Severe COVID-19

Based on the findings of this meta-analysis, the mortality related to COVID-19 two weeks after vaccination was significantly decreased (OR = 0.46, [95% CI, 0.35–0.61], I^2 = 0%). Similarly, mortality one week after vaccination dropped significantly (OR = 0.10, [95% CI, 0.04–0.27], I^2 = 54%). In RCTs, the odds ratio for severe COVID-19 was 0.14 [95% CI, 0.03–0.75], I^2 = 30%), whereas in observational studies, the odds ratio was 0.06 [0.02–0.24], I^2 = 85%. In the same line, the odds ratio of having severe COVID-19 after the 1st dose was 0.15 [0.10–0.25], I^2 = 26%. Analyzing these results, different studies reported a significant reduction in SARS-CoV-2 infection, hospitalizations, and fatalities among those who had been fully vaccinated compared to those who had not been fully vaccinated [29][30][31]. Fiolet et al. [32] recently published a review on different COVID-19 vaccines effectiveness; when the strain was not sequenced, the effectiveness of the mRNA vaccination against hospitalization and mortality was over 87–94%. Similarly, inactivated viral COVID-19 vaccine (CoronaVac) was extremely effective against hospitalization (87.5%) and death (86.3%). In addition, if a breakthrough occurs in a vaccinated individual, the events are usually less severe than in an unprotected person [33]. Similarly, a recently published meta-analysis highlighted that the BNT162b2 and mRNA-1273 vaccines had the best effectiveness in preventing symptomatic COVID-19. The efficacy of comparing different vaccines in preventing serious illness was not different. Moreover, there was no difference in the efficacy of vaccinations to prevent symptomatic COVID-19 among the elderly [34]. Unfortunately, this protective effect wanes with time—5 months or more after vaccination—and vaccine effectiveness decreased against hospitalization and deaths (80.0 and 84.8% with the ChAdOx1-S) and (91.7% and 91.9% with BNT162b2), respectively [35].

2.2. Infection after Vaccination

It is worthy to note that Alagoz et al. [36] hypothesized that if there is a strong adherence to non-pharmacological interventions in the community, the controllable spread of SARS-CoV-2 can be reached sooner than when a substantial part of the population gets vaccinated (e.g., 70–80%). In the current study, COVID-19 vaccines effectively reduced the incidence of symptomatic and asymptomatic infection. On the same lines, the WHO reported that unvaccinated persons account for the great majority of the current SARS-CoV-2 infection [33]. Virus-neutralizing antibodies are principally responsible for the protection provided by presently available vaccinations. These antibodies often inhibit the virus's binding with its cellular receptor or prevent the virus from undergoing the conformational changes essential for fusion with the cell membrane [37]. It's found that vaccination against COVID-19 decreased the number of cases reported within a week of the 2nd dose (OR = 0.06 (95% CI, 0.02–0.21), I^2 = 98%). Type of vaccine and country where study was

conducted were the main predictors of vaccine efficacy and effectiveness. Similarly, the total number of cases diagnosed within 14 days of the 2nd dose decreased significantly, (OR = 0.01 [95% CI, 0.01–0.02], I^2 = 0%). In terms of cases reported 7 days after 2nd dose, the total number of cases decreased significantly with vaccination (OR = 0.03 [95% CI, 0.02–0.05], I^2 = 73%). About 100% of this heterogeneity was explained by meta-regression (vaccine type and country). Regarding symptomatic cases diagnosed 7 days after the 2nd dose, COVID-19 vaccine was effective in reducing the number of symptomatic cases in comparison to placebo or control group (OR = 0.02 [95% CI, 0.02–0.02], I^2 = 0%). The odds ratio of cases reported 14 days after the 2nd dose among vaccinated versus unvaccinated subjects was OR = 0.08, [95% CI, 0.02-0.34], I^2 = 100%). Confirmed cases reported after the 1st and 2nd dose regardless of the duration decreased significantly, OR = 0.14 (95% CI, 0.07–0.4) I^2 = 100% and 0.18 (95% CI, 0.15–0.19), I^2 = 98%, respectively.

In the same vein, many reviews addressed vaccine effectiveness and efficacy. Pormohammad et al. [38] included 25 studies in phase II/III RCTs, the efficacy of mRNA-based and adenovirus-vectored COVID-19 vaccines was 94.6% and 80.2%, respectively. After 3 weeks of vaccinations, the adenovirus-vectored vaccine had the maximum efficacy against receptor-binding domain (RBD) antigen after the 1st and 2nd doses (97.6% and 98.2% respectively). Similarly, a review of phase III studies showed a significant increase in neutralizing antibodies with the 2nd dose of the vaccine [39]. However, it was also advised that when vaccine supply is scarce, countries should vaccinate with a single dose. This may provide better overall protection in the population than vaccinating half the number of individuals with both doses [40].

Many factors can explain the observed difference in efficacy and effectiveness of the COVID-19 vaccines. The Center for Disease Control and Prevention [41] demonstrated that in the real-world, vaccine effectiveness can be affected by several factors, including population host factors (e.g., those who were not included in clinical trials) and virus factors (e.g., variants) as well as programmatic factors (e.g., adherence to dosing schedules or vaccine storage/handling) [42]. Thompson et al. [43] reported that under real-world conditions, complete immunization (14 days after 2nd dose) was 90% effective against SARS-CoV-2 infection, while partial immunization (14 days after 1st dose but before 2nd dose) was 80% effective. In addition, the effectiveness of vaccination varied according to the types of vaccine; Pilishvili et al. [44] stated that vaccine effectiveness for Pfizer–BioNTech and Moderna were 77.6% (95.6% CI, 70.9–82.7) and 88.9% (95.9% CI, 78.7–94.2) after the 1st dose and were 88.8% (95% CI, 84.6–91.8) and 96.3% (95.3–98.4) after the 2nd dose, respectively. Of note, when the SARS-CoV-2 Delta variant became prevalent, the percentage of completely vaccinated people who got SARS-CoV-2 infection grew higher than predicted [31]. The effectiveness of the mRNA vaccine against COVID-19 was 88–100% against Alpha, 76–100% against Beta/Gamma, 47.3–88% against Delta, and 89–100% when the SARS-CoV-2 strain was not sequenced. Oxford/AstraZeneca (AZD1222) was 74.5% effective against Alpha and 67% effective against Delta. CoronaVac was effective against the Alpha/Gamma/D614G strain in 36.8–73.8% of cases [32].

Unfortunately, new data consistently demonstrated that vaccine efficacy against SARS-CoV-2 infection declines with time following immunization [45]. It is worth noting that according to a recently published systematic review and meta-analysis, immunization efficacy against severe COVID-19 infection dropped by around 8% (95% CI, 4–15) during the 6-months period in all age groups. Over the same time, vaccine efficacy against serious illness declined by around 10% (95% CI, 6–15%) in individuals over the age of 50. Vaccine efficacy against symptomatic illness fell by 32% (95% CI, 11–69%) in individuals over the age of 50 [46]. Consequently, WHO has already recommended administering a booster dose of vaccine to people aged 60 years or older as part of the main series to strengthen initial protection [33]. Therefore, people should adhere to public health and social measures even though they have received vaccines to avoid COVID-19 infection and its consequences [47].

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