Proceedings of the 3rd International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/21/20230863

Comparative analysis of efficacy and safety of ChAdOx1 nCov-19 and AD26.COV2.S

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Abstract. Vaccine technology has been going through some radical and incremental advancement over the years for its importance as the most crucial tool in the prevention and elimination of transmissive diseases. Since the outbreak of COVID-19, several vaccine platforms were being studied, developed, and entered the market. Among the platforms, vector viral vaccines attracted particular attention for the cooperation of viral vectors to deliver genetic material of the pathogens. While the mechanism has improved the flexibility of vaccine design and efficacy, the adverse events after vaccination were worth attention at the same time. Taking ChAdOx12 nCov-19 and AD26.COV2.S. as the subjects, the efficacy and safety of the two vaccine platforms were compared and analyzed. In this paper, the initial vaccine efficacy, the resistances against virus variants, and various post vaccination adverse events were looked in more detail to identify the different factors that could affect the performance of viral vector vaccines.

Keywords: vaccine, efficacy, adverse events, safety.

1. Introduction

The outbreak of COVID-19 has been drawing increasing attention to idea of vaccination and development of vaccines. Within one year after the case was discovered, the first COVID-19 vaccine was successfully developed and implemented. Since end of 2020, two viral vector vaccines were under the research and development - ChAdOx12 nCov-19 developed in the UK and AD26.COV2.S developed in the US. The efficacy of the two vaccines were proven to be adequate and the implementation was sped up due to the emergency. However, in April of the same year, the US and several other countries suspended the use of ChAdOx12 nCov-19 due to the concern about blood clots. The incidence was also discovered in AD26.COV2.S. The data was collected from the studies from independent research papers and the comprehensive reports published by US FDA and EMA. The latter had a more comprehensive systematic evaluation of vaccine efficacy and safety; therefore, it is difficult to integrate the results. With the absence of analysis of certain aspects, only a general comparison could be made. Although a clear view of how the two types of vaccine were different in terms of efficacy and safety, a deeper analysis of why they varied in these two areas still needs to be carried out. The efficacy of the two vaccines was compared with consideration of the population characteristics of the test subjects and their performance against different types of virus variants, and the safety analysis focused on the local adverse events and rare adverse events VITT/TTS. The

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purpose is to distinguish the factors that may affect the performance of the vaccines with the same vaccine platform.

2. Comparison of safety and efficacy of ChAdOx12 and AD26.COV2.S

2.1. ChAdOx12

ChAdOx12 was together developed by Oxford University and AstraZeneca and was first licensed in December 2020 in UK. To achieve the desired efficacy, the vaccination facility requires a total of at least two doses to be injected into the deltoid muscle by intramuscular injection at intervals of 4 to 12 weeks. It utilized ChAdOx1 nCov-19, a type of cold-causing chimpanzee adenovirus based on simian adenovirus type Y25 as the vector with COVID-19 virus spike protein-producing gene inserted to produce the antigen spike protein that induces human immune responses and the tissue plasminogen leader sequence which was used to enhance immunogenicity and expression of the protein [1]. The chimpanzee adenovirus type Y25 was chosen to avoid pre-existing immunity to common human adenovirus from vaccines for its unique feature to have chimpanzees as the only natural host. The spike protein-producing gene was modified to increase protein production; the vector has E1 and E3 genes deleted to deprive the vector of replication ability, E4 genes modified to carry human Adenovirus serotype 5 genes for better insertion capability and bettered manufacturing process [1]. After injection, ChAdOx12 nCov-19 can induce strong, durable immune responses inside the human body and offers protection from severe and moderate SARS-CoV-2 symptoms.

2.2. AD26.COV2.S

AD26.COV2.S was under development by the American multinational pharmaceutical cooperation several months after ChAdOx12 nCov-19 was licensed and was licensed in February 2021. The two had the same type of injection. Different from ChAdOx12 nCov-19, only one dose was required by the official. Replication-deficient human adenovirus was chosen to be the vector that carries gene encoding prefusion-stabilized spike protein. The spike protein is stabilized by six prolines proteins making itself a more effective variant in stimulating the creation of antibodies [2].

2.3. Comparison of efficacy

When comparing different types of vaccines, one cannot ignore various factors that can have prominent effects when studying the efficacies of the vaccines, including methodology, population characteristics, and variants of the virus. Specifically in population characteristics, key factors such as age, comorbidity, and severity of symptoms need to be analyzed separately.

2.3.1. Population characteristics. Phase III trials for COVID-19 vaccines were done with populations with different characteristics. A total of four trials in different countries for ChAdOx12 nCov-19 and one trial for AD26.COV2.S were conducted. Study subjects from several countries were selected for the two vaccines, four trials were conducted for ChAdOx12 nCov-19 by experts from several institutes from UK, and two trials for AD26.COV2.S were conducted by US FDA and EMA respectively. All study subjects were adults aged over 18 years. The method of the experiment may have a considerable impact on the efficacy result of the vaccine. Characteristics of which the method designed for the experiment include age, sex, race, ethnicity, country of the study subjects, the period of follow-up investigation and the definition of a main endpoint of each trial are essential factors for the final number. The following Table 1 shows the basic information about the population characteristics of the trials.

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Table 1. Phase III trials for ChAdOx12 nCov-19 and AD26.COV2.S [3].

Vaccine Brand	Subject of Study	Experiment Target
AZD 1222	United Kingdom	Symptomatic cases, more than 14 days after the final dose with no history of infection
	United Kingdom, Brazil, and South Africa	Symptomatic cases, more than 14 days after the final dose with no history of infection
	South Africa	Mild to moderate cases, more than 14 days after the final dose without prior infection
	United States	Prevention of symptomatic cases
AD26.COV2.S	United States, Mexico, South American countries, and South Africa	Moderate to critical cases, more than 14 and 28 days after vaccination with no history of infection

2.3.1.1. ChAdOx12 nCov-19. For the first trial in the table, the participants were recruited in the UK during second half of 2020 and received booster doses during the same time of the year. Among 8534 participants, 78% (6636) were aged 18-55 years and 59% (5065) were females [4]. 520 of them developed SARS-CoV-2 infections between Oct 1, 2020, and Jan 14, 2021. It was observed that the neutralization level of antibodies induced by the vaccine against B.1.1.7 was lower than Victoria lineage. The clinical vaccine efficacy for B.1.1.17 was 70.4% and for non-B.1.1.7 was 81.5% [4].

For the second trial, the participants were recruited from three different countries – Brazil, South Africa, and the UK. The diversity of study subjects was much higher in terms of race where white, black, Asian and other races were all included. The population base of study subjects in the trial was much bigger in addition. During the time between April and November of 2020, a total of 23,848 participants were introduced into the trial and were vaccinated across four studies including a total of 11,750 participants from the United Kingdom, 10,002 participants from Brazil, and 2,096 from South Africa [5]. Half of the participants who met the criteria received 2 doses of ChAdOx12 nCov-19 and another half received the same number of doses of the placebo. The average vaccine efficacy for recipients in the UK was 73.5%, and that for Brazil was 64.2%. Among the UK recipients, those who had a lower first dose showed a much higher vaccine efficacy [5]. The difference between the vaccine efficacy from the UK and Brazil might be due to the different virus variants that were prevalent in these two countries.

The third trial focused specifically on B.1.351. which was the variant discovered in South Africa. Between Jun 24 and Nov 9, 2020, 2,026 adult participants from South Africa were recruited in which half of them received single dose of the vaccine and another the placebo. In the laboratory neutralization process, greater resistance to B.1.351 was shown. In addition, 39 out of 42 participants who developed Covid-19 had this variant. The vaccine efficacy against the variant was only 10.4% [6].

The last ChAdOx12 nCov-19 trial was conducted in the US. The trial showed 79% efficacy in the prevention of the symptomatic cases and 100% in prevention of severe cases that required hospitalization [7]. The trial had 32,499 participants with various ages and ethnic identities. Although it was said to have a consistent vaccine efficacy across these identities, a notably higher efficacy of 80% was observed in the participants aged 65 years and older [7].

2.3.1.2. AD26.COV2.S. US FDA has analyzed the efficacy of AD26.COV2.S in several different subgroups. In each subgroup, more than 14 or 28 days after the vaccination was separately analyzed. As indicated in the tables shown below, the factors such as comorbidity, age, severity of symptoms and country of participants could greatly affect the efficacy of AD26.COV2.S. The vaccine efficacies with consideration of age, comorbidity, the severity of symptoms, region of the subjects and source of confirmation were shown in Tables 2-4 below. All data of vaccine efficacy refers to the condition of

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the first occurrence, including both centrally confirmed and non-centrally confirmed cases except for the Table 3.

Table 2. Moderate to critical cases [8].

Subgroup/Days After Vaccination	≥ 14	≥ 28
Comorbidity		
Yes	64.2%	58.6%
No	67.6%	68.8%
Age group and comorbidity		
18-59, no	65.6%	68.0%
18-59, yes	63.9%	64.0%
≥ 60, no	76.0%	72.4%
≥ 60, yes	64.0%	42.3%

Table 3. Against adjudicated severe/critical cases [8].

Days After Vaccination	≥ 14	≥ 28
Centrally confirmed cases		
Overall	76.7%	84.5%
18-59 years	80.5%	91.7%
≥ 60	68.8%	70.3%
Non-Centrally confirmed cases		
Overall	76.3%	83.5%
18-59 years	76.9%	85.0%
≥ 60	75.1%	80.2%

Table.4. Moderate to critical by country of participation [8].

Country/Days After Vaccination	≥ 14	≥ 28
United States		
Moderate to Severe/Critical	74.4%	72.0%
Severe/Critical	78.0%	85.9%
South Africa		
Moderate to Severe/Critical	52.0%	64.0%
Severe/Critical	73.1%	81.7%
Brazil		
Moderate to Severe/Critical	66.2%	68.1%
Severe/Critical	81.9%	87.6%

2.3.2. Variants of virus. Several variants of the COVID-19 virus are identified in different region of the globe, characterized by specific mutations in the virus that affect their transmissibility, the severity of symptoms and potential resistance to the existing vaccines. Table 5 below shows the effect of new variants on ChAdOx12 nCov-19 and AD26.COV2.S compared with the original virus.

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Table 5. Effect of variants on efficacy [3].

Variants (WHO nomenclature)	First Detection	Transmission and Morality	ChAdOx12 nCov-19	AD26.COV2.S
B.1.1.7	United Kingdom	+ 56% (UK) + 61-64% (UK)	2.1-fold reduction	NA
B.1.551	South Africa	+ 50% (South Africa) NA	3.3-23.45-fold reduction	NA
B.1.1.28.1.P1	Brazil and Japan	+160% (Brazil) NA	9-fold reduction	3.4-fold reduction
B.1.617.2 (and AY sublineages)	India	+ 40-60% (UK) More severe cases than Alpha	3.1-9-fold reduction	1.6-5.4-fold reduction
B.1.617.1	India	NA NA	1-2.6-fold reduction	NA

2.3.3. General comparison. Comparing the data from the vaccine efficacy studies of the two vaccines, the overall performance of ChAdOx12 nCov-19 was better than AD26.COV2.S. However, there is also a significant lack of more detailed analysis from ChAdOx12 nCov-19. On the other hand, ChAdOx12 nCov-19 is more suspectable to different types of variants. Therefore, when comparing the efficacy of the two vaccines, a more specific context is needed. Other reasons why ChAdOx12 nCov-19 had a better efficacy may be due to, first, the formulation of the vaccine where ChAdOx12 nCov-19 utilized chimpanzee adenovirus based on simian adenovirus type Y25 to avoid possible pre-existing immunity.

2.4. Comparison of safety and risks

The safety issues concerning the vaccines ChAdOx12 and AD26.COV2.S are the adverse event following immunization (AEFI). Common post-vaccination adverse events are associated with either local event that occurs near the site of injection or systemic unwell feelings including fatigue, headache, myalgia, etc. that can usually be dealt with regular oral over-the-counter medications with no need for hospitalization. Occasionally, a rare adverse event with a higher grade of severeness was found. Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) was one major rare severe adverse event that was observed in individuals vaccinated with adenovirus vector vaccines, thus including both ChAdOx12 nCov-19 and AD26.COV2.S vaccinated patients. It is a blood coagulation condition accompanied by a low count of platelets.

2.4.1. Incidence of local adverse event. The incidences of a local adverse event, injection-site pain in patients vaccinated with both types of vaccines showed a near 10% difference – 39.24% and 48.6% for ChAdOx12 nCov-19 and AD26.COV2.S vaccinated patients respectively. This may be because ChAdOx12 nCov-19 carries a higher dose of the viral vectors than AD26.COV2.S, and which subsequently may result in a severer inflammation response and thus the pain at the injection site. In addition, the time interval during the doses may also contribute to the injection site pain for the longer the interval, the more robust the immune response. Since ChAdOx12 nCov-19 officially requires two doses for a complete vaccination, the incidence of injection site pain was thus higher.

2.4.2. Incidence of general adverse event. Four main general adverse events were discovered and reported in a higher proportion of participants in the adverse event study, including headache, fatigue, myalgia, and nausea. In ChAdOx12 nCov-19 vaccinated participants, the respective percentages of participants who had been reported to have the four systemic adverse events were 36.20% (headache),

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42.53% (fatigue), 43.04% (myalgia) and 3.54% (nausea) [9]. For AD26.COV2.S vaccinated participants, the percentages are 38.9%, 38.2%, 33.2% and 14.2% [10]. In comparison, higher incidences of fatigue and myalgia were observed in ChAdOx12 nCov-19 vaccinated participants and higher incidences of headache and nausea were observed in AD26.-=COV2.S vaccinated participants. The greatest differences occurred between the incidences of myalgia and nausea where 9.84% and 10.66% differences were observed respectively.

The myalgia observed in participants vaccinated with ChAdOx12 nCov-19 was often together with the symptom of polyarthralgia. The syndrome was acute and could persist for up to 47 days in severe cases. From experimental findings, the syndrome was likely to be caused by adenovirus vector-induced cytokine activation. Mouse model was used to conduct the experiment. The corporation of adenoviral vector has stimulated the innate immune system which subsequently led to an acute inflammation response. The response was accompanied with the secretion of cytokine. The impact of adenoviral vectors on vaccinated individuals depended on their age. For adults below 50 years old, the incidence of cerebral venous sinus thrombosis was often observed. The potential cause, platelet factor 4 – heparin antibodies were unexpected influential in a negative way. The symptom of myalgia is in addition coincidence with that of VITT which was one major identified rare adverse effect of adenovirus vector vaccines that had a higher incidence rate, especially in ChAdOx12 nCov-19 vaccinated individuals. The increase in cytokine secretion may cause and worsen the thrombosis by its ability to recruit leukocytes, the target of activated platelets [11].

2.4.3. Incidence of VITT. Since February 2021, there have been a few cases of uncommon but critical adverse reactions to vaccine-induced immune thrombotic observed in ChAdOx12 and AD26.COV2.S vaccinated individuals in several countries. Within these vaccinated individuals, a higher incidence rate of VITT was discovered in individuals vaccinated with ChAdOx12 nCov-19. In the USA, the rate of VITT was 3.55 x 10-6 % for those who were vaccinated with AD26.COV2.S, in comparison to 2 x 10-5 % to 1 x 10-6 % for those who received with ChAdOx12 in the United Kingdom. In Germany in which both types of vaccines were implemented into the medical system, 5.6 x 10-6 %were for AD26.COV2.S vaccinated people and 1.49 x 10-5 % for ChAdOx12 nCov-19 vaccinated people were reported [12].

The experiment utilized several experimental assays including sodium dodecyl sulfate gel electrophoresis, mass spectrometry, western blot analysis, proteasome activity assays, dynamic light scattering, zeta potential, zebrafish vascular permeability assay and 2 different types of microscopies, immunoelectron and transmission electron microscopy and super-resolution single-molecule light microscopy. Three major results were shown after the experiment.

First, the entire concentration of protein in the ChAdOx12 nCov-19 vaccine sample (102 ng/ L) was roughly 3.4 folds greater than the protein concentration in AD26.COV2.S vaccine sample (29.8 ng/ L). Second, a more complicated protein pattern for pure virus particles for ChAdOx12 compared with AD26.COV2.S sample was displayed by the gel electrophoresis. Third, a higher proportion and number of proteins were identified in ChAdOx12 nCov-19 vaccine sample (44.5% to 59.2%, 1571 31) by mass spectrometric analysis compared with AD26.COV2.S sample (0.26% to 0.96%, 59 14) [12].

One possible reason why the incidence of VITT was higher in ChAdOx12 nCov-19 than AD26.COV2.S was because the host cell protein impurity of ChAdOx12 nCov-19 was higher. Furthermore, platelet factor 4 (PF4) is the key protein identified in vaccine samples that causes VITT. It induces the clustering of vaccine components by forming a charge-dependent complex that contains hexon protein with its high affinity to the hexon protein and then mediates platelet-activating anti-PF4 antibodies that lead to VITT. In addition, EDTA-induced capillary leakage that occurred after the intramuscular injection of ChAdOx12 nCov-19 may also cause the difference in the rate of incidence of VITT.

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3. Conclusions

By analyzing and comparing ChAdOx12 and AD26.COV2.S, the two vaccines from different companies with the same vaccine platform, it is evident that although the former had a higher efficacy performance overall, it had indicated a higher risk of adverse events after vaccination. Factors that may have influenced the result, including the characteristics of study population and experiment settings, are discussed in the analysis of vaccine efficacy in this paper. In addition, when comparing the efficacies of the two vaccines, patients with different conditions were studied, focusing on their age, comorbidities, the severity of their condition, and how their condition was identified. The two vaccines had different level of resistance when it comes to various variants of the Covid-19 virus. Form the statistics of the studies, it appeared that AD26.COV2.S was less affected by the variants. When analyzing the safety of the vaccines, both local and systemic adverse events were studied, and the results showed that both vaccines were involved into in a rare and potentially severe adverse event VITT/TTS. The ChAdOx12 nCov-19 tended to have a higher incidence rate of VITT/TTS than AD26.COV2.S due the presence of its complex protein composition. The mechanism behind the adverse event might also contribute to higher rate of certain local adverse events of ChAdOx12 nCov-19. Because the inconsistencies between the data obtained from the studies done to the two vaccines, some other aspects of comparison might be neglected. When more specific mechanisms behind the vaccines are discovered, there will be a step further digging into the causes of their differences.

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