Analysis and comparison of anti-RBD neutralizing antibodies from AZD-1222, Sputnik V, Sinopharm and Covaxin vaccines and its relationship with age and gender among health care workers

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Abstract

Background

Vaccine efficiency has a significant role in the public perception of vaccination. The current study was designed to evaluate the efficacy of COVID-19 vaccines (AZD-1222, Sputnik-V, Sinopharm, and Covaxin) and the effect of age and gender on vaccine efficacy. We evaluated the efficacy of these vaccine between 214 health care employees in Iran. Blood samples were taken from all participants at day 0 and 14 days after the second dose. Humoral responses were evaluated by SARS-CoV 2 Neutralization Ab Detection kit.

Results

The frequency of immunized individuals in the Sputnik V and AZD-1222 groups was 95% and 93%, respectively. This rate was 73% and 70% for Sinopharm and Covaxin vaccines. Comparison of the results obtained from the effectiveness of the vaccines between female and male groups did not demonstration a significant difference. Moreover, comparison of the results obtained from the effectiveness of vaccines between age groups showed that the rate of immunization in participants < 50 years was significantly higher than participants ≥ 50 years, in the case of Sputnik V and AZD-1222 vaccines.

Conclusions

According to the results, Sputnik V and AZD-1222 vaccines were more effective than Sinopharm and Covaxin vaccines. In addition, aging has a negative effect on the effectiveness of DNA-based vaccines.

1. Introduction

SARS-CoV-2 was first recognized as a COVID-19 agent two years ago (December 2019) [1–3]. SARS-CoV-2 has infected more than 525 million individuals worldwide (May 2022) and has been responsible for more than 6.28 million deaths [4]. SARS-CoV-2 infection usually causes a wide range of symptoms in people, which can range from mild symptoms to severe manifestations and even death. Also, people who have survived severe infections, suffer from post Covid-19 syndrome such as fatigue, shortness of breath, muscle pains, etc. [5–7]. Furthermore, other infections (bacterial, viral, and fungal), cardiovascular problems, and other psychological problems may occur in convalescent patients [6–8]. Due to the health and economic pressures of the COVID-19 epidemic, vaccination is able to reduce this burden by decreasing the mortality rate of SARS-CoV-2 infection. [9, 10].

According to the World Health Organization, more than 137 candidates are currently undergoing clinical development, of which a small number are licensed and approved [11]. The characteristics of an ideal vaccine are: effectiveness after one or two doses of vaccination, protection of target populations such as...
the elderly and people with underlying disease, efficacy and protection for at least 6 months, reduce further transmission of the virus to others [5, 12].

AZD-1222 (Oxford/AstraZeneca), BBIBP-CorV (Sinopharm), Sputnik V (Gamaleya Research Institute) and Covaxin (Bharat Biotech) vaccines were investigate in the current study (February to March 2021).

AZD-1222 and Sputnik V work based on a non-replicating adenoviral vector platform. This platform is based on adenoviruses, which deactivated by removing the E1B and E1A gene, and established in 1972 [13, 14]. The spike antigen cDNA is inserted into non-replicating adenoviral vector, then these vaccines provide the cDNA of the spike protein to infected cells, which leads to spike protein expression in host cells [15]. AZD-1222 and Sputnik V elevate both humoral and cellular immunity [15]. According to the results of clinical trials, AZD-1222 and Sputnik V vaccines have significant immunogenicity and safety, which produce antibodies against spike antigen [2, 16].

Sinopharm and Covaxin are inactivated virus particle vaccines, which are one of the oldest antiviral vaccine platforms. This method was developed in 1940 for influenza vaccines production [17]. However, this method is not appropriate for all viruses [18]. The coronaviruses particles obtained from virus-infected cells and deactivated by means of chemical or physical techniques, including the use of UV, β-propiolactone, etc. [15, 17]. The major problem of these technique is the selection of virus type, and the need to inject with alum adjuvant [19, 20]. BBV-152 or Covaxin vaccine is manufactured by Bharat Biotech, India, and BBIBP-CorV is produced by Sinopharm, China [21]. Clinical trial outcomes confirm that these vaccines are safe and could stimulate impressive cellular and humoral immune responses [22, 23].

During the immediate development of a vaccine in a pandemic, it is critical that a protective response be established within a short period of time (e.g., < 1 month). In addition, previous research programs on vaccines (such as SARS-CoV14 and MERS-CoV13) revealed that both cellular and humoral immune responses are essential for an effective immune response [24].

Covid-19 infection usually stimulate neutralizing antibody production, and the rate of this response in people with COVID-19 infection is 50% and 100% on day 7 and 14 after the onset of symptoms, respectively [25]. On the other hand, serological tests are needed to evaluate the amount of neutralizing antibodies produced in patient and also to recognize donors with high-neutralizing titers for convalescent plasma (CP) therapy [26]. For serum diagnosis, a number of COVID-19 analyze platforms have received FDA emergency usage permissions, which determines the number of antibodies that bind to SARS-CoV-2 spike protein. These methods including ELISA, lateral flow immunoassay, and microsphere immunoassay [26]. In addition, an ideal test should measure levels of neutralizing antibody, which protect against re-infection, because not all spike-binding antibodies can inhibit viral infection.

Studies have shown that age can affect the possibility of Covid-19 infection, on the other hand, increasing age is associated with a decrease in the strength of the immune system [27]. Therefore, it seems necessary to study the effect of vaccines and their relationship with age.
It is critical to study vaccine efficiency during the general vaccination phase. In fact, genetic diversity in different human populations may affect the effectiveness of vaccines. The aim of this investigation was to evaluate the effectiveness of four available COVID-19 vaccines including AZD1222 (AstraZeneca company, British-Swedish), Sputnik V (Gamaleya Research Institute, Russia), BBIBP-CorV (Sinopharm, China), and Covaxin (Bharat Biotech company, India) in inducing anti RBD Immunoglobulin G in a group of participants (in two group of age) who received both doses of vaccine.

2. Results

2.1. Demographic Characteristics

Overall, 214 participants (Mean age: 36.5 ± 8.75, Age range: 19–64 years, F/M ratio: 1.6) were registered in this project. The total number of health care employees in the Birjand hospitals was about 2500, and the vast majority of them had received two dose of Covid-19 vaccine at the time of this study. About 10% of the vaccinated health care employees were included in this study. According to the Cochrane formula, the sample size was 330 persons with 95% confidence level. However, the number of available people who agreed to participate in this study was 280. Some of them did not participate in the second stage of blood sampling and some did not have the second dose of the vaccine. Finally, after screening, 214 people participated in the project. Details of demographic information and frequency of vaccines were summarized in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Outcome</th>
<th>AZD-1222</th>
<th>Sputnik V</th>
<th>Sinopharm</th>
<th>Covaxin</th>
<th>pValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of vaccine</td>
<td></td>
<td>71 (33%)</td>
<td>57 (27%)</td>
<td>63 (29%)</td>
<td>23 (11%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>34 (48%)</td>
<td>36 (63%)</td>
<td>44 (70%)</td>
<td>14 (61%)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>37 (52%)</td>
<td>21 (27%)</td>
<td>19 (30%)</td>
<td>9 (39%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 50 years</td>
<td>61 (86%)</td>
<td>46 (81%)</td>
<td>54 (86%)</td>
<td>23 (100%)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>≥ 50 years</td>
<td>10 (14%)</td>
<td>11 (19%)</td>
<td>9 (14%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Past Covid infection</td>
<td>14%</td>
<td>12%</td>
<td>7%</td>
<td>20%</td>
<td>21%</td>
<td></td>
</tr>
</tbody>
</table>

* One way ANOVA were used with a significance level of < 0.05.

2.2. COVID-19 vaccine efficiency
2.2.1. Comparison of the effectiveness of Sputnik V, AZD-1222, Sinopharm and Covaxin vaccines in all participants

The frequency of IgG seropositivity for RBD protein two weeks after the second dose of vaccines was presented in Fig. 1 and Table 2. Vector-based vaccines showed significantly higher efficacy than inactivated vaccines. Comparison of vaccine efficacy showed that there was no significant difference in immunogenicity between Sputnik V and AZD-1222; however, the production of neutralizing antibodies in Sinopharm and Covaxin vaccines is significantly lower than that of Sputnik V and AZD-1222 vaccines. Moreover, the immunogenicity of Sinofarm and Covaxin vaccines were not significantly different.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The pValue level for comparison of immunogenicity in the four vaccines in the participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sputnik V</td>
</tr>
<tr>
<td>Sputnik V</td>
<td>-</td>
</tr>
<tr>
<td>AZD-1222</td>
<td>0.03 *</td>
</tr>
<tr>
<td>Sinopharm</td>
<td>0.89</td>
</tr>
</tbody>
</table>

2.2.2. Relationship between vaccine efficacy vs. gender and age

In general, there was no significant differences between males and females in rate of seropositivity (84% vs. 84.7%) although the rate was varied for different vaccines (Fig. 2). The rate of seropositivity was significantly lower among older participants (> 50 years group) in case of vector-based vaccines but the difference was not significant in case of Sinopharm (Fig. 3). In the case of the Covaxin, all participants were less than 50 years old.

2.2.3. Relationship between previous COVID19 infection and the efficiency of vaccines

The efficiency of vaccine was evaluated based on a history of previous COVID-19 infection. The rate of seropositivity was significantly higher among convalescent patients in case of AZD-1222, Sinopharm, and Covaxin vaccines, but the difference was not significant in case of Sputnik V (Fig. 4).

According to the kit instructions, if the OD is between 0.8 and 1.1, it is considered as a border line. Out of 214 cases, 13 cases were borderline, the results of them were excluded in the analysis.

3. Discussion
Currently, vaccines are the best strategy for protection against COVID-19 infection. After the COVID-19 outbreak, several types of vaccine with different formulations were introduced and received by billions of people around the world. Induction of a protective immunity by vaccines depends not only on host factors but also vaccine components and structure, so it is necessary to evaluate the efficacy of different vaccines among people with different socio-economic and genetic backgrounds. In the current study, the rate of IgG seropositivity after receiving two doses of four different vaccines was evaluated in a group of participants. The Sputnik V vaccine, which was invented by Gamaleya Research Institute (Russia), has the gene of the SARS-CoV-2 glycoprotein S. The 1st and 2nd doses of Sputnik V vaccine use two different types of adenoviruses as carriers of the spike gene; rAd26 and rAd5 for the first and second doses, respectively. Phase 1/2 clinical trials showed that both formulations of this vaccine were tolerable and safe [28]. “ChadOx1-nCoV-19” or AZD-1222 composed of the replication-deficient simian adenovirus vector, which contains the sequence of the spike protein. According to studies, this vaccine is more tolerable in the elderly, and after a booster dose, it creates an equal immunity in all age categories [28]. “BBIBP-CorV” or Sinopharm vaccine is an inactivated whole virion which is produced by the Beijing Institute of Biological Products and the state-owned Chinese company Sinopharm. It induced high levels of neutralizing antibody in six mammalian species, which can protect them against SARS-CoV-2 infection [29]. “BBV152” or Covaxin is an inactivated whole SARS-CoV-2 virion particle, which is produced by Bharat Biotech Company. This vaccine formulated with a toll-like receptor 7/8 agonist molecule adsorbed to alum. The Covaxin vaccine was developed using the NIV-2020-770 strain (obtained from an Indian patient with COVID-19), has acceptable safety and can effectively elicit cellular and humoral responses [28].

According to the results, Sputnik V and AZD-1222 vaccines are more effective than Sinopharm and Covaxin vaccines. This may be due to differences in the platform of these vaccines [21]. The platform used in Sputnik V and AZD-1222 vaccines is a live viral carrier, which according to previous studies has a high ability to stimulate the immune system [5, 24]. In contrast, the platform used in Sinopharm and Covaxin vaccines is inactive viruses that have less ability to stimulate the immune system [29, 30]. The immunogenicity of Sputnik V and AZD-1222 vaccines was estimated to be about 90%, which is consistent with similar studies [31, 32]. Also, the effectiveness of Sinopharm and Covaxin vaccines was about 70%, which was consistent with most studies [30, 32]. Regarding the effect of age on vaccine efficacy, the results varied depending on the type of vaccine. The efficacy of the vaccine and the production of neutralizing antibodies in the Sputnik V and AZD-1222 vaccines were significantly higher in participants under 50 years old. However, in people who received the Sinopharm or Covaxin vaccine, the production of neutralizing antibodies did not differ significantly between the two age groups. Given that the platform of Sputnik V and AZD-1222 vaccines is a type of live viral vectors, it seems that the use of this platform has different effects between male and female [15].

Also in another study, Voysey et al., determined AZD-1222 vaccine efficacy in the UK, and vaccine efficacy was 95.8%. Their result was similar to ours (93%) [33]. Ewer et al. determined the antibody responses induced by AZD1222 vaccine in adults (Mean age: 18–55), up to 8 weeks after vaccination. Robust immunity induced against the spike antigen, determined by total IgG ELISA. In their studies, no
relationship was found between age and the magnitude of immune response. Anti-SARS-CoV-2 antibody were measurable at day 14 and peaked at day 28 [34]. In another study Wall and colleagues assessed AZD1222-induced neutralizing antibody against SARS-CoV-2 Delta variant of concern. Two doses of AZD1222 produced neutralizing antibody against the wild type strain in all participants (100%). Moreover, 95% and 87% individuals had a measurable neutralizing antibody against the B.1.1.7 and D614G variants, respectively. [35]. Jeewandara et al., measured immune responses to a single dose of the AZD1222 vaccine in health care workers. 93.4% of participants were positive for neutralizing antibody production, regardless of gender and age. Hemagglutination tests for antibodies to the RBD were done in a sub-cohort, and ACE2 blocking antibodies were detected in 97.1% of naive persons [36]. Moreover, Wall et al., investigated the ability of AZD1222 vaccination to elicit neutralizing antibodies against SARS-CoV-2 (Delta) in 106 participants. According to result, 87% of individuals had a measurable neutralizing antibodies against the B.1.1.7 and D614G variants, but only 62% of participants had quantifiable NAbTs against B.1.617.2 (Delta variant) following two doses of AZD1222 [37].

In a study by Logunov et al., Sputnik V vaccine efficacy was determined among adult participants. Vaccine efficacy in this study was 92%, which was very similar to our study (95%) [24]. Moreover, in a study by Claro et al., they assessed the antibody (IgG) response against the RBD of the spike protein and the Nucleocapsid protein (NP) in Venezuela, after the vaccination by Sputnik V. Antibody responses against RBD and nucleocapsid protein were measured by ELISA. All of participants demonstrate a strong IgG immune response against RBD after the second dose, however only 58% of participants had an immune response after 1st dose [38]. In another study by Rossi and colleagues, among health care workers in Argentina, SARS-CoV-2 specific antibody responses were evaluated after vaccination by Sputnik V. IgG anti-spike titers and neutralizing capacity was determined after two doses, and 94% of participants developed spike-specific IgG antibodies. Interestingly, a single Sputnik V dose elicited higher antibody levels in previously infected individuals [39]. Also, Gushchin et al., evaluated neutralizing activity of sera from Sputnik V vaccinated subjects against variants of concern such as alpha variant. The data obtained indicated no significant differences in virus-neutralizing activity against alpha variant [40].

There are many studies on the effect of Sinopharm vaccine on the creation of neutralizing antibodies against SARS-CoV-2. Holt et al., performed a study to evaluate the antibody responses following vaccination with the Sinopharm vaccine in the UAE after two doses (1296 participants). The antibody responses were measured 14–21 days after the second dose by means of chemiluminescence immunoassay technology, and neutralizing antibody testing was carried out by a blocking enzyme-linked immunosorbent assay. According to result, 56% of participants had a positive anti-spike antibody against SARS-CoV-2, which is lower than the our result (73%) [41]. In another study by Jeewandara et al., the kinetics of immune responses following the Sinopharm/BBIBP-CorV was measured in Sri Lankan. SARS-CoV-2 specific total antibodies were evaluated in 83 individuals by ELISA, after the second dose. RBD specific antibodies were measured by ELISA, and about 95% of participants had measurable SARS-CoV-2 specific total antibodies in their study [42]. Moreover, Ferenc and colleagues, determined virus neutralizing antibody responses after second dose of Sinopharm Covid-19 vaccine in 450 participants. Outcomes were examined in a multivariable model for gender and age. Similar to our study, gender was slightly
correlation with the antibody titers, but antibody titers were highly correlated with age. Measurable antibody levels were detect in approximately 90% of subjects under 50 years of age, but production of the antibody was decreased sharply with age [43]. Nevertheless, in our study, age had no significant effect on the efficacy of the Sinopharm vaccine.

Various studies have been performed on the efficacy of the Covaxin vaccine. In a study by Ella, Covaxin vaccine efficacy was measured in Indian hospitals. Participants was followed two weeks after the second vaccination; and vaccine efficacy was reported 77.8%, which was similar to our result (70%) [30]. In another study by Singh et al., antibody response was determined after Covaxin (BBV-152) vaccine among 515 Health Care employees, in India. Anti-spike antibody titer was measured at day 21 after vaccination. The IgG to SARS-CoV-2 directed against the spike protein were assayed with indirect chemiluminescence immunoassay (CLIA). About 44% of participants showed seropositivity after vaccination, which is lower than our result (70%). Also similar to our study, no difference was observed with age and gender [44]. In a study by Kumar, antibody responses to the BBV152 vaccine were measured in healthcare professionals. Serological testing for anti-spike antibodies measurement was performed using chemiluminescence immunoassay. According to their results, about 76% of participants showed seropositivity after vaccination, which is higher than our result (70%) [45].

Finally, in another study, Covid-19 vaccine efficacy was done by Siddique and Ahmed in Pakistan. In this study, the efficacy of various vaccines including Sputnik V, AZD-1222 and Sinopharm vaccines was evaluated. The results showed that the efficacy of Sputnik V, AZD-1222 and Sinopharm vaccines was 92%, 70% and 79%, respectively, which compared to our study, the efficacy of the AZD-1222 vaccine has been less reported [46].

4. Conclusion

The results of this study showed that vector-based vaccine have more efficacy in producing humoral immunity than inactivated vaccines particularly in older people. Further studies need to evaluate the duration of protection immunity acquired by covid-19 vaccines.

5. Methods

5.1 Design study

During May to Aug, 2021, personnel of Birjand University of Medical Sciences including healthcare workers, students and administrative staff who wanted to receive COVID-19 vaccine were invited to participate in the study. Participants donated 5 milliliters of their venous blood before receiving the first dose of vaccine and two weeks after the second dose and completed an online questionnaire. The questionnaire consisted of questions about demographic data, history of previous Covid-19 infection as well as date and type of received vaccines. Sera from collected blood were separated by centrifugation
and stored at -20°C until analysis. To evaluate the vaccine-induced humoral response against COVID-19, sera were checked for anti – RBD IgG by a commercial ELISA kit (ChemoBind Co., Iran) in duplicate.

According to the kit instructions, OD values greater than 1.1 and less than 0.8 and between these values were considered positive, negative and borderline, respectively.

### 5.2. Inclusion/exclusion criteria

The inclusion criteria for this study were injections of both doses of one of the vaccines Sputnik V, AZD-1222, Covaxin, and Sinopharm. Exclusion criteria were have a positive COVID-19 test through the study period and unwillingness to donate blood on time.

### 5.3. Ethical approval

This study was accepted on April 17, 2021 by the Ethics Committee of the Birjand University of Medical University (IR.BUMS.REC.1400.027), and all participants filled out the consent form.

### 5.4. Statistical Analysis

Data analyzed by the SPSS software version 22.0 (SPSS Inc. Chicago, IL, USA). The Chi-square test and Student’s t-test with a significance value \( p < 0.05 \) were used.

### 6. Declarations

**Ethics approval and consent to participate:** The project was found to be in accordance to the ethical principles and the national norms and standards for conducting Medical Research in Iran. This confirmation was issued by the “Research Ethics Committees of Birjand University of Medical Sciences” on 2021.04.19 (Approval ID: IR.BUMS.REC.1400.027).

**Consent for publication:** Not applicable.

**Availability of data and materials:** Not applicable.

**Competing interests:** The authors declare that they have no competing interests.

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**Authors' contributions:** HZ: Conceptualization, design of the work, interpretation of data, and drafted the work. HR: Acquisition, analysis, and interpretation of data. AF: Acquisition and analysis. SN: Design of the work. SM: Interpretation of data. SGR: Drafted the work and substantively revised it. MF:
Conceptualization, design of the work, drafted the work and substantively revised it. All authors read and approved the final manuscript.

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Figures
Figure 1

Frequency of immunized and unimmunized participants after receiving each of the vaccines.

Figure 2

Comparison of immunogenicity in two groups of female and male groups with different vaccines.
Figure 3

Comparison of immunogenicity in two groups of female and male groups with different vaccines. *p<0.05, ns – not significant

Figure 4

Relationship between previous COVID19 infection and the efficiency of vaccines. *p<0.05, ns – not significant