

Discussing the Efficacy and Safety of Covid-19 Vaccine Available in India-

A Mini Review

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Abstract:

Background: Many variants detected after Wuhan-Hu-1 reference which were able to develop the resistance against the neutralizing antibodies induced by vaccine and may cause false negative results in diagnostic test. Novel variant B.1.617 was detected in India and the Covid-19 cases hiked to its maximum; forcing the government towards approving a new vaccine for restricted use in emergency situation to cover a maximum population.

Aims: This review looks at the efficacy, safety, and economical aspects of vaccines that have been authorized in India.

Materials and methods: Wide-ranging assessment and analysis of accessible resources on online database.

Results: The rAd26-s & rAd5-s demonstrate high efficacy as well as safety, followed by BBV152 and AZD1222. Various combinations of the vaccines with different platforms or vectors may induce wide range of immunity than a specific one. As per economical aspect, AZD1222 is more economical than the other two currently approved in India.

Conclusion: There is a lack of clear end point to measure efficacy of the vaccine so the epidemiological studies with huge number of populations is required which may predict the perfect endpoint for efficacy measurement. Until then, inoculation with locally accessible

vaccines and self-awareness about disease transmission prevention are the main options for reducing fatalities, protecting the health-care system, and eventually disease control.

Key Words: Covid-19, Immunization, Vaccine Efficacy, Vaccine Safety.

Highlight

- The goal of vaccination is to reduce deaths, protect the health care system and finally disease control.
- All the vaccine made for immunization were targeting Wuhan-Hu-1 reference virus, after that lots many variants were detected which developed resistance against vaccines available for immunization.
- It is required to carry out the epidemiological studies to establish a clear endpoint for vaccine efficacy measurement.
- Wearing mask, maintaining distance, regular hand washing and avoiding crowded is still the best option to prevent the SARS-CoV-2 infection even after vaccination.

Introduction:

Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is responsible for Coronavirus disease (Covid-19) has spread to 220 countries and has been found to be challenging.¹ As of 10th November 2021, globally there were 250.90 million laboratory-confirmed cases and more than 5.065 million fatalities. In India there were 34.388 million laboratory-confirmed cases and more than 4.16 lakhs fatalities.²

After SARS-CoV-2 was initially infected through the nose, the virus quickly spread to the lungs, using Angiotensin-converting enzyme (ACE) 2 as binding receptor to invade the epithelial cell.^{3,4,5} If the immune system fails to fight SARS-CoV-2 at this stage, the virus moves down to the lungs, where it can develop to fatal levels.⁶ The ACE-2 receptor can be found on the surface of a variety of pulmonary and extrapulmonary cell types, including cardiac, renal, intestinal, and pancreatic cells, endothelial cells⁷ which may be the reason for severe condition in comorbid patients.

The reproduction number (R_0) rate of the virus is very high: 2.24-3.58; can survive on different surfaces for up to 72 hours or more.⁸ So far, SARS-CoV-2 has acquired new mutations at the rate of ~2 changes per month.⁹ At present, compared with the Wuhan-Hu-1 reference, each new sample has about ten mutation sites on average. The variant B.1.1.7,

which was identified for the first time in the UK, may trigger false negative results in diagnostic tests which target the S gene.¹⁰ Recently new variant is detected in India, denoted B.1.617, thought to be more contagious.¹¹ The mutation is caused by random replication errors or due to the host's defense mechanism (called RNA editing).⁹ Which make virus more harmful to the host, rapid spread and complicated to find a targeted medicine or vaccine.

As of 22 April 2021, 91 and 184 vaccines are in clinical and preclinical development, respectively.¹² The target of vaccine research is to obtain direct evidence of vaccine effectiveness against SARS-CoV-2 infection in humans. Candidate vaccines against SARS-CoV-2 may fight infection, disease, or spread, and vaccines that capable to reduce any of these components may help disease control.¹³ The US Food and Drug Administration (FDA) has approved the distribution and use of three vaccines in the US: BNT162b2 vaccine by Pfizer-BioNTech on December 11, 2020, mRNA-1273 vaccine by Moderna on December 18, 2020, and ad26.cov2.s (Janssen Covid Vaccine) by Johnson & Johnson on February 27, 2021. Unfortunately, the Janssen Covid vaccine was halted on April 23, 2021, after six people who were inoculated with it developed a rare and serious form of blood clot.¹⁴ The Drug Controller General of India has approved three vaccines for restricted use in emergency situation in the India: the ChAdOx1 nCoV-19 (AZD1222®) vaccine (AZD1222) by Oxford-AstraZeneca, BBV152 vaccine (BBV152®) by Bharat Biotech on 3rd January 2021 and Gam-COVID-Vac RAd26-s & rAd5-s® by Gamaleya Research Institute of Epidemiology and Microbiology^{15,16}

In this review, we will look at the efficacy, safety, and cost of the Covid-19 vaccines that have been approved by the DCGI in India for limited use in emergency situations.

Methodology:

Various databases (ScienceDirect, PubMed/Medline, Scopus, Google Scholar, Nature, and Cochrane Database of Systematic Reviews) were searched until April 2021. The search strategy employed were “rAd26 and rAd5 and SARS-Cov-2 or Covid-19 or nCoV”, “AZD1222 or ChAdOx1 nCoV-19 and SARS-Cov-2 or nCoV or Covid-19”, “BBV152 and SARS-Cov-2 or Covid-19 or nCoV”, “BNT162b2 mRNA and SARS-Cov-2 or Covid-19 or nCoV”, “mRNA-1273 and SARS-Cov-2 or Covid-19 or nCoV”, “SARS-Cov-2 variants”, “Covid Vaccines and ADR”.

Platforms of Covid-19 Vaccine:

Covid-19 vaccines are developed from various sources. Virus vaccines, nucleic acid vaccines, viral vector vaccines, and protein-based vaccines are among the most important.^{17,18,19} The virus in a viral vaccine should be entirely inactivated and related to the risk of disease transmitted by the vaccine. DNA and RNA fragments stored in plasmids are used in nucleic acid vaccines. When viral proteins are taken up by host cells, they can be generated.^{17,20} Viral vector-based vaccines use viral vectors to introduce genetic sequences encoding antigens into host cells. However, the genetic material encoding the antigen may be lost during the manufacturing process, which may cause the vaccine to fail. The virus protein subunits are isolated and assembled into virus-like particles (VLP) using recombinant methods, which can imitate the structure of wild viruses and elicit a strong immune response, but are not contagious due to a lack of genetic material.^{17,18,19}

Effectiveness of vaccine:

Vaccine trials should prove useful vaccine efficacy in preventing serious diseases, and protection time should be evaluated. The efficacy of vaccine can be evaluated against “infection, severity, and/or shedding/ transmission” keeping as an end point, and those who can able to demonstrate ~50% point estimate can be acceptable as a Covid-19 vaccine (according to WHO).²¹ It appears to be nonspecific, reflecting the complexity of evaluating the clinical efficacy of candidate vaccine.²² As per the FDA, laboratory verified SARS-CoV-2 infection is a good primary endpoint for vaccine efficacy trials, with a 50% chance of success in a placebo-controlled trial.²³ Recently identified variants are showing false negative results in diagnostic test.¹⁰ Also, it may not be an appropriate end point to estimate vaccine efficacy.

Appropriate endpoints may only be predicted in epidemiological studies conducted after the vaccine has been widely deployed. Until we can use the vaccine’s ability to prevent infection, disease, hospital admission, intensive care unit admission, death and transmission as the end points for efficacy measurement.²²

Vaccines authorized in India:

Globally, many vaccines are available some of them are AZD1222® (Oxford-AstraZeneca), mRNA-1273 (Moderna), Janssen (Johnson & Johnson), AZD1222 (Pfizer BioNTech), RAd26-s & rAd5-s V® (Gamaleya), BBV152® (Bharat Biotech), CoronaVac (Sinovac), NVX-Cov2373 (Novavax), BBIBP-CorV (Sinopharm) etc. In India, DCGI has approved three vaccines for restricted use in emergency situation in the India: the AZD1222®, BBV152®, and RAd26-s & rAd5-sV®.^{15,16} As on 25th April, around 140.91 million vaccines have been inoculated²⁴ which is around 10% of total population.

AZD1222®:

The ChAdOx1 nCoV-19 vaccine (AZD1222) is made up of the replication-deficient simian (Chimpanzee) adenovirus vector ChAdOx1, which carries the full-length structural surface glycoprotein of SARS-CoV-2 along with a tissue plasminogen activator leader sequence. ChAdOx1 nCoV-19 expression optimizes the coding sequences for the codon of the spike protein. Two doses are required to administer at a dose of 0.5ml, contain $3.5-6.5 \times 10^{10}$ viral particles as a single intramuscular injection (IM) into the deltoid up to 12 weeks apart (target 4 weeks) which induced maximum humoral and cellular immune responses against SARS-CoV-2.^{25,26,27} It can be kept in the refrigerator at temperatures ranging from +2°C to +8°C. When opened, multi-portion vials should be used as soon as practically possible and within 6 hours if held between 2°C to 25°C.²⁸ It has shown the general efficacy of 70.42% in primary analysis population (Licensing regimen + Exploratory analysis) in the trials carried out in the UK and Brazil.^{26,28} Same vaccine shows only 22% efficacy according to preliminary South African data. It might be the reason of new variant 501Y.V2 (B.1.351), which is resistant to both natural and vaccine-induced immunity.²⁹ Due to the South Africa variant (B.1.351), Shabir AM *et al.* found just 10.4 percent vaccine effectiveness and vaccine did not provide defense against mild-moderate Covid-19. However, the vaccine's effectiveness against the UK strain (B.1.1.7) and Indian strain (B.1.617) of SARS-CoV-2 is comparable to that of other lineages.^{30,31} So it may not be effective in new variants. It is available at rate Rs. 400/- (5.36\$) for state government and Rs. 600/- (8.04\$) for private hospital per dose.³² Injection site tenderness (>60%); injection site discomfort, headache, exhaustion (>50%); myalgia, malaise (>40%); pyrexia, chills (>30 %); and arthralgia, nausea (>20 %) were the most commonly recorded unfavorable reactions. The majority of adverse reactions were mild to moderate in intensity and apparently went away after a few days. By day 7 the incidence of subjects with at least one local or systemic reaction was 4% and 13%, respectively. As compared to the first dose, the second dose's adverse reactions were milder and were

recorded less frequently.^{25,27,28} In the case report reported by Marie S *et al.*, anti-PF4 antibodies were observed 6 to 24 days after receiving the first dose of AZD1222, unrelated to the use of heparin therapy, in a case report of 23 mostly young, usually healthy patients who presented with atypical thrombosis, mainly involving cerebral veins, and thrombocytopenia.³³ With the exception of one patient who presented with fatal intracranial haemorrhage, Andreas G *et al.* confirmed that 11 original patients starting 5 to 16 days after vaccination presented with one or more thrombotic events; nine had cerebral venous thrombosis, three had splanchnic-vein thrombosis, three had pulmonary embolism, and four had other thromboses; six of these patients died.³⁴ Chatterjee S *et al.* has reported a case of myocardial infraction post vaccination after 2 days.³⁵ National Adverse event following immunization (AEFI) has documented which include myocardial infraction, cardiac death, trigger pro-thrombotic state, cardiovascular event, hypertensive emergency and anaphylaxis as adverse events in 11 patients and among them 10 had lost their lives.³⁶ Although a causal link has yet to be established, viral vector, a vaccine additive, or a flaw in the manufacturing process may all play a role.^{33,37}

BBV152@:

The virus strain (NIV-2020-770) with the Asp614Gly mutation, which was isolated and sequenced from a Covid-19 patient, was used to produce BBV152. It is an entire virion β -propiolactone-inactivated SARS-CoV-2 vaccine with a toll-like receptor (TLR) 7/8 agonist molecule absorbed to alum (Algel-IMDG). To induce full cell mediate response, it injects intramuscularly in to deltoid muscle at a volume of 0.5ml/dose in two-dose regimen 28 days apart. It can be stored in the refrigerator at temperatures ranging from +2°C to +8°C, which is ideal for immunization cold chains. A Phase 3 clinical trial with 25,800 participants is ongoing, with interim analysis results indicating vaccine efficacy of 81 percent.^{38,39,40} Sapkal GN *et al.* study shown that this vaccine is effective against B1.1.7 and B.1.617 variants.^{31,41} It is available at the rate of Rs. 600/- (8.04\$) for state government and Rs. 1200/- (16.08\$) for private hospital.⁴² Pain and swelling at the injection site were listed as local adverse effects, while fever, weakness or malaise, myalgia, body aches, headache, nausea or vomiting, anorexia, chills, generalized rash, and diarrhea were listed as systemic adverse events.^{38,39,40} AEFI had document 2 adverse event associated with vaccination which include sweating, dizziness, anxiety, cold extremities, hypotension and anaphylaxis.³⁶ Detail phase 3 clinical trial report will be revealed imminently, which will give more data with respect to the immunization efficacy and undesirable impact of it.

RAAd26-s & rAd5-s®:

Recombinant adenovirus type 26 (rAd26) and recombinant adenovirus type 5 (rAd5), both of which bear the gene for SARS-CoV-2 full-length glycoprotein S, are included in the vaccine (rAd26-s and rAd5-s).^{43,44} For both recombinant adenoviruses, a complete dose of the vaccine contain 10^{10} or 10^{11} viral particles⁴⁵ and given intramuscularly one followed by another with 21 days apart. The antigen transmitted by adenoviral vectors is known to induce both cellular and humoral immunity after a single immunization, making it useful as an emergency pandemic prevention method. A long-lasting immune response can be achieved by combining two immunizations. It is available in two formulation, frozen and lyophilized dry powder vaccine. For injection per dose, frozen vaccine inoculated at a volume of 0.5 mL and lyophilized dry powder vaccine must be reconstituted in 1 mL of sterile water. Frozen vaccine required -18°C and lyophilized dry powder vaccine can storage at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$. It has shown 91.6% vaccine efficacy.^{43,44,45} It is equally effective in case of B.1.1.7 and B.1.617 variant and in case of B.1.351 variant it has shown only minimal efficacy but better than other available vaccines.^{46,47,48,49} It is expected to be accessible in India by end of May 2021 at the rate less than 10\$ per dose.^{50,51} Immunization with this vaccine is linked to mild adverse events such as discomfort at the injection site (58%), hyperthermia (50%), headache (42%), asthenia (28%), muscle and joint pain (28%). There were no severe adverse events identified.^{43,44}

Discussion:

Based on aspects discussed throughout this manuscript; there is no clear end point to measure efficacy of the vaccines, different studies use various endpoints such as laboratory confirmed SARS-CoV-2 infection, severity, and/or shedding/ transmission.^{21,23} The epidemiological studies with huge number of populations may predict the perfect endpoint for efficacy measurement. As per the available data (*Table no. 1*), the efficacy of RAAd26-s & rAd5-s® is comparatively high i.e., 91.6% followed by BBV152® with 80% and AZD1222® 70.42% efficacy after successful inoculation of 2 doses as per respective protocol, all of these vaccines had shown their effectiveness to avert UK variant. But in case of South African variant, RAAd26-s & rAd5-s® has shown minimal efficacy, AZD1222® is less effective and the data for BBV152® is scarcely available. This efficacy against SARS-CoV-2 variants was

discovered in laboratory studies using serum from infected patients with a small sample size, necessitating further tests with a larger number of human participants to determine the exact efficacy against new variants.

National AEFI has detected till date, 13 serious adverse events among which, 11 were from AZD1222® and 2 from BBV152® inoculation, out of 13- 10 lost their lives following vaccination with AZD1222® and 3 people recovered after hospitalization (1 of AZD1222® and 2 of BBV152®).³⁵ AZD1222® vaccinated subjects have shown pain in the injection site, fatigue, headache, myalgia, pyrexia, chills, arthralgia as a mild and myocardial infraction, cerebra venous thrombosis, thrombocytopenia as a severe adverse event.^{25,27,28,36} Similarly, BBV152® vaccinated subjects have shown pain in injection site, fatigue, headache, myalgia, pyrexia, chills, arthralgia, cold extremities as mild and hypotension, anaphylaxis as a severe adverse event.^{36,38,39,40} Still RAd26-s & rAd5-s® is not available in India, data shared from clinical trial and other data from different countries has shown no serious adverse events, only mild adverse events were injection site pain, headache, myalgia, asthenia, pyrexia and arthralgia.^{43,44}

Storage and transportation of vaccines has been a quite challenging task, the storage units and Temperature monitoring device (TMD) requires regular monitoring to ensure proper vaccine stability and function, maintaining the temperature at +2 °C to +8°C except with the frozen RAd26-s & rAd5-s® which requires -18°C. AZD1222® may be economical than compared to the other two with at least Rs. 200/- (2.69\$) per dose as with regard to the expenses behind the logistics for transport through the deeper parts of the country.

Recently new variant B.1.617 detected in India (Maharashtra), which is supposed to be more contagious.¹¹ It might be the reason for hiking Covid-19 cases rapidly, because there is a possibility that the vaccine uses to induce neutralizing antibodies may not work against this mutant (like South African variant). It is necessary to assess the coverage of vaccine for this variant to know the usefulness of vaccination.

All the vaccine made for immunization were targeting Wuhan-Hu-1 reference virus.¹⁰ After that lots many variants were detected which developed resistance against vaccines available for immunization. This raises a question, Are we really safe from SARS-CoV-2 infection after vaccination? Believing a vaccine blindly may result in deadly consequences, the main challenge for scientist and researcher is to develop a vaccine which will have equal efficacy for future variants. It will take long duration as well as huge investment, which may not be

feasible to assure the efficacy within short span of time. Now, the focus of researchers is diverted to induce wide range of immunity by using existing vaccines; therefore, trials of various combinations of the vaccine is ongoing.⁴⁷ As was followed by the manufacturer of RAd26-s & rAd5-s®, where they have used two different viral vectors i.e., rAd26-s and rAd5-s.^{43,44,48}

Table no.1 Head-to-head evaluation of Covid-19 vaccine authorized in India.

Vaccine Name	Type	Doses and Interval	Efficacy				Storage	Adverse Event	Price
			General	UK variant	South African Variant	Indian Variant			
Covishield®	Viral vector ^{26,27,28}	2 doses, 28 days ^{25,26,27}	70.42% ^{26,28}	Effective ³⁰	Not Effective ³⁰	Effective ³¹	+2°C to +8°C ²⁸	Mild: - Injection site pain, fatigue, headache, myalgia, pyrexia, chills, arthralgia Severe: -Myocardial infraction, cerebra venous thrombosis, thrombocytopenia ^{25,26,27,35,36}	Rs.400/- (5.38\$) for state government. Rs. 600/- (8.07\$) for private hospital ³²
Covaxin®	Inactivated virus ^{38,39,40}	2 doses, 28 days ^{38,39,40}	81% ^{38,39,40}	Effective ⁴⁰	Unknown	Effective ³¹	+2°C to +8°C ^{38,39,40}	Mild: - Injection site pain, fatigue, headache, myalgia, pyrexia, chills, arthralgia, cold extremities Severe: - Hypotension, Anaphylaxis ^{36,38,39,40}	Rs. 600/- (8.07\$) for State Government. Rs.1200/- (16.13\$) for private hospital ⁴²
Sputnik V®	Viral vector ^{44,45}	2 doses, 21 days ^{43,44,45}	91.6% ^{43,44,45}	Effective ^{46,47,48}	Minimal effective ^{45,46,47}	Effective ⁴⁹	-18 (Frozen vaccine) +2°C to +8°C (lyophilized) ^{43,44,45}	Injection site pain, headache, myalgia, asthenia, pyrexia, arthralgia. ^{43,44}	Expected less than Rs.750/- (10\$) ^{50,51}

Conclusion:

It is required to carry out the epidemiological studies to establish a clear endpoint for vaccine efficacy measurement. As per available data, RAd26-s & rAd5-s V® vaccine is designed as per present interest by using two different viral vectors to induce neutralizing antibodies having wide range of coverage which has shown comparatively greater efficacy in overall (Old and new variants) than BBV152® and AZD1222® vaccines in the prevention of Covid-19 and has not associated with serious adverse event, further study may be required, considering new variants.

The main goal of vaccination is to reduce deaths, protect the health care system and finally disease control, this is only be possible if more population is vaccinated with locally available Covid-19 vaccine and self-awareness about the prevention of disease transmission. Wearing mask, maintaining distance, regular hand washing and avoiding crowded is still the best option to prevent the SARS-CoV-2 infection even after vaccination.

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