STUDY TITLE: TO STUDY IMMUNOGENECITY AND SAFETY OF COMBINATION VACCINES FOR COVID -19.

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1. **INTRODUCTION:** Vaccination is protective against COVID 19infections. Based on recent studies by ICMR[1] study which included 18 patients and Com- COV study [2,] Combi Vacs trial[3], It has been observed that combination vaccines elicit better immunogenic response. There are a few studies form India on combination vaccines. We plan to do in large number of healthy volunteers.

2. **STUDY OBJECTIVES:**

   a. **Primary objective:**

   To assess the immunogenicity of combination vaccines at 28 days and 45 days after complete vaccination in unvaccinated healthy volunteers.

   b. **Secondary objective:**

   - To assess safety of administration among different vaccine combinations

3. **STUDY POPULATION:**

   This study population includes unvaccinated healthy volunteers

   DESIGN AND DURATION OF THE STUDY: Prospective observational study

   Study duration 3 months

4. **METHODOLOGY:**

   This study shall include volunteers who be tested negative for SARS-CoV-2 by RT PCR and negative baseline antibody titres. Their neutralizing antibodies will be measured and compared at 28 days after 1st dose and at 45 days after complete vaccination.

INCLUSION CRITERIA:

- If you are an adult male or female human volunteer of age 18-65 years (inclusive of both) and not vaccinated for COVID-19/Influenza, willing and able to provide written, signed and dated informed consent
- If you have negative immunoglobulin M (IgM) SARS-CoV-2 antibodies through enzyme immunoassay test result
- If you have negative COVID-2019 Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) test result at the screening visit
- If you had no medical history or evidence of COVID-2019
- If you had no acute infections and/or respiratory diseases within 14 days before enrollment
- If you had no evidence of vaccine-induced reactions or complications after receiving immunobiological products in the past medical history
- If you are willing to give consent to use effective contraception methods during the study
- If you have negative urine pregnancy test at the screening visit (for child-bearing aged women)
- If you have negative human immunodeficiency virus (HIV 1 & 2), syphilis, hepatitis B and C test results

a. EXCLUSION CRITERIA:

- Aged < 18 years of age are excluded from the study
- any vaccination/immunization within 30 days before the enrollment
- any treatment with steroids (except hormonal contraceptives) and/or immunoglobulins or other blood products within 30 days before the enrollment
- any treatment with immunosuppressive therapy within 3 months before the enrollment

- any drug allergy (anaphylactic shock, Quincke's edema, polymorphic exudative eczema, atopy, serum disease), hypersensitivity or allergic reaction to immunobiological products, known allergic reactions to study drug components, acute exacerbation of allergic diseases on enrollment day
- any neoplasms in the past medical history
- donated blood or plasma within 3 months before the enrollment
- any history or evidence of splenectomy
- any immunodeficiency state
- any history or evidence of anorexia or protein deficiency of any origin
- alcohol or drug addiction in the past medical history
- participation in any other interventional clinical trial within 3 months
- any other condition that the study physician considers as a barrier to the trial completion as per the protocol
- pregnancy or breast-feeding
- Subjects who are tested positive for Corona virus disease through RT-PCR SARS CoV-2 Test and positive anti COVID antibodies.

b. SUBJECT RECRUITMENT:

Healthy volunteers will be recruited into the study based on the inclusion criteria and the data shall be collected i.e. Demographics, comorbidities, date of vaccination will be entered in excel. They will be closely followed up upto 8 weeks to observe for any adverse reactions.

c. RANDOMIZATION AND BLINDING: Computer Generated randomisation

d. STUDY METHODS / STUDY PROCEDURE /METHODS OF ASSESSMENT:

This is a prospective observational single-centered study. A total of 200 healthy volunteers will be recruited. They will be given combination vaccines as follows after taking informed consent.

Following are the 4 groups involved in the study:

i. Group 1: Covishield + Covishield (n =50)
ii. Group 2: Covaxin + Covaxin (n=50)
iii. Group 3: Covishield + Covaxin (n=50)
iv. Group 4: Covaxin + Covishield (n=50)

e. Methods: Whole blood (3ml) will be collected from all the healthy volunteers after informed consent and baseline ,28 days and 45 days neutralizing antibodies will be measured by electrochemiluminiscene.

f. DISCONTINUATION CRITERIA:

People who got infected during study period and lost to follow up are excluded in the study.

5. OUTCOME MEASURES

a. Primary:

- To assess the immunogenicity of combination vaccines at 28 days and 45 days in different groups

b. Secondary:

- To assess safety among different vaccine combinations
- To look for break through COVID infection

6. SAMPLE SIZE: 200 (50 IN EACH Group)

7. STATISTICAL ANALYSIS:

All the required data shall be analysed using applicable software.

8. ETHICAL JUSTIFICATION OF THE STUDY:

The study will be conducted in accordance with the International standards of Good Clinical Practices (ICH - GCP) and the Declaration of Helsinki. ICMR guidelines and the Schedule –Y regulations of Clinical research in India shall also be followed.

Institutional Ethics Committee (IEC)

Study would be commenced only after obtaining the approval of the IEC. The investigator will promptly report to the IEC all changes in research activity. The progress of the study and any adverse events if any will be intimated to the IEC as per IEC protocol. Apart from these, the study team would follow any other regulations as per the IECs' standard requirements.

Patient Confidentiality

This study shall follow HIPAA rules by de-identifying the patients. All information obtained on patients shall be kept extremely confidential and shall not be released to anyone outside the study team. The identifiable data i.e., name of the patient would be converted to initials when the data are entered in the study proforma.

9. REFERENCES

1. Covishield and Covaxin Jabs Mix Match Safe: ICMR Study AUG 9 2021. ICMR.gov .in
2. Shaw, R. H. *et al. Lancet* **397**, 2043–2046 (2021).
3. Borobia,A.M. *etal.* Preprint at SSRN https://doi.org/10.2139/ssrn.3854768 (2021).