# STUDY PROTOCOL

**Institution:** Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP)

**Main Coordinator**

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| **TITLE** | **Immunogenicity and safety of an inactivated virus vaccine against SARS-CoV-2 in patients with autoimmune rheumatic diseases** |
| **DISEASES** | Systemic Lupus Erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (APs), dermatomyositis / polymyositis (DM/PM), systemic sclerosis (SS), systemic vasculitis, primary Sjögren's syndrome, primary antiphospholipid syndrome (APS) |
| **BACKGROUND** | The COVID-19 pandemic has progressed rapidly around the world, reaching lethality of up to 20% in different regions (Garcia LF, 2020). More serious cases were observed in elderly patients and with comorbidities, particularly in those with chronic cardiovascular or respiratory diseases, diabetes and hypertension (Garcia LF, 2020; Emmi G, 2020). SARS-Cov-2 infection has raised particular concern in patients with autoimmune rheumatic diseases (DRAI) (Garcia LF, 2020; Emmi G, 2020). Due to chronic inflammatory autoimmune dysregulation and the regular use of immunosuppressive drugs (Fernandez-Ruiz R, 2020), these patients were considered to be at high risk of contracting SARS- |

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| | CoV-2 and potentially having a worse prognosis (Fernandez-Ruiz R, 2020).<br>Vaccine response studies are needed to verify the immunogenicity of the COVID-19 vaccine in immunosuppressed patients with rheumatological diseases. In addition, it is relevant to evaluate the safety of the vaccine in these populations. |
| **OUTCOMES** | Primary Outcome Measure:<br>1. Immunogenicity of CoronaVac in a cohort of ARD patients compared with age- and sex-matched controls without these conditions:<br>- Seroconversion rate of anti-SARS-Cov-2 IgG antibodies<br>- Presence of ≥30% of neutralizing activity of SARS-CoV-2 antibodies<br>2. Safety of CoronaVac in ARD patients compared with controls without these conditions<br>3. Immunogenicity of CoronaVac in a cohort of ARD patients compared with age- and sex-matched controls without these conditions 6 months after the second vaccine dose.<br>4. Immunogenicity of an additional 4$^{th}$ dose of a mRNA (BNT162b2) heterologous SARS-CoV-2 vaccine in poor/non-responders ARD patients previously vaccinated with 3$^{rd}$ of a SARS-CoV-2 inactivated vaccine. |
| **SAMPLE SIZE** | 1. **AUTOIMMUNE RHEUMATIC DISEASES (ARD) PATIENTS**<br>The sample size calculation was based on the previous 15% reduction of seroconversion rate after primo vaccination with the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of ARD patients. Expecting seroconversion rates of 63% in the ARD patient's cohort and 78% in the control group, considering an alpha error of 5% and power of 80%, in 5 : 1 ratio in order to include more ARD patients, the minimum sample required would |

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| | be 445 ARD patients and 89 healthy subjects, sex-matched and with similar ages. Expecting a higher SC rate of 98% for this vaccine, such sample size had a power greater than 99% to detect a 15% reduction in SC of ARD patients. Due to the peak of pandemics ongoing in Brazil during the vaccination period, we invited more patients and controls, expecting a high incidence of previously infected people and a high rate of infections.<br>A sample was calculated for patients with other rare rheumatological diseases, grouped into five diseases (systemic scleroderma, dermatomyositis/myositis, primary Sjogren's syndrome, systemic vasculitis and primary antiphospholipid antibody syndrome) being followed up in Rheumatology outpatient clinic (HCFMUSP). For the calculation, a seroconversion ratio of p1 = 50% is assumed for each disease and p2 = 74.25% as the average seroconversion of healthy controls.<br>The sample size for each rare disease was 50, thus 250 being the number of patients with other diseases.<br><br>2. **CONTROL GROUP:** 271 healthy controls matched for age and sex will be included according to the need for controls for lupus (n = 74), rheumatoid arthritis (n = 61) and ankylosing spondylitis / psoriatic arthritis (n = 136) will be selected to receive the vaccine at HCFMUSP. |
| **STUDY DESIGN** | The study will be prospective observational in a cohort of patients to be vaccinated and that will be compared independently to the healthy, matched control group by sex and age. |
| **POPULATION** | **Inclusion criteria:**<br>- RA patients according to the classification criteria of the European league against rheumatism (EULAR) / American College of Rheumatology (ACR) (Aletaha D, 2010). |

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| | - Patients with spondyloarthritis, more specifically with the diagnosis of axial spondyloarthritis (ASAS criteria 2009) (Rudwaleit M 2009) and psoriatic arthritis (CASPAR 2012 criteria) (Tillet W 2012) will be included in the present study.<br>- SLE patients according to the SLICC classification criteria (Petri M, 2012)<br>- Patients with systemic sclerosis according to the ACR preliminary criteria (Van den Hoogen F et al., 2013)<br>- Adult and pediatric patients with inflammatory myopathies according to the criteria of Bohan and Peter (Bohan A et al., 1975)<br>- Patients with primary vasculitis (Takayasu's arteritis, granulomatosis with polyangiitis, polyarteritis nodosa) (Arend WP et al., 1990; Leavitt RY et al., 1990; Lightfoot RW et al., 1990)<br>- Patients with primary Sjogren's Syndrome (classification criteria of the European Study Group on Diagnostic Criteria for Sjögren's Syndrome) (Vitali C et al., 1996)<br>- Patients with primary APS (Sydney classification criteria) (Miyakis S et al., 2006)<br>- Patients with HIV-related illness<br><br>**Exclusion criteria:**<br>History of anaphylactic response to vaccine components<br>- Acute acute febrile illness<br>- Guillain-Barré syndrome, decompensated heart failure (class III or IV), demyelinating disease.<br>- History of live virus vaccine up to 4 weeks before, virus vaccine inactivated up to 2 weeks before.<br>- History of having received blood products up to 6 months before the study. |

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| | - Individuals who do not accept to participate in the study and / or whose guardians do not agree to participate in the study.<br>- Hospitalized patients<br>- Patients with severe conditions requiring hospitalization<br>- Pre-vaccination positive COVID-19 serology (IgG or neutralization antibodies). |
| **RELEVANT METHODS** | ARD patients and controls will be vaccinated with the vaccine against COVID-19 by HCFMUSP.<br>The vaccination protocol will consist of two doses of the COVID-19 vaccine for patients and controls, in addition to the collection of a blood sample on the day of the 1st vaccine dose (D0), on the day of the 2nd vaccine dose (28 days after first dose) and 40 days after the second dose of the vaccine. An additional (third) dose will be given 6 months after the second dose (D210) and immunogenicity will be assessed 30 days later (D240). Blood collection will also be performed at D210 prior to vaccination (3rd dose) to assess humoral response decay.<br>The serum obtained during collection will be stored in a -70ºC freezer for testing for immunogenicity.<br>Immunogenicity will be assessed using the seroconversion rates of total IgG antibodies against S1 and S2 antigens and neutralizing antibodies to SARS-CoV-2 on the day of the 2nd dose and 40 days after the 2nd dose, using the 2-dose vaccine schedule is 28 days apart. Additionally, immunogenicity will be assessed prior to the third dose vaccination, 6 months after the second dose, and 30 days after the third dose vaccine dose (6 months after the second dose). |
| **SAFETY** | Healthy patients and controls will be advised of the possible side effects of the vaccine. In addition, patients and controls will be |

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| | instructed to note in a standard diary the changes that occur in the period, such as:<br>Local reactions: pruritus, local pain, erythema, induration at the vaccine site,<br>Systemic reactions: tiredness, fatigue, headache, nausea, diarrhea, fever, chills, myalgia, arthralgia and diarrhea, signs of airway infections (cough, sputum, sore throat, ear pain or discharge, nasal congestion or expectoration, dyspnoea, sneezing), fever (axillary temperature> 37.8º C), itchy skin, rash, vertigo, abdominal pain, drowsiness, malaise, flushing, extremity pain / discomfort, back pain, edema, inappetence.<br>In addition, the need for medical care, hospitalizations, severity of infections, sick days, absenteeism at work and treatment received will be raised, regarding a clinical condition compatible with COVID-19.<br>The standardized diary of adverse events will be evaluated by the researchers 28 days after the first dose of vaccine and 40 days after the second dose. The diary includes guidance for telephone communication of any events that require hospital care. If tertiary care is required, the participant will be transferred to our University hospital (Hospital das Clínicas FMUSP). Serious adverse events will be defined as those that result in hospitalization or death. They will be reported to the National Ethics Comitee (CONEP) within 24 hours.<br>Surveillance will be maintained for new cases of COVID-19 through weekly WhatsApp messages. For patients who present symptoms compatible with COVID-19 infection after vaccination, according to the recommended routine for monitoring immunosuppressed patients with a suspicious condition, a nasal swab will be collected to perform PCR for COVID, with sequencing |

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| | for mutant strains in positive cases. for a period of up to 12 months after the 2nd dose of the vaccine. Positive samples will be sequenced by the protocol established at IMT-FMUSP (1) using the MinION platform (Oxford Nanopore Technologies, UK). The extracted RNA is converted into cDNA using the SuperScript IV First-Strand Synthesis System (Thermo Fisher Scientific, USA) and amplification of the complete genome using the Multiplex PCR protocol - version 3, described by Quick 2020 (2). The amplified samples are purified using 1x Ampure XP beads (Beckman Coulter, United Kingdom) and 70% alcohol solution twice. Amplicons are quantified with Qubit dsDNA High Sensitivity Assay Kit fluorophore and assayed in the Qubit 3.0 instrument (Life Technologies, USA (ThermoFisher) as recommended by the manufacturer. Amplicons are normalized to 240 ng and identified with barcodes. the following EXP-NBD104 (1-12) and EXP-NBD114 Native Barcoding Kits (Oxford Nanopore Technologies, UK) and Ligation Sequencing kit (ONT, SQK-LSK109) are used according to protocol (2). The final library is then loaded into the flowcell R9.4.1 and sequenced using the MinION platform (Oxford Nanopore Technologies - ONT) .The programs MinKNOW (version 19.10.1) and RAMPART are used to monitor the sequencing run in real time (https: //artic.network/rampart)<br>After the end of the race, the fast5 files are subjected to base calls and separation of the barcodes (basecalled and demultiplexed) using the Guppy software, version 2.2.7 (Oxford Nanopore Technologies, UK). To obtain the consensus sequences, the fastq5 files are mapped against the reference genome of SARS-CoV-2 isolate Wuhan-Hu 1 (GenBank accession number MN908947) using the program minimap2 (version 2.28.0) and SamTools. |

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| | Bioinformatics analyzes will follow the protocols described by the research group ARTIC (https://artic.network/ncov-2019). |
| **STATISTICAL ANALYSIS** | The results will be presented as mean ± standard deviation (SD) or median for continuous variables and percentage for categorical variables. Data for continuous variables will be compared using Student's t-test or Mann-Whitney to assess differences in immunogenicity (serology) between patients with rheumatic diseases versus healthy controls. Differences between categorical variables (safety and effectiveness) will be assessed using the chi-square or Fisher's exact tests. Statistical significance will be established with $p < 0.05$. |

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