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A comparison of different SARS-CoV-2 vaccine platforms: the CoviCompare project

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To the Editor - Since December 2019 the COVID-19 pandemic has spread from China to across the world. As the pandemic continues, 19 vaccines using different technologies have been authorized and are now being used for large vaccination programs worldwide. These vaccines are based on different vaccine platforms (mRNA, recombinant viruses, adjuvanted recombinant proteins, and inactivated viruses) that have never been compared in terms of immunogenicity using the same standardized immunological readouts.

There are important questions that remain unanswered regarding the durability of the immune response, the need for and timing of booster injections, and the relative efficacy of the different vaccines against variants. Several countries have a limited choice of authorised and available vaccines, and so a given vaccine may be used in a given demographic situation with a subset of a given variant. Local immunological data will help advise the best protection for a given population, as will an analysis of different age groups.

We have implemented a collaborative research program involving scientists and clinicians in France, Guinea and Mali. The CoviCompare project consists of a comprehensive longitudinal analysis of immune innate and adaptive immune responses induced by different vaccine platforms in older (more than 65 years old) versus younger (18 to 45 years old) adults previously infected, or not, by SARS-CoV-2. This project aims to track protection over time in order to assess the need for booster vaccines, as well as the relative efficacy of the different vaccine platforms in different countries against different variants. The project also aims to identify biomarkers by age group, which may help to predict the risk of vaccine failure.

The standard design of each CoviCompare Clinical Trial is a comparative, non-randomised Phase II trial assessing the immunogenicity and safety of a vaccine against SARS-CoV-2 in younger versus older adults. The primary objective is to quantify IgG antibody titers directed against the SARS-CoV-2 spike protein 28 days after the full primary vaccination schedule. Secondary and exploratory objectives will assess all components of the immune response at various time points and up to two years after vaccination (Table 1).

The humoral immune response elicited by the different vaccines will be evaluated by measuring IgG, subclasses of IgG (IgG1, IgG2, IgG3, IgG4), IgA and IgM antibodies against the spike (including the S1-subunit and RBD subdomain) and nucleocapsid protein (NP) of SARS-CoV-2. A 24-month kinetics study of neutralising antibodies[2] will also be performed using the Wuhan ancestral strain and the most relevant variants of concern (VOCs) in circulation at the time of analysis.

Memory B cell responses to diverse SARS-CoV-2 antigens will be assessed using Elispot, B cell receptor repertoire (stereotype and clonotype), defined by next generation sequencing, which may provide insights into the diversity of induced antibodies and their ability to recognize a wide array of variant strains[4].

The mucosal immune response will be evaluated by measuring anti-Spike and anti-NP IgG, IgA and IgM in saliva as well as mucosal secretory IgA and IgM [5].

T-cell responses to the vaccine will be assessed via Elispot and FluoroSpot assay [7] and high-throughput cytometry analysis [7]. Finally, the innate immune response will be characterized using transcriptomics and extensive flow cytometric analysis.

We will also analyze immunosenescence biomarkers at baseline including markers of age-related low grade inflammation (inflammageing), as well as senescence-associated secretory pathways and the DNA damage response. These parameters will be analysed by flow cytometry, a dedicated nanostring panel and by functional assays. This will enable us to identify specific biomarkers that predict poor responses to COVID-19 vaccines in the elderly and should open potential new avenues to investigate and improve the efficacy of these vaccines in this population.

Data generated in this CoviCompare project are high-dimensional, heterogeneous and multi-scale. Machine-learning approaches will be employed to compare the various vaccine platforms, and to decipher and predict immunological responses, including diversity and memory.

In parallel, the project will establish a biobank of serum, saliva and blood cells which will represent a precious reservoir for future experiments, available for the medical and scientific community.

Six independent studies using a standard clinical trial protocol are currently ongoing or scheduled with different vaccine platforms, according to their availability in the various countries. mRNA-based vaccines are already used in CoviCompareM, with mRNA-1273 (Moderna, NCT04748471) and CoviCompareP with BNT162b2 (Pfizer/BioNTech, NCT04824638); Ad26.COV2.S (adenovirus vector from Janssen) is being trailed in CoviCompareJ (NCT05037266) and other trials are in preparation with other vaccine platforms, including inactivated virus and purified adjuvanted protein-based vaccines.

The CoviCompare project has already fully recruited volunteers for CoviCompareM and P trials, which are ongoing with the financial support of the French Ministry of Research (MESRI, Ministère de l'Enseignement supérieur, de la Recherche et de l'Innovation). The third clinical trial began in October 2021 with the Janssen vaccine and will recruit volunteers in both France and Mali. In addition, studies evaluating inactivated and subunit vaccines will be conducted in Mali and Guinea, with the sponsorship of the ANRS Emerging Infectious Diseases (ANRS|MIE).

Studying vaccine efficacy in African countries will ensure that much-needed independent data is generated about vaccines that are widely used in Africa[8]. This will help inform the design of effective national immunization policies in the region and contribute to local confidence in these vaccines.

The CoviCompare project will allow us to define the differential durability of immune responses between vaccine platforms and the diversity of immune responses that allow different variant virus neutralization. Our hope is that this project will help to identify immune correlates of protection and identify differences in cellular and humoral responses according to age and gender, as well as in those who are naïve or previously infected with SARS-CoV-2.

Author Contributions

DM, ET, MPK, and OL managed the project and wrote the manuscript. All authors contributed to the project and reviewed the manuscript.

Competing interests

B.C. has been a scientific board member for Sanofi Pasteur and Astrazeneca and received personal fees as a speaker for Pfizer. E.B.N. has been a scientific board member for Pfizer, Sanofi Pasteur, and Janssen with all honoraria payed to her institution. E.T. has received personal fees as a speaker or consultant for BMS and Kephren and research grants from Servier, OSE therapeutics, and Imcheck. S.v.d.V. has a provisional patent on SARS-CoV-2 diagnostics and a research grant from Sanofi Pasteur on an unrelated subject. O.L. has received personal fees from Sanofi Pasteur, grants, personal fees and non-financial support from Pfizer, Janssen and Sanofi Pasteur, Merck Sharp & Dohme and grants and non-financial support from GlaxoSmithKline. All other authors declare no conflicts.

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Humoral immune responses
Spike serology, isotypes and subclasses
Neutralization and pseudoneutralization assays using SARS-CoV-2 (Wuhan strain and variants of concern)
Immunoprofiling/LIPS SARS-CoV-2 (S-S1 S2 RBD)
Serology for other coronaviruses
T cell-mediated responses
Fluorospot T cell assays
T cell specific phenotyping (subgroup of Fluorospot)
Memory B cell responses
Memory B cell Elispot
B cell receptor repertoire
Innate immune responses
Transcriptomic analysis (3'RNA sequencing)
Cytokines (Simoa) and anti-cytokines (ELISA)
Innate and B cell phenotyping
Mucosal immune response testing
IgA, IgM and IgG salivary anti-S and anti-RBD
IgA and IgG salivary anti-S ultrasensitive
ADCC/neutralization