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▶ **To cite this version:**

Diana Molino, Christine Durier, Anne Radenne, Corinne Desaint, Jacques Ropers, et al.. A comparison of Sars-Cov-2 vaccine platforms: the CoviCompare project. Nature Medicine, 2022, 28 (5), pp.882-884. 10.1038/s41591-022-01785-4 . hal-03693493

HAL Id: hal-03693493
https://hal.science/hal-03693493

Submitted on 30 Jun 2022

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

Diana Molino[1], Christine Durier[2], Anne Radenne[3], Corinne Desaint[2], Jacques Ropers[3], Soizic Courcier[1] , Louis Victorien Vieillard[1], Claire Rekacewicz[1], Beatrice Parfait[4], Victor Appay[5], Frédéric Batteux[6], Emmanuel Barillot[7] ,Michel Cogné[8] , Béhazine Combadière[9] ,Christiane S. Eberhardt[10], Guy Gorochov[11] , Philippe Hupé [7,12], Laetitia Ninove[13], Stéphane Paul[14] , Isabelle Pellegrin [5], Sylvie van der Werf[15], Maeva Lefebvre[16], Elisabeth Botelho Nevers[17], Inmaculada Ortega Perez[18], Marie Jaspard[24,25], Samba Sow[20], Jean Daniel Lelièvre[21], Xavier de Lamballerie[13], Marie Paule Kieny[22], Eric Tartour[23] , Odile Launay[1] and the CoviCompare Consortium

Affiliations

[1]. Université Paris Cité ; Inserm CIC 1417 Cochin Pasteur ; Innovative clinical research network in vaccinology (I-REIVAC) ; AP-HP. Hôpital Cochin ; Paris, France
[2] INSERM SC10-US019, Villejuif, France
[3] AP-HP. Hôpitaux Universitaires Pitié Salpêtrière - Charles Foix, Unité de Recherche Clinique des Hôpitaux Universitaires Pitié Salpêtrière, Paris, France
[4] AP-HP. Hôpital Cochin, Fédération des Centres de Ressources Biologiques–Plateforme de Ressources Biologiques Centre de Ressources Biologique Cochin, Paris, France
[5]CHU Bordeaux, Laboratory of Immunology and Immunogenetics ; Université de Bordeaux, CNRS UMR 5164, INSERM ERL 1303, ImmunoConcEpT, Bordeaux, France
[6] AP-HP. Hôpital Cochin, Service d'Immunologie Biologique et Plateforme d'immunomonitoring vaccinal, Paris, France
[7] Institut Curie, PSL Research University-INSERM U900- MINES ParisTech, PSL, Paris, France
[8]Laboratory of Immunology - Research unit INSERM U 1236, B cell Ig Remodelling Singularities (BIGRES), Faculty of Medicine, French Blood Center (EFS Bretagne) & University Hospital, Rennes, France
[9]Centre d'Immunologie et des Maladies Infectieuses - Paris (Cimi-Paris), Inserm U1135, Paris, France. Sorbonne Université 91 Boulevard de l'hôpital. 75013 Paris
[10] University of Geneva, Faculty of Medicine; Division of General Pediatrics, Department of Woman, Child and Adolescent Medicine and Center for Vaccinology, Geneva, Switzerland
[11]Sorbonne Université ; Inserm, Centre d'Immunologie et des Maladies Infectieuses (CIMI-Paris), Département d'Immunologie, AP-HP ; Hôpital Pitié-Salpêtrière, Paris, France
[12] CNRS, UMR144, Paris, France
[13] Aix Marseille Univ, IRD 190, INSERM 1207, IHU Méditerranée Infection,Unité des Virus Émergents, Marseille, France.
[14] Inserm, U1111, CNRS, UMR530, Immunology and Immunomonitoring laboratory, iBiothera; CIRI – GIMAP, UCBL 1, UJM, CIC 1408, Saint-Etienne, France.
[15] Université Paris Cité, Institut Pasteur, Unité Génétique Moléculaire Virus à ARN UMR 3569 CNRS, Paris, France
[16] CHU de Nantes ; Inserm CIC1413, Maladies Infectieuses et Tropicales, Centre de Prévention des Maladies Infectieuses et Transmissibles, Nantes, France.
[17] Inserm CIC 1408, axe vaccinologie, CHU de Saint-Etienne, Service d'Infectiologie, Saint-Etienne, France
[18] ANRS | Emerging Infectious Diseases, 75013 Paris, France
[20]The Center for Vaccine Development, Bamako, Mali
[21] INSERM U955, Créteil, France, Vaccine research Institute, Créteil, France
[22] Inserm, 101, 75013 Paris, France
[23] AP-HP, Hôpital Européen Georges Pompidou, INSERM U970, PARCC, Paris, France
[24] ALIMA, The Alliance for International Medical Action, Paris, France
[25] University of Bordeaux, National Institute for Health and Medical Research (Inserm), Research Institute for Sustainable Development (IRD), Bordeaux Population Health Center, UMR 1219, Bordeaux, France

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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.

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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

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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.

Acknowledgments

We thank all the participants included in CoviCompare trial and the Covicompare consortium (Diana Molino, Christine Durier, Anne Radenne, Corinne Desaint, Jacques Ropers, Soizic Courcier, Louis Victorien Vieillard, Claire Rekacewicz, Beatrice Parfait, Victor Appay, Frédéric Batteux, Emmanuel Barillot ,Michel Cogné , Béhazine Combadière, Christiane S. Eberhardt, Guy Gorochov , Philippe Hupé, Laetitia Ninove, Stéphane Paul , Isabelle Pellegrin, Sylvie Van Der Werf, Maeva Lefebvre, Elisabeth Botelho Nevers, Inmaculada Ortega Perez, Marie Jaspard, Samba Sow, Jean Daniel Lelièvre, Xavier de Lamballerie, Marie Paule Kieny, Eric Tartour, Odile Launay, Amélie Dublineau**,** Nozomi Watanabe, Marion Bonetton, Sébastien A Gauthier, Gilbert Mchantaf, Axel Levier, Alpha Diallo, Rebecca Bauer, Diane Carette, Lebbah Said,Fadima Cheick Haidara, Camilla Ducker, Claire-Anne Siegrist, Inna Kuperstein, Andrei Zinovyev, Alice Montoyo, Xavier Anglaret, Denis Malvy, Carine Labruyere, Silvy Laporte, Marie Lachatre, Bertrand Dussol, Dominique Delplanque, Florent Valour, Giovanna Melica, Henri Mondor Creteil, Jean-Jacques Kiladjian, Zoha Maakaroun-Vermess, Paul Laubet, Christian Duale, Clermont Ferrand, Catherine Mutter, Renaud Verdon, Séverine Ansart, Jean-François Nicolas, Abdoul Habib Beavogui, Berthe-Marie Imbert, Samantha Montagne, Alexandre Evrard, Marc Berger, Denis Vivien, Christophe Leroyer, Annachiara de sandre Giovanolli, Frédérique Bertholon, Vinca Icard, Bijan Ghaleh, Alexandre Traverse-Glehen, Caroline Barau, Jean Marc Lessinger, Michel Billing, Bruno Cassinat, Michael Hisbergues)

Funding was received from ANRS |Emerging Infectious Diseases, Ministère des Solidarités et de la Santé, Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation and the Coalition for Epidemic Preparedness Innovations (CEPI).

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199 **Table 1. Immune responses measured in CoviCompare**

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

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