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## References

1. Zhang, Q. et al. *Nature* https://doi.org/10.1038/s41586-022-04447-0 (2022).
2. Sancho-Shimizu, V. et al. *J. Exp. Med.* **218**, e20210446 (2021).
3. Andreakos, E. et al. *Nat. Immunol.* **23**, 159–164 (2022).
4. Arkin, L. M. et al. *J. Invest. Dermatol.* **141**, 2791–2796 (2021).
5. Consiglio, C. R. et al. *Cell* https://doi.org/10.1016/j.cell.2020.09.016 (2020).
6. Cheng, M. H. et al. *Proc. Natl Acad. Sci. USA* **117**, 25254–25262 (2020).
7. Brodin, P. *Immunity* https://doi.org/10.1016/j.immuni.2022.01.014 (2022).
8. Sahanic, S. et al. *Clin. Infect. Dis.* https://doi.org/10.1093/cid/ciab978 (2021).
9. Gaebler, C. et al. *Nature* **591**, 639–644 (2021).
10. Rosene, K. A., Copass, M. K., Kastner, L. S., Nolan, C. M. & Eschenbach, D. A. *Ann. Intern. Med.* **96**, 865 (1982).

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## Author contributions

P. B., G.C., L.T., C.O., I.T., J.L.-R., T.H.M. and J.L.C. wrote the manuscript with input from members of the COVID Human Genetic Effort consortium.

## Competing interests

The authors declare no competing interests.

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# A comparison of Sars-Cov-2 vaccine platforms: the CoviCompare project

To the Editor — Since December 2019, the COVID-19 pandemic has spread from China 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 efficacies of the different vaccines against different variants. Several countries have a limited choice of authorized 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 on the best protection for a given population, as will an analysis of different age groups.

To this end, we have implemented a collaborative research program involving

**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 |

LIPS SARS-CoV-2 (S S1 S2 RBD), luciferase immunoprecipitation system (LIPS) assays using the SARS-CoV-2 ectodomain of the trimeric full spike protein (S) and subdomains S1 (amino acids 1–698), S2 (amino acids 686–1208) and the receptor-binding domain (RBD); Simoa, single-molecule array; ADCC, antibody-dependent cell toxicity.

scientists and clinicians in France, Guinea and Mali. The CoviCompare project consists of a comprehensive longitudinal analysis of innate and adaptive immune responses induced by different vaccine platforms in older adults (≥65 years old) versus younger adults (18–45 years old) who were previously infected, or were not infected, with 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-randomized phase 2 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 is completed. Secondary and exploratory objectives will assess all components of the immune response at various time points and for up to two years after vaccination (Table 1).

The humoral immune response elicited by the different vaccines will be evaluated by measuring IgG, IgG subclass (IgG1, IgG2, IgG3, IgG4), IgA and IgM antibodies against the spike protein (including the S1 subunit and RBD subdomain) and nucleocapsid protein (NP) of SARS-CoV-2. A 24-month kinetics study of neutralizing antibodies[1] 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 assays of B cell receptor repertoire (serotype 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[2,3].

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[4]. T cell responses to the vaccine will be assessed via ELISpot and FluoroSpot assays[5,6] and high-throughput flow cytometric analysis[6]. 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 (inflammaging), as well as senescence-associated secretory pathways and the DNA-damage response. These parameters will be analyzed by flow cytometry, using a dedicated NanoString panel and through 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 for investigating and improving the efficacy of these vaccines in this population[7].

Data generated in the 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 various countries. mRNA-based vaccines are under investigation in the CoviCompareM (with mRNA-1273, Moderna; NCT04748471) and CoviCompareP (with BNT162b2, Pfizer/BioNTech; NCT04824638) studies; the CoviCompareJ study is trialing an adenovirus vector (Ad26.COV2.S, Janssen; 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 the CoviCompareM and CoviCompareP trials, which are ongoing with the financial support of the French Ministry of Research (Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation; MESRI). The CoviCompareJ trial with the Janssen vaccine trial began in October 2021 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 are 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 across cohorts and the diversity of immune responses that allow differential 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 naive to or were previously infected with SARS-CoV-2. ❐

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## References

1. Carrat, F. et al. *Infection* **50**, 257 (2022).
2. Eberhardt, C. S. et al. *J. Virol.* **94**, e02127–19 (2020).
3. Bender, S. et al. *Blood* **135**, 1750–1758 (2020).
4. Sterlin, D. et al. *Sci. Transl. Med.* **13** (2021).
5. Hassan, A. O. et al. *Cell* **183**, 169–184.e113 (2020).
6. Sirima, S. B. et al. *Lancet Infect. Dis.* **20**, 585–597 (2020).
7. Knopp, P. et al. *Eur. Geriatr. Med.* **11**, 1089–1094 (2020).
8. Makoni, M. *Lancet Respir. Med.* **8**, e79–e80 (2020).

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## Author contributions

D.M., E.T., M.P.K. and O.L. 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 paid to her institution. E.T. has received personal fees as a speaker or consultant for BMS and Kephren and research grants from Servier, OSE Immunotherapeutics 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, Sanofi Pasteur and Merck Sharp & Dohme, and grants and non-financial support from GlaxoSmithKline. All other authors declare no conflicts.