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

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

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

72

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

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

89 The humoral immune response elicited by the different vaccines will be evaluated by
90 measuring IgG, subclasses of IgG (IgG1, IgG2, IgG3, IgG4), IgA and IgM antibodies
91 against the spike (including the S1-subunit and RBD subdomain) and nucleocapsid
92 protein (NP) of SARS-CoV-2. A 24-month kinetics study of neutralising antibodies² will
93 also be performed using the Wuhan ancestral strain and the most relevant variants of
94 concern (VOCs) in circulation at the time of analysis.

95 Memory B cell responses to diverse SARS-CoV-2 antigens will be assessed using
96 Elispot, B cell receptor repertoire (stereotype and clonotype), defined by next generation
97 sequencing, which may provide insights into the diversity of induced antibodies and their
98 ability to recognize a wide array of variant strains⁴.

99 The mucosal immune response will be evaluated by measuring anti-Spike and anti-
100 NP IgG, IgA and IgM in saliva as well as mucosal secretory IgA and IgM⁵.

101 T-cell responses to the vaccine will be assessed via Elispot and FluoroSpot assay⁷
102 and high-throughput cytometry analysis⁷. Finally, the innate immune response will be
103 characterized using transcriptomics and extensive flow cytometric analysis.

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

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

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

118 Six independent studies using a standard clinical trial protocol are currently ongoing or
119 scheduled with different vaccine platforms, according to their availability in the various
120 countries. mRNA-based vaccines are already used in CoviCompareM, with mRNA-
121 1273 (Moderna, NCT04748471) and CoviCompareP with BNT162b2 (Pfizer/BioNTech,
122 NCT04824638); Ad26.COVS (adenovirus vector from Janssen) is being trailed in
123 CoviCompareJ (NCT05037266) and other trials are in preparation with other vaccine
124 platforms, including inactivated virus and purified adjuvanted protein-based vaccines.

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

132 Studying vaccine efficacy in African countries will ensure that much-needed
133 independent data is generated about vaccines that are widely used in Africa⁸. This will
134 help inform the design of effective national immunization policies in the region and
135 contribute to local confidence in these vaccines.

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

142 **Author Contributions**

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

145 146 **Competing interests**

147

148 B.C. has been a scientific board member for Sanofi Pasteur and Astrazeneca and
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158

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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