Of course, we concentrated not only on COVID-19 but also on other diseases. In total, we helped the population with 31 patient-education videos, 43 social-media appearances and 13 printed patient-information leaflets (Fig. 1i).

What does the future hold? It is hard to predict, but it is certainly up to us. We strongly believe that disseminating the model and highlighting the successes it achieves can help. It is an excellent sign that Semmelweis University has already invited us to build the TM cycle in Budapest; moreover, several European and American universities have already expressed interest in introducing the TM cycle model or further developing their existing models. Is this model perfect? Certainly not, but it represents a considerable advance. ❐

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Competing interests

The authors declare no competing interests.

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A French cohort for assessing COVID-19 vaccine responses in specific populations

To the Editor—The COVID-19 vaccination campaign started in France on 27 December 2020. It has been rolled out in different priority phases according to the risk of developing a severe form of COVID-19 and the risk of being exposed to the causative coronavirus SARS-CoV-2. By 5 May 2021, four vaccines against COVID-19 were approved by the European Medicines Agency and were available in France: COMIRNATY (the COVID-19 mRNA vaccine BNT162b2; BioNTech–Pfizer); COVID-19 Vaccine Moderna (mRNA-1273; Moderna); VAXZEVRIA (ChAdOx1-nCoV19; AstraZeneca–Oxford University); and COVID-19 Vaccine Janssen (Ad26.COV2.S; Janssen). Specific populations are defined as people at risk of developing severe forms of the disease and in whom the immunogenicity and efficacy of vaccines against that disease may differ from that of the general population (e.g., recipients of solid-organ transplants or patients undergoing hemodialysis). The safety, immunogenicity and efficacy of vaccines in specific populations, which are heterogeneous groups of patients, are affected by the nature and intensity of the underlying disease(s), the age of the patient and any other treatments the patient is taking, and are possibly affected by the vaccine platform used. So far, no or only limited data on specific populations are available from published results of phase 3 trials of authorized vaccines against COVID-19. Initial immunogenicity data available for some of these specific populations showed low antibody responses to the SARS-CoV-2 spike protein in patients who received solid-organ transplantation[1–4], patients undergoing hemodialysis[5,6], patients receiving chemotherapy or immunotherapy for solid cancer or hematologic malignancies[7,8], and patients receiving infliximab for inflammatory bowel disease[9]. Most of these studies reported small sample sizes.

To assess the immune response of COVID-19 vaccines in different specific populations, INSERM (Institut National de la Santé et de la Recherche Médicale) and ANRS-MIE (Agence Nationale de Recherche sur le Sida–Maladies Infectieuses Emergentes), in collaboration with the COVIREIVAC network, ten national disease-specific societies and seven patients' associations (France Rein, Transhépate, ARSEP Foundation, CNAO, FFD, EGMOS and TRT5 CHV), launched, on 25 March 2021, the ANRS0001S COV-POPART study (ClinicalTrials.gov NCT04824651). COV-POPART is a national multi-center prospective multi-cohort study of specific populations vaccinated against COVID-19 that aims to include 10,700 patients.

Patients with solid cancer ($n = 800$), solid-organ transplantation ($n = 700$), hematopoietic stem cell transplantation ($n = 350$), chronic renal failure with or without dialysis ($n = 350$), multiple sclerosis or neuromyelitis optica spectrum disorders ($n = 600$), autoimmune inflammatory rheumatic diseases ($n = 600$), systemic autoimmune diseases ($n = 600$), hypogammaglobulinemia ($n = 300$), obesity (1,400), diabetes mellitus ($n = 1{,}400$) and/or infection with human immunodeficiency virus ($n = 1{,}400$) will be included. All adults affected by at least one of these chronic conditions, without a history of COVID-19 and not yet vaccinated, will be included in one of the 35 participating centers, which represent more than 250 clinical sites. A control group without any of the above-mentioned underlying conditions will also be included ($n = 1{,}850$; 18–74 years of age ($n = 1{,}400$) and ≥75 years of age ($n = 450$)).

The main objective will be to analyze the humoral immune response by assessing IgG antibody to the SARS-CoV-2 spike protein (by ELISA), IgG antibody to the SARS-CoV-2 receptor-binding domain (by ELISA) and specific neutralizing antibody to SARS-CoV-2 (by classical in vitro neutralization assay) at 1 month, 6 months, 12 months and 24 months after the first dose (Janssen vaccine) or second dose (all other vaccines) of the vaccine regimen (Fig. 1). Secondary objectives will be to compare the kinetics and strength of the immune responses of each subpopulation (e.g., recipients of solid-organ transplantation) with those of the control group and to

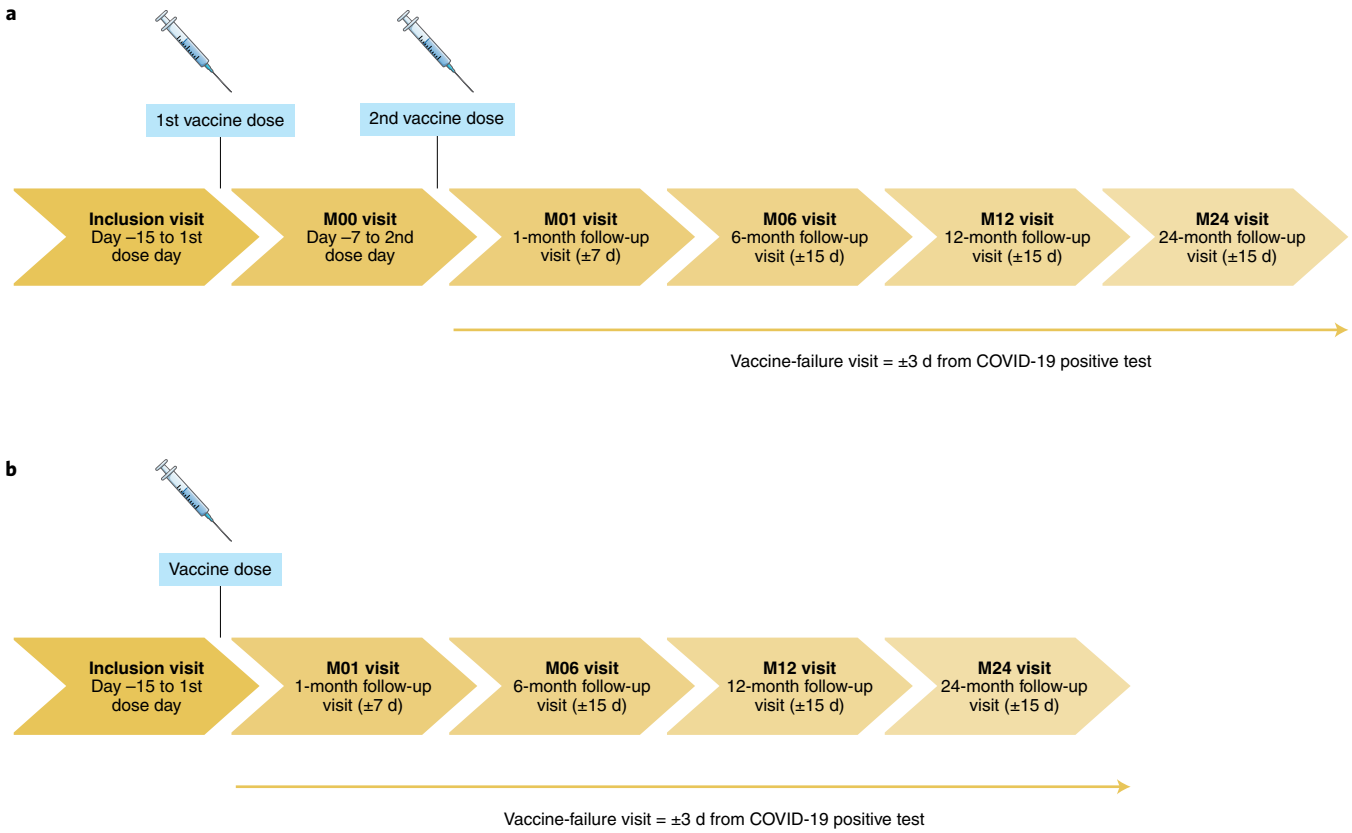

Fig. 1 | COV-POPART study designs. a, Study design for a two-dose vaccine regimen. **b**, Study design for a one-dose vaccine regimen.

make this comparison between specific subpopulations; to assess the factors (such as age, disease stage, treatment, type of vaccine, etc.) associated with the kinetics and strength of the immune responses in each subpopulation; and to characterize the immunology and virology of any vaccination failures, defined as a positive RT-PCR result for SARS-CoV-2 (performed because of clinical symptoms or during routine follow-up) at least 7 days and 15 days after the completion of vaccination (for the two-dose regimen and one-dose regimen, respectively).

In the case of vaccine failure, an additional visit will be required during which specific samples will be collected, including peripheral blood mononuclear cells, blood RNA and DNA, and nasopharyngeal swabs for sequencing of SARS-CoV-2.

In addition, a smaller ancillary study (30–40 participants from each subpopulation) will assess and characterize in-depth antigen-specific T cell responses, and will analyze the gene expression of the immune response through the use of transcriptomics.

Serological and immunological analysis will be centralized to allow standardization of tests and better comparison between patient cohorts of the immunogenicity of vaccines against COVID-19. A new biobank will be implemented to allow future comparisons and assessments. Samples will be made available to other researchers upon request to the scientific committee of the cohort.

Finally, given concerns about the development of thrombotic thrombocytopenia after immunization with ChAdOx1-nCoV19, the French Haute Autorité de Santé advocated, on 8 April 2021, for the use of an mRNA vaccine as a second dose in those below 55 years of age who received a prime dose of ChAdOx1-nCoV19. To assess the immune response of this new heterologous prime–boost COVID-19 vaccine regimen, researchers have added to the COV-POPART study an additional cohort of 200 patients affected by this mixed schedule.

Data collected from participants in the COV-POPART study will be linked to the French Health Data Hub (https://www.health-data-hub.fr/). This will allow the collection of data on cause of death, hospitalizations and monitoring of pre-existing health conditions during the follow-up.

The COV-POPART study will explore responses to vaccines against COVID-19 in a large number of at-risk patients by determining the strength and duration of their immune response and factors associated with this. By sharing the data as quickly as possible, the COV-POPART study will add valuable information that may allow possible adaptations of vaccine recommendations for certain subgroups or may serve as a basis for the implementation of clinical trials on enhanced vaccine regimens, including additional boost with standard or higher doses or adjuvanted vaccines. Finally, the COV-POPART study is intended to be adaptive to include new subpopulations (e.g., pediatric populations) depending on the evolution of the French immunization guidelines or to explore questions that may arise during follow-up, such as the evaluation of added boosting doses, new mixed-vaccine regimens or new authorized vaccines against COVID-19. ❐

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Fractionation of COVID-19 vaccine doses could extend limited supplies and reduce mortality

To the Editor—COVID-19 continues to pose a major threat to public health. Public-health and social measures have been implemented to control transmission, but they are emergency measures that are difficult to sustain in the longer term. There are now 15 vaccines against COVID-19 being used worldwide. However, shortages in the supply of vaccines have been a particular problem for low-income countries, which have collectively received only 0.2% of all vaccines delivered worldwide for approximately 10% of the world's population. Fractionation of vaccine doses (Fig. 1) is a potential solution to this global shortage of vaccines that has not been given sufficient attention and consideration.