Effect of a first shot of covid-19 vaccination on symptoms of long covid: an emulated trial nested in the ComPaRe e-cohort

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Background

According to the United Kingdom Office for National Statistics, 10% of people who were infected with SARS-CoV-2 still experience symptoms after three months, including those whose acute infection was asymptomatic [1].

There are anecdotal stories of long-COVID symptoms improving after vaccination by eliminating any virus or viral remnants left in the body, or by rebalancing the immune system[2]. A UK survey (unpublished) of 900 people with long COVID, reported that 57% saw an overall improvement in their symptoms, 24% no change and 19% a deterioration after their first dose of vaccine [2]. A preprint study compared 44 patients with long covid symptoms who had been vaccinated to 22 who didn't. It found a small overall improvement in long-COVID symptoms [3].

Design

Emulation of a target trial following the framework designed by Hernan et al. [4]

	Target trial	Emulation
Eligibility criteria	- Adult patients (age > 18 years old) - Self-reported long covid, defined as having at least one symptom among a list of 53 persisting more than three weeks past the initial infection and with at least one symptom at the time of inclusion [5] - Confirmed or suspected infection - Exclusion of patients whose date of first symptoms is <3 months before the inclusion date - Exclusion of patients with contraindication to vaccination (history of anaphylactic shock)	- Adult patients (age > 18 years old) - Self-reported long covid, defined as having at least one symptom among a list of 53 persisting more than three weeks past the initial infection and with at least one symptom at baseline [5] - Confirmed or suspected infection - Exclusion of patients whose date of first symptoms is <3 months before baseline - Exclusion of patients with a history of allergy (as a safe proxy to patients who may have had an anaphylactic reaction)
Treatment strategies	Vaccination at baseline No vaccination	Same

Treatment assignment	Random allocation to a strategy at baseline. Patients are aware of the strategy to which they have been assigned	We will classify individuals according to the strategy that their data were compatible With, at baseline. We will emulate randomization by adjusting for baseline confounders
Outcomes	Long covid ST and IT (self-reported) at 120 days	Same
Follow-up	Starts at baseline and ends 120 days after baseline	Same
Causal contrast	intention-to-treat and per-protocol effect	Observational analog per-protocol effect

Data sources

ComPaRe e-cohort (the Community of Patients for Research) is an ongoing citizen science project based on an e-cohort of patients with chronic conditions (www.compare.aphp.fr). Patients join the project to donate time to accelerate research on their conditions. They can do this by answering regular patient-reported outcomes and patient-reported experience instruments, suggesting ideas for new research or participating in the set-up or analysis of research projects. The recruitment started in January 2017 and is still ongoing, with about 47 000 patients included in May 2021. All participants provide electronic consent before participating in the e-cohort. Conditions are self-reported by patients by using the International Classification of Primary Care-Version 2 [6]. In October 2020, "Covid-19" was added as a condition in ComPaRe.

Patients reporting a Covid-19 condition (laboratory confirmed with a positive testing for SARS-CoV2 by PCR swab and/or a serological assay or not (i.e. suspected infection)) receive an online questionnaire asking them the initial date of symptoms and whether they had symptoms persisting more than three weeks past the initial infection (hereafter defined as "patients with long covid").

Those with long COVID are followed-up every 60 days with online questionnaires. At each observation time, patients are first asked whether they still had symptoms related to COVID-19. Those reporting the persistence of symptoms complete the long COVID symptom tool (ST) and impact tool (IT), a pair of validated patient reported instruments assessing respectively 53 long symptoms and 6 dimensions of patients' lives that can be affected by the disease. Those reporting no longer having symptoms were asked to report the date when they no longer experienced any symptoms.

All patients enrolled in ComPaRe are asked every 45 days whether they received Covid-19 vaccination.

This study will use the data from all patients with long covid (laboratory confirmed or not) in ComPaRe who reported their vaccination status and who were enrolled in the cohort from inception up to 01/05/2021 (so as to have at least 120 days of follow-up in September 2021).

Participants

Inclusion criteria:

- Adult patients (age > 18 years old)

- Confirmed or suspected infection COVID-19 infection. We choose to include suspected COVID-19 patients because, during the 1st wave in France, a high number of patients were infected by the SARS-CoV2 but were not tested
- Unresolved long covid, defined as having, at baseline, at least one symptom among the 53 assessed by the long COVID ST [5]

Exclusion criteria:

- Patients whose date of first symptoms is <3 months before baseline. Indeed, in France, recommendations are to delay vaccination for patients who had had COVID-19 for 3 months past the date of symptom onset.
- Reported history of allergy, as a proxy to history of anaphylaxis, which is considered a contraindication to vaccination.

Treatment strategies

Treatment group: Receipt of at least one dose from the following vaccines: ChAdOx1 (Astra Zeneca); BNT162b2 mRNA (Pfizer-BioNTech); mRNA-1273 (Moderna) or Ad26.COV2. S (Johnson & Johnson) within 60 days from baseline.

Control group: No vaccination within 60 days from baseline

Vaccination status is assessed every 45 days in ComPaRe using a self-reported questionnaire.

Outcomes

Outcomes are evaluated at 120 days after baseline.

- Long covid symptom tool (ST), defined as the number of different symptoms experienced by patients during the last 30 days [5].
    - Time to complete remission of symptoms (defined as the first time after baseline when patients report that they no longer any symptoms of COVID-19)
- Long covid impact tool (IT), defined as the sum of scores of 6 items related to the impact of the disease on patients' everyday life [5].
    - Long COVID IT scores can be expressed as a binary outcome, by using the PASS of the score.

For patients in the vaccination group, we will report whether patients self-reported having a serious adverse event after vaccination.

Statistical analysis

We will emulate a target trial of Covid-19 vaccination among patients with long covid using observational data from the ComPaRe e-cohort.

General principles

For each patient, we will divide his/her follow-up into consecutive shorter periods defined by the "observation time points" of follow-up (time at which he responds to the online questionnaires hereafter called "VX", X being at maximum 3 for patients enrolled in December 2020) – on average periods will be 60 days-.

For each patient and for each period, we will identify whether he/she received the 1st dose of COVID-19 vaccine during the period. For each vaccinated patient, we will match one patient who

has not been vaccinated in the same period (e.g., vaccinated patients in the V1-V2 period will be matched to unvaccinated patients in the V1-V2 period) by propensity score matching (see below).

Newly vaccinated persons will be eligible for inclusion in the study, even if they had previously been selected as a control, similar to what was done in the study from Dagan et al. [7]

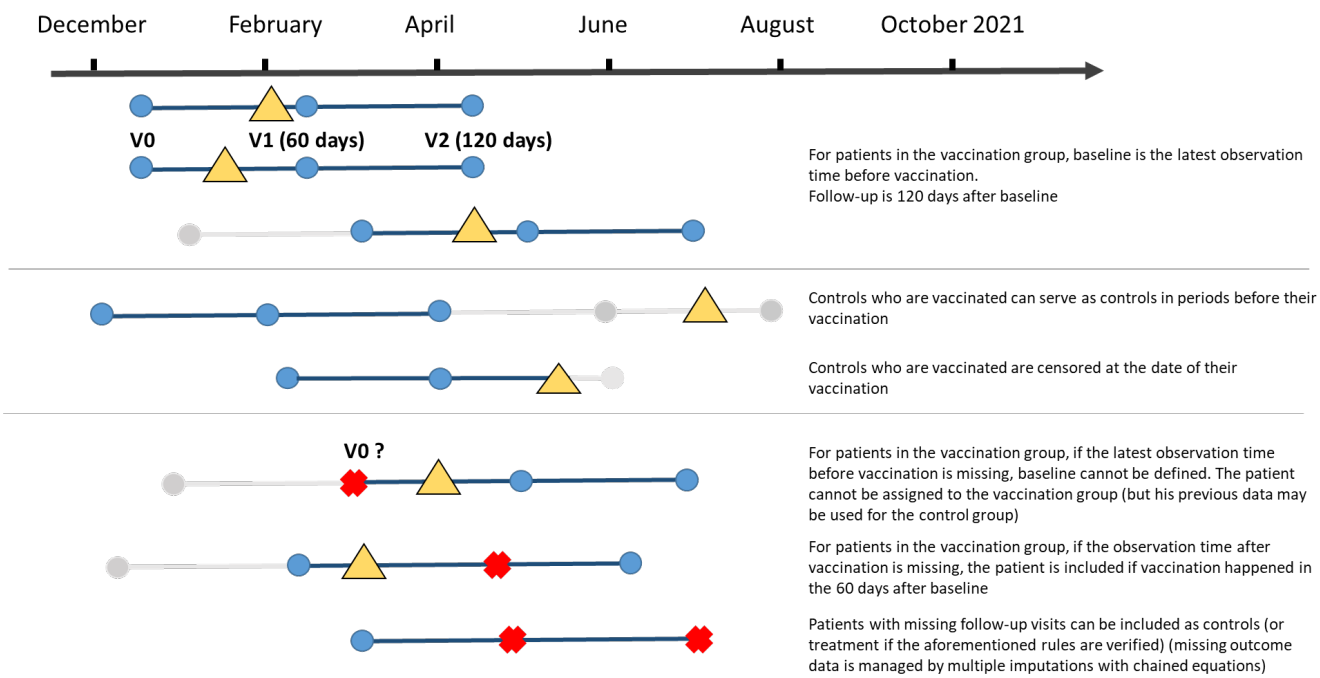
For each person, follow-up ends at the earliest of the following events: vaccination (for unvaccinated controls), or the end of the follow-up (120 days).

Missing baseline and outcome data will be obtained by multiple imputation using chained equations using baseline and follow-up data. However, dates of missing observation points are not created.

Missing observation times

In the treatment (vaccination) group, if patients received vaccination before their first observation time OR if the latest observation time before receiving COVID-19 vaccination was missing, baseline could not be defined and these patients and they could not be assigned to the treatment group. However, they could still be eligible for the control group.

In the treatment (vaccination) group, if the earliest observation time after receiving COVID-19 vaccination was missing, we considered that they were eligible in the period going from the latest observation time before receiving COVID-19 (t0) to (t0 + 60 days).



Propensity score matching

Controls will be matched using PS matching. The PS will be developed using a non-parsimonious logistic model with the following variables:

- sex,
- age at baseline
- Educational level (Associate's degree or Higher education vs. other)
- delay since initial symptoms
- Hospitalization for COVID-19 (YES/NO)

- Hospitalization in ICU for COVID-19 (YES/NO)
- Number of comorbidities (continuous)
- confirmed / suspected covid-19 (confirmed vs. suspected)
- severity at baseline (long covid ST)
- impact at baseline (long covid IT)

Missing baseline and outcome data

Missing baseline and outcome data will be obtained by multiple imputation using chained equations using baseline and follow-up data.

Subgroups

Results will be analyzed globally and in

- a subgroup focused on patients with a confirmed COVID-19 infection

- subgroups evaluating a different version of the intervention:

1) are considered in the vaccination group only patients who received COVID-19 vaccination within 30 days from baseline. Patients who receive COVID-19 vaccination between 30 and 60 days from baseline are excluded from analysis. This analysis reduces the heterogeneity in length of follow-up. It is based on the hypothesis that choice of the date of vaccination relatively to the inclusion in the cohort is not associated with the treatment effect

2) are considered in the vaccination group only patients who received the Pfizer vaccine.

Sensitivity analyses

We will perform a sensitivity analysis restricted to patients who have been included in only one period (i.e., excluding patients included twice in the study, once as an unvaccinated patient and then as a vaccinated patient)

1. Office for National Statistics, *The prevalence of long COVID symptoms and COVID-19 complications*. 2020: London, UK.
2. Marshall, M., *The four most urgent questions about long COVID.* Nature, 2021.
3. Arnold, D., et al., *Are vaccines safe in patients with Long COVID? A prospective observational study.* medRxiv, 2021.
4. Hernan, M.A. and J.M. Robins, *Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available.* Am J Epidemiol, 2016. **183**(8): p. 758-64.
5. Tran, V.T., et al., *Development and validation of the long covid symptom and impact tools, a set of patient-reported instruments constructed from patients' lived experience.* Clin Infect Dis, 2021.

6. World Health Organization. *International Classification of Primary Care, Second edition (ICPC-2)*. 2003 [cited 2020 04/04]; Available from: https://www.who.int/classifications/icd/adaptations/icpc2/en/.
7. Dagan, N., et al., *BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting.* N Engl J Med, 2021. **384**(15): p. 1412-1423.