Long COVID Phenotyping and Vaccine Effectiveness Methods

November 16 Community Call: OHDSI Studies

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Long COVID Phenotyping
Introduction

Background
While many people fully recover after COVID-19, a substantial proportion continue to suffer from long-term complications such as persistent tiredness, chronic pain or breathing difficulties. The combination of these is also called “long COVID”. Current vaccines prevent severe infections leading to hospitalisations or death, but we do not know yet if they also prevent long COVID.

Aim
To characterise long COVID using UK primary care data.
Our approach

#1: Systematic review

An updated systematic review to characterise Long COVID symptoms as recorded in real world data vs. self-reported data

Authors: Annika Jödicke, Kristin Koslka, Victoria Strauss, Daniel Prieto Alhambra
Version, Date: V2, 3rd November 2021

Background

Rationale: Several definitions for "post-acute COVID-19 syndrome" or "long COVID" are currently used in the literature, characterising persistent symptoms that continue for weeks or months following the acute COVID-19 disease. With more and more different symptoms being reported, the definition is rapidly evolving. While systematic reviews were already conducted to summarise symptoms and diagnoses characterising long COVID, differences in types of symptoms depending on the study setting, reporting source and time are less well described. However, for the conduction of observational studies it is crucial to understand which symptoms are reported in the respective real-world study settings. Moreover, an "operational definition" or "clinical phenotype" is needed to facilitate research on long covid using real world data.

Objective: Aim: To summarise symptoms and diagnoses characterising long COVID based on the current literature as of September 2021

#2: OHDSI Phenotype Library
The journey to a Long COVID phenotype

How it started...

March 2021: Columbia DBMI PASC Characterization

- COVID diagnosis, pre-coordinated COVID measurement, lab-confirmed test positive (measurement or observation)

index:

March 2021: Columbia DBMI PASC Characterization

- Symptom: Asthenia (low energy)
- Symptom: Cough
- Symptom: Depression
- Symptom: Dizziness
- Symptom: Fatigue
- Symptom: Headache
- Symptom: Insomnia
- Symptom: Myalgia
- Symptom: Nausea
- Symptom: Neuropsychiatric symptoms
- Symptom: Shortness of breath
- Symptom: Sleep disturbances
- Symptom: Tiredness
- Symptom: Vision changes

March 2021: NIH National COVID Cohort Collaborative PASC Study

- Initial characterization of PASC symptoms

October 2021: NIH National COVID Cohort Collaborative

- With no phenotype, the team took a XGBoost machine learning (ML) model approach to identify potential long-COVID patients
- Anchored on labeled Long COVID clinic visits

How it’s going...

WHO Delphi Consensus (Oct 2021)

“Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist beyond the initial illness. Symptoms may also fluctuate over time.”
Call for community collaboration

- Phenotype WG: Long COVID Subgroup
  - Building phenotypes for 25 WHO Delphi symptoms
  - Building composite phenotype for Long COVID
  - Network validation with interested OHDSI sites
Vaccine Effectiveness Methods
Introduction

Background
Studying COVID-19 vaccine effectiveness is challenging:
• Staged roll-out of the COVID vaccination campaign
• Person-level confounding
• Population-level confounding such as infection rates and vaccination rates in the community

Aim
To test, if our proposed observational analyses adequately account for confounding
**Method**

**Aim:** To test if the proposed observational analyses adequately account for confounding.

“In the first 10-12 days after vaccination there is not yet a protective effect of the vaccine against COVID-19”

Emulate the null-effect from RCT in observational study:
Use observational study design to assess difference in COVID-19 infections between vaccinated and unvaccinated people in the first 10 days.

Polack et al. NEJM, 2020
### Staggered cohort study design

Four staggered cohort studies based on UK Government vaccination priority groups:

<table>
<thead>
<tr>
<th>Study period</th>
<th>Enrolment periods</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/01–27/01</td>
<td>28/01–28/02</td>
<td>01/03–13/04</td>
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### STUDY COHORT
- **Age ≥ 75 (risk groups 2+3)**
  - Vaccinated
  - Unvaccinated

### STUDY COHORT
- **Age ≥ 65, clinically extremely vulnerable/ at-risk patients (risk groups 4-6)**
  - Vaccinated
  - Unvaccinated

### STUDY COHORT
- **Age ≥ 50 (risk groups 7-9)**
  - Vaccinated
  - Unvaccinated

### STUDY COHORT
- **Age ≥ 18 (risk group 10)**
  - Vaccinated
  - Unvaccinated

Additional details include eligibile unvaccinated adults in risk groups 2+3.
Study characteristics

**Study design:** Staggered cohort studies

**Outcome:** COVID-19 in the first 10 days after vaccination

**Exposure:** COVID Vaccines

**Statistical analyses:**
- **Relative Risk** estimated by Poisson regression with IPW (each cohort study)

**Propensity Score:**
- **Person-level confounding:** Baseline characteristics
- **Population-level confounders** at index date: e.g. regional infection rate*, cumulative vaccination rate*

- **Unmeasured confounding:** Negative control outcomes
- **Meta-analysis** to pool 4 cohort study specific effect estimates
Once we have phenotypes for Long COVID … and our study design adequately accounts for confounding…

Vaccine effectiveness for long COVID prevention

**Objective 1**
Estimate the effect of vaccines on the development of long COVID, comparing vaccinated vs. unvaccinated persons

**Objective 2**
Compare the effectiveness of Oxford/AstraZeneca vs BioNTech/Pfizer vaccine in prevention of long COVID
Looking forward to collaborate 😊


Timelines:
Long COVID phenotyping: ~ January 2022
Vaccine effectiveness method: package finished by ~ March 2022

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