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.

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Our approach

#1: Systematic review

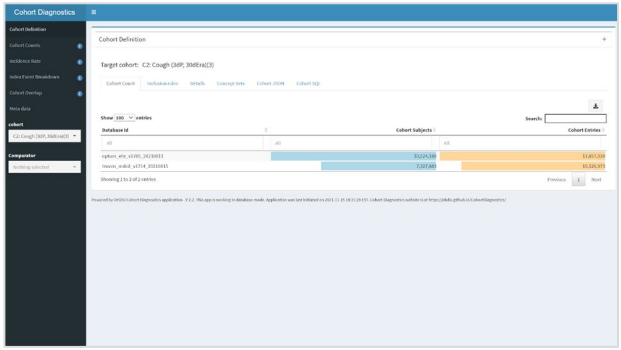
Protocol Systematic Literature Review

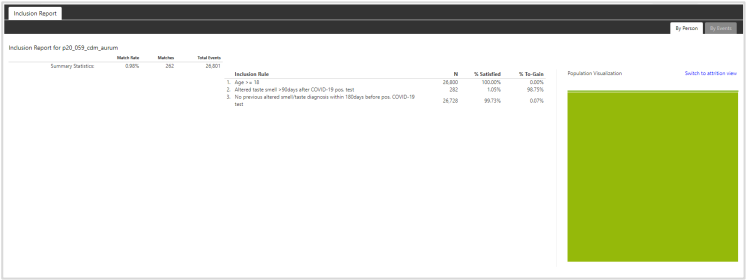
An updated systematic review to characterise Long COVID symptoms as recorded in real world data vs. self-reported data

Authors	Annika Jödicke, Kristin Kostka, 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[1-3]. With more and more different symptoms being reported, the definition is rapidly evolving.[1-8] While systematic reviews were already conducted to summarise symptoms and diagnoses characterising long COVID[9,10], 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

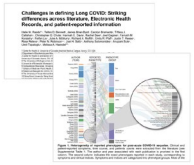
Index:
COVID diagnosis, pre-coordinated COVID measurement, lab-confirmed test positive (measurement or observation)

March 2021: Columbia DBMI PASC Characterization

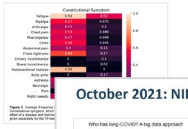
Symptoms:

- Altered smell and taste
- Myalgia
- Joint pain
- Anxiety disorders
- Chest Pain
- Dyspnea
- Malaise or Fatigue
- Cough
- Alopecia
- Sleep disorder without apnea
- Dementia or memory impairment
- Tachycardia or Palpitations
- Adult Rash
- Myocarditis
- Lung Disorder
- PASC Depression
- Acute Kidney Injury
- Fever
- Mood Changes

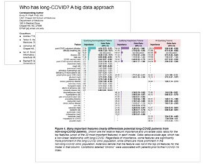
March 2021: NIH National COVID Cohort Collaborative PASC Study



- Initial characterization of PASC symptoms



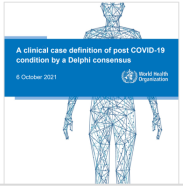
October 2021: NIH National COVID Cohort Collaborative



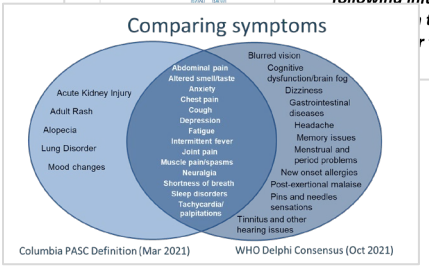
- With no phenotype, the team took a XGBoost machine learning (ML) model approach to identify potential long-COVID patients
- Anchored on labeled Long COVID clinic visits

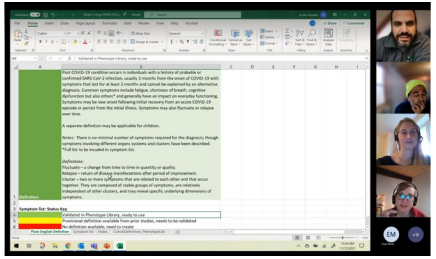
How it's going…

WHO Delphi Consensus (Oct 2021)



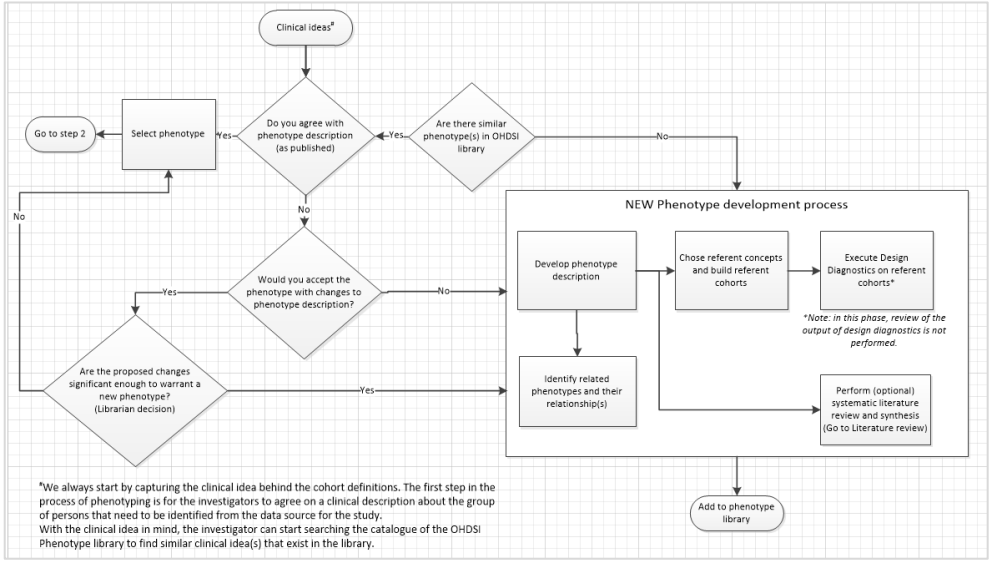
"Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, 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 the initial illness. Symptoms may also fluctuate or 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

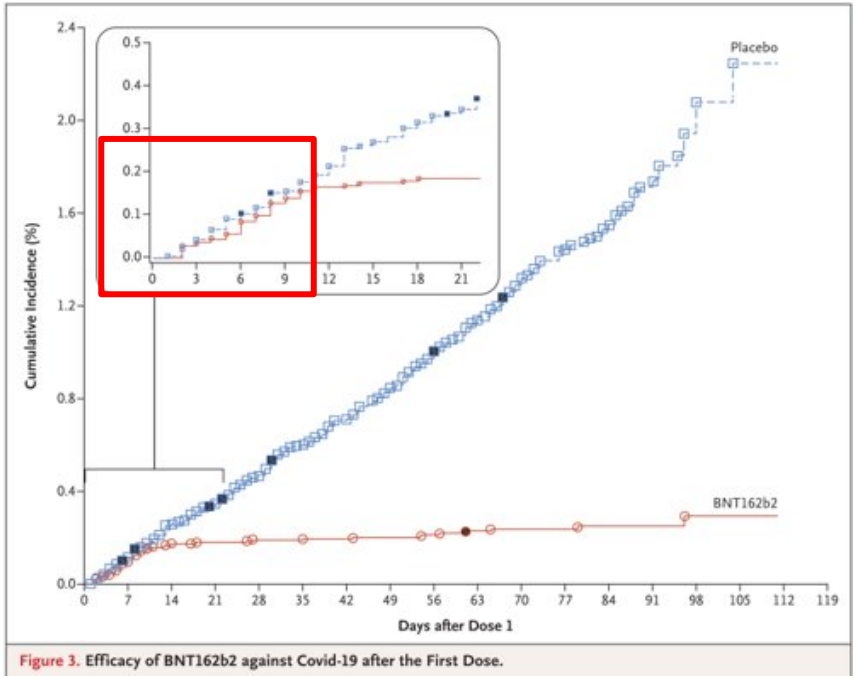


Figure 3. Efficacy of BNT162b2 against Covid-19 after the First Dose.

Polack et al. NEJM, 2020

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.

Staggered cohort study design

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

<table>
<tr><td rowspan="3"></td><td colspan="5">Study period</td></tr>
<tr><td colspan="4">Enrolment periods</td><td>Follow-up</td></tr>
<tr><td>04/01–27/01</td><td>28/01– 28/02</td><td>01/03-13/04</td><td>14/04–31/07</td><td></td></tr>
<tr><td rowspan="2">STUDY COHORT
Age ≥ 75
(risk groups 2+3)</td><td>Vaccinated</td><td colspan="4"></td></tr>
<tr><td>Unvaccinated</td><td colspan="4"></td></tr>
<tr><td colspan="2" rowspan="2">STUDY COHORT
Age ≥ 65,
clinically extremely vulnerable/ at-risk patients
(risk groups 4-6)
+
Eligible unvaccinated adults in risk groups 2+3</td><td>Vaccinated</td><td colspan="3"></td></tr>
<tr><td>Unvaccinated</td><td colspan="3"></td></tr>
<tr><td colspan="3" rowspan="2">STUDY COHORT
Age ≥ 50 (risk groups 7-9)
+
Eligible unvaccinated adults in risk groups 2-6</td><td>Vaccinated</td><td colspan="2"></td></tr>
<tr><td>Unvaccinated</td><td colspan="2"></td></tr>
<tr><td colspan="4" rowspan="2">STUDY COHORT
Age ≥ 18 (risk group 10)
+
Eligible unvaccinated adults in risk groups 2-10</td><td>Vaccinated</td><td></td></tr>
<tr><td>Unvaccinated</td><td></td></tr>
</table>

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

Vaccine effectiveness for long COVID prevention

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 ☺

Protocol: https://github.com/oxford-pharmacoepi/NIHR-LongCOVID

Timelines:

Long COVID phenotyping: ~ January 2022

Vaccine effectiveness method: package finished by ~ March 2022

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