OHDSI COVID-19
International Study-A-Thon

The meeting will begin shortly.

Collaborating to design and execute observational research and generate real-world evidence to inform the global pandemic

March 26-29, 2020
To improve health by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care.
We regret to inform you that the 2020 European Symposium "From data to impact: the journey towards improving clinical practice" is cancelled due to the COVID-19 outbreak.
OHDSI COVID-19 Study-a-thon kickoff
26Mar2020 3amEST

https://www.ohdsi.org/covid-19-updates/
When we started on 26 March 2020
## Tracking our collaboration
### 26Mar2020 3amET

### OHDSI COVID-19 Study-a-thon Study Tracker

<table>
<thead>
<tr>
<th>Analytic use case</th>
<th>Study</th>
<th>Lit Review and protocol development</th>
<th>Phenotype development and evaluation</th>
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<tbody>
<tr>
<td><strong>Characterization</strong></td>
<td>COVID-19 positive patients</td>
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<td>Influenza, symptoms, and complications</td>
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<td>Invasive treatments for respiratory distress</td>
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<tr>
<td><strong>Prediction</strong></td>
<td>1) Who presenting with flu, symptoms, or complications will be admitted to hospital?</td>
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*To be done*  
*Completed*
## Where are we now?

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What have we done?

In only **88** hours, we have:

- Convened **351** participants brought together from **30** countries
- Held **12** Global Huddles, **>100** collaborator calls, **>13,000** chat messages
- Engaged **15** concurrent channels
- Reviewed **>10,000** publications
- Drafted **9** protocols
- Released **13** study packages
- Designed **355** cohort definitions
- Assembled a distributed data network with **37** partners signed on to execute studies
3 things that we did in 4 days together that nobody has ever done before

• First large-scale characterization of COVID patients in US and Asia (Ed)
• First prediction model externally validated on COVID patients to support triage to ‘flatten the curve’ (Jenna)
• Largest study ever conducted on the safety of hydroxychloroquine (Dani)
3 things we’re about to do that nobody has ever done before

• Designed self-controlled case series to examine safety of IL6 and JAK inhibitors….package is running

• Designed and implemented international study to evaluate protease inhibitors….package is running (Albert)

• Designed and implemented a study to evaluate impact of ACE inhibitor amongst Covid….need more COVID data (Daniel)
Ground rules for presentation

• We will be sharing the journey we’ve been on through all our studies
  – Celebrate the tremendous progress
  – Highlight the rigorous analytical methods and scientific best practices applied through the week
  – Share *preliminary* results, which should not be over-interpreted but provide an exciting view of the journey ahead
Collaborative literature review

Jenny Lane
University of Oxford
Pre Study-a-thon...

AIM TO SUPPORT STUDY TEAMS, ESPECIALLY IN ESTIMATION

DMARDs

Antivirals
Systematic approach

PubMed
Embase (1974)
Clinicaltrials.gov
ICTRP
BioRxiv & medRxiv

5458 DMARD Articles
(Hydroxychloroquine/ csDMARDs
Biologics- IL6 & JAK inhibitors)

4800 Antiviral Articles
Protease Inhibitors (Lopinavir/ ritonavir)
Hep C/ H1N1 / Ebola/ Influenza
Results

Rayyan ([https://rayyan.qcri.org](https://rayyan.qcri.org)) to collaboratively screen
Data extraction files (efficacy, safety, mechanism of action)
Written summaries for protocols & manuscripts
Updated searches
Chinese clinical trial registry
Clinical guidelines
The Team & Final Products

- 5 continents; core team 15, 25 in total
- Data scientists to clinicians
- Teams -> files -> Competency Literature Review -> HCQ / IL6 / HepC Study Channel
- BIG thanks to everyone!!
OHDSI Data Network in Action

Kristin Kostka
IQVIA
United Nations of OMOP (Our Global Network)

- 37 databases participating
  - Insurance claims, EHRs, Administrative data, Registries
  - 10 countries on 3 continents
- 8 databases with COVID+ patients (and growing)
- Everyone adopted OMOP CDMv5+
Executing 9 OHDSI network studies concurrently...

**Expectation**

**Reality**
Process for managing 9 OHDSI network studies concurrently

1. Intake Requests
2. Test Packages
3. Assign Tasks/Priority
4. Provide Technical Support for Sites
5. Get Results to SFTP
Mobilizing our action plan

Thank you HIRA, AUSOM, Tufts, CUMC, Stanford, UC Denver, Vanderbilt, SIDIAp and Veteran's Affairs/VINCI!
A snapshot of our journey...
Phenotype development and evaluation

Anna Ostropolets
Columbia University
Systematic process we followed

Building blocks

- Literature review
- Concept sets: Atlas and Concept Prevalence
- Empirical evaluation: Cohort Diagnostics and PheValuator

Phenotypes

Using building blocks to create composite phenotypes
Three lesson we learned

1. To create composite phenotypes we first have to create and validate building blocks. Example: pneumonia is used in 29 different phenotypes.

2. Phenotypes are driven by their intended use. Example: how to find influenza?
   - Narrow: diagnosis of influenza or test result
   - Broad: suspected, confirmed, symptoms (fever AND (cough OR dyspnea OR malaise OR fatigue OR myalgia))

3. Phenotypes require knowledge of the data: data exploration is a must!
Exploring the data: creating comprehensive concept sets
Exploring the data: capturing coding practices

Malaise

Malaise OR (malaise and fatigue)

Incidence rate dropped, need to add fatigue
Final Results

- Literature reviews done for 36 phenotypes
- 355 cohorts created in atlas-covid19.ohdsi.org
- 114 validated and reviewed cohorts for prediction, estimation and characterization on atlas.ohdsi.org
- Results of Covid19CohortEvaluation are posted on data.ohdsi.org
Next Steps

- Complete the remaining cohorts for characterization
- Finalize the CohortEvaluation package for all cohorts and run across the OHDSI network
- Write a paper about our phenotyping experience
Clinical characterization of COVID-19

Ed Burn
Characterisation in OHDSI: Defining Cohorts

- A cohort is a set of persons who satisfy one or more inclusion criteria for a duration of time
Characterisation in OHDSI: Cohort characterisation

- OHDSI approaches characterization through descriptive statistics of all conditions, drug and device exposures, procedures and other clinical observations that are present in the person’s history.
Characterisation in OHDSI: Incidence

Incidence rates and proportions are statistics that are used in public health to assess the occurrence of a new outcome in a population during a time-at-risk (TAR)
Our to do list

- Elucidating research questions
- Writing protocols
  - Develop study packages
  - Review results
- Disseminate results
Research questions


2. Characterization of individuals tested for COVID-19

3. Characteristics and outcomes of COVID-19 in children
Research questions


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Research questions


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Protocols

Research questions

D Protocol template

1. Table of contents
2. List of abbreviations
3. Abstract
4. Amendments and Updates
5. Milestones
6. Rationales and Background
7. Study Objectives
   - Primary hypotheses
   - Secondary Hypotheses
   - Primary Objectives
   - Secondary Objectives
8. Research methods
    - Study Design
    - Data Source(s)
    - Study population
    - Exposures
    - Outcomes
    - Covariates
9. Data Analysis Plan
Protocols

Characterization and outcomes of individuals tested for COVID-19: evidence from the OHDSI network


Protocol

Characteristics and outcomes of COVID-19 in Children in 2019-2020: evidence from the OHDSI network
Preparing study packages
Characteristics of adults hospitalized with influenza

- 2009 vs 2014-2019

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proportion Target</th>
<th>Proportion Comparator</th>
<th>StdDiff</th>
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<tbody>
<tr>
<td>Age group</td>
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<tr>
<td>15-29</td>
<td>1.8%</td>
<td>0.2%</td>
<td>-1.1</td>
</tr>
<tr>
<td>20-24</td>
<td>3.2%</td>
<td>0.9%</td>
<td>-2.3</td>
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<tr>
<td>25-29</td>
<td>5.0%</td>
<td>1.2%</td>
<td>-3.8</td>
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<tr>
<td>30-34</td>
<td>6.3%</td>
<td>1.0%</td>
<td>-5.3</td>
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<td>35-39</td>
<td>6.4%</td>
<td>1.7%</td>
<td>-4.7</td>
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<td>40-44</td>
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<td>1.8%</td>
<td>-0.6</td>
</tr>
<tr>
<td>45-49</td>
<td>8.5%</td>
<td>2.0%</td>
<td>-6.5</td>
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<tr>
<td>50-54</td>
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<tr>
<td>90-94</td>
<td>1.2%</td>
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</table>
Characteristics of adults hospitalized with influenza

- 2009 vs 2014-2019
Characteristics of adults who have tested positive for COVID-19

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Columbia University Irving Medical Center N</th>
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<tbody>
<tr>
<td>Gender: female (%)</td>
<td>67</td>
</tr>
<tr>
<td>Charlson score (median [IQR])</td>
<td>6</td>
</tr>
<tr>
<td>Acute respiratory disease (%)</td>
<td>29.6</td>
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<tr>
<td>Chronic obstructive lung disease (%)</td>
<td>19.7</td>
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<tr>
<td>Gastroesophageal reflux disease (%)</td>
<td>24.2</td>
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<tr>
<td>Hyperlipidemia (%)</td>
<td>41.8</td>
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<tr>
<td>Hypertensive disorder (%)</td>
<td>60.4</td>
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<tr>
<td>Pneumonia (%)</td>
<td>32.2</td>
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<tr>
<td>Renal impairment (%)</td>
<td>39.7</td>
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<tr>
<td>Urinary tract infectious disease (%)</td>
<td>15.7</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>20.4</td>
</tr>
<tr>
<td>Heart disease (%)</td>
<td>60.7</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>30.1</td>
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<tr>
<td>Malignant neoplasmic disease (%)</td>
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Characteristics of adults who have tested positive for COVID-19

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<tr>
<td>N</td>
<td>1,076</td>
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<tr>
<td>Medication use</td>
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<tr>
<td>Anti-inflammatory and antirheumatic products (%)</td>
<td>33.2</td>
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<tr>
<td>Antithrombotic agents (%)</td>
<td>77.3</td>
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<tr>
<td>Beta blocking agents (%)</td>
<td>41.1</td>
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<tr>
<td>Calcium channel blockers (%)</td>
<td>36.3</td>
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<tr>
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<td>16.1</td>
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<td>Lipid modifying agents (%)</td>
<td>46.5</td>
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  - Review results
  - Disseminate results
The journey through patient-level prediction

Peter Rijnbeek
Erasmus MC
Complementary evidence to inform the patient journey

Clinical characterization: What happened to them?

Patient-level prediction: What will happen to me?

Population-level effect estimation: What are the causal effects?

observation

inference

causal inference
Among a target population (T), we aim to predict which patients at a defined moment in time (t=0) will experience some outcome (O) during a time-at-risk. Prediction is done using only information about the patients in an observation window prior to that moment in time.
Important questions to ask!

• What decision is the prediction model intended to inform?

• When is the decision made in the context of the patient’s health experience and interaction with the healthcare system?

• Who is the decision-maker, and from which stakeholder vantage point are we evaluating the decision?

• What is the trade-off between True Positive, False Positive, True Negative, False Negative?

• Etc.
OHDSI aims to develop a systematic process to learn and evaluate large-scale patient-level prediction models using observational health data in a data network.
Design and implementation of a standardized framework to generate and evaluate patient-level prediction models using observational healthcare data

Jenna M Reps, Martijn J Schuemie, Marc A Suchard, Patrick B Ryan, Peter R Rijnbeek

Published: 27 April 2018

Abstract

Objective

To develop a conceptual prediction model framework containing standardized steps and describe the corresponding open-source software developed to consistently implement the framework across computational environments and observational healthcare databases to enable model sharing and reproducibility.

R-package

www.github.com/OHDSI/PatientLevelPrediction

• Vignettes
• Videos
• Online training material

Book-of-OHDSI
https://ohdsi.github.io/TheBookOfOhdsi/

Study Results
www.data.ohdsi.org

The prediction chapter and the publication are added on top of our channel in Teams
Problem pre-specification. A study protocol should unambiguously pre-specify the planned analyses.

Transparency. Others should be able to reproduce a study in every detail using the provided information. All analysis code should be made available as open source on the OHDSI Github.

Team Effort:
- Problem Definition + Questions
- Literature Research -> Prior work, Rationale
- Study Protocol Development
The Target Cohort (T) and Outcome Cohort (O) can be defined using ATLAS or custom code (see later today).

For model development all outcomes (O) of patients in the Target Cohort (T) are used.

We extract data for the patients in the Target Cohort (T) and we select all patients that experience the outcome (O).

Team Effort:
- Literature Review
- Cohort Definition

Work done with the phenotype group
Data is extracted from the OMOP CDM using the Feature Extraction R-Package. This allows for specification of the candidate predictors and time windows.
The Journey: Model Development

**Problem Definition**

**Data Extraction**

**Training**

**Internal Validation**

**External Validation**

**Dissemination**

---

**Model training** and **Internal validation** is done using a train test split:

1. Person split: examples are assigned randomly to the train or test set, or

2. Time split: a split is made at a moment in time (temporal validation)

<table>
<thead>
<tr>
<th>Train set</th>
<th>Test set</th>
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<tr>
<td>2014-01-15</td>
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- Study Package Development
- Study Execution
**The Journey: External Validation**

- **Problem Definition**
- **Data Extraction**
- **Training**
- **Internal Validation**
- **External Validation**
- **Dissemination**

**External validation** is performed using data from multiple populations not used for training.

- **Train**
  - 1 → Model

- **Apply**
  - 2
  - 3
  - 4

- **Evaluate**
  - Auc2, Cal2
  - Auc3, Cal3
  - Auc4, Cal4

- • Data Partners
Dissemination of study results should follow the minimum requirements as stated in the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.

- Internal and external validation
- Sharing of full model details
- Sharing of all analyses code to allow full reproducibility

Website to share protocol, code, models and results for all databases

---

PLP Aims Study-A-Thon

Build and evaluate models developed on Flu patients to:

1) Test them on COVID patients if data becomes available
2) Have tools ready to learn on COVID patients

And,

Replicate some of the models found in literature
Team Effort

51 Participants in our channel and literature study

Thank you all for the great collaboration in the PLP team
Patient-level prediction #1: Amongst patients presenting with COVID-19, influenza, or associated symptoms, who are most likely to be admitted to hospital in next 30d?

Jenna Reps
Janssen Research and Development
Background

• Can we predict who is going to be hospitalized at the point they have their first outpatient visit with flu/covid19 or flu-like symptoms?

• This could be used to aid the 'do I hospitalize or send this patient home?' decision that doctors will need to make

• Simple model could potentially be used for phone screen (patient calls medical staff and model answers questions)
Methods

T1: GP/OP/ER visits of patients presenting with Covid-19, flu or flu-like symptoms AND no symptoms or pneumonia in prior 60d

O1: Hospitalizations with pneumonia (narrow)
O2: Hospitalizations with pneumonia or ARDS or sepsis or AKI (broad)
O3: Hospitalizations with pneumonia or ARDS or sepsis or AKI requiring intensive services or resulting in death in 30d (severe)
O4: Death (severe)

TAR: 0-30d
## Preliminary results

<table>
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<tr>
<th>Analysis</th>
<th>Dev</th>
<th>Val</th>
<th>T</th>
<th>O</th>
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<th>TAR end</th>
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<th>AUPRC</th>
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<td>GP/OPYER visits of patients presenting with Covid flu or flu-like symptoms AND no symptoms or pneumonia in prior 60d</td>
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Discussion and next steps


• External validation of OHDSI score model

• External validation existing risk models
Patient-level prediction #2: Amongst patients at GP presenting with virus or associated symptoms with/without pneumonia who are sent home, who are most likely to require hospitalization in next 30d?

Ross D. Williams
Erasmus MC
Background

A large proportion of patients presenting with symptoms will be sent home.

Some of these patients will go on to experience disease progression.

This model can act as a safety net for a clinician and reassurance for the patient.
Methods

T1: Visit with COVID or Influenza or flu-like symptoms and with NO pneumonia and NO admission
T2: same as T1 except WITH pneumonia

O1: Hospitalizations with pneumonia or ARDS or sepsis or AKI requiring intensive services
O2: Hospitalizations with pneumonia or ARDS or sepsis or AKI requiring intensive services or resulting in death in 30d
TAR: 2-30d
<table>
<thead>
<tr>
<th>Analysis</th>
<th>Dev</th>
<th>Val</th>
<th>T</th>
<th>O</th>
<th>Model</th>
<th>TAR start</th>
<th>TAR end</th>
<th>AUC</th>
<th>AUPRC</th>
<th>T Size</th>
<th>Count</th>
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Preliminary results
Discussion and next steps

COVID-19 validation and external validation

Model parsimonisation

Tool creation
  – how can we best present the model for application?

Model dissemination
Patient-level prediction #3: Amongst patients hospitalized with pneumonia, who are most likely to require intensive services or die?

Aniek Markus
Erasmus MC
Background

- Lack of evidence of factors associated with disease severity
- Enables close monitoring of high risk patients
- Indicator for short-term demand of intensive services
Methods

• T [IV]: Hospitalization with pneumonia
• T [EV]: Hospitalization with COVID-19

• O1: Patients requiring intensive services* or death
• O2: Death

* Includes ventilation, intubation, tracheotomy, or ECMO.
## Preliminary results

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Dev</th>
<th>Val</th>
<th>T</th>
<th>O</th>
<th>Model</th>
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<th>TAR end</th>
<th>AUC</th>
<th>AUPRC</th>
<th>T Size</th>
<th>O Count</th>
<th>Incidence (%)</th>
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<td>Lasso Logistic Regression</td>
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<td>[COVID-19 OR 2019 VL] persons who die</td>
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<td>[COVID-19 OR 2019 VL] persons who die</td>
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Discussion and next steps

• Developing more parsimonious models
  – easier to use and understand in practice

• External validation in COVID-19 data

• In the future: also train models in COVID-19 data
Population-level Estimation #1:
Hydroxychloroquine

Dani Prieto-Alhambra
University of Oxford
BACKGROUND
What have we achieved?

TWO RQs

1. What is the safety profile of hydroxychloroquine?

2. What is its potential anti-viral efficacy?
METHODS

DESIGN
1. Comparative cohort HCQ (t) vs SSZ (o) in RA patients
2. SCCS (regardless of indication)

PARTICIPANTS
1. RA diagnosis + new use of HCQ or SSZ
2. HCQ use (on/off) + outcome of interest (“case”)
METHODS (2)

OUTCOMES

1. Serious adverse events, including: arrhythmia, cv disease, vte, liver failure, kidney failure, GI bleeds, mortality
2. Flu/viral infections, hospitalized pneumonia (not in SCCS)

ANALYSES

1. PS stratification + negative control outcome calibration
   – On treatment and ITT (up to 5y)
2. Age and season-adjusted SCCS
## RESULTS (VTE)

### Power

<table>
<thead>
<tr>
<th>DATA SOURCE</th>
<th>N HCQ</th>
<th>N SSZ</th>
<th>T events HCQ</th>
<th>C events SSZ</th>
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<tr>
<td>CCAE</td>
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<td>57,236</td>
<td>1,752</td>
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RESULTS (VTE)

Diagnostics (CCAE)

✓ PS overlap
✓ Covariate balance
✓ Negative control outcomes
### RESULTS (3)

**Risk estimates**

**OHDSI COVID-19 Studyathon: Hydroxychloroquine population-level effect estimation**

#### Analysis

<table>
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<th>Target</th>
<th>Data source</th>
<th>HR</th>
<th>LB</th>
<th>UB</th>
<th>P</th>
<th>Cal.HR</th>
<th>Cal.LB</th>
<th>Cal.UB</th>
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<td>CCAE</td>
<td>0.99</td>
<td>0.82</td>
<td>1.20</td>
<td>0.92</td>
<td>1.00</td>
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<td>New users of sulfasalazine with prior rheumatoid arthritis</td>
<td>CPRD</td>
<td>1.06</td>
<td>0.81</td>
<td>1.38</td>
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<td>1.01</td>
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<td>Venous thromboembolic (pulmonary embolism and deep vein thrombosis) events</td>
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<td>0.98</td>
<td>0.58</td>
<td>1.63</td>
<td>0.94</td>
<td>0.72</td>
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<td>0.97</td>
<td>0.87</td>
<td>1.07</td>
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<td>0.88</td>
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## RESULTS (3)

### Risk estimates

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<th>Cal.LB</th>
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<th>Cal.P</th>
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<td>No prior outcome in last 30d, 5 PS strata, TAR on-treatment+14d</td>
<td>CCAE</td>
<td>0.99</td>
<td>0.82</td>
<td>1.20</td>
<td>0.92</td>
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<td>1.63</td>
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<td>0.89</td>
<td>1.22</td>
<td>0.64</td>
<td>1.06</td>
<td>0.84</td>
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<td>0.51</td>
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<td>0.97</td>
<td>0.88</td>
<td>1.07</td>
<td>0.56</td>
</tr>
</tbody>
</table>
DISCUSSION

COMPLETED
✓ The biggest study to date on the safety of HCQ
✓ Reassuringly, no consistent signals found

WORK IN PROGRESS
• Running across the whole network (where possible)
• SCCS

OUTSTANDING
• Anti-viral efficacy (new user design in COVID19 infectees)
Population-level Estimation #1: Safety of HIV/HepC protease inhibitors

Albert Prats
University of Oxford
SARS-Coronavirus-2

A little piece of enveloped RNA!

Antiviral searches globally
Antiviral drugs, non-specific

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Efficacy</th>
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</thead>
<tbody>
<tr>
<td>Interferons</td>
<td>Activate cytoplasmic enzymes affecting viral messenger RNA translation and protein synthesis; evidence of minor efficacy in MERS-CoV in combination with ribavirin</td>
<td>4</td>
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</table>

Antiviral drugs, antiretrovirals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC09</td>
<td>HIV protease inhibitor; to be used in combination with ritonavir</td>
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<tr>
<td>Azvudine</td>
<td>Azidocytidine nucleoside analogue; HIV reverse transcriptase inhibitor</td>
<td>4</td>
</tr>
<tr>
<td>Danoprevir</td>
<td>Hepatitis C virus NS3 protease inhibitor; to be used in combination with ritonavir</td>
<td>1</td>
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<tr>
<td>Darunavir</td>
<td>HIV protease inhibitor; used in combination with cobicistat, a CYP3A inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Lopinavir + ritonavir</td>
<td>Both HIV reverse transcriptase inhibitors; ritonavir is mainly used to enhance the action of other drugs by inhibition of CYP3A4; in vitro and possible clinical efficacy in SARS-CoV</td>
<td>2</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>Nucleotide analogue; inhibitor of RNA-dependent RNA polymerase; used to treat Ebola and Marburg viruses; effective in vitro against SARS-CoV-1 and MERS and blocks infection with 2019-nCoV in vitro</td>
<td>2</td>
</tr>
</tbody>
</table>

Adapted from: [https://www.cebm.net/covid-19/registered-trials-and-analysis/](https://www.cebm.net/covid-19/registered-trials-and-analysis/) at 29-March
Antivirals Background

HIV antivirals

SARS

? COVID

Hepatitis C antivirals

in-vitro

X SARS

? COVID

Effectiveness
Does it work?

Safety
Does it harm patients?

Gastrointestinal events
Liver Injury
Pancreatitis
etc ...

Arrythmia
Liver Injury
Hematologic
etc ...
Safety: Does it harm patients?

HIV Antivirals Estimation

Ritonavir/lopinavir
All HIV protease inhibitors

NNRTIs
Integrase inhibitors

SCCS

Cohort study of HIV treatment naïve patients (PS stratification)
HIV Antivirals Estimation

Ritonavir/lopinavir

All HIV protease inhibitors

VS

Hydroxychloroquine

Cohort study of SARS-CoV-2 Patients (PS stratification)

Hospital treated pneumonia

Poor outcomes
Hep C Antivirals Estimation

Hepatitis C protease inhibitors

Peginterferon alfa-2b

Ribavirin

SCCS

Cohort study
Pairwise Comparisons
(PS stratification)
Hepatitis C protease inhibitors

Peginterferon alfa-2b

Ribavirin

Hydroxychloroquine

Hep C Antivirals Estimation

Cohort study pairwise comparisons of SARS-CoV-2 Patients (PS stratification)

Hospital treated pneumonia

Poor pneumonia outcomes

Does it work?
Progress

Protocol

Safety Analyses

Effectiveness Analyses

Paper writing

Done!

SCCS Cohorts

Cohorts

Background and methods
Population-level Estimation #3: Association of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) on COVID incidence and complications

Daniel Morales
University of Dundee
• People with hypertension (HTN) have worse COVID-19 outcomes
  • Speculation that ACE/ARBs taken for HTN may be detrimental
    – Coronaviruses interact with RAS ACE-2 receptor, allowing them to enter the cell
    – ACE & ARBs upregulate ACE-2 receptors (limited data)
    – RAS ACE-2 expressed in lung, kidney, heart, GI tract
  • Speculation that ARBs may be protective
    – Prevent the angiotensin I receptor from being stimulated
    – Regulate ACE-2 and reduce angiotensin production by ACE and increase production of the vasodilator angiotensin(1-7)

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### Background

<table>
<thead>
<tr>
<th>Authors</th>
<th>COVID Patients</th>
<th>Location</th>
<th>Key Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guan et al</td>
<td>1099</td>
<td>China</td>
<td>24% HTN in severe disease (vs 13%)</td>
</tr>
<tr>
<td>Zhou</td>
<td>191</td>
<td>China</td>
<td>HTN Univariate OR 3.1 (1.6-6.0) for death</td>
</tr>
<tr>
<td>Wang et al</td>
<td>138</td>
<td>China</td>
<td>HTN admissions 31%, HTN ICU 58%</td>
</tr>
<tr>
<td>Wu et al</td>
<td>201</td>
<td>China</td>
<td>HTN admissions 19%, HTN ARDS 27%</td>
</tr>
</tbody>
</table>
Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?

The most distinctive comorbidities of 32 non-survivors from a group of 52 intensive care unit patients with novel coronavirus disease inhibitors and ARBs, which results in an upregulation of ACE2.5 ACE2 can also be increased by thiazolidinediones and ibuprofen. These data suggest that ACE2 expression is increased in diabetes and treatment with ACE inhibitors and ARBs increases ACE2 expression. Consequently, the increased expression of ACE2 would facilitate infection with COVID-19. We therefore hypothesise that diabetes and hypertension treatment with

EMA advises continued use of medicines for hypertension, heart or kidney disease during COVID-19 pandemic

Press release 27/03/2020

EMA is aware of recent media reports and publications which question whether some medicines, for instance angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs, or sartan medicines), could worsen coronavirus disease (COVID-19). ACE inhibitors and ARBs are most commonly used for treating patients with high blood pressure, heart failure or kidney disease.

Clinical Hypotheses

1. Prevalent ACE or ARB use is associated with a difference in risk of COVID-19 infection relative to an active comparator in hypertensive patients

2. Prevalent ACE or ARB use in COVID-19+ patients is associated with a difference in risk of intensive outcomes relative to an active comparator in hypertensive patients
Protocol for Hypothesis 1

Inclusion:
- ACEI drug era that overlaps with index date \[\text{ACEI Exposure within 60 days prior}\].
- And history of hypertension any time prior to index date.
- And no exposure to Other antihypertensive within 180 days prior.

First event
Incident COVID-19 diagnosis

End of follow-up:
- End Exposure
- Death
- End of observation period

Cohort Entry
2019-12-01

Follow-up

1 year observation in database
Protocol for Hypothesis 2

Covariates (-1 to 365 days)

Exposure (-1 to 60 days)

Inclusion:
- ACEI drug era that overlaps with index date [ACEI Exposure within 60 days prior*]
- And history of hypertension any time prior to index date
- And no exposure to Other antihypertensive within 180 days prior

1 year observation in database

Follow-up

Cohort Entry
- Incident
  - COVID-19 diagnosis

Outcome
- ICU, endotracheal intubation, artificial ventilation, extracorporeal membrane oxygenation, mortality
- Composite event of all previous outcomes

End of follow-up:
- 30 days
- End Exposure
- Death
- End of observation period
Prevalent users of ARBs, with COVID-19, history of hypertension
Specification

Comparisons:
- ACE vs CCB
- ACE vs THZ
- ARB vs CCB
- ARB vs THZ
- RAS vs Discontinued RAS

Outcomes:
- ICU Care
- Ventilation
- ECMO
- All-cause mortality
- MI, HF, Stroke, CV death
- AKI
- LEGEND negative controls

Design:
- Logistic regression outcome (30/60/90 days) (cohort 2)
- PS matched / stratified (including age, gender, month)
- Potential for large-scale PS with larger cohorts
Results

• HIRA: study executes and preliminary results (coming in next presentation)

• Columbia University Medical Center/NYP
  – Successfully ran the main cohort of HTN, recent ACE, no other anti-HTN drugs, sufficient lookback => about 20 patients
  – Analysis using SQL showed we can increase patient numbers using less recent ACE (note we have 30d prescriptions with 5 refills = 180d)
  – Do not have hospital disposition yet, but have inferred ICU, for example, via medications given
  – (Do have a subpopulation on hydroxychloroquine)
Acknowledgments

Key participants:

- Kees van Bochove
- Mitchell Conover
- George Hripcsak
- Christophe Lambert
- Michael Matheny
- Daniel Morales
- Fredrik Nyberg
- Nicole Pratt
- Daniel Prieto Alhambra
- Marc Suchard
- Cynthia Sung
- Seng Chan You

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Apologies if your name is not here; let Marc know – he haphazardly compiled this list
Summary of COVID-19 Study w/ HIRA Data

March 29/30, 2020
SUMMARY OF “OPENDATA4COVID19” PROJECT W/ HIRA DATA

WE’VE GOT 1,772 VISITORS FROM 32 COUNTRIES FOR 3 DAYS
- More than 160 individual researchers have registered from 15 countries
- Nearly, 30 research projects are submitted for analysis
  (disease characterization, relationship b/w baseline condition and death,
   relationship baseline drug intake and death, patient-level prediction using
   machine learning program, etc.)
- Ongoing project
SUMMARY OF “OPENDATA4COVID19” PROJECT W/ HIRA DATA

FUTURE CONSIDERATIONS

- Wonderful experience
- Data update issues
- Further opportunities
# CHARACTERIZATION OF PATIENTS WITH COVID-19

<table>
<thead>
<tr>
<th>Covariate Name</th>
<th>HIRA Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td>1.9%</td>
</tr>
<tr>
<td>20-24</td>
<td>10.9%</td>
</tr>
<tr>
<td>25-29</td>
<td>13.9%</td>
</tr>
<tr>
<td>30-34</td>
<td>10.5%</td>
</tr>
<tr>
<td>35-39</td>
<td>11.6%</td>
</tr>
<tr>
<td>40-44</td>
<td>9.4%</td>
</tr>
<tr>
<td>45-49</td>
<td>7.2%</td>
</tr>
<tr>
<td>50-54</td>
<td>5.7%</td>
</tr>
<tr>
<td>55-59</td>
<td>6.5%</td>
</tr>
<tr>
<td>60-64</td>
<td>5.7%</td>
</tr>
<tr>
<td>65-69</td>
<td>3.9%</td>
</tr>
<tr>
<td>70-74</td>
<td>3.3%</td>
</tr>
<tr>
<td>75-79</td>
<td>4.1%</td>
</tr>
<tr>
<td>80-84</td>
<td>3.2%</td>
</tr>
<tr>
<td>85-89</td>
<td>1.8%</td>
</tr>
<tr>
<td>90-94</td>
<td>0.5%</td>
</tr>
<tr>
<td>Gender: female</td>
<td>51.9%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>race = Korean</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

### Medical history: General
- Chronic liver disease: 5.5%
- Chronic obstructive lung disease: 3.4%
- Crohn’s disease: <0.2%
- Dementia: 4.3%
- Depressive disorder: 11.7%
- Diabetes mellitus: 16.9%
- Gastroesophageal reflux disease: 29.8%
- Gastrointestinal hemorrhage: 2.7%
- Human immunodeficiency virus infection: <0.2%
- Hyperlipidemia: 29.9%
- Hypertensive disorder: 21.7%
- Lesion of liver: 4.7%
- Obesity: 0.3%
- Osteoarthritis: 13.8%
- Pneumonia: 13.8%
- Psoriasis: 1.4%
- Renal impairment: 3.9%
- Rheumatoid arthritis: 3.3%
- Schizophrenia: 1.4%

### Medication use
- Agents acting on the renin-angiotensin system: 13.8%
- Antibacterials for systemic use: 74.4%
- Antidepressants: 12.5%
- Antiepileptics: 11.8%
- Antiinflammatory and antirheumatic products: 63.2%
- Antineoplastic agents: 3.2%
- Antipsoriatrics: 0.8%
- Antithrombotic agents: 36.7%
- Beta blocking agents: 10.6%
- Calcium channel blockers: 14.0%
- Diuretics: 10.4%
- Drugs for acid related disorders: 66.5%
- Drugs for obstructive airway diseases: 24.9%
- Drugs used in diabetes: 9.7%
- Immunosuppressants: 2.9%
- Lipid modifying agents: 16.8%
- Opioids: 65.8%
- Psycheotics: 29.7%
- Psychostimulants, agents used for ADHD and nootropics: 8.2%
### Evidence Explorer

#### Target
- Prevalent ARB user as monotherapy for HTN within 30 days before COVID-19 diagnosis

#### Comparator
- Prevalent dCCB user as monotherapy for HTN within 30 days before COVID-19 diagnosis

#### Outcome
- All-cause mortality

#### Analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Data source</th>
<th>HR</th>
<th>LB</th>
<th>UB</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without PS adjustment-Logistic (age/gender/year/month)</td>
<td>HIRA</td>
<td>1.21</td>
<td>0.14</td>
<td>10.32</td>
<td>0.86</td>
</tr>
<tr>
<td>Without PS adjustment-Cox (age/gender/year/month)</td>
<td>HIRA</td>
<td>1.21</td>
<td>0.15</td>
<td>10.07</td>
<td>0.86</td>
</tr>
<tr>
<td>Minimum PS stratification -Cox</td>
<td>HIRA</td>
<td>1.21</td>
<td>0.15</td>
<td>10.07</td>
<td>0.86</td>
</tr>
<tr>
<td>Minimum PS stratification -Logistic</td>
<td>HIRA</td>
<td>1.21</td>
<td>0.14</td>
<td>10.05</td>
<td>0.86</td>
</tr>
<tr>
<td>Full PS stratification -Cox</td>
<td>HIRA</td>
<td>1.21</td>
<td>0.15</td>
<td>10.07</td>
<td>0.86</td>
</tr>
<tr>
<td>Full PS stratification -Logistic</td>
<td>HIRA</td>
<td>1.21</td>
<td>0.14</td>
<td>10.05</td>
<td>0.86</td>
</tr>
<tr>
<td>Unadjusted with all demographic covariates (+14 / logistic)</td>
<td>HIRA</td>
<td>2.42</td>
<td>0.23</td>
<td>52.80</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Showing 1 to 7 of 7 entries
PREDICTION OF HOSPITALIZATION AMONG PATIENTS SYMPTOMS RELATED WITH VIRAL INFECTION OR DIAGNOSIS OF COVID-19

Led by Peter Rijnbeek (Erasmus University, Netherland)
Thank you!
The journey ahead

Patrick Ryan
Janssen Research and Development
Columbia University
Thank you literature review team!
Thank you phenotype team!
Thank you network execution team!
Thank you characterization team!
Thank you prediction team!
Thank you estimation teams!
Thank you infrastructure support teams!
The journey ahead

• Study-a-thon may be finishing today, but this is only the START of our journey today
  – Thanks to Erasmus MC, The MSTeams collaboration platform will continue to be available to support OHDSI collaborations
  – ATLAS-COVID19.ohdsi.org will remain available for collaborative development of analyses
  – Each study team needs to determine their own strategy for dissemination
    • Data.ohdsi.org to make results publicly available as soon as possible
    • Publications to be drafted by the community will be open access
Many more important questions need answering…

Our ask of all of you:
• Keep asking good questions....
  – post your thoughts on the OHDSI forums
• ....and continue to collaborate with each other to help:
  – translate those questions into analysis designs...
  – implement those designs into study packages....
  – execute those packages to generate results....
  – share results across the community to synthesis reliable real-world evidence
We like to thank the large group of community members that worked extremely hard to make these four days possible.

We like to thank the Data Partners that have participated in this effort, and those who will join the journey shortly.

We like to thank you for your active participation in these four days.
Questions & Answers
• This disease isn’t stopping yet, and neither will we
• We will remain committed to generating reliable real-world evidence to meet the needs of public health
• Thank you for continuing on the journey with us