How RWE can inform the COVID-19 pandemic response:

Lessons from OHDSI and EHDEN for global, speedy and reliable drug safety research

Dani Prieto-Alhambra, MD PhD

Prof of Pharmaco-epidemiology

Oxford University

AGENDA

- OHDSI and EHDEN
- Maximising reproducibility and speed through international collaboration
- "If it's not good, I'll tell you right, I'm not gonna get hurt by it": the rise and fall of hydroxychloroquine

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OHDSI community

We're all in this journey together...

Different stakeholders: academia, medical product industry, regulators, government, payers, technology providers, health systems, clinicians, patients
Different disciplines: computer science, epidemiology, statistics, biomedical informatics, health policy, clinical sciences

OHDSI's community engagement

- Active community online discussion: forums.ohdsi.org
  - **>3,800** distinct users have made **>24,400** posts on **>4,200** topics
  - Implementers, Developers, Researchers, CDM Builders, Vocabulary users, OHDSI in Korea, OHDSI in China, OHDSI in Europe
- Weekly community web conferences for all collaborators to share their research ideas and progress
- >25 workgroups for solving shared problems of interest
  - ex: Common Data Model, Population-level Estimation, Patient-level Prediction, Phenotype, NLP, GIS, Oncology, Women of OHDSI

OHDSI's community engagement

- Quarterly tutorials in OHDSI tools and best practices, taught by OHDSI collaborators for OHDSI collaborators

- OHDSI Symposiums held annually in North America, Europe and Asia to provide the community opportunities to showcase research collaborations (2020 Global Symposium virtual Oct 18-22)
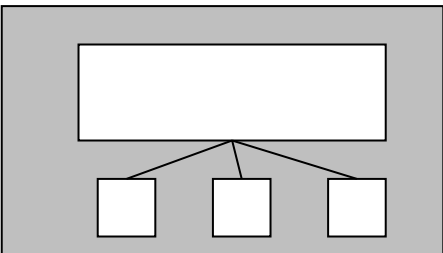
- Follow us on Twitter @OHDSI and LinkedIn

Common data model to enable standardized analytics
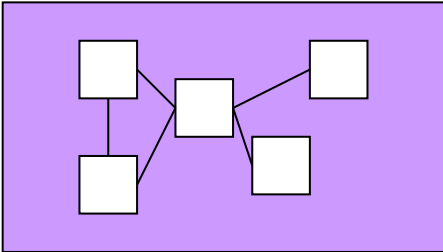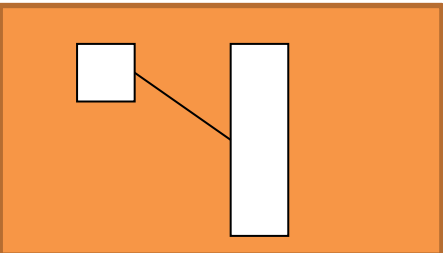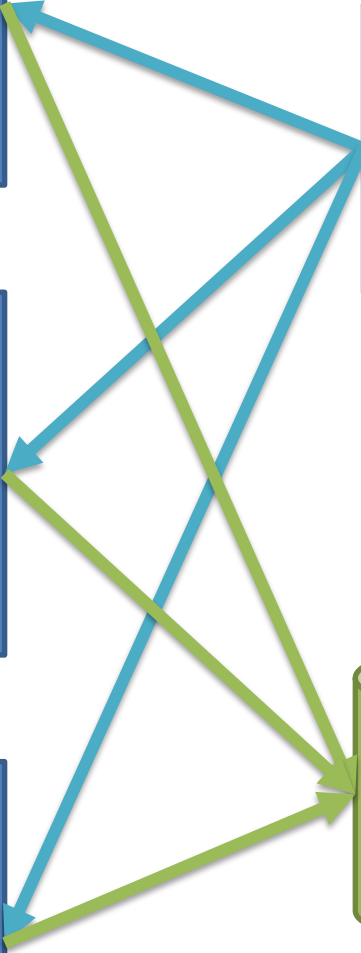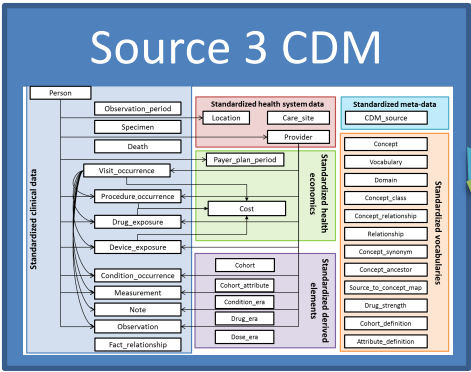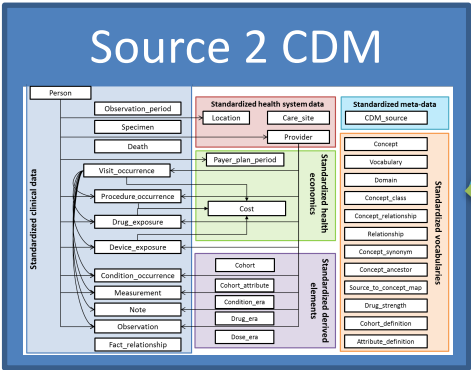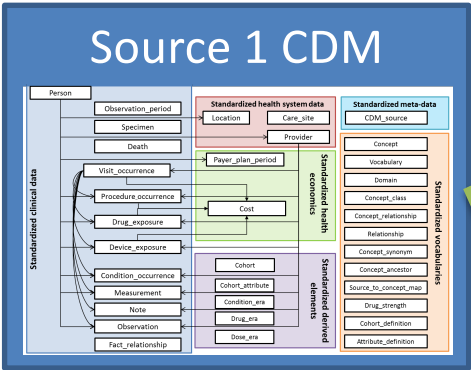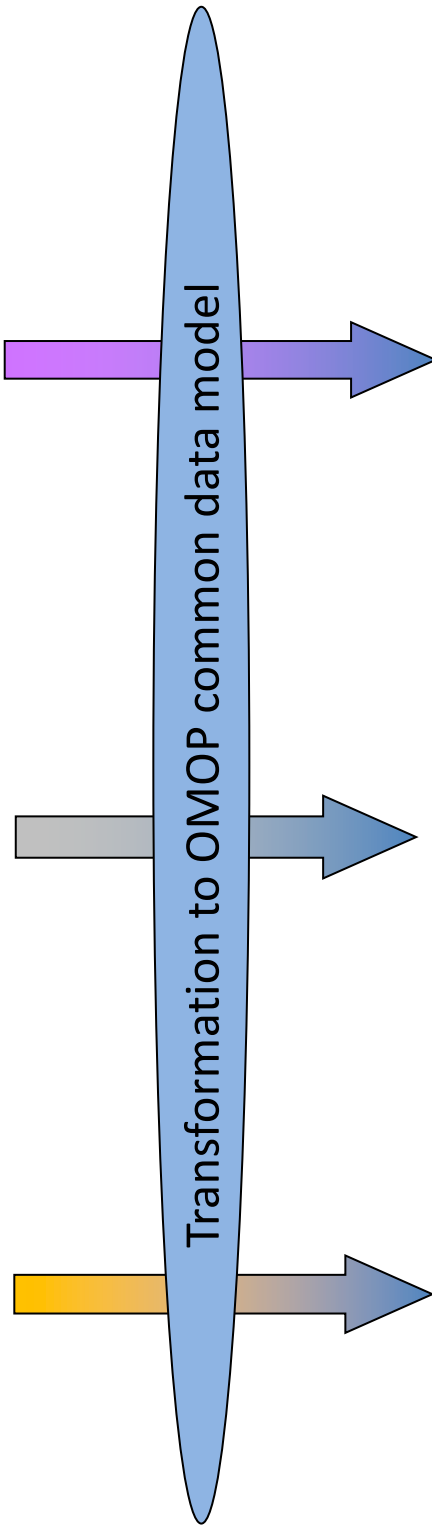
Complementary evidence to inform the patient journey
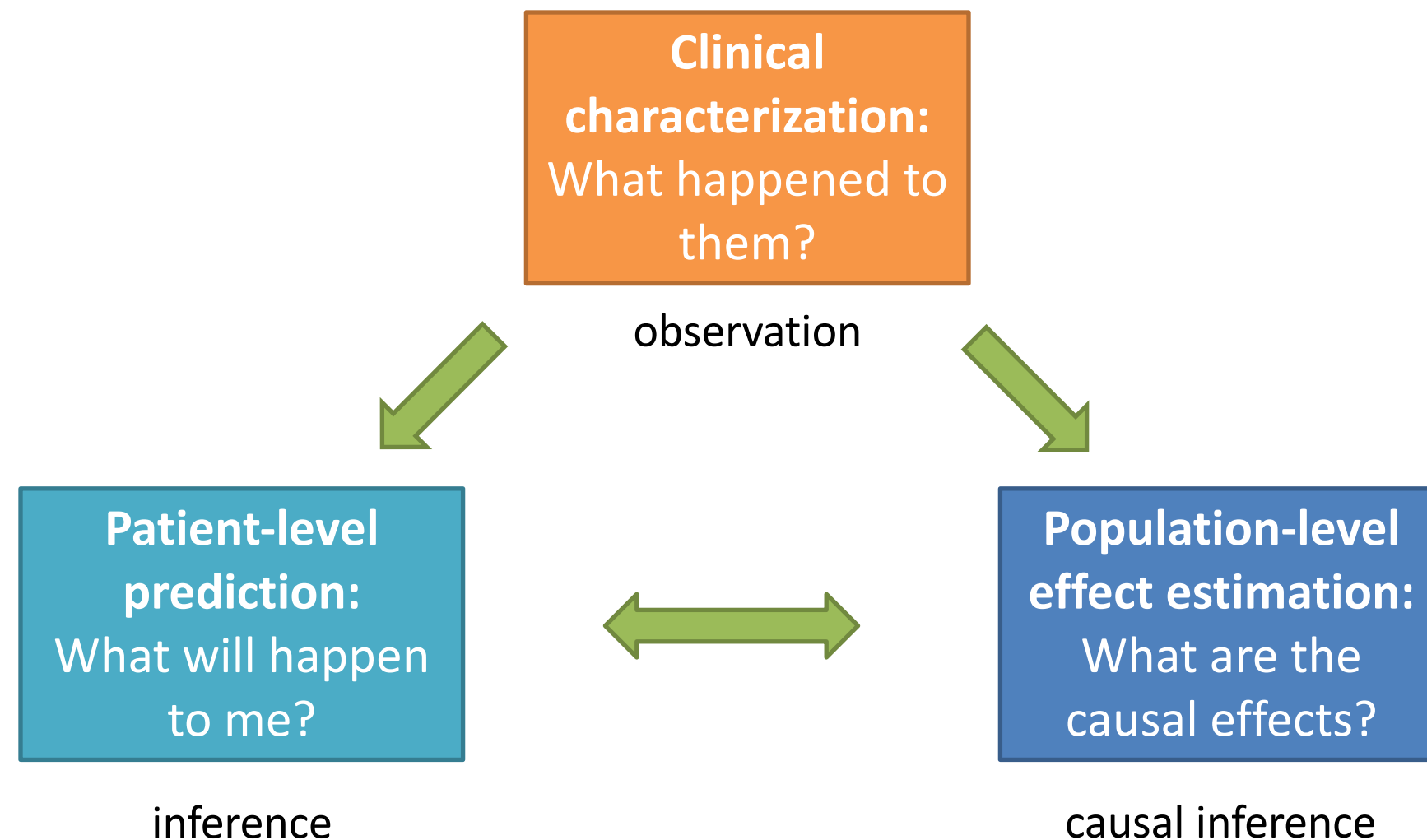
Driving agenda of full transparency

- All artifacts of our analytics pipeline are made available to the public

- In doing so, we are encouraging others to do the same

- Transparency is key to

  - **Reproducibility**

  - **Interpretability**

  - **Trustworthiness**

ETL documentation

Data Quality Dashboard

Protocol

Standardized Analytics Packages

Study Diagnostics

Interactive Results
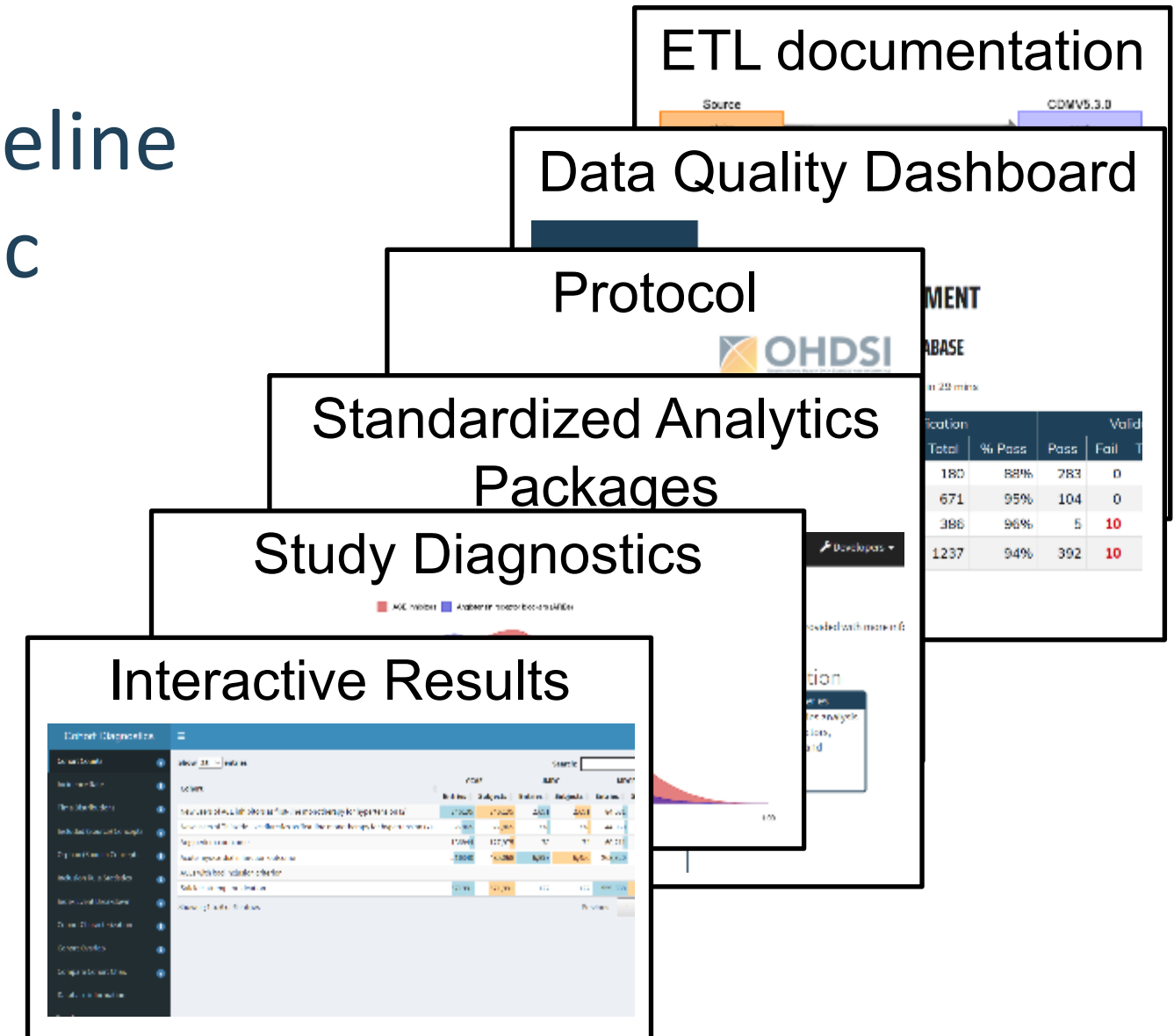
OHDSI COVID-19 Data Network

USA (8)	EUROPE (7)	ASIA-PACIFIC (3)
Premier (National – Hospital Billing)	CPRD (UK – Electronic Health Records)	HIRA (South Korea – Administrative Claims)
HealthVerity (Claims linked to diagnostic testing)	SIDIAP (Spain – Electronic Health Records)	DCMC (South Korea – Electronic Health Records)
Optum EHR (National – Electronic Health Records)	SIDIAP-H (Spain – EHR hospital linkage	Nanfang Hospital (China – Electronic Medical Records)
IQVIA Open Claims (National – Administrative Claims)	HM Hospitales (Spain – Hospital Billing)	
Department of Veterans Affairs (National – Electronic Health Records)	ICPI (Netherlands – Electronic Health Records)	
Stanford University (CA – Electronic Health Records)	LPD France (France – Electronic Health Records)	
Tufts University (MA – Electronic Health Records)	Germany DA (Germany – Electronic Health Records)	
Columbia University (NY – Electronic Health Records)		

Together, OHDSI has studied:

- **>4.5m** patients tested for SAR-COV-2
- **>1.2m** patients diagnosed or tested positive for COVID-19
- **>249k** patients hospitalized 4 COVID-19

- In April EHDEN launched a call to any institution in Europe holding relevant COVID-19 data to apply in order to contribute to research collaboration

- 75 applicants, **25 grants** awarded
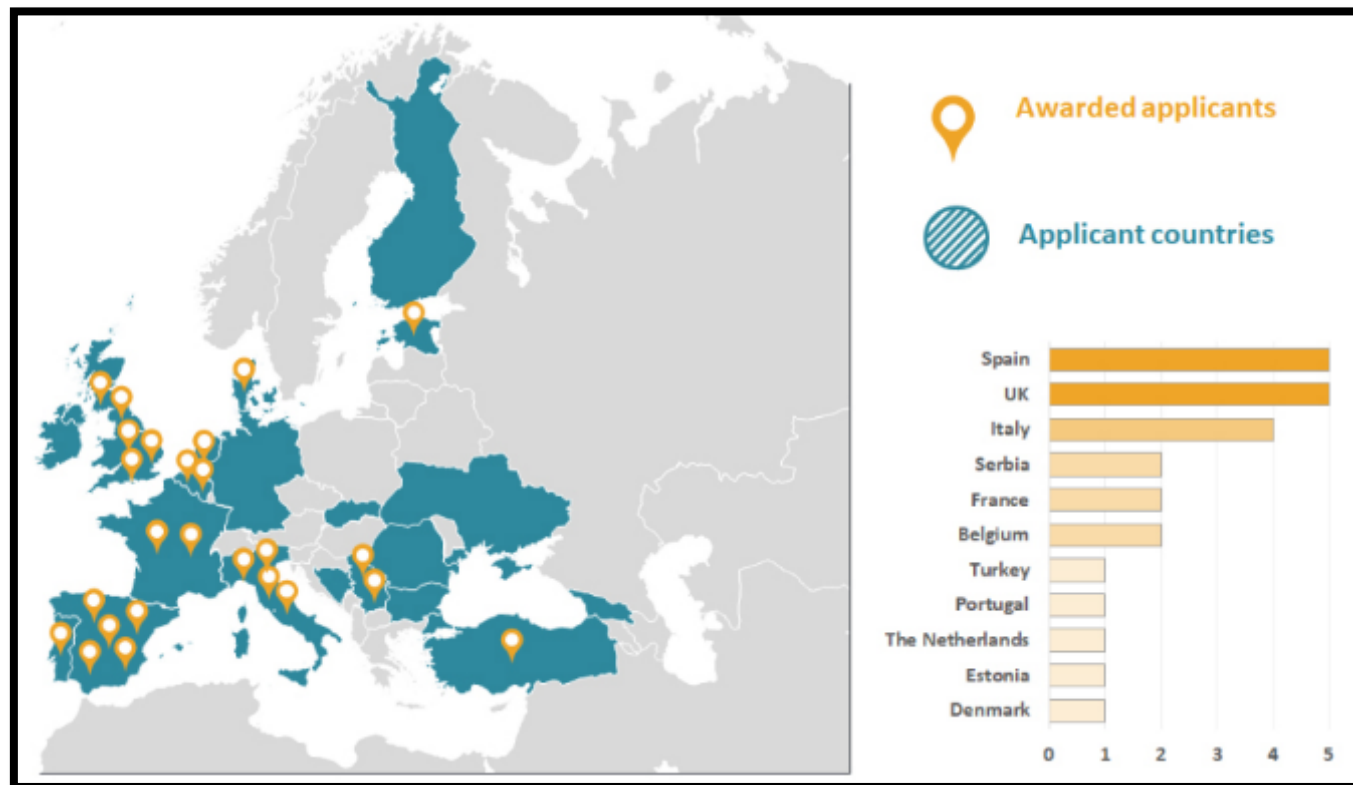
- Highlights:

  - **Health Data Hub** – medical records for the *entire French population*, millions of active patients, 70K COVID diagnoses made

  - **UK Biobank** – *large longitudinal research study* of 500K participants from England, Scotland, and Wales, has 330 positive COVID19 cases

  - **Istanbul University Faculty of Medicine** – 2.5M patients, 1.5M active patients, more than 7K COVID19 patients seen, *work done at this data partner would be applicable for the whole country*

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The original plan …

OHDSI Europe 2020

- 300 to 350 people
- In Oxford
- Talking science
- Learning

Instead … #flattenthecurve

How can we help?

- System overload –> Capacity issues …

- What is the phenotype, prognosis, and care needs? [Characterisation]

- Who is at high (or low) risk of complications? [Prediction]

World ▶ Europe US Americas Asia Australia Middle East Africa Inequality Global development

Coronavirus outbreak

London woman dies of suspected Covid-19 after being told she was 'not priority'

Kayla Williams, 36, from Peckham, south London, died a day after calling 999

Coronavirus – all updates

How can we help (2)?

- Clinical guidelines …

How can we help (3)?

- Drug (regulatory) approvals …

China backs use of Roche's Actemra for coronavirus

Anti-inflammatory drug will be used in patients with lung complications

Article by **Phil Taylor**

5th March 2020

From: **Healthcare**

China has given a green light to use Roche's anti-inflammatory drug Actemra in coronavirus patients with lung complications as it tries to find ways to tackle the **COVID-19** outbreak.

Tags

Roche
Actemra
Coronavirus
COVID-19

Donald Trump says malaria drug has shown 'very encouraging results' in treating coronavirus

View 3 comments

Jimmy McCloskey Thursday 19 Mar 2020 3:47 pm

1.9k SHARES

Causal Effects / Estimation

- What is the safety of the most commonly used repurposed therapies?

How can we help (4)?

- Extensive use of the combination of HCQ + AZM in countries hit in March …
  - 70% HCQ / 32% HCQ+AZM

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial [preprint]

What have we done?

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

- Convene **351** participants from **30** countries
- Hold **12** Global Huddles, **>100** collaborator calls, **>13,000** chat messages
- Engage **15** concurrent channels
- Review **>10,000** publications
- Draft **9** study protocols
- Release **13** study packages
- Design **355** cohort definitions
- Assemble a distributed data network with **37** partners signed on to execute studies

https://www.ohdsi.org/covid-19-updates/

3 things that we did in 4 days that nobody had ever done before

- First large-scale characterization of COVID patients in Europe, US and Asia

- First prediction model externally validated on COVID patients to informe shielding strategies

- Largest study ever conducted on the safety of hydroxychloroquine
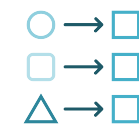
Desired attributes for reliable evidence

Desired attribute	Question	Researcher	Data	Analysis		Result
Repeatable	Identical	Identical	Identical	Identical	=	Identical
Reproducible	Identical	Different	Identical	Identical	=	Identical
Replicable	Identical	Same or different	Similar	Identical	=	Similar
Generalizable	Identical	Same or different	Different	Identical	=	Similar
Robust	Identical	Same or different	Same or different	Different	=	Similar
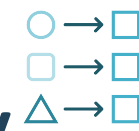
Minimum requirements to achieve reproducibility

Desired attribute	Question	Researcher	Data	Analysis		Result
Reproducible	Identical	Different	Identical	Identical	=	Identical
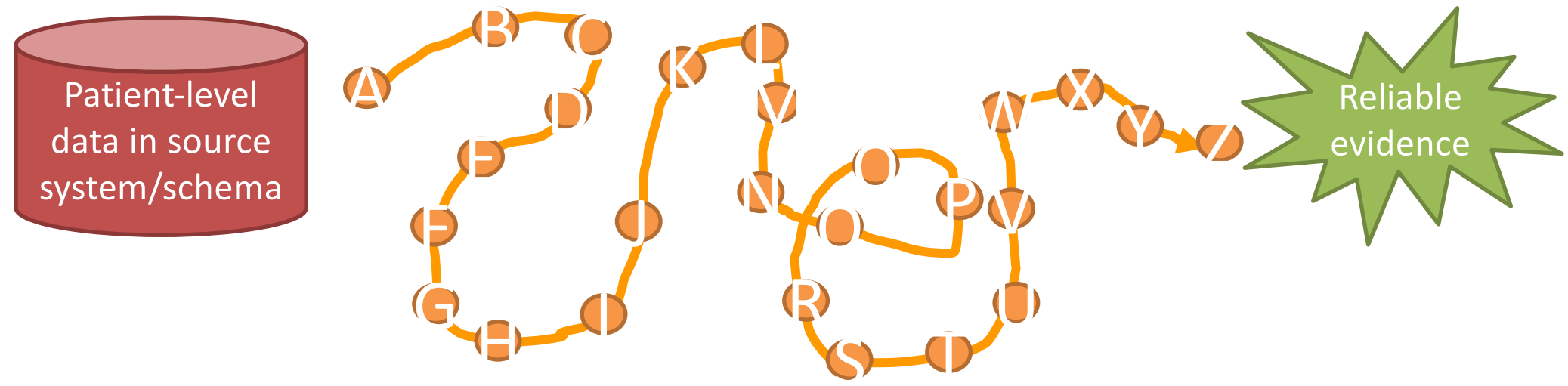
- Complete documented specification that fully describes all data manipulations and statistical procedures

- Original source data, no staged intermediaries

- Full analysis code that executes end-to-end (from source to results) without manual intervention
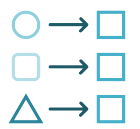
How a cdm + common analytics can support reproducibility

Desired attribute	Question	Researcher	Data	Analysis		Result
Reproducible	Identical	Different	Identical	Identical	=	Identical
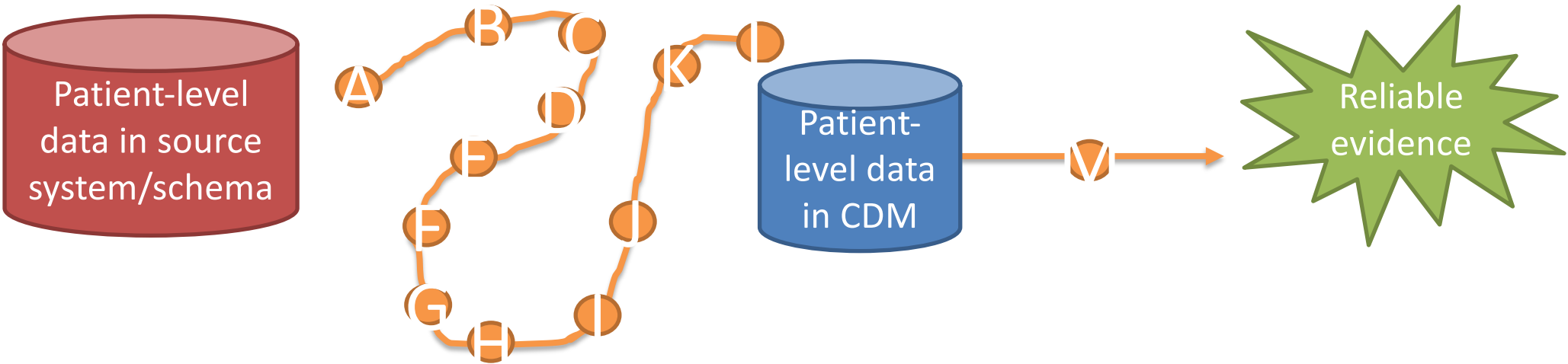
- CDM splits the journey into two segments: 1) data standardization, 2) analysis execution

- ETL specification and source code can be developed and evaluated separately from analysis design

- CDM creates opportunity for re-use of data step and analysis step

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Complementary evidence to inform the patient journey
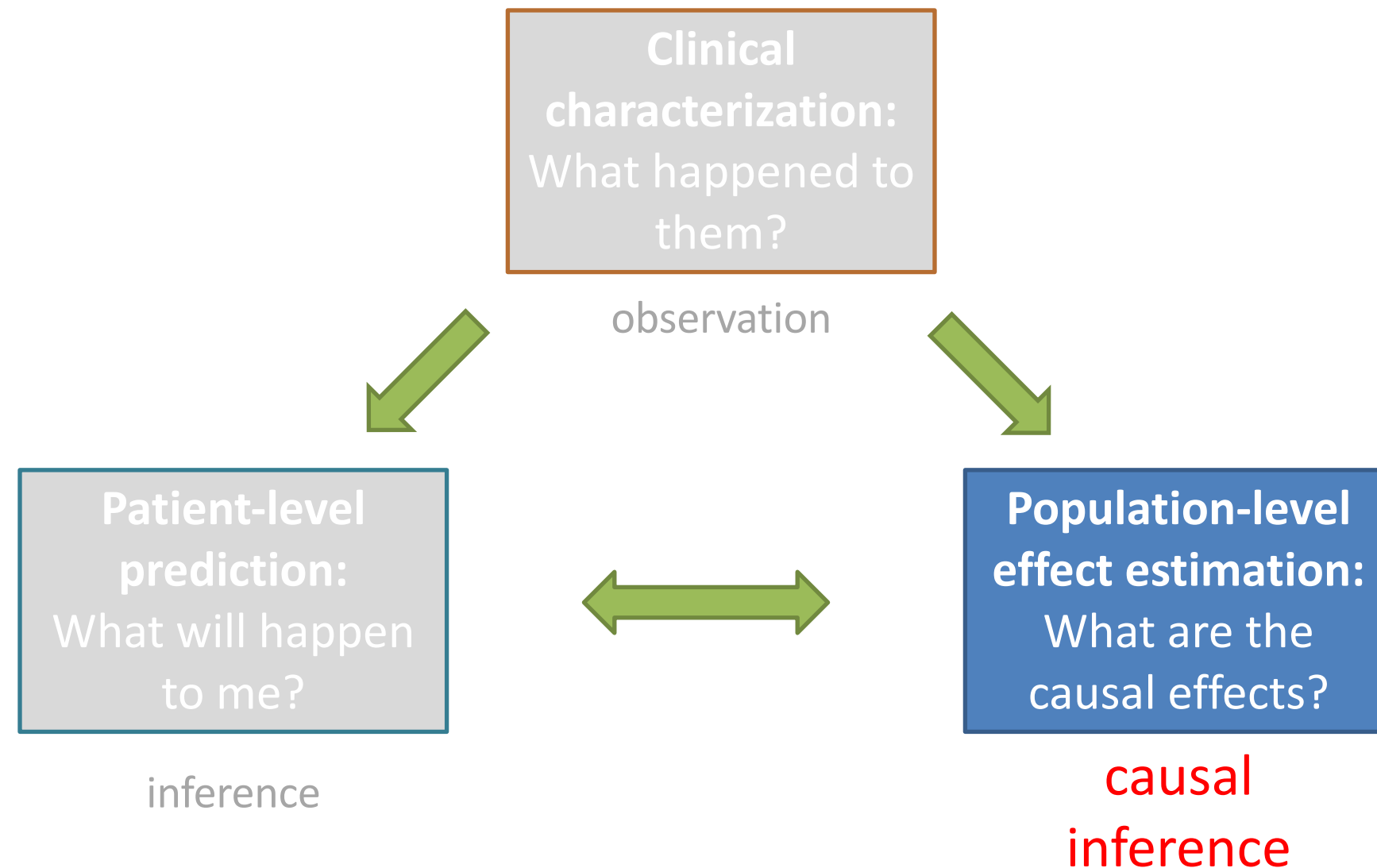
~~Safety~~ **Risks of HCQ ± AZM, in light of rapid wide-spread use for COVID-19:**

a multinational, network cohort and self-controlled case series study

Primum non nocere (First, do no harm)

Hydroxychloroquine …

- Cheap, generic drug
- Indicated for RA, SLE and malaria prophylaxis
- Relatively safe, but:
  – Retinal toxicity
  – QT lengthening

- "In vitro" activity vs SARSCov2
- Great publicity …

Coronavirus: Trump says he is taking unproven drug hydroxychloroquine

🕐 19 May 2020

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Coronavirus pandemic

Trump: "If it's not good, I'll tell you right, I'm not going to get hurt by it"

Potential public health impact: CHARYBDIS DUS results
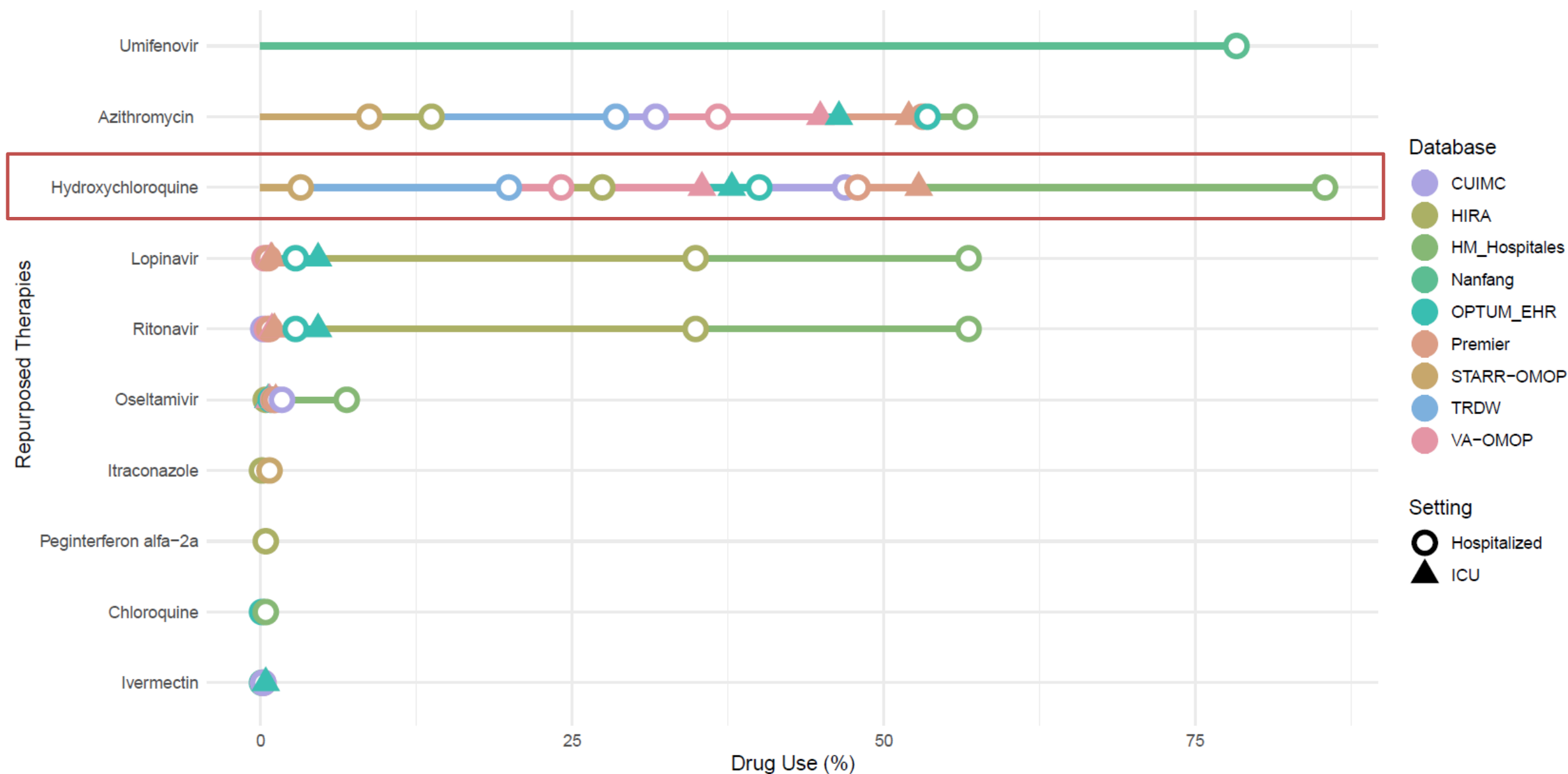
Aim/s

We used historical data from >900,000 previous users of HCQ for other indications (RA) to learn:

- What is the risk of serious adverse events (leading to hospital admission) associated with HCQ (vs SSZ as active comparator)?
- What is the risk of serious adverse events associated with the addition of AZM (vs AMX as active comparator) amongst users of HCQ?

Methods

Data source/s: Routine data (electronic medical records and claims) from Germany, Japan, Spain, S Korea, US, and the UK

Design: Comparative cohort analysis (+ SCCS, not covered today)

Participants:
- Age 18+ , 1+ years of data 'visibility'
- Diagnosis of Rheumatoid Arthritis + use of one of the study drugs/ combinations

Methods (2)

Follow-up:

- 30-day (from initiation of study drug/combination)
- On treatment (for as long as treatment is continued)

Analyses:

1. Federated analytics -> db-specific findings -> meta-analysis
2. Building large-scale propensity scores
3. Diagnostics (imbalances observed confounders + negative control outcomes for unobserved confounders) -> analyses only conducted if OK
4. Propensity score stratification + NCO calibration

RESULTS

http://evidence.ohdsi.org/Covid19EstimationHydroxychloroquine

Patient counts

Data source	HCQ	SSZ
AmbEMR	57,140	15,268
CCAE	65,935	22,173
Clinformatics	50,698	17,221
CPRD	9,114	11,388
DAGermany	3,884	5,045
IMRD	8,843	8,452
MDCD	7,982	2,177
MDCR	15,690	5,150
OpenClaims	617,628	182,776
OptumEHR	76,844	21,549
VA	31,824	14,276
Meta-analysis	*945,582*	*305,475*

Short-term (30-day) main event/s safety

HCQ vs SSZ

Outcome	Database	CalHR (95% CI) [I2]
CV-related mortality	Clinformatics	1.04 (0.31-3.41)
	VA	2.47 (0.45-13.69)
	Meta-analysis	1.36 (0.51-3.63) [<0.01]
Chest pain or angina	AmbEMR	1.08 (0.71-1.66)
	CCAE	0.91 (0.72-1.14)
	Clinformatics	0.82 (0.66-1.01)
	CPRD	0.90 (0.36-2.23)
	DAGermany	0.41 (0.08-2.06)
	IMRD	1.11 (0.39-3.17)
	MDCD	0.96 (0.58-1.59)
	MDCR	0.93 (0.66-1.30)
	OpenClaims	0.91 (0.83-1.00)
	OptumEHR	1.15 (0.95-1.40)
	VA	1.04 (0.73-1.48)
	Meta-analysis	0.96 (0.84-1.09) [<0.01]
Heart failure	AmbEMR	1.17 (0.56-2.45)
	CCAE	1.40 (0.50-3.90)
	Clinformatics	1.20 (0.74-1.95)
	CPRD	1.32 (0.09-19.00)
	DAGermany	0.65 (0.10-4.06)
	IMRD	5.14 (0.29-89.87)
	MDCD	1.83 (0.36-9.40)
	MDCR	0.75 (0.42-1.34)
	OpenClaims	0.94 (0.80-1.11)
	OptumEHR	1.25 (0.91-1.73)
	VA	1.28 (0.70-2.34)
	Meta-analysis	1.05 (0.89-1.25) [<0.01]

0.175 0.25 0.5 1 2 4 6
Favors HCQ   CalHR   Favors SSZ

Short-term (30-day) main event/s

HCQ vs SSZ

AZM vs AMX

Outcome	Database	CalHR (95% CI) [I2]		CalHR (95% CI) [I2]	
CV-related mortality	Clinformatics	1.04 (0.31-3.41)		1.76 (0.56-5.57)	
	VA	2.47 (0.45-13.69)		1.98 (1.00-3.91)	
	Meta-analysis	1.36 (0.51-3.63) [<0.01]		2.19 (1.22-3.95) [<0.01]	
Chest pain or angina	AmbEMR	1.08 (0.71-1.66)		1.42 (0.78-2.59)	
	CCAE	0.91 (0.72-1.14)		1.02 (0.82-1.25)	
	Clinformatics	0.82 (0.66-1.01)		1.22 (0.98-1.52)	
	CPRD	0.90 (0.36-2.23)			
	DAGermany	0.41 (0.08-2.06)			
	IMRD	1.11 (0.39-3.17)			
	MDCD	0.96 (0.58-1.59)		0.98 (0.57-1.69)	
	MDCR	0.93 (0.66-1.30)		1.10 (0.77-1.56)	
	OpenClaims	0.91 (0.83-1.00)		1.23 (1.10-1.36)	
	OptumEHR	1.15 (0.95-1.40)		1.08 (0.84-1.40)	
	VA	1.04 (0.73-1.48)		0.81 (0.51-1.28)	
	Meta-analysis	0.96 (0.84-1.09) [<0.01]		1.15 (1.05-1.26) [<0.01]	
Heart failure	AmbEMR	1.17 (0.56-2.45)		1.08 (0.51-2.31)	
	CCAE	1.40 (0.50-3.90)		1.01 (0.55-1.86)	
	Clinformatics	1.20 (0.74-1.95)		1.18 (0.77-1.80)	
	CPRD	1.32 (0.09-19.00)			
	DAGermany	0.65 (0.10-4.06)			
	IMRD	5.14 (0.29-89.87)			
	MDCD	1.83 (0.36-9.40)		0.96 (0.39-2.35)	
	MDCR	0.75 (0.42-1.34)		1.33 (0.79-2.22)	
	OpenClaims	0.94 (0.80-1.11)		1.29 (1.11-1.51)	
	OptumEHR	1.25 (0.91-1.73)		0.97 (0.66-1.42)	
	VA	1.28 (0.70-2.34)		1.89 (1.13-3.15)	
	Meta-analysis	1.05 (0.89-1.25) [<0.01]		1.22 (1.02-1.45) [0.23]	

0.175 0.25   0.5   1   2   4   6
Favors HCQ   CalHR   Favors SSZ

0.175 0.25   0.5   1   2   4   6
Favors AZM   CalHR   Favors AMX

Long-term (on treatment) main event/s

Outcome	Database	HCQ vs SSZ CalHR (95% CI) [I2]	AZM vs AMX CalHR (95% CI) [I2]
CV-related mortality	Clinformatics	1.97 (1.25-3.12)	1.12 (0.80-1.58)
	CPRD	0.74 (0.23-2.37)	
	VA	1.69 (1.27-2.25)	1.22 (0.91-1.65)
	Meta-analysis	1.65 (1.12-2.44) [0.25]	1.20 (0.96-1.50) [<0.01]
Chest pain or angina	AmbEMR	1.07 (0.86-1.35)	0.94 (0.72-1.22)
	CCAE	1.00 (0.88-1.14)	0.98 (0.90-1.08)
	Clinformatics	0.99 (0.82-1.19)	1.01 (0.91-1.13)
	CPRD	0.92 (0.49-1.72)	
	DAGermany	0.86 (0.51-1.45)	
	IMRD	0.81 (0.52-1.28)	
	MDCD	1.07 (0.85-1.34)	1.14 (0.85-1.52)
	MDCR	1.06 (0.91-1.23)	1.13 (0.97-1.32)
	OpenClaims	1.00 (0.79-1.27)	0.96 (0.91-1.02)
	VA	1.02 (0.92-1.14)	0.88 (0.73-1.05)
	Meta-analysis	1.01 (0.79-1.30) [<0.01]	0.98 (0.94-1.02) [<0.01]
Heart failure	AmbEMR	1.04 (0.74-1.45)	0.99 (0.66-1.50)
	CCAE	0.96 (0.72-1.28)	1.02 (0.79-1.31)
	Clinformatics	1.04 (0.83-1.30)	0.93 (0.77-1.11)
	CPRD	1.40 (0.57-3.43)	
	DAGermany	0.49 (0.22-1.09)	
	IMRD	1.30 (0.56-3.02)	
	MDCD	0.85 (0.55-1.31)	0.96 (0.63-1.48)
	MDCR	0.94 (0.77-1.16)	1.12 (0.93-1.35)
	OpenClaims	1.03 (0.81-1.32)	0.98 (0.91-1.05)
	VA	1.04 (0.90-1.20)	1.13 (0.91-1.40)
	Meta-analysis	1.04 (0.80-1.33) [<0.01]	0.99 (0.94-1.05) [<0.01]

SAE (others)

Follow-up	Outcome	HCQ vs SSZ CalHR (95% CI) [I2]		AZM vs AMX	
30-day	All-cause mortality	0.76 (0.44-1.32) [0.21]		1.36 (0.94-1.97) [<0.01]	
	Myocardial infarction	1.15 (0.92-1.43) [<0.01]		1.07 (0.88-1.30) [<0.01]	
	Cardiovascular events	1.01 (0.87-1.16) [<0.01]			
	Cardiac arrhythmia	0.90 (0.78-1.03) [<0.01]			
	Bradycardia	0.88 (0.66-1.16) [<0.01]		0.93 (0.70-1.25) [<0.01]	
	Transient ischemic attack	1.17 (0.90-1.53) [<0.01]		1.01 (0.71-1.44) [0.2]	
	Stroke	1.16 (0.93-1.45) [<0.01]		1.11 (0.91-1.36) [<0.01]	
	Venous thromboembolism	0.96 (0.81-1.13) [<0.01]		0.99 (0.83-1.18) [0.17]	
	Gastrointestinal bleeding	1.09 (0.89-1.33) [<0.01]		1.02 (0.85-1.22) [0.03]	
	Acute renal failure	1.03 (0.88-1.20) [<0.01]			
	End stage renal disease	1.07 (0.59-1.93) [0.11]		1.14 (0.76-1.69) [<0.01]	
	Hepatic failure	0.67 (0.45-1.01) [<0.01]		0.88 (0.56-1.39) [<0.01]	
	Acute pancreatitis	0.97 (0.72-1.30) [<0.01]		0.94 (0.69-1.27) [<0.01]	
On-treatment	All-cause mortality			0.95 (0.83-1.08) [0.19]	
	Myocardial infarction	1.11 (0.86-1.44) [<0.01]		1.02 (0.95-1.09) [<0.01]	
	Cardiovascular events	1.02 (0.79-1.31) [<0.01]		1.01 (0.95-1.07) [0.29]	
	Bradycardia	1.09 (0.84-1.42) [<0.01]		0.92 (0.84-1.00) [<0.01]	
	Transient ischemic attack	1.04 (0.80-1.35) [<0.01]		1.02 (0.94-1.11) [<0.01]	
	Stroke			0.99 (0.92-1.06) [<0.01]	
	Venous thromboembolism	1.00 (0.77-1.30) [0.29]		1.06 (0.97-1.15) [0.28]	
	Gastrointestinal bleeding			1.01 (0.93-1.10) [0.13]	
	Acute renal failure	1.18 (0.91-1.52) [0.3]		0.98 (0.93-1.02) [<0.01]	
	End stage renal disease	1.23 (0.92-1.63) [<0.01]		0.93 (0.82-1.05) [<0.01]	
	Hepatic failure	1.06 (0.79-1.42) [<0.01]		0.93 (0.77-1.12) [0.07]	
	Acute pancreatitis	0.99 (0.76-1.29) [<0.01]		1.02 (0.92-1.14) [<0.01]	

0.25 0.5 1 2 4
Favors HCQ   CalHR   Favors SSZ

0.25 0.5 1 2 4
Favors AZM   CalHR   Favors AMX

Safety of hydroxychloroquine

- Findings:
  - In history use in RA population, HCQ alone is generally safe but in combination with AZ it shows a doubling of risk of 30-day cardiovascular mortality.

THE LANCET Rheumatology

Articles

Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study

Jennifer C E Lane*, James Weaver*, Kristin Kostka, Talita Duarte-Salles, Maria Tereza F Abrahao, Heba Alghoul, Osaid Alser, Thamir M Alshammari, Patricia Biedermann, Juan M Banda, Edward Burn, Paula Casajust, Mitchell M Conover, Aedin C Culhane, Alexander Davydov, Scott L DuVall, Dmitry Dymshyts, Sergio Fernandez-Bertolin, Kristina Fišter, Jill Hardin, Laura Hester, George Hripcsak, Benjamin Skov Kaas-Hansen, Seamus Kent, Sajan Khosla, Spyros Kolovos, Christophe G Lambert, Johan van der Lei, Kristine E Lynch, Rupa Makadia, Andrea V Margulis, Michael E Matheny, Paras Mehta, Daniel R Morales, Henry Morgan-Stewart, Mees Mosseveld, Danielle Newby, Fredrik Nyberg, Anna Ostropolets, Rae Woong Park, Albert Prats-Uribe, Gowtham A Rao, Christian Reich, Jenna Reps, Peter Rijnbeek, Selva Muthu Kumaran Sathappan, Martijn Schuemie, Sarah Seager, Anthony G Sena, Azza Shoaibi, Matthew Spotnitz, Marc A Suchard, Carmen O Torre, David Vizcaya, Haini Wen, Marcel de Wilde, Junqing Xie, Seng Chan You, Lin Zhang, Oleg Zhuk, Patrick Ryan, Daniel Prieto-Alhambra, on behalf of the OHDSI-COVID-19 consortium

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COVID-19: reminder of risk of serious side effects with chloroquine and hydroxychloroquine < Share

News 23/04/2020

Chloroquine and hydroxychloroquine are known to potentially cause heart rhythm problems, and these could be exacerbated if treatment is combined with other medicines, such as the antibiotic azithromycin, that have similar effects on the heart.

Recent studies[1,2] have reported serious, in some cases fatal, heart rhythm problems with chloroquine or hydroxychloroquine, particularly when taken at high doses or in combination with the antibiotic azithromycin.

Safety of hydroxychloroquine #2

- Psychiatric safety of hydroxychloroquine: EMA was concerned about risk of neuropsychiatric events associated with HCQ based on spontaneous reports.

Findings:

- No increased risk of depression, suicidal ideation or psychosis for new users of HCQ with RA.

- Utilized claims and electronic medical records from 10 databases across 3 different countries
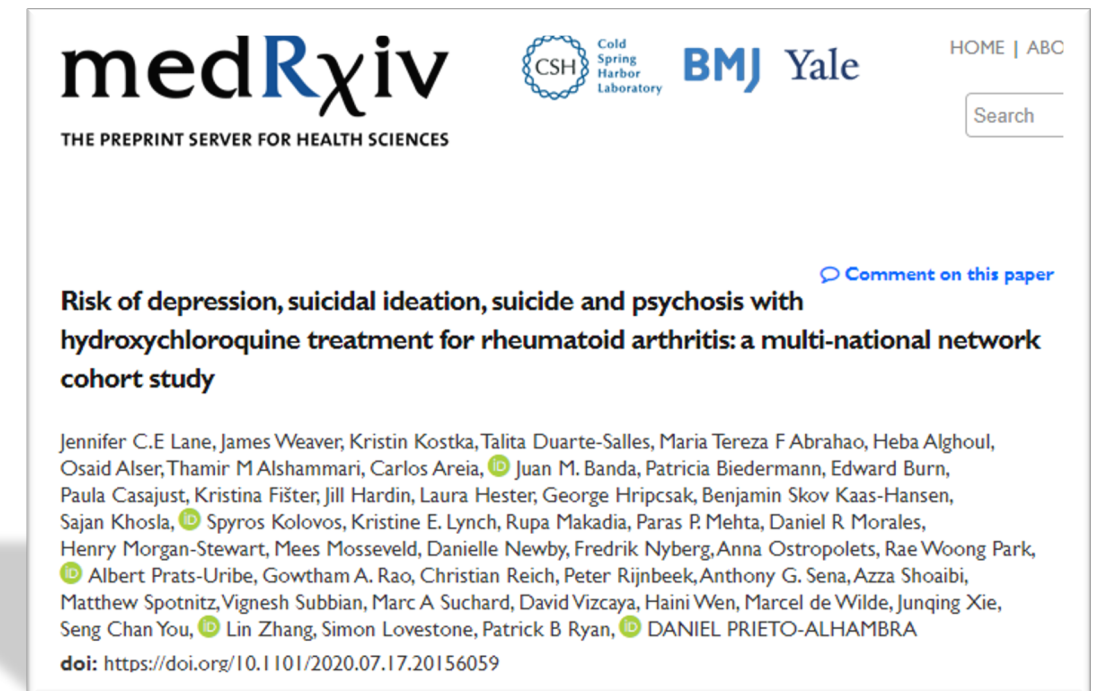
Under review at *Rheumatology*

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ENCePP
European Network of Centres for
Pharmacoepidemiology and
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EMA/95098/2010 Rev.8

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology

(Revision 8)

Foreword to 8th Revision

ENCePP Guide supports strong observational research for the COVID-19 pandemic

The rapid progression of the COVID-19 pandemic has generated several hypotheses on the safety and effectiveness of therapeutic interventions, such as repurposed medicines. The need for quick answers triggered the initiation of observational studies carried-out with fast data collection, analysis and reporting. In a pandemic situation, the same methodological standards as those applied in any other circumstance should nevertheless be used to provide valid and reliable evidence supporting rapid treatment decisions by clinicians and regulators. Adherence to existing guidance on the appropriate design and conduct of pharmacoepidemiologic studies is therefore of utmost importance. ENCePP believes that this 8th Revision of the Guide on Methodological Standards in Pharmacoepidemiology should be the backdrop against which observational studies related to the COVID-19 pandemic should be conducted.

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The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
(Revision 8)

In the context of a pandemic where rapid answers to research questions are needed, combining data across different databases affords insight into the generalisability of the results and may improve precision if outcomes or exposure of interest are rare or when there is interest in subgroup effects. It may also inform on specific patterns of drug utilisation. Chapter 4.6. on research networks for multi-database studies describes the different models that can be applied for combining data or results from multiple databases. An example of a collaboration in the context of the COVID-19 pandemic is the study published by Lane et al. using data from 14 multinational sources of claims data or electronic medical records. This study followed the model of a general common data model (CDM) described in Chapter 4.6.2.5.

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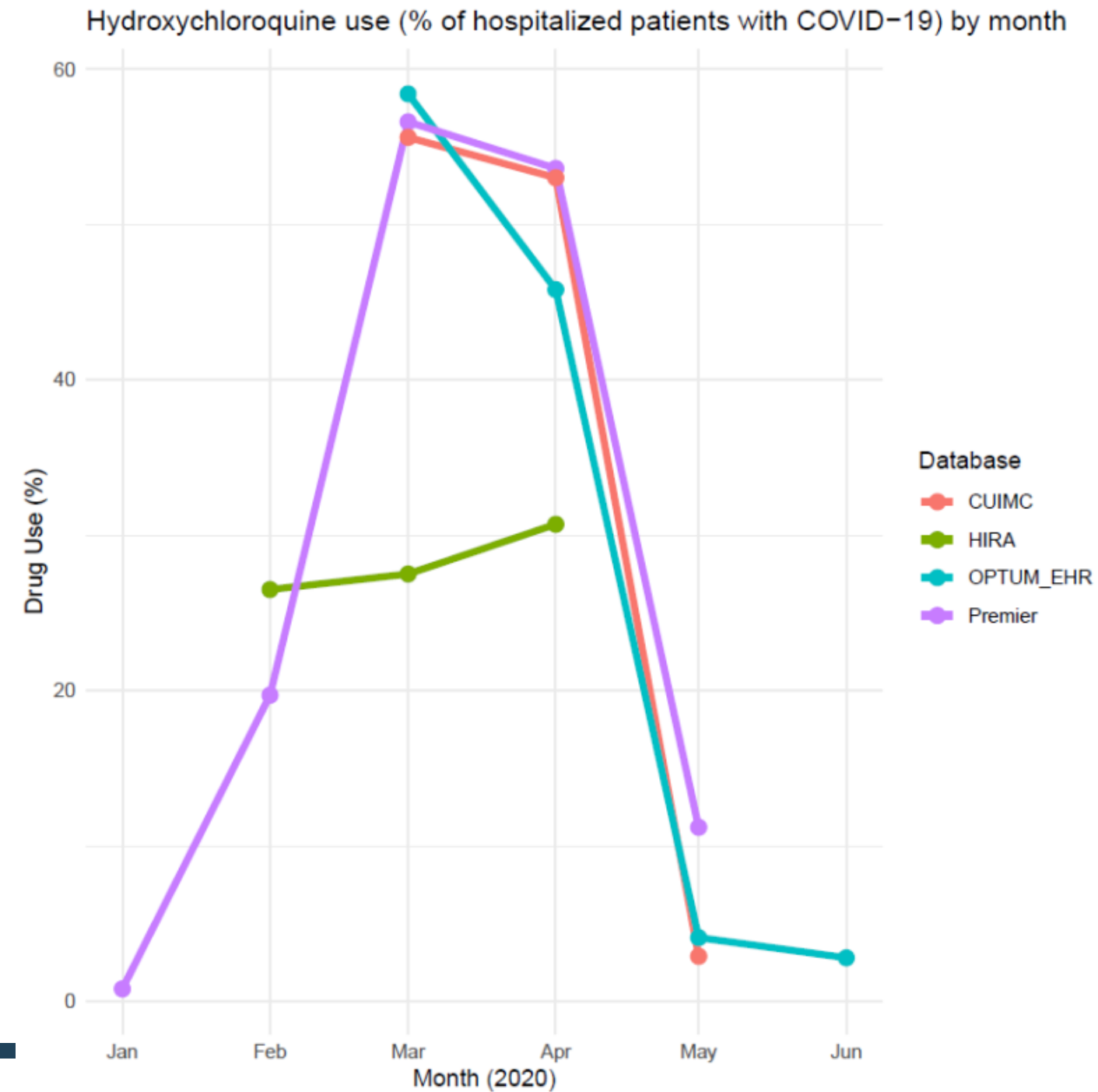
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As stated by Watson et al. in relation to one of the published studies, lack of transparency and uncertainties about research standards applied raise doubts about published results. Morales et al. supported the reproducibility of their study by publishing the study protocol in the EU PAS Register ahead of time, providing a start-to-finish executable code, facilitating the sharing and exploration of the complete result set with an interactive web application and asking clinicians and epidemiologists to perform a blinded evaluation of propensity score diagnostics for the treatment comparisons.

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The rise and fall of hydroxychloroquine

Hydroxychloroquine use (% of hospitalized patients with COVID−19) by month

Questions?