The real-world data response to a changing world

Dr Jennifer Lane
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University of Oxford
Vision
The European Health Data & Evidence Network (EHDEN) aspires to be the trusted observational research ecosystem to enable better health decisions, outcomes and care.

Mission
Our mission is to provide a new paradigm for the discovery and analysis of health data in Europe, by building a large-scale, federated network of data sources standardized to a common data model.
EHDEN IS ABOUT...

**Federation**
Creation of an EU-wide architecture for federated analyses of real world data

**Harmonisation**
Harmonise more than 100 million anonymised health records to the OMOP common data model

**Education**
The establishment of an EHDEN Academy, webinars and face-to-face training sessions to train all stakeholders

**Community**
Establish a self-sustaining open science collaboration in Europe, supporting academia, industry, regulators, payers, government, NGOs and others

**Outcomes**
Enabling outcomes driven healthcare at a European level
EHDEN CONSORTIUM

Start date: 1 Nov 2018
End date: 30 Apr 2024
Duration: 66 months

22 partners

Almost €29 million

Universities, public bodies and research organisations

SME & Mid-sized companies

Non-profit organisations

EFPIA & Associated partners
The EHDEN Federated Data Network

### Local Governance

<table>
<thead>
<tr>
<th>EMR</th>
<th>LIMS</th>
<th>Rx</th>
<th>Dx</th>
<th>Admin</th>
</tr>
</thead>
</table>

- **Local Database**
- **OMOP Database**

### Analysis query

- **Aggregated results**

### EHDEN will develop new tools and dashboards.

### The EHDEN platform

- **Many different open source tools** (cohort builder, estimation, incidence rate, ....)

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**ATLAS**

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5
The OMOP Common Data Model

V 5.0.1

Patient-centric
Tabular
Extendable
Built for analytics
Relational design
THE OMOP COMMON DATA MODEL

Standardized clinical data
Standardized health economies
Standardized derived elements
Standardized vocabularies
Standardized meta-data
Standardized health system data

Person
Observation
Location
Care
Fact relationship

CDM source

Patient-centric
Tabular
Extendable
Built for analytics
Relational design

v 5.0.1
EHDEN WILL ENSURE COMPLIANCE WITH E.G., GDPR/DGA

Compliance with citizen and data protection regulations

Ethical Advisory Board

Development of a FDN code of conduct (concentric circles of trust view)

‘Privacy by design’
(data remains local behind socio-technical firewalls)

Evolving framework for data protection as regulation and implementation evolves
Aiming to double Data Partners in 2021!
FAST OBSERVATIONAL RESEARCH IS FEASIBLE (STUDY-A-THON)

“To compare the risk of post-operative complications and mortality between unicompartmental vs total knee replacement.”

Monday
- Group consensus on the problem
- Draft cohort definitions

Tuesday
- Review clinical characterisation
- Draft patient-level prediction design

Wednesday
- Review patient-level prediction results
- Externally validate prediction model

Thursday
- Draft population-level effect estimation design
- Review population-level effect estimation diagnostics

Friday
- Review of results
- Plan for completing publications

(EHDEN 1st Study-a-thon, Oxford, December 2018); published Lancet Rheumatology Dec 2019
COVID-19 PANDEMIC BEGINS

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.
What is the phenotype, prognosis and care needs? [characterization]
Who is at high or low risk? [prediction]
What is the safety of the most commonly used medications repurposed for treatment? [causal inference/estimation]
OHDSI COVID-19
International Study-A-Thon

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

March 26-29, 2020
1. Influenza Hospital Admission in next 30 days
2. Pneumonia Relapse & Admission in next 30 days
3. Pneumonia & ICU/Mortality

2. Characterisation of individuals tested for COVID-19
3. Characteristics and outcomes of COVID-19 in children

1. DMARDs
2. Antivirals
3. ACEi/ARBs

- Super File
**HCQ Safety: Distributed Database Network Study**

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>Patients</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA</td>
<td>US (Veterans)</td>
<td>12M</td>
<td>Claims</td>
</tr>
<tr>
<td>DAGermany</td>
<td>Germany (general population)</td>
<td>37M</td>
<td>EHR</td>
</tr>
<tr>
<td>IMRD</td>
<td>UK (general population)</td>
<td>15M</td>
<td>EHR</td>
</tr>
<tr>
<td>AmbEMR</td>
<td>US (general population)</td>
<td>49M</td>
<td>EHR</td>
</tr>
<tr>
<td>OpenClaims</td>
<td>US (general population)</td>
<td>300M</td>
<td>Claims</td>
</tr>
<tr>
<td>CPRD</td>
<td>UK (general population)</td>
<td>13M</td>
<td>EHR</td>
</tr>
<tr>
<td>CCAE</td>
<td>US (commercially insured, &lt;65y)</td>
<td>142M</td>
<td>Claims</td>
</tr>
<tr>
<td>MDCD</td>
<td>US (Medicaid enrollees)</td>
<td>26M</td>
<td>Claims</td>
</tr>
<tr>
<td>MDCR</td>
<td>US (commercially insured, ≥65y)</td>
<td>10M</td>
<td>Claims</td>
</tr>
<tr>
<td>IPCI</td>
<td>Netherlands (general population)</td>
<td>2.5M</td>
<td>EHR</td>
</tr>
<tr>
<td>JMDC</td>
<td>Japan (insured general population)</td>
<td>5.5M</td>
<td>Claims</td>
</tr>
<tr>
<td>Clinformatics</td>
<td>US (commercially insured)</td>
<td>85M</td>
<td>Claims</td>
</tr>
<tr>
<td>OptumEHR</td>
<td>US (general population)</td>
<td>93M</td>
<td>EHR</td>
</tr>
<tr>
<td>SIDIAP</td>
<td>Catalonia (general population)</td>
<td>7.7M</td>
<td>EHR</td>
</tr>
</tbody>
</table>

14 database
6 countries
7 administrative claims
7 electronic health records

**Real world heterogeneity of patient experience**

Data partners contributing to this study remain custodians of their individual patient-level health information and hold either exemption from institutional review boards or approval for participation.
**HCQ SAFETY: COMPARATIVE COHORT STUDY DESIGN**

**Eligibility criteria:**
- First exposure after Sept 1, 2000
- ≥365 days prior observation
- ≥18 years at index
- RA diagnostics any time prior or on index

**Treatment strategies:**
1. HCQ vs SSZ
2. HCQ+AZM vs HCQ+AMX

**Causal contrasts:**
- On-treatment effect
- Fixed 30d effect

**Outcomes:**
- 16 severe adverse events
- No prior outcome (30d)

**Analysis plan:**
- Cox PH model
- Meta-analysis if $I^2<40\%$

**Baseline covariates for confounding adjustment from observed sources:**
- Demographics
- Conditions, drugs, procedures, devices, measurements observed during the 365 and 30 days before and including index date
- Comorbidity and risk scores

**Index date:**
- Day 0

**TAR start:**
- Day 1

**Baseline covariates for confounding adjustment from unobserved sources:**
- 65 negative controls

**Infographic:** Jamie Weaver
### HYDROXYCHLOROQUINE & CV RISK

#### HCQ vs SSZ incidence rates (/1k PYs) and meta-analytic calibrated hazard ratios (95% CIs)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HCQ IR</th>
<th>SSZ IR</th>
<th>cHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality</td>
<td>3.68</td>
<td>3.86</td>
<td>1.36 (0.51-3.63)</td>
</tr>
<tr>
<td>Chest pain/angina</td>
<td>59.86</td>
<td>57.90</td>
<td>0.96 (0.84-1.09)*</td>
</tr>
<tr>
<td>Heart failure</td>
<td>16.28</td>
<td>14.34</td>
<td>1.05 (0.89-1.25)*</td>
</tr>
</tbody>
</table>

Figure 2: Source-specific and meta-analytic specific severe adverse event risk estimates for HCQ versus SSZ and HCQ plus AZM versus HCQ plus AMX new users during 30-day (intention-to-treat) follow-up

Amb@EMR=IQVIA Ambulatory EMR. AMX=amoxicillin. AZM=azithromycin. CCAE=IBM Commercial Claims and Encounters. CPRD=Clinical Practice Research Datalink. DAGermany=IQVIA Disease Analyzers Germany. EMR=electronic medical record. HCQ=hydroxychloroquine. HR=hazard ratio. IMRD=IQVIA UK Integrated Medical Record Data. MDCD=IBM Multi-state Medicaid. MDCH=IBM Medicare Supplemental Database. Optum@EMR=Optum de-identified Electronic Health Record. SSZ=sulfasalazine. VA=US Department of Veterans Affairs.

*Significant at p < 0.05.
### HCQ+AZM vs HCQ+AZM incidence rates (/1k PYs) and meta-analytic calibrated hazard ratios (95% CIs)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AZM IR</th>
<th>AMX IR</th>
<th>cHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality</td>
<td>22.70</td>
<td>9.08</td>
<td>2.19 (1.22-3.95)</td>
</tr>
<tr>
<td>Chest pain/angina</td>
<td>75.13</td>
<td>59.12</td>
<td>1.15 (1.05-1.26)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>31.32</td>
<td>21.32</td>
<td>1.22 (1.02-1.45)</td>
</tr>
</tbody>
</table>

Figure 2: Source-specific and meta-analytic-specific severe adverse event risk estimates for HCQ versus SSZ and HCQ plus AZM versus HCQ plus AMX new users during 30-day (intention-to-treat) follow-up.
Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study


doi: https://doi.org/10.1101/2020.04.08.20054551

This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and should not be used to guide clinical practice.

KEY PUBLICATIONS

Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study

Journal article

LANE J. et al. (2020)
COVID-19: reminder of risk of serious side effects with chloroquine and hydroxychloroquine

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 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.

Chloroquine and hydroxychloroquine are currently authorised for treating malaria and certain autoimmune diseases. In addition to side effects affecting the heart, they are known to potentially cause liver and kidney problems, nerve cell damage that can lead to seizures (fits) and low blood sugar (hypoglycaemia).
Cloroquina/Hidroxicloroquina: precauciones y vigilancia de posibles reacciones adversas en pacientes con COVID-19

- Estos medicamentos pueden ocasionar trastornos del ritmo cardíaco, específicamente prolongación del intervalo QT del ECG. Este riesgo aumenta con dosis altas y cuando se administra con otros medicamentos que también comparten este posible riesgo como azitromicina.
- No es aconsejable por tanto la combinación de cloroquina o hidroxicloroquina con otros medicamentos que comparten el riesgo de prolongar el intervalo QT del ECG, especialmente en pacientes con factor de riesgo de un intervalo QT prolongado. En caso de necesitar administrar en alguna de estas condiciones, se realizará una vigilancia estrecha del paciente.
- Se recomienda informar a los pacientes que comiencen el tratamiento sobre los posibles signos y síntomas que sugieran un trastorno del ritmocardiaco que consulten con el médico que les realiza seguimiento en caso de que aparezcan.
Rise and Fall of Hydroxychloroquine

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

February 2020

March 2020
09 March Yao, X. et al. - Hydroxychloroquine shows superior in vitro activity to CQ
19 March President Trump promotes HCQ in press conference
20 March Gautret, P. et al. - Open-label non-randomized clinical trial shows effectiveness
28 March US Food and Drug Administration issued an emergency use authorisation
31 March Chen, Z et al. - Preprint of an RCT suggests that HCQ reduces time to clinical recovery

April 2020
10 April Lane, J CE et al. - Observational data shows AZT + HCQ may increase cardiovascular mortality
24 April FDA and EMA caution against the use of HCQ due to potential hearth rhythm problems

May 2020
07 May Geleris, J. et al. - Lack of effectiveness of hydroxychloroquine on observational data
28 May WHO halts SOLIDARITY HCQ trial arm

June 2020
08 June RECOVERY trial press note shows that HCQ has no effect on COVID-19
15 June FDA revokes emergency use ruling for hydroxychloroquine

Prats-Uribe et al 2021 BMJ
Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study

Jennifer C. E. Lane, MRCs, James Weaver, MSC, Kristin Kostka, MPH, Talita Duarte-Salles, PhD
Maria Teresa F. Abrahao, MD, Heba Alghoouf, MD, Ozaid Alser, MD, Thamir M Alshammari, MD
Patricia Biedermann, MD, Juan M. Banda, PhD, Edward Burn, MSC, Paula Casajust, MSc, Mitchell M. Conover, PhD
Aedin C. Culhane, PhD, Alexander Davydov, MD, Scott A. DuVal, MD, Dmitry Dymshyts, MD
Sergio Fernandez-Serritellas, MSc, Kristina Filser, PhD, Jill Hardin, PhD, Laura Hester, PhD
Prof George Hripcsak, MD, Benjamin Skov Kaas-Hansen, MD, Seamus Kent, PhD, Sajjan Khosa, MSc
Spyros Kolovos, PhD, Christoph A. Lambert, PhD, Prof. Johan van der Lei, PhD, Kristine E. Lynch, PhD
Rupa Maladis, PhD, Andrea V. Margulis, ScD, Michael E. Matheny, MD, Paros Mehta, BA, Daniel R. Morales, PhD
Henry Morgan-Stewart, PhD, Mees Mossavadi, MSc, Danielle Newby, PhD, Prof. Frederik Nyberg, PhD
Anna Ostropolets, MD, Prof. Rae Woong Park, MD, Albert Prats-Urube, MPH, Gowtham A. Rao, MD
Christian Reich, MD, Jenna Reps, PhD, Peter Rijnbeek, PhD, Selva Muthu Kumaran Sathappan, MSc
Martijn Schuermans, PhD, Sarah Seager, BA, Anthony G. Sena, BA, Azza Shoaiibi, PhD, Matthew Spottitz, MD
Prof. Marc A. Suchard, MD, Carman O. Torre, MSc, David Vizcaya, PhD, Haiyu Wan, MSc, Marcel de Wilde, BSc
Junqing Xie, MSc, Seng Chan You, MD, Lin Zhang, MD, Oleg Zhou, PhD, Patrick Ryan, PhD
Prof. Daniel Prieto-Alhambra, PhD, on behalf of the OHDSI-COVID-19 consortium

Original article
Risk of depression, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multinational network cohort study

First large-scale characterisation of COVID-19 patients in Europe, Asia & US

First prediction model externally validated on COVID-19 patients to inform shielding strategies

Largest study ever conducted on the safety of hydroxychloroquine
**IMPACT TO DATE**

**RAPID EXPANSION OF COLLABORATIVE COMMUNITY**
**RAPID & AVAILABLE EVIDENCE**
**REGULATORY CHANGE**
**PEER REVIEW PUBLICATIONS**

1. Drug Utilisation Study
2. 3 PLEs (HCQ; HCQ psych effects; ARBs)
3. 1 Phenotyping hospitalized patients with COVID-19
   Characterisations- obesity, paediatrics, cancer

More to come:
Drug use during pandemic
Characteristion, HIV, pregnancy, summary of all

@rebecca_mason_art
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