

The Charybdis project – use of real-world data from multiple countries and opportunities for regulatory purpose

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- Why CHARYBDIS?
- Aims & Methods
- Data sources and main outputs
- Final remarks and opportunities for regulatory purpose



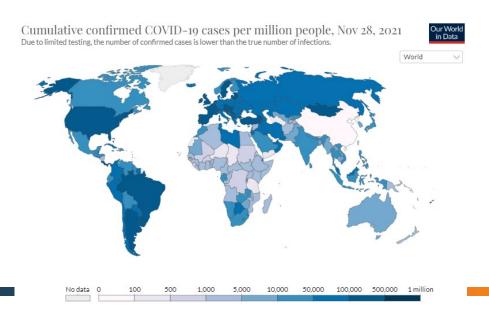
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Why CHARYBDIS?

COVID-19 -> new disease -> need to understand its natural history







Why CHARYBDIS?

- Many published characterization studies
 - Small sample size
 - Few countries
 - Granularity of information
 - Hospital settings

Clinical and virological data of the first cases of COVID-19 in Europe: a case series

Francolo-Xavier Lescore", Life Boosdme", Duc Nguyen, Marion Partney, Paul-Henri Wicky, Sylvie Behillit, Alexandre Geymant Moude Bouscombert Duchang, Flora Donati, Quentin Le Hingrat, Vincent Enoug Madhira Houbou-Fidouh, Martine Halette, Alexandra Mallier Jean-Christophe Lucat, France Mentre, Xavier Duvol, Diane Gincamps, Denis Maley, Jean-François Terrait, Brune Lina*, Sphie van-der-Werf*

Clinical features of patients infected with coronavirus in Wuhan, China

arraham Chang, Ting Yu, Jissen Kin, Yourn Min, Warquan Wu, Koulet Kin, Wan Yor, Har Li, Min Liu nglir Wang, Annymang Jiang, Zhanchang Gao, Q Jin, Jianwe Wang F, Bin-Cast

and treatment and clinical outcomes of these patients

Methods All patients with suspected 2009 of all were admitted to a designator collected and analysed data on patients with laboratory-confirmed 2015-oca. France), where RNA extraction, real-time RT-PCR, and virus isolation and titration procedures were done.

harmoptysis (two [5%] of 3%, and diardroro june [2%] of 36). Dyspance develoy Feb 29, 2020. time from illness occurt to despenses \$-0 days (SQR 5-0-13-05, 36 (63%)) of 45 pa

Background On Dec 31, 2019, China reported a cluster of cases of pneumonia in people at Wuhan. Hubei Province. The responsible pathogen is a novel conseavirus, named severe acute respiratory syndrome conseavirus 2 30.500,006 (SARS-GoV-2). We report the relevant features of the first cases in Europe of confirmed infection, named communitus disease 2019 (COVID-19), with the first patient diagnosed with the disease on Jan 24, 2020.

Methods In this case series, we followed five patients admitted to Bichat-Claude Bernard University Hospital (Paris, France) and Pellegrin University Hospital (Bordeaux, France) and diagnosed with COVID-19 by semi-quantitative Indeposed A recent cluster of porumento cases in Walon, China, was ca RT-PCR on nanopharyngeal swabs. We assessed patterns of clinical disease and vital load from different samples. 2019 novel coronavirus (2019 oCeV). We report the epidemiological, clinical, bit juasophasyngeal and blood, urine, and stool samples), which were obtained once daily for I days from hospital admission, and once every 2 or 3 days until gatient discharge. All samples were refrigerated and shipped to laboratories in the National Reference Center for Respiratory Viruses (The Institut Pasteur, Paris, and Hospices Civils de Lyon, Lyon,

emutional Severe Acute Respiratory and Emerging Infection Consortio Findings The patients were three men (aged 31 years, 48 years, and 80 years) and two women (aged 30 years and Researchers also directle communicated with patients or their families to su 46 years), all of Chinese origin, who had travelled to France from China around mid-January, 2020. There different clinical evolutions are described: (1) two passessymptomatic women diagnosed within a day of exhibiting symptoms. with high nasopharyngeal titres of SARS-CoV-2 within the first 24 h of the illness onset (5-2 and 7-4 log,, copies per findings by Jan 2, 2020, 41 admitted broughtd patients had been identified as h. 1000 cells, respectively) and viral RNA detection in stools; (2) a two-step disease progression in two young men. infection. Most of the infected patients were men (10 (77%) of 4% less than h. with a secondary worsening around 10 days after disease conset despite a decreasing viral load in masopharyngeal. Formus, so: nebeling dishere pight (1995), hopertonion più (1995), and codiovacule samples; and (5) an 80-year-old man with a rapid evolution towards multiple organ failure and a persistent high et 0 years (QQR ex 0-58-0), 27 paths of 41 patients had been exposed to bluer viral load in lower and upper respiratory tract with systemic virus dissemination and virus detection in plasma. The Inigae (31 (44%); Ion common symptoms were spottern production (5 (50) 80-year-old patient died on day 14 of illness (Feb 14, 2020); all other patients had recovered and been discharged by

pretation We illustrated three different clinical and biological types of evolution in five patients infected with (11) [1955], RNAsmis (sh) [1956], scate cardiac injury (for [1255] and econdary SARS-GNV2 with detailed and comprehensive viral sampling strategy. We believe that these findings will contribute masses (not in the comprehensive viral sampling strategy. to a better understanding of the natural history of the disease and will contribute to advances in the implementation. ## (### ## Online) of more efficient infection control strategies.

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sion of coronavirus 2019 (Covid-19) was detected in the state Community transof Washington in February 2020.

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Covid-19 in Critically Ill Patients

in the Seattle Region - Case Series

Pavan K. Bhatraju, M.D., Bijan J. Ghassemieh, M.D., Michelle Nichols, M.D.

Richard Kim, M.D., Keith R. Jerome, M.D., Arun K. Nalla, Ph.D., Alexander L. Greninger, M.D., Sudhakar Pipavath, M.D., Mark M. Wurfel, M.D., Ph.D., Laura Evans, M.D., Patricia A. Kritek, M.D., T. Eoin West, M.D., M.P.H.,

Andrew Luke, M.D., Arthory Gerbino, M.D., Chris R. Dale, M.D., Jason D. Goldman, M.D., Shane O'Mahony, M.D.,

and Carmen Mikacenic, M.D.

ABSTRACT

intensive care unit (ICU) with confirmed infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Clinical data were obtained through review of medical records. The data reported here are those available through March 23,



Here, we characterize the first 393 consecutive this letter at NEIM.orgi. two hospitals in New York City.

18 years of age or older with confirmed Covid-19 symptoms were cough (79.4%), fever (77.1%),

TO THE EDITOR: The world is in the midst of the col and structured abstraction tool (details are coronavirus disease 2019 (Covid-19) pandemic,12 provided in the Methods section in the Suppleand New York City has emerged as an epicenter. mentary Appendix, available with the full text of

patients with Covid-19 who were admitted to Among the 393 patients, the median age was 62.2 years, 60.6% were male, and 35.8% had This retrospective case series includes adults obesity (Table 1). The most common presenting

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLI

Clinical Characteristics of Coronavirus Disease 2019 in China

W. Guan, Z. Ni, Yu Hu, W. B. Du, L. Li, G. Zeng, K. S. Li, Jin-lin Wang, 2 Jian-ming Wang, J. Liu, and N. Zhong, for the

Clinical characteristics of COVID-19 in 104 people with SARS-CoV-2 infection on the Diamond Princess cruise ship: a retrospective analysis



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to the Findings As 54 (52%) we o died. (COVID-16 ng non! as being asy on ada but develop ras unics with partient this unline publication has been g. 2 to 73 years (IQ corrected. The corrected version

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Critical Care Medicine, Center of Respiratory Medicine, National of Respiratory Medicine. Sciences, Politing Union Mindical College, Beiling, China (F.Zhou MI), G.Fan MS, Z.Liu MD TWong MD, X Gu/PAD, H U/MD, Y Zhang MD, Prof B Car MDS Department of Tuberculosis and Resolvations Discourse (T.Yu-985) YORK MICH SCHOOL MICK YORK MIC

5040-5795-2030055-3

Laboratory () Korg RO), and Pulmonary Hospital, Wohan.

→ @ Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective

Q LO

Fei Zhou", Ting Yu", Ronghui Du", Guohui Fan", Ying Liu", Zhibo Liu", Jie Xiang", Yeming Wang, Bin Song, Xiaoying Gu, Lulu-Guan, Yuar Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao

tanut 2020, 355, 1058-62 Background Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus diseases Published Online (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiologi March 5, 2000 clinical characteristics of patients with COVID-19 have been reported but risk factors for mortality and a https://doi.org/10.1016/ clinical course of illness, including viral shedding, have not been well described.

Methods In this retrospective, multicentre cohort study, we included all adult inpatients (a18 years old) with lab confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) who ha finding size [270] - torappeared at the location discharged or had died by Jan 31, 2020. Demographic, clinical, treatment, and laboratory data, including mman 12,2000 samples for viral RNA detection, were extracted from electronic medical records and compared between st *Control sparty and non-survivors. We used univariable and multivariable logistic regression methods to explore the risk Inpartment of Polymorary and associated with in-hospital death.

> Findings 191 patients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) were included study, of whom 137 were discharged and 54 died in hospital. 91 (48%) patients had a comorbidity, with hyper being the most common (58 [30%] patients), followed by diabetes (36 [19%] patients) and coronary heart Otoma-Austony of Medical (15 [856] patients). Multivariable regression showed increasing odds of in-hospital death associated with ol (odds ratio 1-10, 95% Cl 1-03-1-17, per year increase; p=0-0043), higher Sequential Organ Failure Assessment score (5 · 65, 2 · 61-12 · 23; p · 0 · 0001), and d-dimer greater than 1 µg/ml. (18 · 42, 2 · 64-128 · 55; p · 0 · 0013) on adr Median duration of viral shedding was 20-0 days (IQR 17-0-24-0) in survivors, but SARS-CoV-2 was detectal death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days.

> Interpretation The potential risk factors of older age, high SOFA score, and d-dimer greater than 1 µg/m1. cor STATE PROFESSIONAL Clinicians to identify patients with poor prognosis at an early stage. Prolonged viral shedding provides the r. Department of Closest for a strategy of isolation of infected patients and optimal antiviral interventions in the future.

> Funding Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences; National Science G tourt of Polosoway and Distinguished Young Scholars; National Key Research and Development Program of China; The Beijing Scie Critical Care Medicine, Wolfare Technology Project; and Major Projects of National Science and Technology on New Drug Creation and Develo

We identified patients from nine Seattle-area hospitals who were admitted to the

CORRESPONDENCE

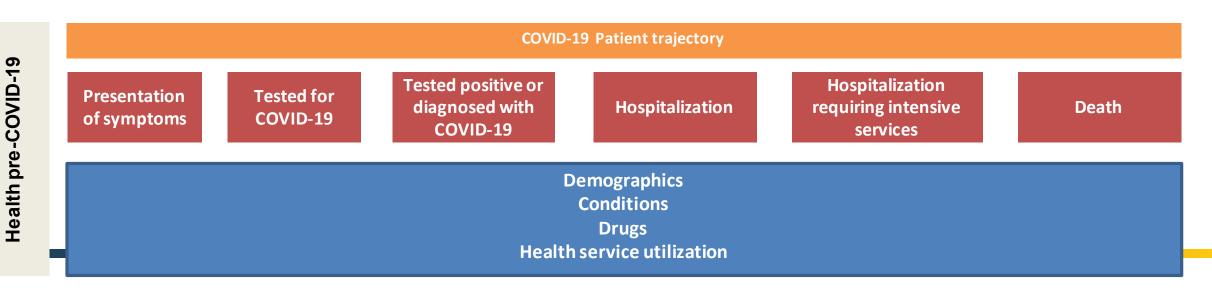
Clinical Characteristics of Covid-19 in New York City

interpretation The 20th of all infection caused clusters of severe respiratory illness sensual to severe acute responsery ronavirus and was associated with ICU admission and high mortality. Major gaps in our knowledge of the origin, epidemiology, duration of human transmission, and clinical spectrum of disease need fulfillment by future



Why CHARYBDIS?

- But many unanswered questions:
 - Who gets tested, infected and hospitalized?
 - Age and gender
 - Most frequent comorbidities
 - Treatment history
 - What are their symptoms and outcomes?
 - How different is COVID-19 from influenza?





OHDSI: a global pandemic requires a global response

OHDSI's Mission: To improve health by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care

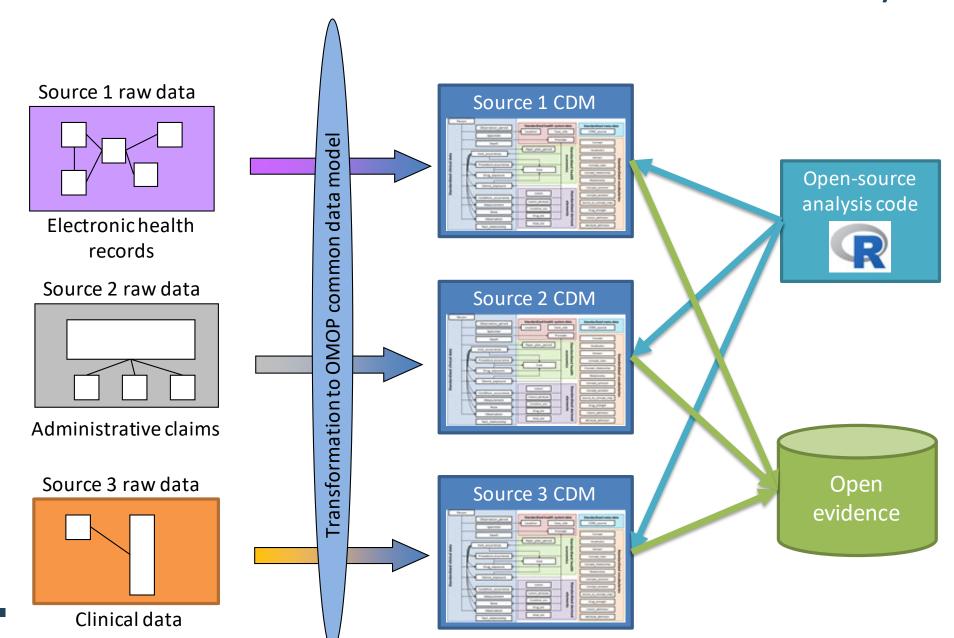


Stakeholders: academia, medical product industry, regulators, government, payers, technology providers, health systems, clinicians, patients **Disciplines:** computer science, epidemiology, statistics, biomedical informatics, health policy, clinical sciences

records



Common data model to enable standardized analytics





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Characterizing Health Associated Risks, and Your Baseline Disease In SARS-COV-2 (CHARYBDIS)

1) Describe the baseline demographic, clinical characteristics, treatments, symptoms and outcomes of interest among individuals with COVID-19 overall and stratified by sex, age and specific comorbidities

2) Describe characteristics and outcomes of influenza patients between September 2017 and April 2018 compared to the COVID-19 population

FULL STUDY PROTOCOL AVAILABLE AT https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis



CHARYBDIS – Target cohorts

Persons **tested** for SARS-CoV-2

Persons **tested positive** for SARS-CoV-2

Persons with a **COVID-19 diagnosis** or a SARS-CoV-2 **positive test**

Persons **hospitalized** with a COVID-19 diagnosis record or a SARS-CoV-2 positive test

Persons hospitalized and requiring **intensive services** with a COVID-19 diagnosis record or a SARS-CoV-2 positive test

Persons with **Influenza** diagnosis or positive test 2017-2018

Persons hospitalized with influenza diagnosis or positive test 2017-2018
Persons hospitalized with influenza diagnosis or positive test and requiring intensive services 2017-2018

COHORT DEFINITIONS AVAILABLE AT:

https://atlas.ohdsi.org/



CHARYBDIS – Stratification factors

COVID-19 and...

- Asthma
- Cancer
- Cardiac Outcomes
- Chronic Kidney Disease
- COPD
- Elderly
- End-Stage Renal Disease

- Gender Differences
- Heart Disease
- Hepatitis C
- HIV infection
- Hypertension
- Immune Disorders
- Obesity

- Pediatrics
- Pregnant Women
- Tuberculosis
- Type 2 Diabetes
- Dementia
- Gender

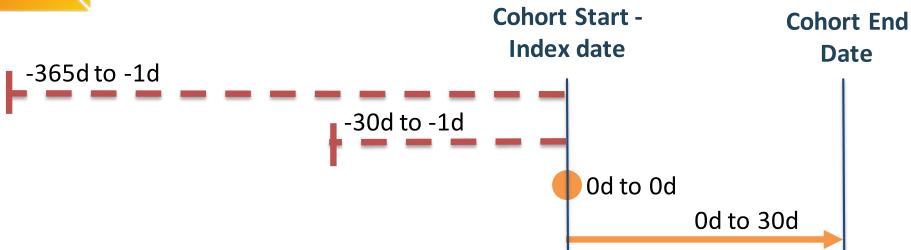
... And more!



PHENOTYPE DEFINITIONS AVAILABLE AT: https://atlas.ohdsi.org/



CHARYBDIS – Characterization framework



Pre-index characteristics:

- Sex
- Age group (5-year strata)
- Condition groups (SNOMED + descendants)
- Drug groups (ATC/RxNorm + descendants)

Index and post-index characteristics:

- Condition groups (SNOMED + descendants)
- Drug start groups (ATC/RxNorm + descendants)
- Symptoms
- Outcomes
- Procedural treatments

R package to run available at:

https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis



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Snapshot of the CHARYBDIS Data Network

Canada North Atlantic	Unit Kingu Oland Goly Ukraine Sprin Italy Turkey	Kazakhstan Mongolia China South Korea
USA (13)	EUROPE (9, 6 countries)	ASIA-PACIFIC (3, 2 countries)
Columbia University (NY – EHR)	CPRD (UK – EHR)	HIRA (South Korea – Administrative Claims)
Department of Veterans Affairs (National – EHR)	IQVIA DA Germany (Germany – EHR)	DCMC (South Korea – EHR)
HealthVerity (Claims linked to diagnostic testing)	HM Hospitales (Spain – Hospital Billing)	Nanfang Hospital (China – EMR)
IQVIA Open Claims (National – Administrative Claims)	Hospital del Mar (Spain – EHR)	
IQVIA Hospital Charge Data (Hospital Billing)	IPCI (Netherlands – EHR)	
Optum EHR (National – EHR)	IQVIA LPD France (France – EHR)	
Optum SES (National – EHR linked to Socio-economic data)	IQVIA LPD Italy (Italy – EHR)	
Oregon Health 2 Sciences University (EHR)	SIDIAP (Spain – EHR)	
Premier (National – Hospital Billing)	SIDIAP-H (Spain – EHR Hospital linkage)	
Stanford University (CA – EHR)		
Tufts University (MA – EHR)		
University of Colorado Anschutz Medical Campus (CO – EHR)		
University of Washington Medicine COVID Research Dataset (WA – EHR)		



Snapshot of the CHARYBDIS Data Network

Canada O O O O O O O O O O O O O O O O O O O	Unit Colored C	Kazakhstan Mongolia China South Korea ASIA-PACIFIC (3, 2 countries)
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IQVIA Hospital Charge Data (Hospital Billing)	IPCI (Netherlands – EHR)	T. II. CURCUL II. II. I
Optum EHR (National – EHR)	IQVIA LPD France (France – EHR)	Together, OHDSI has studied:
Optum SES (National – EHR linked to Socio-economic data)	IQVIA LPD Italy (Italy – EHR)	• >17.2m persons tested for SAR-COV-2
Oregon Health 2 Sciences University (EHR)	SIDIAP (Spain – EHR)	>4.5m persons diagnosed or tested positive for COVID-19 >890k persons hospitalized with COVID-
Premier (National – Hospital Billing)	SIDIAP-H (Spain – EHR Hospital linkage)	
Stanford University (CA – EHR)		
Tufts University (MA – EHR)		19
University of Colorado Anschutz Medical Campus (CO – EHR)		

University of Washington Medicine COVID Research Dataset (WA – EHR)



CHARYBDIS – Outputs

- >2,000 papers reviewed literature review team
- 107 definitions of COVID-19 and conditions phenotypes team
 - https://atlas.ohdsi.org/#/cohortdefinitions
- >100,000 variables x cohort x strata x database:
 - https://data.ohdsi.org/Covid19CharacterizationCharybdis/
- 16 scientific manuscripts
 - 7 papers published
 - 5 pre-prints to be published
 - 4 papers in preparation or recently submitted

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





CHARYBDIS – Example of findings









Comments (I)

Deep phenotyping of 34,128 patients hospitalised with COVID-19 and a comparison with 81,596 influenza patients in America, Europe and Asia: an international network study

© Edward Burn, Seng Chan You, Anthony G. Sena, Kristin Kostka, Hamed Abedtash, Maria Tereza F. Abrahão, Amanda Alberga, Heba Alghoul, Osaid Alser, Thamir M Alshammari, Maria Aragon, Carlos Areia, Juan M. Banda, Jaehyeong Cho, Aedin C Culhane, Alexander Davydov, Frank J DeFalco, Talita Duarte-Salles, Scott DuVall, Thomas Falconer, Sergio Fernandez-Bertolin, Weihua Gao, Asieh Golozar, Jill Hardin, George Hripcsak, Vojtech Huser, Hokyun Jeon, Yonghua Jing, Chi Young Jung, Benjamin Skov Kaas-Hansen, Denys Kaduk, Seamus Kent, Yeesuk Kim, Spyros Kolovos, Jennifer C.E. Lane, Hyejin Lee, Kristine E Lynch, Rupa Makadia, Michael E. Matheny, Paras P. Mehta, Daniel R Morales, Karthik Natarajan, Fredrik Nyberg, Anna Ostropolets, Rae Woong Park, Jimyung Park, Jose D. Posada, Albert Prats-Uribe, Gowtham Rao, Christian Reich, Yeunsook Rho, Peter Rijnbeek, Lisa M. Schilling, Martijn Schuemie, Nigam H. Shah, Azza Shoaibi, Seokyoung Song, Matthew Spotnitz, Marc A. Suchard, Joel N. Swerdel, David Vizcaya, Salvatore Volpe, Haini Wen, Andrew E. Williams, Belay B. Yimer, Lin Zhang, Oleg Zhuk, Daniel Prieto-Alhambra, Patrick Ryan doi: https://doi.org/10.1101/2020.04.22.20074336

Posted on June 28, 2020

Article | Open Access | Published: 06 October 2020

Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study

Edward Burn, Seng Chan You, [...]Patrick Ryan

Nature Communications 11, Article number: 5009 (2020) | Cite this article

17k Accesses | 16 Citations | 456 Altmetric | Metrics

- COVID-19 is no flu
 - o Healthier
 - Younger
 - Less history of medicines
 - Worse outcomes





CHARYBDIS – Example of findings









THE PREPRINT SERVER FOR HEALTH SCIENCES

Comment on this paper

Heterogeneity and temporal variation in the management of COVID-19: a multinational drug utilization study including 71,921 hospitalized patients from China, South Korea, Spain, and the United States of America

Osaid Alser, Trats-Uribe, Anthony G. Sena, Lana Yin Hui Lai, Waheed-Ul-Rahman Ahmed, Heba Alghoul, Osaid Alser, Thamir M Alshammari, Carlos Areia, William Carter, Paula Casajust, Dalia Dawoud, Asieh Golozar, Djitendra Jonnagaddala, Paras P. Mehta, Mengchun Gong, Daniel R. Morales, Fredrik Nyberg, Jose D. Posada, Martina Recalde, Elena Roel, Karishma Shah, Nigam H. Shah, Lisa M. Schilling, Vignesh Subbian, David Vizcaya, Andrew Williams, Lin Zhang, Ying Zhang, Hong Zhu, Li Liu, Peter Rijnbeek, George Hripcsak, Jennifer CE Lane, Edward Burn, Christian Reich, Marc A. Suchard, Talita Duarte-Salles, Kristin Kostka, Patrick Ryan, Daniel Prieto-Alhambra

doi: https://doi.org/10.1101/2020.09.15.20195545

Posted on September 28, 2020

thebmj covid-1

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Research • Education •

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Campaign

Research

Use of repurposed and adjuvant drugs in hospital patients with covid-19: multinational network cohort study

BMJ 2021; 373 doi: https://doi.org/10.1136/bmj.n1038 (Published 11 May 2021)

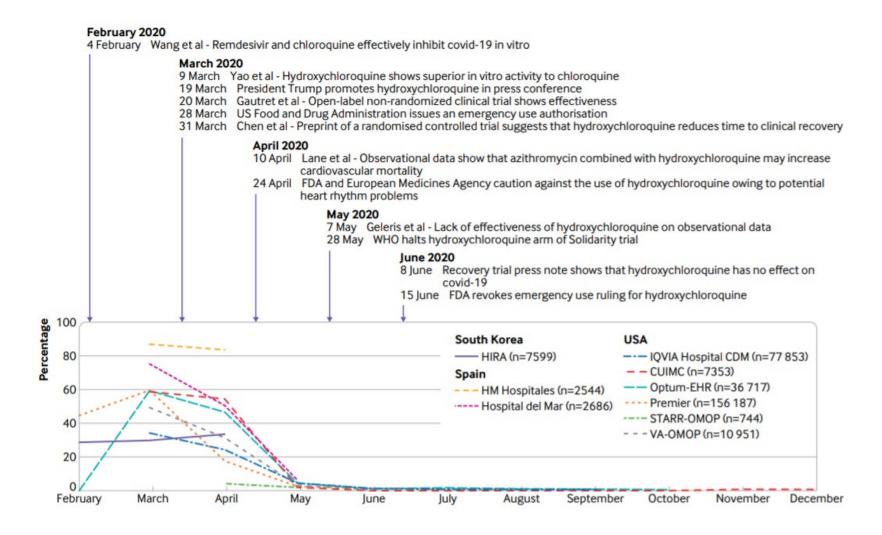
Cite this as: BMJ 2021;373:n1038

- Geographical and temporal variation
- Hydroxychloroquine, azithromycin, lopinavirritonavir, and umifenovir -> most prescribed repurposed drugs
- Antithrombotics, antibiotics, H2 receptor antagonists, and corticosteroids -> most used adjunctive treatments.



The rise and fall of drugs for COVID-19 treatment - hydroxychloroquine

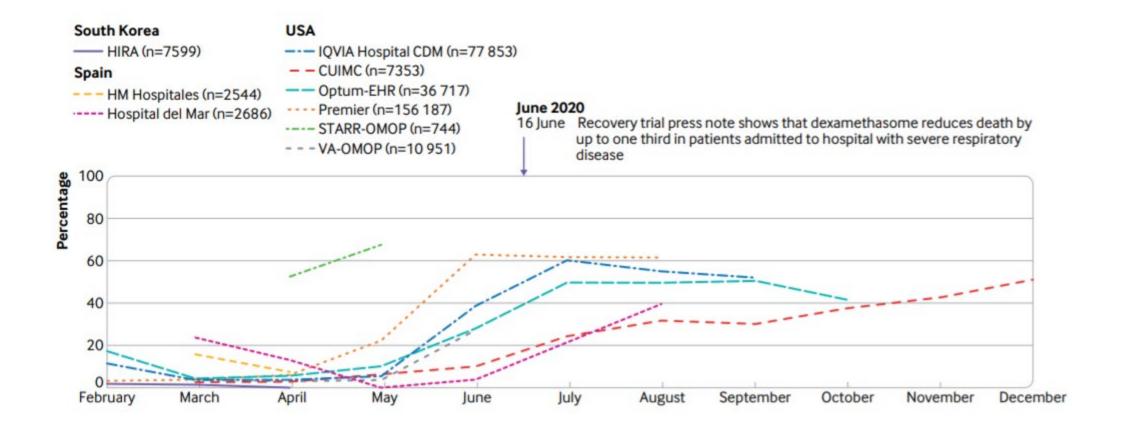






The rise and fall of drugs for COVID-19 treatment - dexamethasone







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CHARYBDIS – Final remarks and opportunities for regulatory purpose

- Need of a global community to face a global problem
 - We were able to create the biggest COVID-19 Data Network in the world, and
 - to provide reliable and timely evidence to inform the pandemic
- Importance of leadership and international collaboration in science
 - 11 study leads, 130 co-authors, 25 data partners, hundreds of calls
- Value of the use of a common data model in RWD to provide comprehensive, valid and reliable evidence
 - Large sample size
 - Speed and quality
 - Heterogeneity of settings and data



CHARYBDIS – Final remarks and opportunities for regulatory purpose

- Open collaboration requires full transparency
 - The project was approved by local ethics committees
 - Protocol and analysis code: https://github.com/ohdsi-studies/Covid19CharacterizationCharybdis
 - Phenotype definitions: https://atlas.ohdsi.org/
 - Results (interactive R shiny application):
 http://data.ohdsi.org/Covid19CharacterizationCHARYBDIS/
 - Manuscripts published as pre-prints while awaiting peer-review
 - Generation of <u>reliable</u> and <u>reproducible</u> evidence



OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

OHDS COVID-19 Study-A-Thon ohdsi.org/covid-19-updates























































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