



Jose R Arribas

Infectious Diseases Unit
La Paz University Hospital

 @jrribas

IX JORNADAS DE ASPECTOS ÉTICOS DE LA INVESTIGACIÓN BIOMÉDICA

Nuevas reflexiones sobre la investigación relacionada con la salud en seres humanos

22/23
NOVIEMBRE
2022
MADRID



¿Lo hicimos todo bien con la COVID-19?

Luces y sombras de la investigación



DISCLOSURES

- Gilead
- Merck
- GSK
- Lilly
- Roche
- Pfizer
- Sobi

SOMBRAS

Unidad de Aislamiento del Carlos III acogerá posibles portadores del coronavirus que presenten "criterios de gravedad"





15



El Objetivo 
@ObjetivoLaSexta



José R. Arribas, especialista en enfermedades infecciosas del [@HospitalULaPaz](#): “El foco está en los países asiáticos. Si uno tiene síntomas de gripe en España, probablemente lo que tenga es gripe”

[#ObjetivoCoronavirus](#)



11:07 p. m. 16 feb. 2020 Twitter Web App

Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)

16-24 February 2020

The Global Response & Next Steps

- 1. The COVID-19 virus is a new pathogen that is highly contagious, can spread quickly, and must be considered capable of causing enormous health, economic and societal impacts in any setting. It is not SARS and it is not influenza. Building scenarios and strategies only on the basis of well-known pathogens risks failing to exploit all possible measures to slow transmission of the COVID-19 virus, reduce disease and save lives.**



Jose R Arribas

@jrribas



En los hospitales con COVID-19
Nos estamos quedando sin equipos de protección
Nos podemos quedar sin camas de UVI
La respuesta frente a COVID-19 debe ser prioridad
nacional
Por favor RT

7:53 a. m. **10 mar. 2020** · Twitter for iPhone

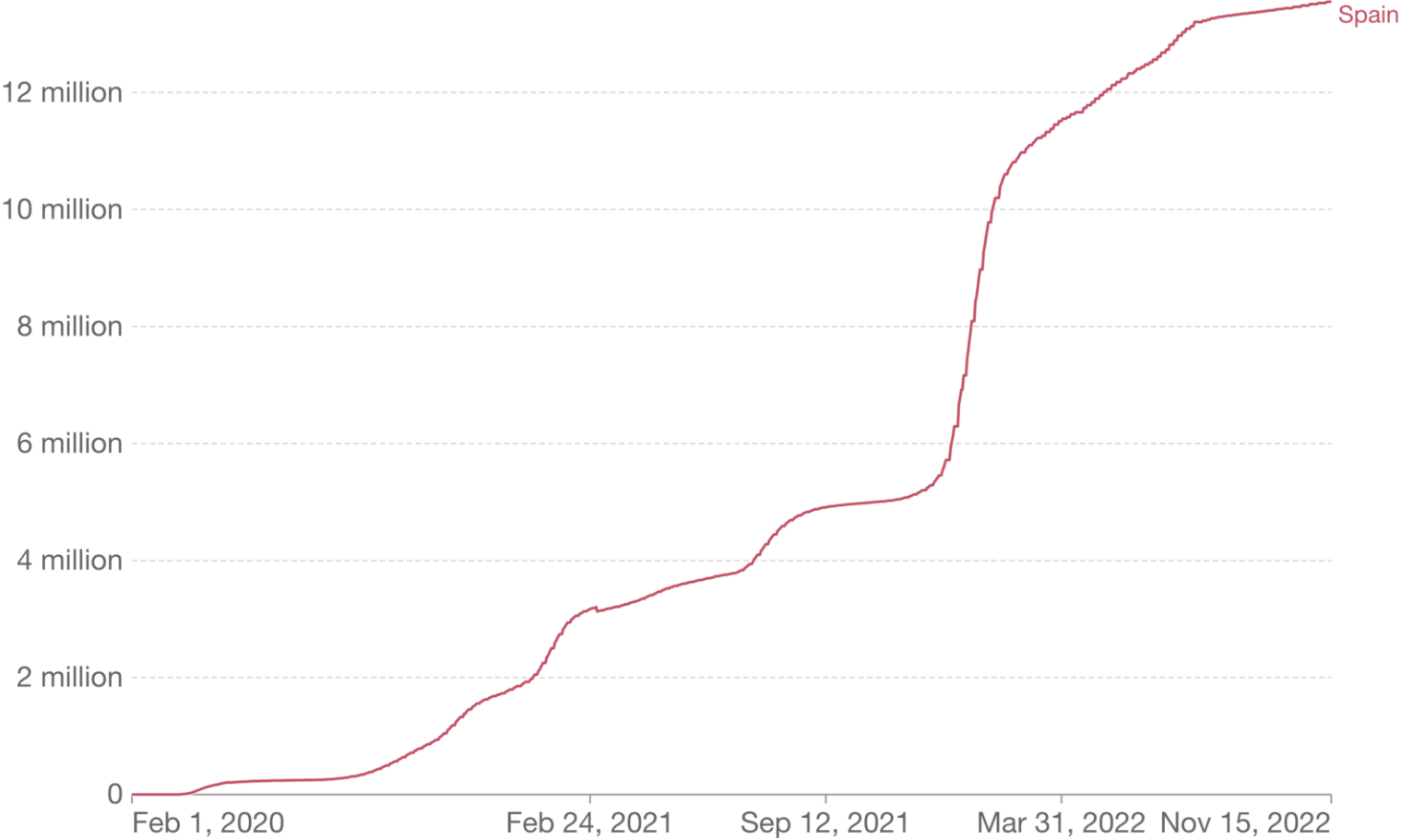
 Ver estadísticas del Tweet

11,2 mil Retweets **204** Tweets citados **7.997** Me gusta

Cumulative confirmed COVID-19 cases



Due to limited testing, the number of confirmed cases is lower than the true number of infections.



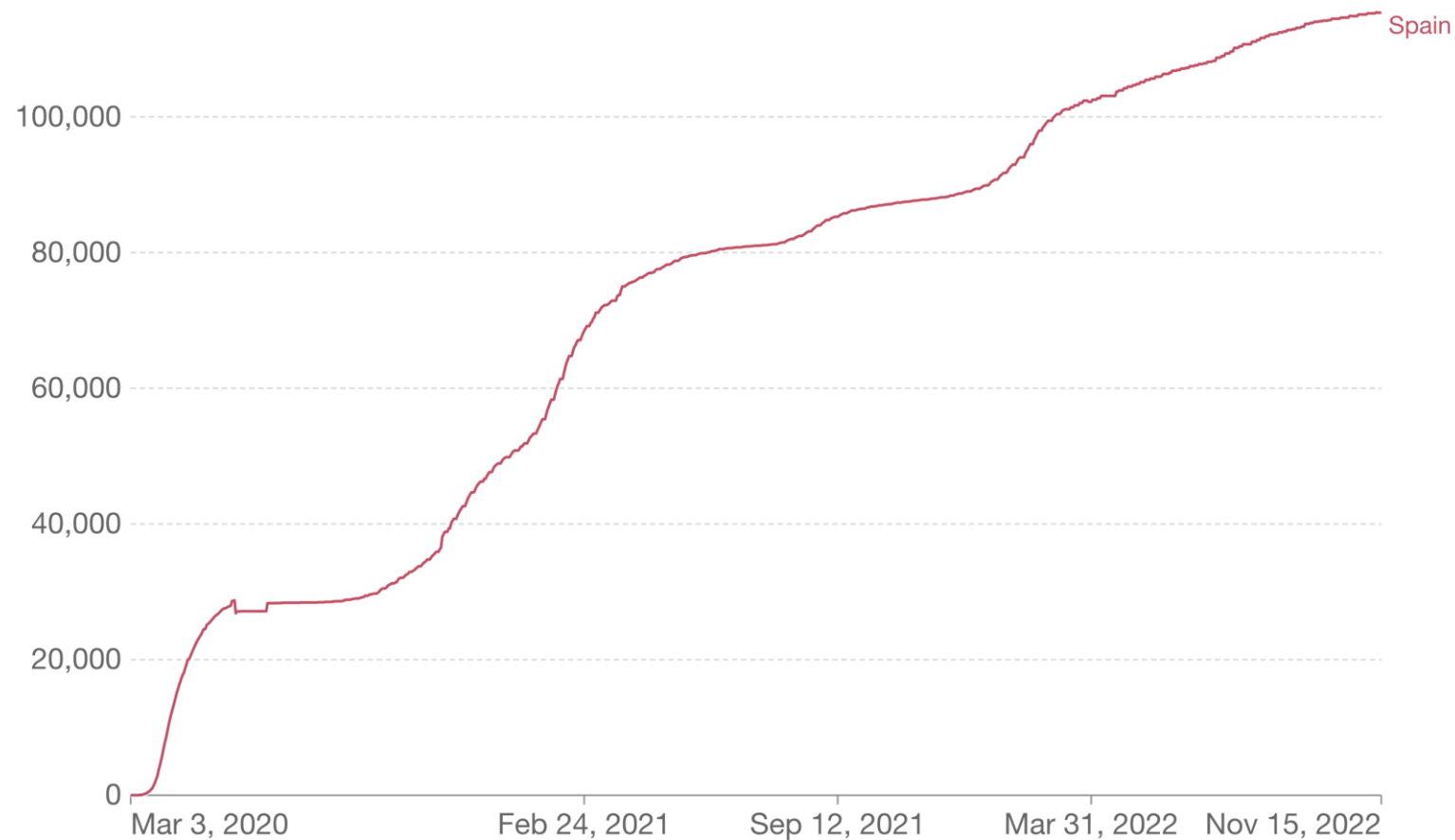
Source: Johns Hopkins University CSSE COVID-19 Data

CC BY

Cumulative confirmed COVID-19 deaths



Due to varying protocols and challenges in the attribution of the cause of death, the number of confirmed deaths may not accurately represent the true number of deaths caused by COVID-19.



Source: Johns Hopkins University CSSE COVID-19 Data

CC BY

4/Marzo/2020

JORNADA VIRTUAL
DE ACTUALIZACIÓN EN
SARS - CoV-2 Y COVID-19

Jose Ramón Arribas

*Hospital La Paz
Madrid*

 @jrarribas



4/Marzo/2020

**No hay ningún tratamiento
directo con eficacia
demostrada**

Potential repurposing candidates for 2019-nCoV

4/Marzo/2020

- Favipiravir
- Ribavirin
- Galidesivir
- Favipiravir plus interferon- α (ChiCTR2000029600)
- Favipiravir plus baloxavir marboxil (an approved influenza inhibitor targeting the cap-dependent endonuclease) (ChiCTR2000029544).
- Chloroquine and is being evaluated in an open-label trial (ChiCTR2000029609)
- Convalescent plasma

Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury



	Outcomes of corticosteroid therapy*	Comment
MERS-CoV	Delayed clearance of viral RNA from respiratory tract ²	Adjusted hazard ratio 0.4 (95% CI 0.2–0.7)
SARS-CoV	Delayed clearance of viral RNA from blood ⁵	Significant difference but effect size not quantified
SARS-CoV	Complication: psychosis ⁵	Associated with higher cumulative dose, 10 975 mg vs 6780 mg hydrocortisone equivalent
SARS-CoV	Complication: diabetes ⁷	33 (35%) of 95 patients treated with corticosteroid developed corticosteroid-induced diabetes
SARS-CoV	Complication: avascular necrosis in survivors ⁸	Among 40 patients who survived after corticosteroid treatment, 12 (30%) had avascular necrosis and 30 (75%) had osteoporosis
Influenza	Increased mortality ⁹	Risk ratio for mortality 1.75 (95% CI 1.3–2.4) in a meta-analysis of 6548 patients from ten studies
RSV	No clinical benefit in children ^{10,11}	No effect in largest randomised controlled trial of 600 children, of whom 305 (51%) had been treated with corticosteroids

CoV=coronavirus. MERS=Middle East respiratory syndrome. RSV=respiratory syncytial virus. SARS=severe acute respiratory syndrome. *Hydrocortisone, methylprednisolone, dexamethasone, and prednisolone.

Table: Summary of clinical evidence to date



Jose R Arribas

Infectious Diseases Unit
La Paz University Hospital

 @jrribas



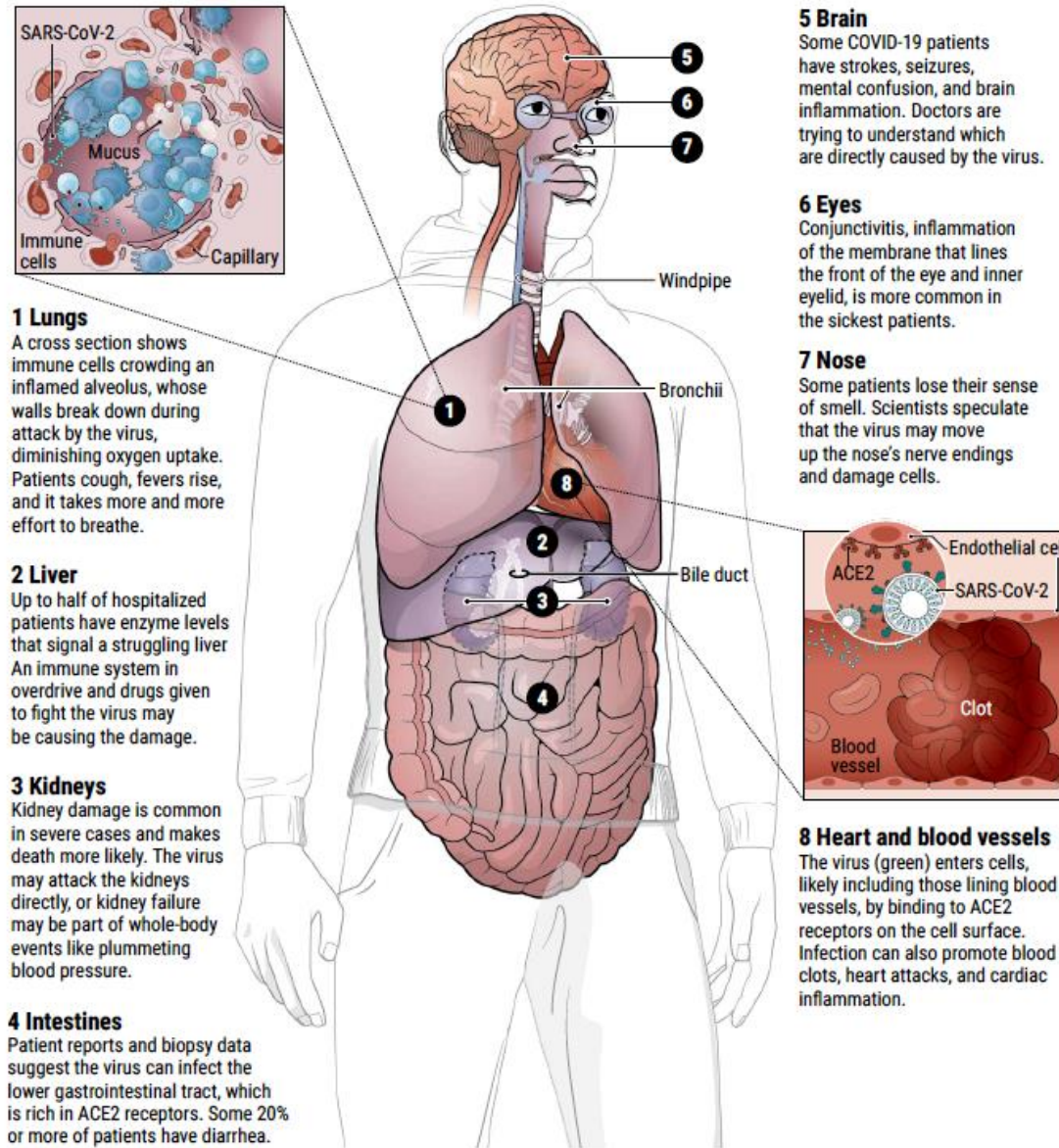
¿Lo hicimos todo bien con la COVID-19?

Luces y sombras de la investigación

Casi 3 años después

Fármacos





V. ALTOUNIAN/SCIENCE

COVID-19 TREATMENT

O₂, VNI, VM

**NEUMÓLOGOS
INTENSIVISTAS**

**ANTIVIRALS
MONOCLONAL ANTIBODIES**

**INFECTOLOGOS
INTERNISTAS
TROPICALISTAS**

ANTICOAGULATION

**INTERNISTAS
HEMATOLOGOS
CARDIOLOGOS**

IMMUNOMODULATION

**INTERNISTAS
REUMATOLOGOS
INMUNOLOGOS**

IMMUNOSUPPRESSED

LONG COVID

DECISIONES TERAPEUTICAS CUANDO NO HAY TRATAMIENTOS EFICACES

TRATAR

- “Si no hago algo se va a morir”
- “X funciona in vitro”
- “Tiene sentido utilizarlo”
- “En el hospital X lo están usando”
- “Hay datos en animales”
- “A mi me ha ido bien”
- “Lo ha dicho un experto”
- “No es ético que le pueda tocar placebo”
- “No podemos esperar a los resultados de los ensayos”
- “No tengo ningún ensayo clínico disponible”

NO TRATAR

- Si no hacemos un EECC nunca sabremos si X es eficaz
- X puede ser tóxico e ineficaz
- El voluntario al menos tiene un X% de que le toque tratamiento activo
- Es ahora cuando es más importante hacer el EECC



The Covid Drug Wars That Pitted Doctor vs. Doctor

How much freedom should front-line clinicians have in treating Covid-19 patients with unproven drugs? The question opened up a civil war in some hospitals.

VIEWPOINT

Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics

- A common interpretation of off-label use and compassionate use of drugs is that if the patient died, they died from the disease, but if the patient survived, they survived because of the given drug. This is not true.
- If the disease is not 100% lethal and it is not known whether the experimental drug would help or harm a patient (ie, a situation with true equipoise), then it is ethical to conduct an RCT. Without a control group, it is not possible to accurately determine the harms of any experimental drug

PROTOCOLOS, PROTOCOLOS, PROTOCOLOS



PROTOCOLO GLOBAL DE TRATAMIENTO COVID19

HULP ADULTOS

COD: COVID

EDICION 16

Fecha: 11/08/2020



**BRIGHAM AND
WOMEN'S HOSPITAL**

**Brigham and Women's Hospital
COVID-19 Critical Care Clinical Guidelines**

Updated: 3/23/2020



Trial search



Nation,
Province(City)



Code of
disease



Primary
sponsor(s)



Secondary
sponsor(s)



Funding
source



Recruiting
status



Register
status



Measure



Ethical
committee



Study type

Trial search

Filter Options

Public title	<input type="text" value="COVID"/>	Scientific title	<input type="text"/>	Subject ID	<input type="text"/>
Registration Status	<input type="text" value="All"/>	Registration number	<input type="text"/>	Secondary ID	<input type="text"/>
<input type="button" value="Search"/>		More Options			

311 trials have been registered

Historical versions	Registration number	Public title	Type	Registration time
Historical Versions	ChiCTR2000030471	Efficacy and safety of lipoic acid injection in reducing the risk of progression in common patients with novel coronavirus pneumonia (COVID-19) Maoming People's Hospital	Interventional	2020/03/02

[Home](#) > Search Results

[Modify Search](#)

[Start Over](#)

8617 Studies found for: **COVID**

Also searched for **SARS-CoV-2**. [See Search Details](#)



m agencia española de
medicamentos y
productos sanitarios



Buscar



PARA LA BÚSQUEDA 'COVID' SE HAN ENCONTRADO **220** RESULTADOS



Contents lists available at [ScienceDirect](#)

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag



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



20 patientes
16 controles

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

P Gautret, [JC Lagier](#), P Parola, L Meddeb... - International journal of ..., 2020 - Elsevier

Background Chloroquine and hydroxychloroquine have been found to be efficient on SARS-CoV-2, and reported to be efficient in Chinese COV-19 patients. We evaluate the effect of hydroxychloroquine on respiratory viral loads. Patients and methods French Confirmed COVID-19 patients were included in a single arm protocol from early March to March 16 th, to receive 600mg of hydroxychloroquine daily and their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithromycin ...

[☆] Save Cite **Cited by 5902** [Related articles](#) [All 25 versions](#)



Donald J. Trump ✓

@realDonaldTrump



HYDROXYCHLOROQUINE & AZITHROMYCIN, taken together, have a real chance to be one of the biggest game changers in the history of medicine. The FDA has moved mountains - Thank You! Hopefully they will BOTH (H works better with A, International Journal of Antimicrobial Agents).....

10:13 AM · Mar 21, 2020 · [Twitter for iPhone](#)



Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag



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



20 pacientes
16 controles

Annals of Internal Medicine

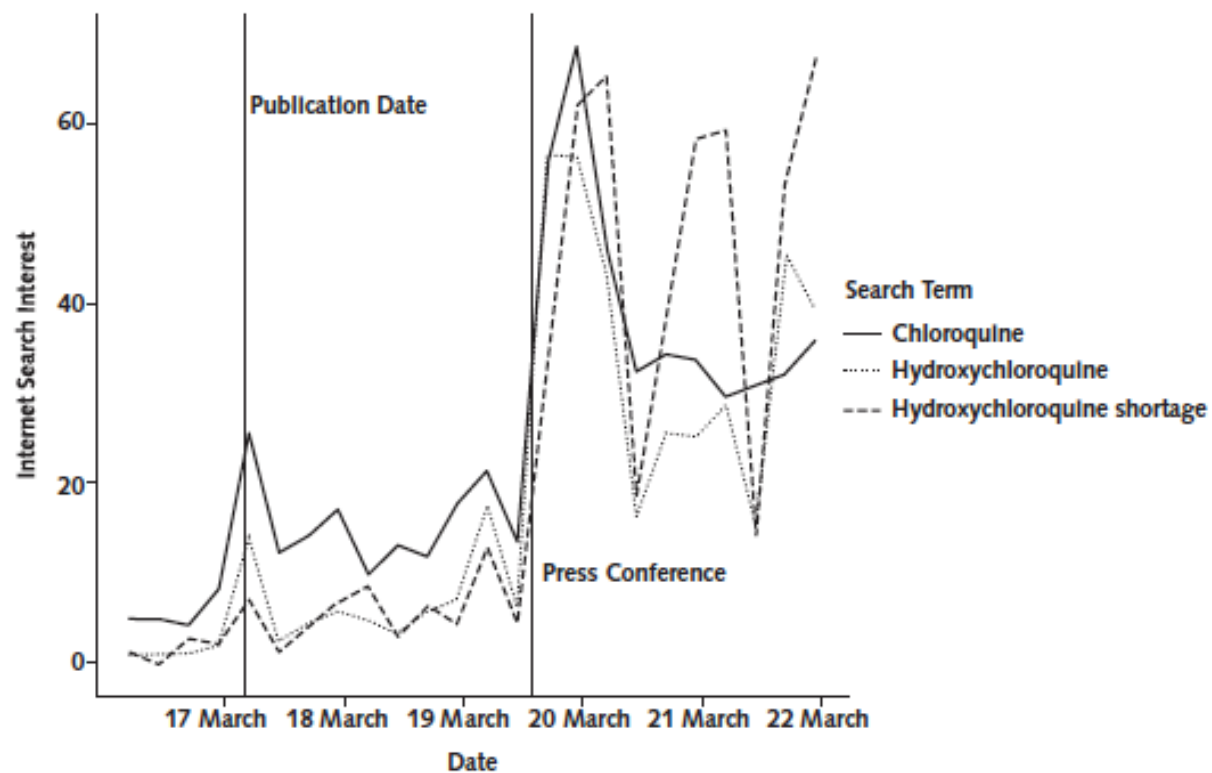
IDEAS AND OPINIONS

A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19

Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020;56(1):105949.

Kim AHJ, Sparks JA, Liew JW, et al. A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19. *Annals of internal medicine* [Internet] 2020; Available from: <https://annals.org/aim/fullarticle/2764065/rush-judgment-rapid-reporting-dissemination-results-its-consequences-regarding-use>

Figure. Global Google Trends search patterns for “hydroxychloroquine,” “chloroquine,” and “hydroxychloroquine shortage,” 16 to 22 March 2020.



The spike on 17 March corresponded with the publication of Gautret and colleagues' report (4). The second spike on 20 March followed the U.S. presidential press conference in which hydroxychloroquine was described as a treatment of coronavirus disease 2019.

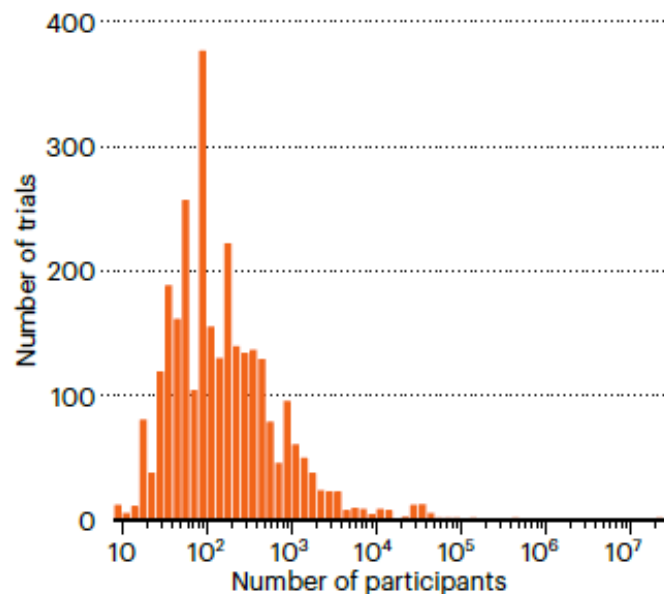


Some US protesters against COVID-19 restrictions promoted drugs not backed by evidence.

HOW COVID BROKE THE EVIDENCE PIPELINE

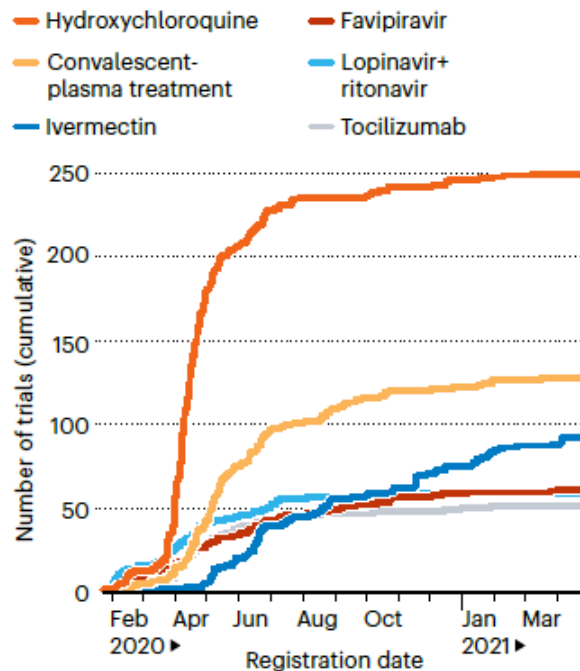
SMALL SAMPLES

In one database of COVID-19 trials, 40% stated that they were enrolling fewer than 100 patients — a sample size that is generally too small to be useful.

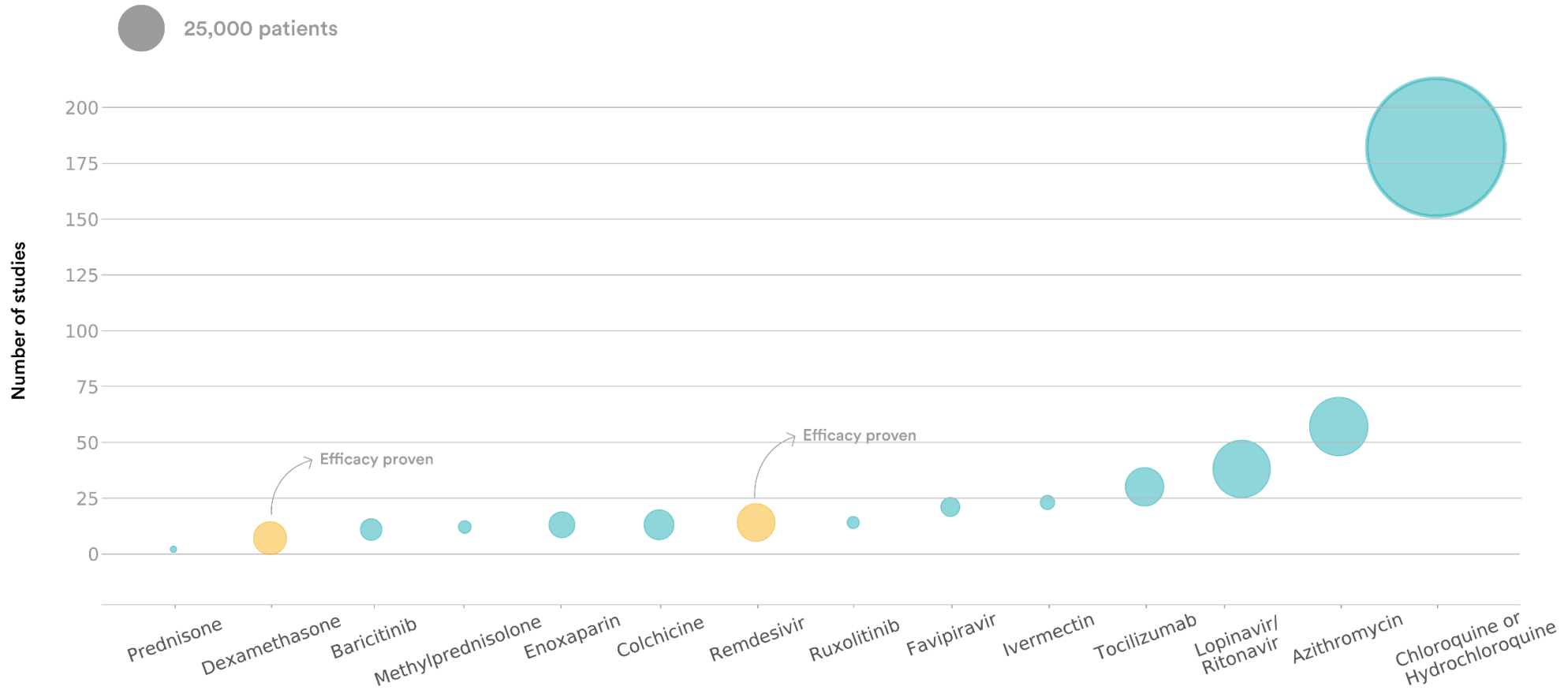


TOO MANY TRIALS?

Studies assessing drugs against COVID-19 included 250 trials of hydroxychloroquine — a duplication that researchers say represents wasted effort.



Top Drugs Based on Enrollment Count and Study Numbers





EDITORIALS

Waste in covid-19 research

A deluge of poor quality research is sabotaging an effective evidence based response

Of the 145 registered trials of hydroxychloroquine, for example, 32 have a planned sample size of ≤ 100 , 10 have no control group, and 12 are comparative but non-randomised



correspondence

COVID-19 clinical trials: learning from exceptions in the research chaos

Of the >2,000 planned drug studies examining COVID-19 treatments (<https://www.covid-trials.org>), most have delivered little or no directly useful information¹.

1. Tikkinen KAO, Malekzadeh R, Schlegel M, Rutanen J, Glasziou P. COVID-19 clinical trials: learning from exceptions in the research chaos. Nat Med [Internet] 2020 [cited 2022 Nov 10];26(11):1671–2. Available from: <https://www.nature.com/articles/s41591-020-1077-z>

HOW COVID BROKE THE EVIDENCE PIPELINE

ments prove to be ineffective – or even harmful – in trials. “The COVID-19 pandemic has arguably been one of the greatest challenges to evidence-based medicine since the term was coined in the last century,” Carley and his colleagues wrote of the problems they were seeing¹.

MOTIVACIONES PARA HACER UN ENSAYO CLÍNICO DURANTE UNA PANDEMIA

INDIVIDUALES

- ACADÉMICAS: Quiero ser autor, si es posible primero o ultimo
- DE PRESTIGIO: Que me vean mis colegas
- ECONÓMICAS: Mayor en los ensayos de la industria
- MÉDICAS: Quiero ofrecer a mi paciente al menos la posibilidad de ser tratado con un fármaco *potencialmente* eficaz

COLECTIVAS

- Necesitamos saber, rápidamente, si un fármaco funciona

MOTIVACIONES PARA HACER UN ENSAYO CLÍNICO DURANTE UNA PANDEMIA

INDIVIDUALES

- ACADÉMICAS: Quiero ser autor, si es posible primero o ultimo
- DE PRESTIGIO: Que me vean mis colegas
- ECONÓMICAS: Mayor en los ensayos de la industria
- MÉDICAS: Quiero ofrecer a mi paciente al menos la posibilidad de ser tratado con un fármaco *potencialmente* eficaz



MUCHOS EECC CON MUESTRAS PEQUEÑAS
NO ADAPTATIVOS

COLECTIVAS

- Necesitamos saber, rápidamente si un fármaco funciona



POCOS EECC CON MUESTRAS MUY GRANDES
ADPTATIVOS

PUBLISH OR PERISH

Vs.

DO THE RIGHT CLINICAL TRIAL OR PERISH

PREPRINTS, PREPRINTS, PREPRINTS



Cold
Spring
Harbor
Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

COVID-19 SARS-CoV-2 preprints from [medRxiv](#) and [bioRxiv](#)

bioRxiv posts many COVID-19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.



Cold
Spring
Harbor
Laboratory

BMJ Yale

[HOME](#) | [SUBMIT](#) | [FAQ](#) | [BLOG](#) | [ALERTS / RSS](#) | [ABOUT](#)

medRxiv

THE PREPRINT SERVER FOR HEALTH SCIENCES

[Advanced Search](#)

ARTICLES | ONLINE FIRST

RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Prof Mandeep R Mehra, MD   • Sapan S Desai, MD • Prof Frank Ruschitzka, MD • Amit N Patel, MDPublished: May 22, 2020 • DOI: [https://doi.org/10.1016/S0140-6736\(20\)31180-6](https://doi.org/10.1016/S0140-6736(20)31180-6) •  Check for updates

Summary

Introduction

Methods

Results

Discussion

Supplementary

Material

References

Article Info

Figures

Tables

Summary

Background

Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although generally safe when used for approved indications such as autoimmune disease or malaria, the safety and benefit of these treatment regimens are poorly evaluated in COVID-19.

Methods

We did a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in six continents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagnosis were included in one of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed the control group. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis or while they were on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outcomes of interest were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias (non-sustained or sustained ventricular tachycardia or

Press Release

News +++ Information +++ News +++ Information +++ News +++ Information +++ News +++ Information

Vestibulum ante ipsum primis in faucibus metus

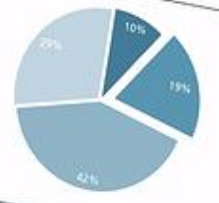
Nullam quis ante. Etiam sit amet orci eget eros faucibus tincidunt. Duis leo. Sed fringilla mauris sit amet nibh. Donec sodales sagittis magna. Sed consequat, leo eget bibendum magna mi a libero. Fusce vulputate eleifend nunc. Vestibulum purus quam, scelerisque ut, mollis sed, nonummy id, metus. Nullam accumsan lorem in dui. Cras ultricies mi eu turpis hendrerit fringilla. Vestibulum ante ipsum primis in faucibus orci luctus et ultrices posuere cubilia Curae; In ac dui quis mi consectetia. Nam pretium turpis et arcu.

Curabitur arcu tortor, suscipit eget, imperdiet nec, suspendet lacus, ipsum. Sed aliquam ultrices mauris. Integer ante arcu, accumsan a, consectetur eget, posuere ut, mauris. Praesent adipiscing. Phasellus ullamcorper ipsum rutrum nunc. Nunc nonummy metus. Vestibulum volutpat pretium libero. Cras id dui. Aenean ut eros et nisl sagittis vestibulum. Nullam nulla eros, ultrices sit amet, nonummy id, imperdiet

leo dolor, tempus non, auctor et, hendrerit quis, nisi. Curabitur ligula sapien, tincidunt non, euismod vitae, posuere imperdiet, leo massa. Sed cursus turpis vitae tortor. Donec posuere vulputate arcu. Phasellus accumsan faucibus orci luctus et ultrices posuere cubilia Curae; Sed aliquam, nisi quis porttitor congue, elit erat euismod orci, ac placerat dolor lectus quis orci. Phasellus consetetuer vestibulum elit. Aenean tellus metus, bibendum sed, posuere ac, mattis non, nunc. Vestibulum fringilla pede sit amet augue. In turpis Pellentesque posuere. Praesent turpis. Aenean posuere, tortor sed cursus feugiat, nunc augue blandit nunc, eu sollicitudin urna dolor sagittis lacus. Donec elit libero, sodales nec, volutpat a, hendrerit congue. Ut varius tincidunt libero. Phasellus dolor. Maecenas vestibulum mollis diam. pede. Sed

ut neque. Pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. In dui magna, posuere eget, vestibulum et, tempor auctor, justo. In ac felis quis tortor malesuada pretium. Pellentesque auctor neque nec urna. Proin sapien ipsum, porta a, auctor quis, euismod ut, mi. Aenean viverra rhoncus pede. Pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. Ut non enim eleifend felis pretium feugiat. Vivamus quis mi. Phasellus a est, Phasellus magna. In hac habitasse platea dictumst. Curabitur at lacus ac velit ornare

Curabitur vestibulum aliquam leo. Praesent egestas neque eu enim. In hac habitasse platea dictumst. Fusce a quam. Etiam ut purus mattis mauris sodales aliquam. Curabitur nisi. Quisque malesuada placerat nisl. Nam ipsum risus, rutrum vitae, vestibulum eu, molestie vel, lacus. Sed augue ipsum, vestibulum eu, molestie vel, et, malesuada adipiscing, dui. Vestibulum facilisis, purus nec pulvinar lacus, ligula mi congue nunc, vitae euismod ligula urna in dolor. Mauris sollicitudin fermentum libero. Praesent nonummy mi in odio. Nunc interdum lacus sit amet orci. Vestibulum rutrum, mi nec tum





Source <https://www.cambridgeblog.org/2019/08/information-overload-in-the-legal-sphere/>

LUCES



This international clinical trial aims to identify treatments that may be beneficial for people hospitalised with suspected or confirmed COVID-19

GLOBAL CUMULATIVE TOTALS

48092 Participants

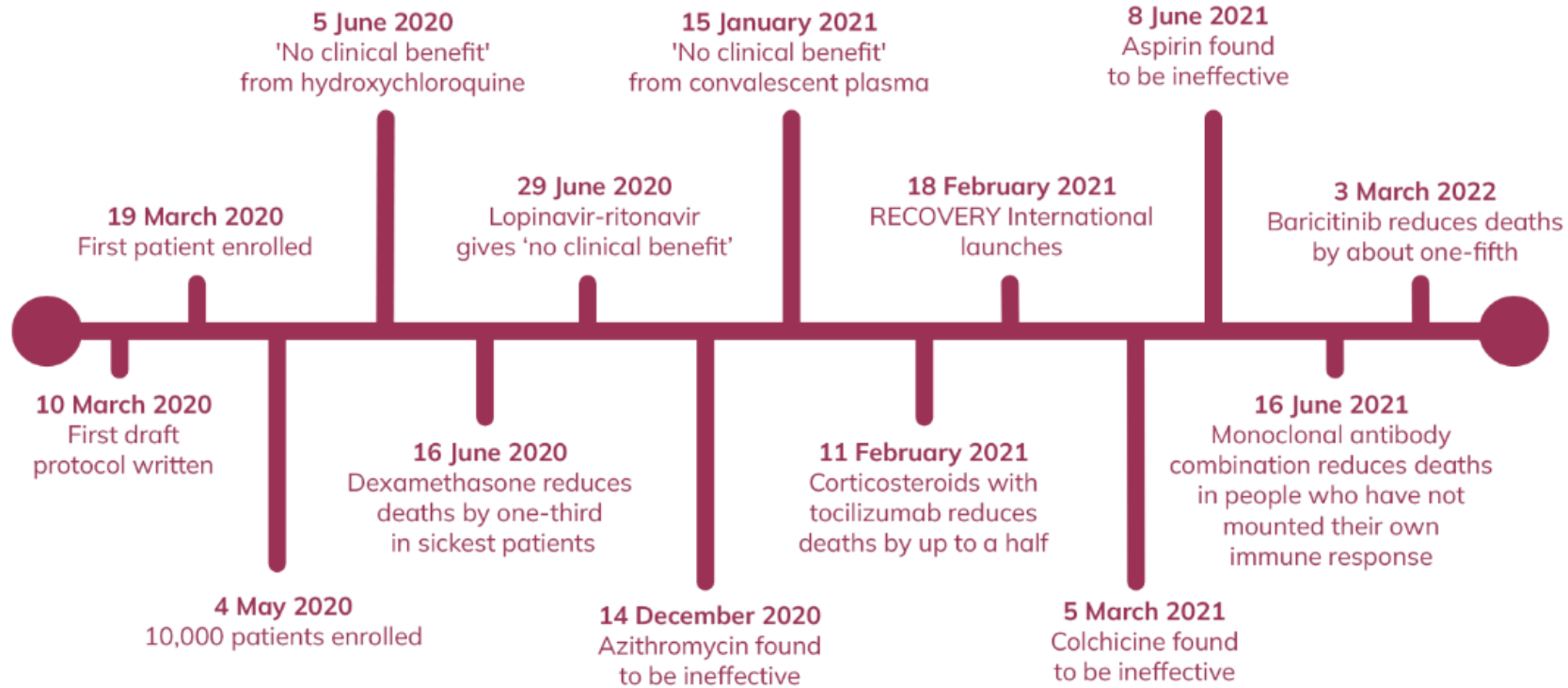
199 Active sites

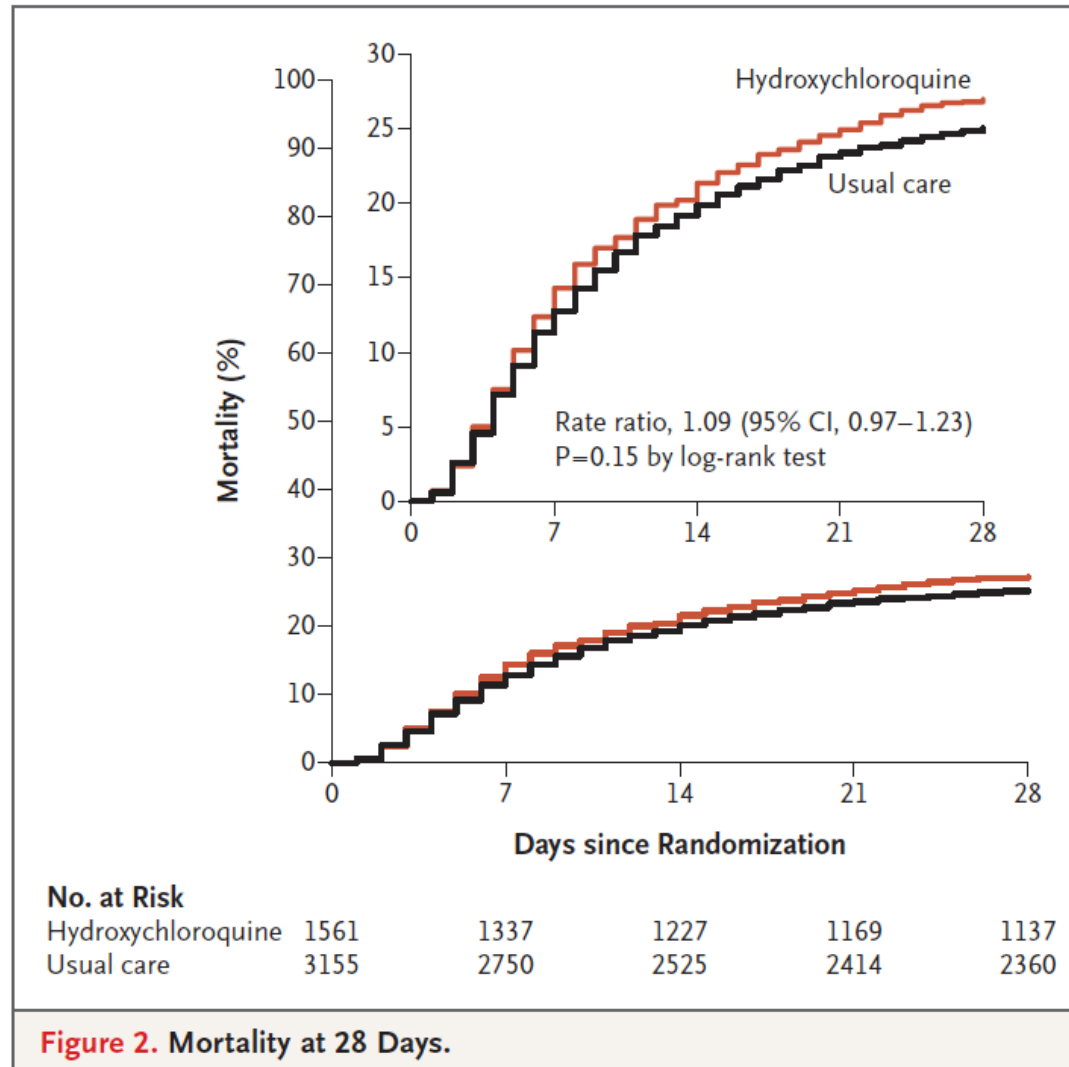


RECOVERY

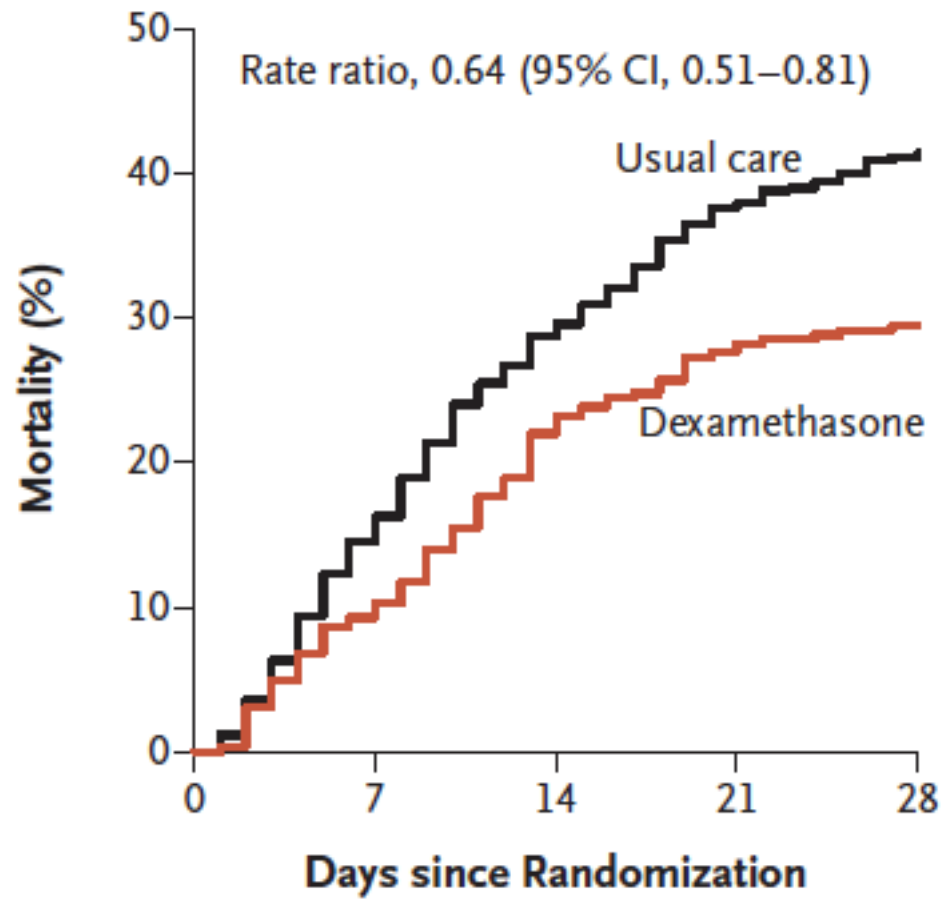
Randomised Evaluation of COVID-19 Therapy

2 years on





B Invasive Mechanical Ventilation (N=1007)



No. at Risk

Usual care	683	572	481	424	400
Dexamethasone	324	290	248	232	228



<https://twitter.com/home>

Health Information

Grants & Funding

News & Events

Research & Training

Institutes at NIH

About NIH

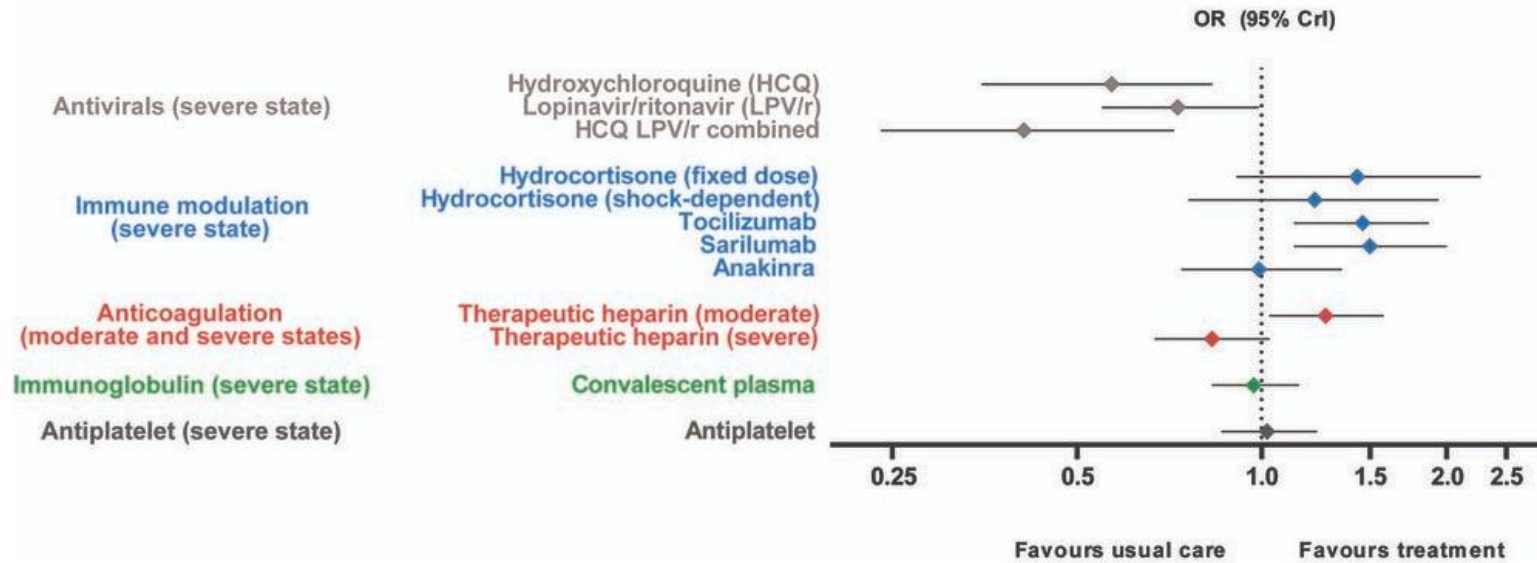
COVID-19 [COVID.gov](#) | [NIH Research information](#) | [Español](#) | [NIH staff guidance \(NIH Only\)](#)



[Home](#) » [Research & Training](#) » [Medical Research Initiatives](#)

ACCELERATING COVID-19 THERAPEUTIC INTERVENTIONS AND VACCINES (ACTIV)

REMAP-CAP results



Accelerating clinical trial implementation in the context of the COVID-19 pandemic: challenges, lessons learned and recommendations from DisCoVeRy and the EU-SolidAct EU response group

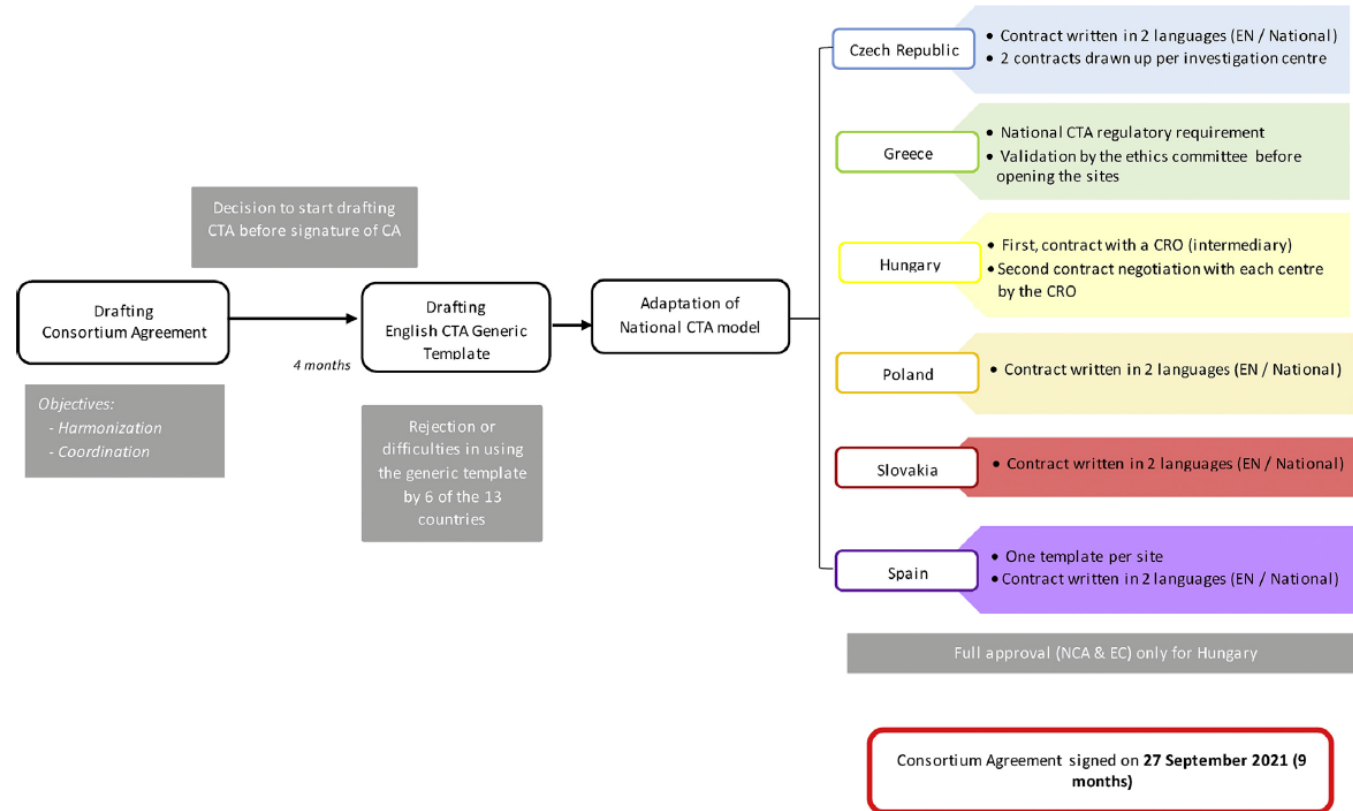


Fig. 1. Flowchart highlighting the legal hurdles encountered in DisCoVeRy. Acronyms: CA, Consortium Agreement; CTA, Clinical Trial Agreement; CRO, Contract Research Organization; EN, English.



**KEEP CALM
AND DO LARGE
CLINICAL TRIALS**