JAMA Insights

Herd Immunity and Implications for SARS-CoV-2 Control

Saad B. Omer, MBBS, MPH, PhD; Inci Yildirim, MD, PhD, MSc; Howard P. Forman, MD, MBA

Herd immunity, also known as *indirect protection*, *community immunity*, or *community protection*, refers to the protection of susceptible individuals against an infection when a sufficiently large proportion of immune individuals exist in a population. In other words, herd immunity is the inability of infected individuals to propagate an epidemic outbreak due to lack of contact with sufficient numbers of susceptible individuals. It stems from the individual immunity that may be gained through natural infection or through vaccination. The term *herd immunity* was initially introduced more than a century ago. In the latter half of the 20th century, the use of the term became more prevalent with the expansion of immunization programs and the need for describing targets for immunization coverage, discussions on disease eradication, and cost-effectiveness analyses of vaccination programs.[1]

Author Audio Interview

JAMA Patient Page page 2113

Eradication of smallpox and sustained reductions in disease incidence in adults and those who are not vaccinated following routine childhood immunization with conjugated *Haemophilus influenzae* type B and pneumococcal vaccines are successful examples of the effects of vaccine-induced herd immunity.[1]

Herd Immunity Threshold

The *herd immunity threshold* is defined as the proportion of individuals in a population who, having acquired immunity, can no longer participate in the chain of transmission. If the proportion of immune individuals in a population is above this threshold, current outbreaks will extinguish and endemic transmission of the pathogen will be interrupted. In the simplest model, the herd immunity threshold depends on the basic reproduction number (R_0; the average number of persons infected by an infected person in a fully susceptible population) and is calculated as $1 - 1/R_0$ (**Figure**).[2,3] The effective reproduction number incorporates partially immune populations and accounts for dynamic changes in the proportion of susceptible individuals in a population, such as seen during an outbreak or following mass immunizations. A highly communicable pathogen, such as measles, will have a high R_0 (12-18) and a high proportion of the population must be immune to decrease sustained transmission. Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, most of the studies estimated the SARS-CoV-2 R_0 to be in the range of 2 to 3.[2] Assuming no population immunity and that all individuals are equally susceptible and equally infectious, the herd immunity threshold for SARS-CoV-2 would be expected to range between 50% and 67% in the absence of any interventions.

Duration of Protection

For both naturally acquired and vaccine-induced immunity, the durability of immune memory is a critical factor in determining population-level protection and sustaining herd immunity. In the case of measles, varicella, and rubella, long-term immunity has been achieved both with infection as well as vaccination. With seasonal coronaviruses, durable immunity has not been observed or has been short lived.[4] For infections that produce transient immunity, the pool of susceptible individuals soon increases in the absence of a vaccine and outbreaks reappear. With an effective vaccine and vaccine program, herd immunity can be sustained (even if periodic vaccination is required to do so) and outbreaks can be curtailed as long as the community maintains the necessary levels.

Role of Heterogeneity

Nominal herd immunity thresholds assume random mixing between individuals in a population. However, daily life is more complicated; individuals mix nonrandomly and some individuals have higher numbers of interactions than others. Empirically validated network models have shown that individuals who have higher numbers of interactions get infected earlier in outbreaks.[5] This may contribute to slowing of community spread of an infection before reaching the nominal herd immunity threshold. However, there is uncertainty regarding the precise effect of heterogeneity in social mixing on herd immunity against SARS-CoV-2.

T-Cell Cross-reactivity

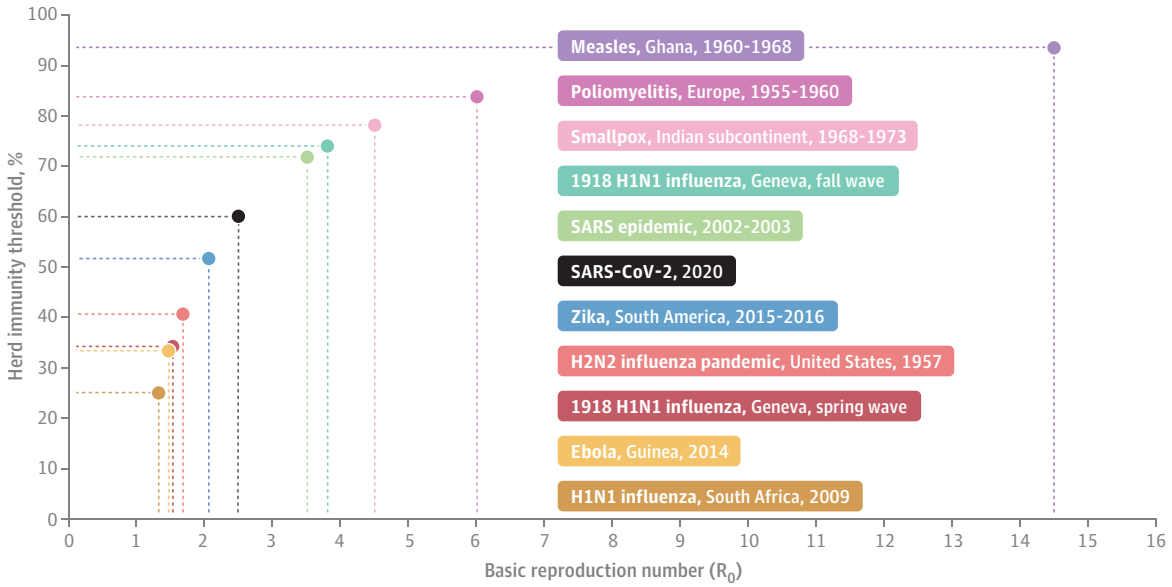
T-cells are important mediators of immunity. Recent reports have suggested that cross-reactivity with other coronaviruses may confer relative protection of the population from coronavirus disease 2019 (COVID-19).[6] It is less clear that T-cell cross-reactivity could provide sterilizing immunity (ie, that the host could not carry nor transmit infection) as opposed to reducing the severity of illness.

Infection-Based Herd Immunity as Policy

An infection-based herd immunity approach (ie, letting the low-risk groups become infected while "sequestering" the susceptible groups) has been proposed to slow the spread of SARS-CoV-2. However, such a strategy is fraught with risks. For example, even with modest infection fatality ratios, a new pathogen will result in substantial mortality because most, if not all, of the population would not have immunity to the pathogen. Sequestering the high-risk populations is impractical because infections that initially transmit in low-mortality populations can spread to high-mortality populations. Moreover, so far, there is no example of a large-scale successful intentional infection-based herd immunity strategy.

There are only rare instances of seemingly sustained herd immunity being achieved through infection. The most recent and well-documented example relates to Zika in Salvador, Brazil. Early in the COVID-19 pandemic, as other countries in Europe were locking down in late February and early March of 2020, Sweden made a decision against lockdown. Initially, some local authorities and journalists described this as the *herd immunity strategy*: Sweden would do its best to protect the most vulnerable, but otherwise aim to see sufficient numbers of citizens become infected with the goal of achieving true infection-based herd immunity. By late March 2020, Sweden abandoned this strategy in favor of active interventions; most universities and high schools were closed to students, travel restrictions were put in place, work from home was encouraged, and bans on groups of more than 50 individuals were enacted. Far from achieving herd immunity, the

Figure. Herd Immunity Thresholds by Disease



The locations included are the locations in which the threshold was measured.

seroprevalence in Stockholm, Sweden, was reported to be less than 8% in April 2020,[7] which is comparable to several other cities (ie, Geneva, Switzerland,[8] and Barcelona, Spain[9]).

The population of the United States is about 330 million. Based on World Health Organization estimates of an infection fatality rate of 0.5%, about 198 million individuals in the United States are needed to be immune to reach a herd immunity threshold of approximately 60%, which would lead to several hundred thousand additional deaths. Assuming that less than 10% of the population has been infected so far,[10] with an infection-induced immunity lasting 2 to 3 years (duration unknown), infection-induced herd immunity is not realistic at this point to control the pandemic. SARS-CoV-2 vaccines will help to reach the herd immunity threshold, but the effectiveness of the vaccine(s) and the vaccine coverage are to be seen.

Conclusions

Herd immunity is an important defense against outbreaks and has shown success in regions with satisfactory vaccination rates. Importantly, even small deviations from protective levels can allow for significant outbreaks due to local clusters of susceptible individuals, as has been seen with measles over the past few years. Therefore, vaccines must not only be effective, but vaccination programs must be efficient and broadly adopted to ensure that those who cannot be directly protected will nonetheless derive relative protections.

ARTICLE INFORMATION

Author Affiliations: Yale Institute for Global Health, New Haven, Connecticut (Omer, Yildirim); Departments of Internal Medicine and Epidemiology of Microbial Diseases, Yale Schools of Medicine and Public Health, New Haven, Connecticut (Omer); Section of Infectious Diseases and Global Health, Department of Pediatrics, Yale School of Medicine, New Haven, Connecticut (Yildirim); Yale School of Public Health, New Haven, Connecticut (Forman); Yale School of Management, New Haven, Connecticut (Forman).

Corresponding Author: Saad B. Omer, MBBS, MPH, PhD, Yale University, 1 Church St, New Haven, CT 06510 (saad.omer@yale.edu).

Published Online: October 19, 2020. doi:10.1001/jama.2020.20892

Conflict of Interest Disclosures: Dr Yildirim reported being a member of the mRNA-1273 Study Group. No other disclosures were reported.

REFERENCES

1. Fine P, Eames K, Heymann DL. "Herd immunity": a rough guide. *Clin Infect Dis*. 2011;52(7):911-916. doi:10.1093/cid/cir007

2. Reproduction number (R) and growth rate (r) of the COVID-19 epidemic in the UK: methods of estimation, data sources, causes of heterogeneity, and use as a guide in policy formulation. *The Royal Society*. Preprint posted August 24, 2020. Accessed October 16, 2020. https://royalsociety.org/-/media/policy/projects/set-c/set-covid-19-R-estimates.pdf

3. van den Driessche P. Reproduction numbers of infectious disease models. *Infect Dis Model*. 2017;2(3):288-303.

4. Edridge AWD, Kaczorowska J, Hoste ACR, et al. Seasonal coronavirus protective immunity is short-lasting. *Nat Med*. Published online September 14, 2020. doi:10.1038/s41591-020-1083-1

5. Christakis NA, Fowler JH. Social network sensors for early detection of contagious outbreaks. *PLoS One*. 2010;5(9):e12948. doi:10.1371/journal.pone.0012948

6. Mateus J, Grifoni A, Tarke A, et al. Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. *Science*. 2020;370(6512):89-94. doi:10.1126/science.abd3871

7. Initial results from ongoing investigation of antibodies to COVID-19 virus. Public Health Agency of Sweden. Published May 20, 2020. Accessed September 30, 2020. https://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2020/maj/forsta-resultaten-fran-pagaende-undersokning-av-antikroppar-for-covid-19-virus/

8. Stringhini S, Wisniak A, Piumatti G, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. *Lancet*. 2020;396(10247):313-319. doi:10.1016/S0140-6736(20)31304-0

9. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al; ENE-COVID Study Group. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. *Lancet*. 2020;396(10250):535-544. doi:10.1016/S0140-6736(20)31483-5

10. Anand S, Montez-Rath M, Han J, et al. Prevalence of SARS-CoV-2 antibodies in a large nationwide sample of patients on dialysis in the USA: a cross-sectional study. *Lancet*. Published online September 25, 2020. doi:10.1016/S0140-6736(20)32009-2

RESEARCH LETTER

COVID-19 and Excess All-Cause Mortality in the US and 18 Comparison Countries

The US has experienced more deaths from coronavirus disease 2019 (COVID-19) than any other country and has one of the highest cumulative per capita death rates.[1,2] An unanswered question is to what extent high US mortality was driven by the early surge of cases prior to improvements in prevention and patient management vs a poor longer-term response.[3] We compared US COVID-19 deaths and excess all-cause mortality in 2020 (vs 2015-2019) to that of 18 countries with diverse COVID-19 responses.

Supplemental content

Methods | We compared the US with Organisation for Economic Co-operation and Development countries with populations exceeding 5 million and greater than $25 000 per capita gross domestic product. For each country, we calculated the COVID-19 per capita mortality rate and grouped countries by mortality: (1) low (COVID-19 deaths, <5/100 000), (2) moderate (5-25/100 000), and (3) high (>25/100 000).[1] We used Poisson regression for comparisons across countries.

We calculated the difference in COVID-19 deaths between each country and the US through September 19, 2020 (week 38) under 3 scenarios: if the US had a comparable per capita COVID-19 mortality rate to each country from the start of the pandemic (February 13) or if the US mortality rate became comparable to other countries beginning May 10 or June 7, to allow lag time for policy interventions.[3] (See the Supplement for formulas.)

We also considered all-cause mortality per capita for countries with publicly available data through July 25, 2020 (week 30). This measure is robust to country-level differences in COVID-19 death coding and captures indirect pandemic effects. We estimated excess all-cause mortality (the difference between mean 2020 deaths and deaths in corresponding weeks of 2015-2019) for each country and the US,

Table 1. COVID-19 Mortality in the US Compared With That of Other Countries[a]

Country	Date COVID-19 cases surpassed 1 per million	COVID-19 deaths per 100 000			Excess US COVID-19 deaths (% of reported deaths)		
		Since the start of the pandemic	Since May 10, 2020	Since June 7, 2020	Since the start of the pandemic	Since May 10, 2020	Since June 7, 2020
Low mortality (COVID-19 deaths, <5/100 000)							
South Korea	2/20/20	0.7	0.2	0.2	196 161 (99)	120 625 (61)	88 771 (45)
Japan	2/23/20	1.2	0.7	0.5	194 711 (98)	119 090 (60)	87 939 (44)
Australia	3/1/20	3.3	2.9	2.9	187 661 (94)	111 747 (56)	79 849 (40)
Moderate mortality (COVID-19 deaths, 5-25/100 000)							
Norway	2/29/20	5.0	1.0	0.5	182 099 (92)	118 074 (59)	87 655 (44)
Finland	3/2/20	6.1	1.4	0.3	178 373 (90)	116 698 (59)	88 432 (45)
Austria	3/1/20	8.6	1.7	1.0	170 247 (86)	115 874 (58)	86 066 (43)
Denmark	3/4/20	10.9	2.1	0.8	162 600 (82)	114 438 (58)	86 669 (44)
Germany	3/1/20	11.3	2.4	0.9	161 393 (81)	113 422 (57)	86 521 (44)
Israel	3/2/20	14.0	11.2	10.6	152 393 (77)	84 676 (43)	54 529 (27)
Switzerland	2/29/20	20.6	2.8	1.2	130 654 (66)	112 205 (57)	85 402 (43)
Canada	3/6/20	24.6	12.4	4.0	117 622 (59)	80 631 (41)	76 235 (38)
High mortality (COVID-19 deaths, >25/100 000)							
The Netherlands	3/3/20	36.2	5.2	1.5	79 318 (40)	104 177 (52)	84 514 (43)
France	3/1/20	46.6	7.5	3.2	45 142 (23)	96 763 (49)	78 947 (40)
Sweden	2/29/20	57.4	23.5	10.3	9581 (5)	44 210 (22)	55 607 (28)
Italy	2/23/20	59.1	9.1	3.1	4136 (2)	91 604 (46)	79 120 (40)
United Kingdom	3/3/20	62.6	16.3	5.0	−7459 (−4)	67 927 (34)	73 103 (37)
Spain	2/29/20	65.0	8.6	4.6	−15 204 (−8)	93 247 (47)	74 163 (37)
Belgium	3/2/20	86.8	12.4	4.2	−87 057 (−44)	80 475 (41)	75 572 (38)
United States	3/7/20	60.3	36.9	27.2			

[a] Data on coronavirus disease 2019 (COVID-19) deaths are from February 13, 2020, through September 19, 2020 (n = 198 589 US deaths). In columns 4-6, due to large sample sizes, all mortality rates are statistically significantly different from the corresponding US mortality rates ($P < .001$). Scenarios in the last 3 columns assume that compared with the country in a given row, (A) the US had a comparable cumulative mortality rate; (B) the US mortality rate was unchanged until May 10 (n = 77 180 deaths), when it became comparable to the other country's death rate; and (C) the US mortality rate was unchanged until June 7 (n = 109 143 deaths), when it became comparable to the other country's death rate.

Table 2. Excess All-Cause Mortality in the US Compared With That in Other Countries[a]

Country	Excess all-cause mortality per 100 000			Excess US deaths from all causes (% of reported deaths)		
	Since the start of the pandemic	Since May 10, 2020	Since June 7, 2020	Since the start of the pandemic	Since May 10, 2020	Since June 7, 2020
Moderate mortality (COVID-19 deaths, 5-25/100 000)						
Norway	−2.6	−4.3	−2.1	235 610 (100)	102 598 (44)	63 952 (27)
Denmark	5.1	1.9	1.8	218 664 (93)	96 375 (41)	57 910 (25)
Israel	8	7.5	5.4	209 376 (89)	77 932 (33)	46 091 (20)
Germany	10.0	1.4	−0.2	202 547 (86)	97 905 (42)	63 952 (27)
Canada	13.3	−3.7	−7.6	192 009 (81)	102 598 (44)	63 952 (27)
Switzerland	17.0	−3.6	−2.7	179 545 (76)	102 598 (44)	63 952 (27)
Austria	17.1	3.2	1.4	179 208 (76)	92 042 (39)	59 375 (25)
Finland	19.1	8.7	5.4	172 706 (73)	74 116 (31)	46 264 (20)
High mortality (COVID-19 deaths, >25/100 000)						
Sweden	50.8	14.9	3.7	68 540 (29)	53 429 (23)	51 864 (22)
France	51.5	5.9	2.6	66 167 (28)	83 301 (35)	55 512 (24)
The Netherlands	55.1	0.1	−0.7	54 282 (23)	102 157 (43)	63 952 (27)
Belgium	67.8	−4.6	−6.4	12 638 (5)	102 598 (44)	63 952 (27)
United Kingdom	94.5	13.7	−1.2	−75 196 (−32)	57 659 (24)	63 952 (27)
Spain	102.2	2.1	1.8	−100 768 (−43)	95 784 (41)	57 948 (25)
United States	71.6	31.2	19.4			

[a] Data on deaths are through July 25, 2020 (week 30, n = 235 610 excess US deaths compared with 145 546 reported COVID-19 deaths). Countries lacking publicly available all-cause mortality data through this time are omitted. Excess deaths were estimated by week, compared with 2015-2019, beginning when a country surpassed 1 COVID-19 case per million population. In columns 3-5, due to large sample sizes, all mortality rates are statistically significantly different from the corresponding US mortality rates ($P < .001$). Scenarios in the last 3 columns assume that compared with the country in a given row: (A) the US had a comparable cumulative mortality rate; (B) the US excess all-cause mortality rate was unchanged until May 10 (week 20, n = 133 012 deaths), when it became comparable to the other country's death rate; and (C) the US excess all-cause mortality rate was unchanged until June 7 (week 24, n = 171 659 deaths), when it became comparable to the other country's death rate. Totals are truncated to avoid exceeding US estimated deaths. Due to reporting lags, these data include less follow-up time than Table 1, which in some cases produces lower cumulative death rates.

compared rates across countries using Poisson regression with country and week fixed effects (Supplement), and estimated the difference in excess all-cause mortality between each country and the US as described above. We used R software (version 4.0.2) for all analyses.

Results | On September 19, 2020, the US reported a total of 198 589 COVID-19 deaths (60.3/100 000), higher than countries with low and moderate COVID-19 mortality but comparable with high-mortality countries (**Table 1**). For instance, Australia (low mortality) had 3.3 deaths per 100 000 and Canada (moderate mortality) had 24.6 per 100 000. Conversely, Italy had 59.1 COVID-19 deaths per 100 000; Belgium had 86.8 per 100 000. If the US death rates were comparable to Australia, the US would have had 187 661 fewer COVID-19 deaths (94% of reported deaths), and if comparable with Canada, 117 622 fewer deaths (59%).

While the US had a lower COVID-19 mortality rate than high-mortality countries during the early spring, after May 10, all 6 high-mortality countries had fewer deaths per 100 000 than the US. For instance, between May 10 and September 19, 2020, Italy's death rate was 9.1/100 000 while the US's rate was 36.9/100 000. If the US had comparable death rates with most high-mortality countries beginning May 10, it would have had 44 210 to 104 177 fewer deaths (22%-52%) (Table 1). If the US had comparable death rates beginning June 7, it would have had 28% to 43% fewer reported deaths (as a percentage overall).

In the 14 countries with all-cause mortality data, the patterns found for COVID-19–specific deaths were similar for excess all-cause mortality (**Table 2**). In countries with moderate COVID-19 mortality, excess all-cause mortality remained negligible throughout the pandemic. In countries with high COVID-19 mortality, excess all-cause mortality reached as high as 102.1/100 000 in Spain, while in the US it was 71.6/100 000. However, since May 10 and June 7, excess all-cause mortality was higher in the US than in all high-mortality countries (Table 2).

Discussion | Compared with other countries, the US experienced high COVID-19–associated mortality and excess all-cause mortality into September 2020. After the first peak in early spring, US death rates from COVID-19 and from all causes remained higher than even countries with high COVID-19 mortality. This may have been a result of several factors, including weak public health infrastructure and a decentralized, inconsistent US response to the pandemic.[4,5]

Limitations of this analysis include differences in mortality risk: the US population is younger but has more comorbidities compared with the other countries.[6] In addition, since late August death rates have increased in several countries, and how mortality will compare with the US throughout fall remains unknown.

Alyssa Bilinski, MSc
Ezekiel J. Emanuel, MD, PhD

Author Affiliations: Interfaculty Initiative in Health Policy, Harvard Graduate School of Arts and Sciences, Cambridge, Massachusetts (Bilinski); University of Pennsylvania Perelman School of Medicine, Philadelphia (Emanuel).

Corresponding Author: Ezekiel J. Emanuel, MD, PhD, Perelman School of Medicine, University of Pennsylvania, Medical Ethics and Health Policy, 423 Guardian Dr, Blockley Hall, Ste 1412, Philadelphia, PA 19104 (MEHPchair@upenn.edu).

Accepted for Publication: October 2, 2020.

Published Online: October 12, 2020. doi:10.1001/jama.2020.20717

Author Contributions: Ms Bilinski had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design; acquisition, analysis, or interpretation of data; and drafting of the manuscript: Both authors.
Critical revision of the manuscript for important intellectual content: Emanuel.
Statistical analysis: Bilinski.
Obtained funding: Emanuel.
Administrative, technical, or material support: Emanuel.
Supervision: Emanuel.

Conflict of Interest Disclosures: Dr Emanuel reported receiving personal fees and nonfinancial support from Blue Cross Blue Shield Minnesota, Bergen University, United Health Group, Futures Without Violence, Children's Hospital of Philadelphia, Washington State Hospital Association, the Association of Academic Health Centers, Blue Cross Blue Shield of Massachusetts, Lumeris, Roivant Sciences, Medical Specialties Distributors, Vizient University Health System Consortium, the Center for Neurodegenerative Disease Research, Genentech Oncology, the Council of Insurance Agents and Brokers, America's Health Insurance Plans, the Montefiore Physician Leadership Academy, Medical Home Network, the Healthcare Financial Management Association, Ecumenical Center–UT Health, the American Academy of Optometry, the Associação Nacional de Hospitais Privados, the National Alliance of Healthcare Purchaser Coalitions, Optum Labs, the Massachusetts Association of Health Plans, the District of Columbia Hospital Association, Washington University, Optum, Brown University, McKay Lab, the American Society for Surgery of the Hand, the Association of American Medical Colleges, America's Essential Hospitals, Johns Hopkins University, the National Resident Matching Program, Shore Memorial Health System, Tulane University, Oregon Health and Science University, Blue Cross Blue Shield, and the Center for Global Development, as well as nonfinancial support from the Delaware Healthcare Spending Benchmark Summit, Geisinger Health System, RAND Corporation, Goldman Sachs, The Atlantic, Village MD, and Oncology Analytics. Dr Emanuel is also a venture partner at Oak HC/FT, and a partner at Embedded Healthcare LLC and COVID-19 Recovery Consulting. Ms Bilinski reported no disclosures.

Funding/Support: This research was partially funded by the Colton Foundation.

Role of the Funder/Sponsor: The Colton Foundation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank David Cutler, PhD, of the Harvard University Department of Economics, for helpful feedback, for which he received no compensation.

Additional Information: Data and code are publicly available on GitHub.

1. COVID-19 data. European Centre for Disease Prevention and Control. Accessed September 25, 2020. https://www.ecdc.europa.eu/en/covid-19/data

2. Viglione G. How many people has the coronavirus killed? *Nature*. 2020;585(7823):22-24. doi:10.1038/d41586-020-02497-w

3. Lyu W, Wehby GL. Shelter-in-place orders reduced COVID-19 Mortality and reduced the rate of growth in hospitalizations: study examine effects of shelter-in-places orders on daily growth rates of COVID-19 deaths and hospitalizations using event study models. *Health Aff (Millwood)*. 2020;39(9):1615-1623. doi:10.1377/hlthaff.2020.00719

4. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis*. 2020;20(6):669-677. doi:10.1016/S1473-3099(20)30243-7

5. Maani N, Galea S. COVID-19 and underinvestment in the public health infrastructure of the United States. *Milbank Q*. 2020;98(2):250-259. doi:10.1111/1468-0009.12463

6. Chaudhry R, Dranitsaris G, Mubashir T, Bartoszko J, Riazi S. A country level analysis measuring the impact of government actions, country preparedness and socioeconomic factors on COVID-19 mortality and related health outcomes. *EClinicalMedicine*. 2020;25:100464. doi:10.1016/j.eclinm.2020.100464

Pediatric Magnet Ingestions After Federal Rule Changes, 2009-2019

Magnet ingestions among children have become a serious health risk after the 2009 introduction of high-powered, rare-earth magnets, commercially sold as small (3- to 6-mm) recreational objects.[1,2] These neodymium magnets are 5 to 10 times more powerful than traditional ferrite magnets and are sold as sets for entertainment and toys (eg, Bucky Balls building sets, jewelry kits, spinning toys).[3] Ingestion of multiple magnets, or a magnet with a metal object, can result in bowel obstruction, perforation, and death when magnets attach through bowel walls.[4] After reports of pediatric injuries and deaths related to ingested neodymium magnets, the Consumer Product Safety Commission (CPSC) initiated campaigns to limit sales in 2012 with voluntary recalls and safety standards.[5] Other CPSC efforts included awareness campaigns, legislative advocacy, and lawsuits.[1] In October 2014, the CPSC published its final rule, Safety Standard for Magnet Sets, prohibiting sales of these small high-powered magnet sets.[3] In November 2016, this rule was legally remanded by the US Court of Appeals 10th Circuit after being challenged by Zen Magnets LLC, resulting in a resurgence of these magnets on the market.[6] This study examined trends in US emergency department (ED) visits for pediatric magnet ingestions over the period of the changes in federal regulations.

Methods | Data from the National Electronic Injury Surveillance System (NEISS), a national sample of US injury-related ED visits, were obtained for January 1, 2009, through December 31, 2019. Magnet ingestions were identified for children aged 17 years or younger with NEISS diagnosis codes of ingested object (41) or aspirated object (42). Only narratives with the key word *magnet* were included. We used US Census data, NEISS sample weights, and clusters to calculate age-specific weighted rates of ED visits for ingestions per 100 000 persons of the population. An interrupted time-series analysis using linear regression modeling examined trends during 3 periods: (1) 2009-2012, before CPSC involvement; (2) 2013-2016, during the CPSC federal rule (including increasing CPSC regulations); and (3) 2017-2019, after the CPSC rule was vacated. Mean ED visit rates for each period and slope changes between periods were calculated. Analysis of variance was used to compare demographics. A 2-sided $P < .05$ was considered significant. Data were analyzed with SAS version 9.3 (SAS Institute Inc) using SURVEYFREQ, SURVEYREG, and SURVEYLOGISTIC, and R for regression analyses (2020; R Foundation). This study was deemed exempt by the Partners Healthcare Institutional Review Board.

Results | A total of 36 701 ED visits were identified for ingested or aspirated objects; 1421 met criteria for magnet

VIEWPOINT

Answering Key Questions About COVID-19 Vaccines

Jesse L. Goodman, MD, MPH
Medicine and Infectious Disease, Georgetown University School of Medicine, Washington, DC.

John D. Grabenstein, RPh, PhD
Immunization Action Coalition, St Paul, Minnesota.

M. Miles Braun, MD, MPH
Lombardi Comprehensive Cancer Center, Georgetown University School of Medicine, Washington, DC.

The US government is investing in rapid development of vaccines against coronavirus disease 2019 (COVID-19), several relying on new technologies.[1] In the US, 4 vaccine candidates are in phase 3 studies with initial results expected soon. If studies succeed, 1 or more vaccines may become available within a few months. Clinicians are likely among the first to be offered COVID-19 vaccines and have a key role in helping patients make decisions about vaccination.[2] Providing evidence-based information will be particularly important in an environment of polarization and mistrust. This Viewpoint focuses on common questions patients are likely to ask about COVID-19 vaccines.

How Much Does a Vaccine Reduce the Risk of COVID-19 and Its Complications?

The US Food and Drug Administration (FDA) guidance set as an expectation for licensure that a COVID-19 vaccine would prevent disease or decrease its severity in at least 50% of people who are vaccinated.[3]

In reviewing the results of a study it is important to know there is a margin of error in estimating the percentage of cases or complications prevented. For example, a study might report a reduction in disease from 100 cases in the placebo group to 50 in those vaccinated. This difference would meet the standard of 50%, but it will be important to explain to patients the uncertainty surrounding that value. While the study showed a 50% reduction in illness, the confidence interval for the efficacy estimate might be 30% to 80%, meaning efficacy may be as low as 30% or as high as 80%. It will also be important to understand whether a vaccine reduces not only mild but also more severe disease, as well as hospitalizations and deaths. However, studies may have insufficient numbers of patients with severe outcomes to definitively evaluate those end points.

How Safe Is a Vaccine Candidate?

Clinicians will want to know how safety was evaluated, including whether studies have been completed, as planned, with 15 000 or more people vaccinated and followed up for time periods sufficient to detect most safety issues (eg, 2 months). It is also important for vaccine developers to present all safety data, including from outside the US.

It is likely that vaccination will be associated with mild adverse events like soreness at the injection site, fever, fatigue, and myalgias. While such symptoms may be unpleasant, so long as they are not severe and resolve quickly, and patients anticipate them, these symptoms are not usually worrisome, unless they lead to additional health care encounters.

More serious reactions, such as otherwise unexplained neurologic or inflammatory processes, would raise concerns. While patients need to understand that serious adverse events may occur coincidentally following receipt of a vaccine, these adverse events could be signals of a safety problem. Comparing rates of adverse events between vaccine and placebo recipients can help determine whether a signal is vaccine-related, but for small numbers of rare events it may be inconclusive.

Patients should understand that rare adverse events may only be detected as a vaccine is widely used. Patients will want assurance that the US has mobilized enhanced safety systems to monitor, evaluate, and communicate about the safety of COVID-19 vaccines after they are released.[4]

Will the Vaccine Be Effective for All Patients?

COVID-19 is more common and severe among individuals often underrepresented in clinical trials, including older individuals, people with chronic illnesses, and persons in racial/ethnic minority populations. Different groups may not have the same responses to vaccination. When results become available, it will be important to evaluate the characteristics of people included in the trial and determine whether they are similar to patients seen in the practice setting. A given vaccine may be more appropriate for some patients than others, and knowing those differences will be important.

Trials involving children and pregnant women will start once vaccine safety is demonstrated in others, making it unlikely vaccines will initially have FDA indications for these groups. In considering use of a vaccine in patients not within FDA indications, available evidence and recommendations from the CDC's Advisory Committee on Immunization Practices (ACIP) should be consulted.

Was Important Information Made Public and Reviewed by Independent Experts?

It is important to know whether all relevant information that might support or contradict the findings of a vaccine trial has been made public. For example, preliminary reports might not include all patients studied or might include only selected results. It must be clear if any information is missing and the reasons for that missing information should be provided.

In addition, it is important that the study has been reviewed by experts without personal or financial interests in the research, as done by major medical journals. Such review helps reduce the risk of errors or bias.

Is a Vaccine Licensed or Provided Under an Emergency Use Authorization?

FDA has a long track record of licensing vaccines that have protected individuals against diseases like measles, polio, and pneumonia. FDA has stated it will apply its usual high standards to COVID-19 vaccines.[5] These standards mean clinicians can have confidence in what is known about the safety and efficacy of a licensed vaccine.

However, FDA could make an as-yet unapproved vaccine available through an Emergency Use Authorization (EUA). Rather than proven safety and effectiveness, EUAs

Corresponding Author: Jesse L. Goodman, MD, MPH, Medicine and Infectious Disease, Georgetown University School of Medicine, 3900 Reservoir Rd, Washington, DC 20057 (jesse.goodman@georgetown.edu).

only require FDA determine a product "may" be effective and that benefits are likely to outweigh risks.

In some circumstances an EUA may be appropriate. For example, substantial data demonstrating safety and efficacy may be available, but it may take additional months for the developer to submit all documentation to FDA or for FDA to review data required for licensure but unrelated to safety or efficacy. Or early results may document convincing safety and efficacy, but it may be months until final data on all enrolled patients are available.

FDA officials have stated,[6] and affirmed in recent guidance,[7] that they would only issue a COVID-19 vaccine EUA with substantial evidence of safety and efficacy. Nonetheless, there is widespread concern a vaccine might be prematurely authorized under political pressure.[8] Clinicians will want to know that any EUA is based on science, with supporting data publicly available, and that those issuing an EUA have not been pressured to do so.

If a vaccine is released under an EUA, clinicians should inform patients that the vaccine is not FDA licensed. Key questions will include why the vaccine is not licensed and what information FDA may be waiting for. If clinical trials have not been completed, there will be questions about how much confidence exists regarding estimated efficacy. Other important considerations include whether adequate safety data from all participants have been analyzed, and whether FDA has ensured the vaccine meets manufacturing and quality standards.[3,7]

FDA has indicated that prior to any decision it will bring potential EUAs or approvals to an advisory committee, allowing outside expert input and enhancing transparency of the evaluation.[3] Furthermore, after FDA makes its determination, CDC and ACIP normally provide recommendations about who should receive a vaccine. If these steps are not followed, or if, in an unprecedented action, the secretary of the Department of Health and Human Services or White House, rather than FDA, were to issue an EUA, it should be apparent. If so, the foundation of scientific expertise and integrity that clinicians rely on to make recommendations to patients would be compromised, and use of a vaccine would need to be carefully considered in that harsh light.

Will All COVID- 19 Vaccines Be the Same?

Different vaccines are likely to perform and be used differently. Clinicians will need to be aware of any differences between vaccines including dose numbers and schedules, as well as safety and efficacy. Importantly, some vaccines may be preferred for certain populations. Clinicians should understand the basics of how different vaccines perform and, if more than one is available, be able to recommend the best for a given patient.

Can Vaccinated People Stop Worrying About COVID-19?

While a vaccine will help protect individual patients and those around them, a large proportion of the population must be immunized and protected before transmission is substantially reduced. Especially for 2-dose regimens, this will take months. No vaccine will be 100% effective and a vaccine that protects against developing clinical illness may not prevent transmission to others. Also, the duration of naturally occurring immunity to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown and may wane with time.[9] Therefore, the likely duration of protection by new COVID-19 vaccines is unknown.

For these reasons, even after vaccines become available, SARS-CoV-2 will be a continuing concern. Effective public health measures, such as social distancing, limiting the size of gatherings, and wearing masks, will be needed for at least several more months, and potentially longer.

Conclusions

Many individuals are hesitant about receiving COVID-19 vaccines. Reasons include the novelty and rapid development of the vaccines, as well as the politicization of the pandemic and inconsistent messages from scientists and government leaders. It is critical that clinicians stay well informed about emerging data so that they can help patients make sound decisions about the vaccines needed to help end the pandemic.

ARTICLE INFORMATION

Published Online: October 16, 2020. doi:10.1001/jama.2020.20590

Conflict of Interest Disclosures: Dr Goodman reported receiving personal fees and nonfinancial support from GlaxoSmithKline and Intellia Therapeutics, and nonfinancial support from US Pharmacopeia outside the submitted work. Dr Grabenstein reported having stock equity in Merck & Co, consulting fees from Valneva, personal fees from serving on the Janssen advisory board, and personal fees from the VBI advisory board outside the submitted work. No other disclosures were reported.

Additional Contributions: We thank Norman W. Baylor, PhD, Biologics Consulting; Luciana L. Borio, MD, In-Q-Tel; Bruce G. Gellin, MD, MPH, Sabin Vaccine Institute; Peter J. Hotez, MD, PhD, Baylor College of Medicine; Glen J. Nowak, PhD, University of Georgia; Paul A. Offit, MD, Children's Hospital of Philadelphia; and Walter A. Orenstein, MD, Emory University, for their input and Nicole Lurie, MD, MSPH, Coalition for Epidemic Preparedness Innovations (CEPI), Harvard Medical School, for her helpful review.

Additional Information: Dr Goodman reported that he served as the chief scientist of the FDA from January 2009 to March 2014.

REFERENCES

1. O'Callaghan KP, Blatz AM, Offit PA. Developing a SARS-CoV-2 vaccine at warp speed. *JAMA*. 2020;324(5):437-438. doi:10.1001/jama.2020.12190

2. Mergler MJ, Omer SB, Pan WK, et al. Association of vaccine-related attitudes and beliefs between parents and health care providers. *Vaccine*. 2013;31(41):4591-4595. Published online July 27, 2013. doi:10.1016/j.vaccine.2013.07.039

3. FDA Center for Biologics Evaluation and Research. Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry. June 2020. Accessed October 12, 2020. https://www.fda.gov/media/139638/download

4. Lurie N, Sharfstein JM, Goodman JL. The development of COVID-19 vaccines: safeguards needed. *JAMA*. 2020;324(5):439-440. doi:10.1001/jama.2020.12461

5. Shah A, Marks PW, Hahn SM. Unwavering regulatory safeguards for COVID-19 vaccines. *JAMA*. 2020;324(10):931-932. doi:10.1001/jama.2020.15725

6. Owermohle S. Politico Prescription Pulse. Marks: prepare for "EUA-plus" for Covid vaccines. September 11, 2020. Accessed September 29, 2020. https://www.politico.com/newsletters/prescription-pulse/2020/09/11/marks-prepare-for-eua-plus-for-covid-vaccines-790343

7. FDA Center for Biologics Evaluation and Research. Emergency Use Authorization for vaccines to prevent COVID-19: guidance for industry. Accessed October 13, 2020. https://www.fda.gov/media/142749/download

8. Rushing coronavirus "Holy Grail" vaccine could turn into a curse. *USA Today*. September 8, 2020. Accessed September 29, 2020. https://www.usatoday.com/story/opinion/todaysdebate/2020/09/08/rushing-coronavirus-holy-grail-vaccine-could-become-curse-editorials-debates/5743934002/

9. Huang AT, Garcia-Carreras B, Hitchings MDT, et al. A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease. *medRxiv*. Preprint posted April 17, 2020. doi:10.1101/2020.04.14.20065771

JAMA | Original Investigation

Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19
A Randomized Clinical Trial

Wesley H. Self, MD, MPH; Matthew W. Semler, MD; Lindsay M. Leither, DO; Jonathan D. Casey, MD, MSc; Derek C. Angus, MD, MPH; Roy G. Brower, MD; Steven Y. Chang, MD, PhD; Sean P. Collins, MD; John C. Eppensteiner, MD; Michael R. Filbin, MD; D. Clark Files, MD; Kevin W. Gibbs, MD; Adit A. Ginde, MD, MPH; Michelle N. Gong, MD, MS; Frank E. Harrell Jr, PhD; Douglas L. Hayden, PhD; Catherine L. Hough, MD, MSc; Nicholas J. Johnson, MD; Akram Khan, MD; Christopher J. Lindsell, PhD; Michael A. Matthay, MD; Marc Moss, MD; Pauline K. Park, MD; Todd W. Rice, MD; Bryce R. H. Robinson, MD, MS; David A. Schoenfeld, PhD; Nathan I. Shapiro, MD, MPH; Jay S. Steingrub, MD; Christine A. Ulysse, MS; Alexandra Weissman, MD, MPH; Donald M. Yealy, MD; B. Taylor Thompson, MD; Samuel M. Brown, MD, MS; for the National Heart, Lung, and Blood Institute PETAL Clinical Trials Network

IMPORTANCE Data on the efficacy of hydroxychloroquine for the treatment of coronavirus disease 2019 (COVID-19) are needed.

OBJECTIVE To determine whether hydroxychloroquine is an efficacious treatment for adults hospitalized with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This was a multicenter, blinded, placebo-controlled randomized trial conducted at 34 hospitals in the US. Adults hospitalized with respiratory symptoms from severe acute respiratory syndrome coronavirus 2 infection were enrolled between April 2 and June 19, 2020, with the last outcome assessment on July 17, 2020. The planned sample size was 510 patients, with interim analyses planned after every 102 patients were enrolled. The trial was stopped at the fourth interim analysis for futility with a sample size of 479 patients.

INTERVENTIONS Patients were randomly assigned to hydroxychloroquine (400 mg twice daily for 2 doses, then 200 mg twice daily for 8 doses) (n = 242) or placebo (n = 237).

MAIN OUTCOMES AND MEASURES The primary outcome was clinical status 14 days after randomization as assessed with a 7-category ordinal scale ranging from 1 (death) to 7 (discharged from the hospital and able to perform normal activities). The primary outcome was analyzed with a multivariable proportional odds model, with an adjusted odds ratio (aOR) greater than 1.0 indicating more favorable outcomes with hydroxychloroquine than placebo. The trial included 12 secondary outcomes, including 28-day mortality.

RESULTS Among 479 patients who were randomized (median age, 57 years; 44.3% female; 37.2% Hispanic/Latinx; 23.4% Black; 20.1% in the intensive care unit; 46.8% receiving supplemental oxygen without positive pressure; 11.5% receiving noninvasive ventilation or nasal high-flow oxygen; and 6.7% receiving invasive mechanical ventilation or extracorporeal membrane oxygenation), 433 (90.4%) completed the primary outcome assessment at 14 days and the remainder had clinical status imputed. The median duration of symptoms prior to randomization was 5 days (interquartile range [IQR], 3 to 7 days). Clinical status on the ordinal outcome scale at 14 days did not significantly differ between the hydroxychloroquine and placebo groups (median [IQR] score, 6 [4-7] vs 6 [4-7]; aOR, 1.02 [95% CI, 0.73 to 1.42]). None of the 12 secondary outcomes were significantly different between groups. At 28 days after randomization, 25 of 241 patients (10.4%) in the hydroxychloroquine group and 25 of 236 (10.6%) in the placebo group had died (absolute difference, −0.2% [95% CI, −5.7% to 5.3%]; aOR, 1.07 [95% CI, 0.54 to 2.09]).

CONCLUSIONS AND RELEVANCE Among adults hospitalized with respiratory illness from COVID-19, treatment with hydroxychloroquine, compared with placebo, did not significantly improve clinical status at day 14. These findings do not support the use of hydroxychloroquine for treatment of COVID-19 among hospitalized adults.

TRIAL REGISTRATION ClinicalTrials.gov: NCT04332991

JAMA. 2020;324(21):2165-2176. doi:10.1001/jama.2020.22240
Published online November 9, 2020.

Visual Abstract

Editorial page 2161

Audio and Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network members who participated in this trial are listed in the eAppendix in Supplement 3.

Corresponding Author: Wesley H. Self, MD, MPH, Department of Emergency Medicine, Vanderbilt University Medical Center, 1313 21st Ave S, Oxford House 312, Nashville, TN 37232 (wesley.self@vumc.org).

Through September 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused more than 30 million confirmed cases of coronavirus disease 2019 (COVID-19), resulting in more than 1 million deaths globally.[1,2]

Hydroxychloroquine has been widely promoted as a potential therapy for COVID-19 due to its anti-inflammatory effects and in vitro studies suggesting antiviral activity.[3-9] Hydroxychloroquine was adopted into routine care for hospitalized adults with COVID-19 at many hospitals.[10-12] However, lack of evidence on efficacy and safety led multiple groups, including the National Institutes of Health (NIH) and Infectious Diseases Society of America, to recommend clinical trials to evaluate hydroxychloroquine as a potential treatment for patients with COVID-19.[13-15]

This trial—Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among Inpatients With Symptomatic Disease (ORCHID)—was conducted to test the hypothesis that, compared with placebo, hydroxychloroquine improves clinical outcomes for adults hospitalized with COVID-19.

Key Points

Question Does treatment with hydroxychloroquine improve clinical outcomes of adults hospitalized with coronavirus disease 2019 (COVID-19)?

Findings In this randomized clinical trial that included 479 hospitalized adults with respiratory symptoms from COVID-19, the distribution of the day 14 clinical status score (measured using a 7-category ordinal scale) was not significantly different for patients randomized to receive hydroxychloroquine compared with placebo (adjusted odds ratio, 1.02).

Meaning These findings do not support the use of hydroxychloroquine for treatment of COVID-19 among hospitalized adults.

Methods

Trial Design and Oversight

Details of the trial's rationale and design were previously published[16] and are available in the trial protocol and statistical analysis plan included in Supplement 1 and Supplement 2, respectively. We conducted a multicenter, blinded, randomized clinical trial comparing hydroxychloroquine vs placebo among hospitalized adults with respiratory illness from COVID-19. Patients were enrolled between April 2, 2020, and June 19, 2020, at 34 hospitals in the US within the Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network (eTable 1 in Supplement 3). The final outcome assessment was scheduled on July 17, 2020. The trial was funded by the National Heart, Lung, and Blood Institute (NHLBI) of the NIH. A central institutional review board at Vanderbilt University Medical Center approved the study. A data and safety monitoring board (DSMB) appointed by the NHLBI provided trial oversight. The Food and Drug Administration (FDA) issued an investigational new drug exemption (IND No. 149243). Patients or legally authorized representatives provided informed consent for participation, primarily using electronic consent procedures, including electronic consent forms and video conferencing for informed consent discussions, to reduce the risk of spreading the virus and to conserve personal protective equipment.[16]

Patient Population

Adults (aged ≥18 years) who were hospitalized for less than 48 hours with laboratory-confirmed SARS-CoV-2 infection and symptoms of respiratory illness for less than 10 days were enrolled. The main exclusion criteria were more than 1 dose of hydroxychloroquine or chloroquine in the prior 10 days; QTc interval greater than 500 ms; prior receipt or planned administration of select medications that prolong the QTc interval; and seizure disorder. Full eligibility criteria are listed in eTable 2 in Supplement 3. Race and ethnicity were reported in this study because the efficacy of hydroxychloroquine for COVID-19 might vary by race or ethnicity. Race and ethnicity were reported by the participant or surrogate; categories of race and ethnicity were provided in the trial's case report form.

Due to delays in SARS-CoV-2 testing early in the pandemic, the trial was initially designed to enroll hospitalized patients with suspected or confirmed SARS-CoV-2 infection, but after testing capacity increased, eligibility criteria were narrowed to include only laboratory-confirmed cases. Prior to this change, 2 patients without laboratory confirmation of SARS-CoV-2 infection were enrolled; these patients were included in the primary analysis.

Randomization

Using a centralized electronic system, we randomly assigned enrolled patients to hydroxychloroquine or placebo in a 1:1 ratio stratified by enrolling hospital using randomization block sizes of 2 and 4. Allocation was concealed. Patients, treating clinicians, trial personnel, and outcome assessors were blinded to group assignment.

Trial Interventions

The first dose of the trial drug was administered within 4 hours of randomization. Patients assigned to the hydroxychloroquine group received 400 mg of hydroxychloroquine sulfate in pill form twice a day for the first 2 doses and then 200 mg in pill form twice a day for the subsequent 8 doses, for a total of 10 doses over 5 days.[7] Patients assigned to the placebo group received matching placebo in the same dosing frequency. Patients discharged from the hospital before day 5 continued the trial medication after discharge to complete the 10-dose course.

An important safety consideration for hydroxychloroquine is QTc prolongation.[17,18] Hence, trial personnel systematically assessed the QTc interval between 24 and 48 hours after administration of the first dose of trial drug. Additional doses of the trial drug were held for a QTc greater than 500 ms. Study personnel monitored daily for administration of medications with potential interactions with hydroxychloroquine and did not administer the trial drug if the participant received a concomitant medication with a high risk for interaction (eTable 3 in Supplement 3).

Open-label, clinical use of hydroxychloroquine and chloroquine was not allowed during the 5-day course of trial drug. Treating clinicians determined all other aspects of patient care. Concomitant medications were recorded through hospital discharge.

Outcomes

The primary outcome was clinical status 14 days after randomization assessed with a 7-category ordinal scale (the COVID Outcomes Scale) recommended by the World Health Organization.[19] The scale consisted of 7 mutually exclusive categories: 1, death; 2, hospitalized, receiving extracorporeal membrane oxygenation (ECMO) or invasive mechanical ventilation; 3, hospitalized, receiving noninvasive mechanical ventilation or nasal high-flow oxygen therapy; 4, hospitalized, receiving supplemental oxygen without positive pressure or high flow; 5, hospitalized, not receiving supplemental oxygen; 6, not hospitalized and unable to perform normal activities; and 7, not hospitalized and able to perform normal activities. To distinguish between category 6 and category 7, study personnel assessed the patient's performance of usual activities with questions consistent with validated health status measures.[20,21] Patients who were discharged from the hospital were contacted by telephone for assessment of the COVID Outcome Scale at 7, 14, and 28 days after randomization.

The trial included 12 secondary outcomes: scores on the COVID Outcomes Scale at 2, 7, and 28 days after randomization; all-cause all-location mortality at 14 and 28 days after randomization; time to recovery, defined as time to reach COVID Outcome Scale category 5, 6, or 7; the composite of death or receipt of ECMO through 28 days; and support-free days through 28 days, including hospital-free, oxygen-free, intensive care unit (ICU)–free, ventilator-free, and vasopressor-free days.[22] Data on the occurrence of several safety events with potential mechanistic links to hydroxychloroquine were also systematically collected between randomization and 28 days later, including cytopenia, plasma aspartate aminotransferase or alanine aminotransferase concentration greater than twice the local laboratory upper limit of normal, cardiac arrest treated with cardiopulmonary resuscitation, symptomatic hypoglycemia, ventricular tachyarrhythmia, and seizure. Serious adverse events, defined as untoward medical events leading to death, a life-threatening experience, prolongation of hospitalization, or persistent or significant disability or incapacity in the judgment of the site investigator, were also reported. Definitions for all outcomes are available in the statistical analysis plan (Supplement 2).

Statistical Analysis

The trial was analyzed by comparing patients randomized to hydroxychloroquine vs those randomized to placebo, with the placebo group serving as the referent. The primary outcome was analyzed with a multivariable proportional odds model with the following prespecified covariables: age, sex, baseline (prerandomization) COVID Outcomes Scale category, baseline Sequential Organ Failure Assessment (SOFA) score,[23] and duration of acute respiratory symptoms prior to randomization. An adjusted odds ratio (aOR) greater than 1.0 indicated more favorable outcomes on the COVID Outcomes Scale among patients randomized to hydroxychloroquine compared with placebo.

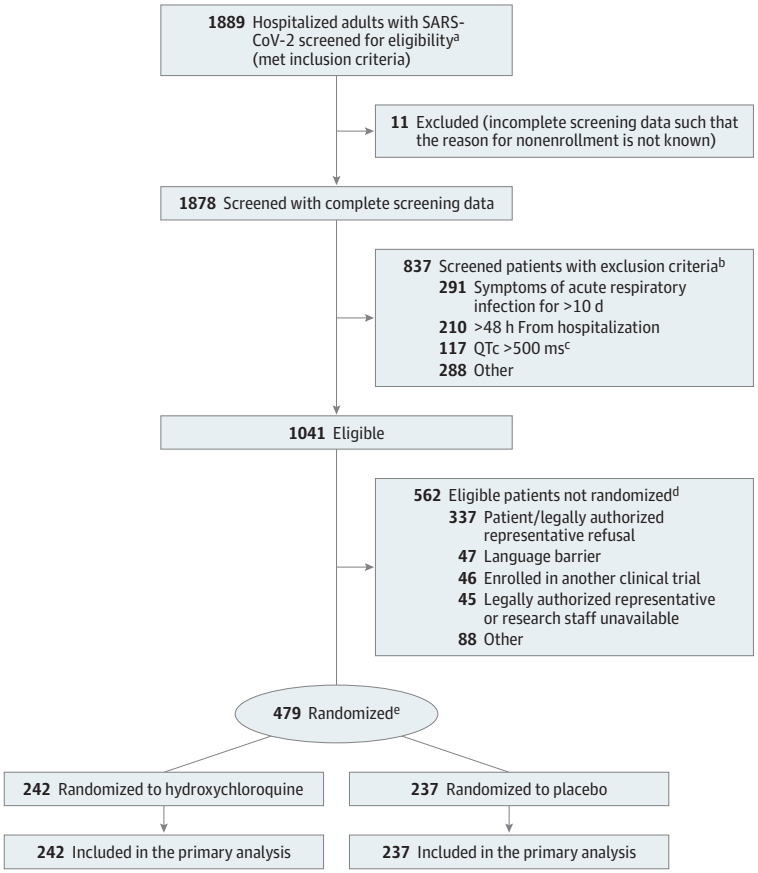
Due to the paucity of information available on COVID-19 at the beginning of the trial for estimation of event rates and treatment effects, we used a bayesian framework to guide serial interim analyses. Interim analyses for the DSMB to evaluate trial data were planned after approximately 102, 204, 306, 408, and 510 patients reached follow-up time for the primary outcome. Enrollment was planned to continue until the DSMB recommended stopping the trial for evidence of efficacy, futility, or harm, based on evaluation of all available data, including data internal and external to the trial. At interim analyses, the DSMB was presented with the probability that the aOR for the primary outcome met each of 3 separate thresholds: greater than 1.0 with a skeptical prior (evidence of efficacy); less than 1.1 with a noninformative prior (evidence of futility); and less than 0.7 with a noninformative prior (evidence of harm) (eTable 4 in Supplement 3). Although there were no mandatory stopping criteria, the investigators suggested and specified in the statistical analysis plan that the DSMB strongly consider stopping the trial if the probability of efficacy (aOR > 1.0) was greater than 95%, the probability of futility (aOR < 1.1) was greater than 90%, or the probability of harm (aOR < 0.7) was greater than 70%. Based on statistical simulation of a range of possible treatment effect sizes, the investigators anticipated that enrolling approximately 510 patients would provide sufficient data for the DSMB to draw conclusions regarding hydroxychloroquine and support recommendations about stopping or continuing the trial.[16] The minimal clinically important difference between groups on the COVID Outcomes Scale was unknown. Enrollment of 510 patients would provide 90% power to detect an aOR of 1.82, which the investigators considered a moderate effect size, using a 2-sided significance level of .05.

Sensitivity analyses for the primary outcome included (1) a modified population limited to patients with laboratory-confirmed SARS-CoV-2 infection; (2) a modified population limited to patients who received at least 1 dose of trial drug; and (3) a post hoc analysis including enrolling site as a random effect in the multivariable proportional odds model.

Heterogeneity of treatment effect by prespecified baseline characteristics was evaluated by adding an interaction term between randomized group assignment and the baseline characteristic of interest in the primary model.[24] Baseline characteristics evaluated in heterogeneity of treatment effect analyses included baseline COVID Outcomes Scale category, hospital location at randomization (ICU vs outside an ICU), baseline SOFA score, duration of symptoms prior to randomization, age, sex, and race/ethnicity.

Secondary outcomes were analyzed using regression models including the same covariables as the primary model (details are provided in the statistical analysis plan in Supplement 2). Survival and hospital discharge through day 28 were analyzed using proportional hazards regression. For the time-to-hospital discharge model, death was treated as

Figure 1. Participant Flow in a Randomized Clinical Trial of Hydroxychloroquine vs Placebo in Patients Hospitalized With Respiratory Symptoms of Coronavirus Disease 2019 (COVID-19)



[a] Between April 2 and April 21, 2020, screened patients included both those with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and those with suspected SARS-CoV-2 infection. Between April 21, 2020, and the end of the trial (June 19, 2020), only patients with laboratory-confirmed SARS-CoV-2 infection were screened.

[b] Exclusion criteria were not mutually exclusive.

[c] QTc was assessed as a study procedure during the screening process; patients must have had a QTc less than 500 ms at the time of screening to be eligible for the trial.

[d] Reasons for not randomizing were not mutually exclusive.

[e] Randomization was stratified by enrolling hospital.

a competing risk, and the subdistribution hazard ratio was reported.[25] A treatment × time interaction was used to test the proportional hazards assumption for the survival and time to discharge models; the proportional hazards assumption was determined to be met for both models.

Post hoc analyses included a comparison of persistent symptoms at 14 and 28 days after randomization between the hydroxychloroquine and placebo groups and evaluation of the primary outcome among patients who received each of the following medications during the same hospitalization as trial enrollment: remdesivir, azithromycin, and corticosteroids.

In presentation of final trial results, between-group differences were reported using point estimates and 2-sided 95% CIs. Results with a 95% CI that did not include the null (eg, a 95% CI for an aOR that did not include 1.0) were considered statistically significant. The widths of confidence intervals were not adjusted for multiplicity and thus findings for analyses of secondary outcomes should be interpreted as exploratory. For patients who remained hospitalized 14 days after randomization, primary outcome ascertainment was completed by medical record review. For patients who were discharged prior to 14 days after randomization, primary outcome ascertainment was completed by telephone calls. Patients who could not be reached by telephone for the primary outcome assessment at day 14 had the COVID Outcomes Scale score carried forward from a day 7 follow-up call if such a call was successfully completed or had a category 6 score (not hospitalized and unable to perform normal activities) imputed if no prior follow-up calls were successfully completed. Mortality was not imputed when vital status was unknown. Analyses were performed using SAS version 9.4 (SAS Institute) and R rms package version 6.0 and rmsb package version 0.0.1 (R Project for Statistical Computing).

Stopping the Trial

On June 19, 2020, enrollment was stopped for futility based on recommendations from the DSMB after it reviewed information both internal and external to the trial. Enrollment was stopped at the fourth interim analysis, which included 371 patients with primary outcome data and an additional 108 patients who had not reached 14 days after randomization for primary outcome assessment. At that time, trial data did not meet the prespecified threshold for futility (defined as >90% probability of an aOR < 1.1 for the primary outcome) but demonstrated an 81% probability for an aOR less than 1.1. Furthermore, a post hoc conditional power analysis showed less than 1% probability of the trial reaching the prespecified threshold for efficacy (defined as >95% probability of an aOR > 1.0) if it continued to a sample size of 510 participants (eTable 5 in Supplement 3). At that time,

Table 1. Baseline Patient Characteristics

Characteristic	No. (%)	
	Hydroxychloroquine (n = 242)	Placebo (n = 237)
Age, median (IQR), y	58 (45-69)	57 (43-68)
Sex		
Female	107 (44.2)	105 (44.3)
Male	135 (55.8)	132 (55.7)
Race/ethnicity	n = 232	n = 227
Hispanic/Latinx	91 (39.2)	87 (38.3)
Non-Hispanic		
White	72 (31.0)	65 (28.6)
Black	57 (24.6)	55 (24.2)
American Indian or Alaska Native	5 (2.2)	8 (3.5)
Asian	4 (1.7)	7 (3.1)
Native Hawaiian or Other Pacific Islander	2 (0.9)	4 (1.8)
Multirace	1 (0.4)	1 (0.4)
Living at home in the community prior to hospitalization	190 (78.5)	183 (77.2)
Body mass index, median (IQR)[a]	31.3 (26.4-37.2)	31.1 (27.2-36.5)
No.	226	219
Chronic conditions		
Hypertension	136 (56.2)	117 (49.4)
Diabetes	88 (36.4)	78 (32.9)
Chronic kidney disease	28 (11.6)	14 (5.9)
Coronary artery disease	19 (7.9)	23 (9.7)
Chronic obstructive pulmonary disease	18 (7.4)	21 (8.9)
Location at time of randomization	n = 228	n = 224
Hospital ward	157 (68.9)	132 (58.9)
Intensive care unit	37 (16.2)	54 (24.1)
Emergency department	34 (14.9)	38 (17.0)
Symptoms of acute respiratory infection		
Shortness of breath	175 (72.3)	168 (70.9)
Cough	143 (59.1)	140 (59.1)
Fever (temperature >37.5 °C)	138 (57.0)	132 (55.7)
Duration of symptoms prior to randomization, median (IQR), d	5 (3-7)	5 (3-7)
Time between hospital presentation and randomization, median (IQR), h[b]	22.2 (14.6-33.1)	22.7 (14.1-29.9)
No.	240	234
COVID Outcomes Scale category at randomization[c]		
2: Hospitalized, receiving ECMO or invasive mechanical ventilation	13 (5.4)	19 (8.0)
3: Hospitalized, receiving noninvasive ventilation or nasal high-flow oxygen	28 (11.6)	27 (11.4)
4: Hospitalized, receiving supplemental oxygen without positive pressure or high flow	116 (47.9)	108 (45.6)
5: Hospitalized, not receiving supplemental oxygen	85 (35.1)	83 (35.0)
Vasopressor use at enrollment	8 (3.3)	20 (8.4)
Total SOFA score at enrollment, median (IQR)[d]	2 (1-4)	2 (1-4)
Laboratory measurements[e]		
White blood cell count, median (IQR), $\times 10^3/\mu L$ (normal range, 3.9-10.7)	6.0 (4.3-7.9)	5.9 (4.1-7.7)
No.	224	218
Platelet count, median (IQR), $\times 10^3/\mu L$ (normal range, 135-371)	199 (151-247)	200 (147-251)
No.	237	230
Creatinine, median (IQR), mg/dL (normal range, 0.57-1.11)	0.90 (0.75-1.47)	0.90 (0.75-1.25)
No.	235	231
Aspartate aminotransferase, median (IQR), U/L (normal range, 5-40)	39 (29-62)	45 (31-70)
No.	173	184
Alanine aminotransferase, median (IQR), U/L (normal range, 0-55)	30 (18-47)	34 (23-62)
No.	174	183

(continued)

Table 1. Baseline Patient Characteristics (continued)

Characteristic	No. (%)	
	Hydroxychloroquine (n = 242)	Placebo (n = 237)
Bilateral infiltrates on chest imaging[f]	147/230 (63.9)	145/230 (63.0)
QTc interval, median (IQR), ms[g]	430 (414-452)	435 (416-452)
No.	242	236

Abbreviations: COVID, coronavirus disease; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

SI conversion factors: To convert aspartate aminotransferase and alanine aminotransferase to μkat/L, multiply by 0.0167; creatinine to μmol/L, multiply by 88.4.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Defined as the time of the first contact with an acute care hospital during the health care episode that resulted in the hospitalization during which the patient was enrolled. For patients who initially presented to the emergency department, time of hospital presentation was the time of emergency department arrival. For patients directly hospitalized without presenting to the emergency department, time of hospital presentation was the time of arrival at the admission unit.

[c] The COVID Outcomes Scale is a 7-category ordinal scale that classifies a patient's clinical status.[19] Lower scores indicate more severely ill clinical status. Patients in the following categories at baseline were not eligible for enrollment: category 1 (death); category 6 (not hospitalized and unable to perform normal activities); and category 7 (not hospitalized and able to perform normal activities).

[d] The SOFA score[23] categorizes illness severity based on organ dysfunction across 6 organ systems: respiratory, coagulation, liver, cardiovascular, central nervous system, and kidney. SOFA scores range from 0 to 24, with higher scores indicating greater illness severity. A SOFA score of 2 indicates moderate dysfunction in 1 organ system or mild dysfunction in 2 organ systems.

[e] Laboratory normal ranges were reported base on the clinical laboratory normal ranges from Vanderbilt University Medical Center. Normal ranges may vary across laboratories.

[f] Reported chest imaging interpretations were based on final interpretation from radiologists.

[g] Reported QTc was based on automated readings.

new information about hydroxychloroquine from sources external to the trial reviewed by the DSMB included (1) a June 5, 2020, press release from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) platform trial leadership stating that results from their trial suggested no survival benefit from hydroxychloroquine[26]; (2) a June 15, 2020, revision to the FDA Emergency Use Authorization for remdesivir recommending against co-administration of remdesivir and hydroxychloroquine due to the potential of hydroxychloroquine reducing the efficacy of remdesivir[27]; and (3) a June 16, 2020, press release from the Medicines and Healthcare products Regulatory Agency instructing all clinical trials of hydroxychloroquine in the United Kingdom to suspend recruitment.[28]

Results

Patients

During the 78-day enrollment period, 1889 patients were screened; 1041 patients met eligibility criteria and 479 patients were randomized (**Figure 1**). The most common reasons for exclusion among screened patients were duration of respiratory symptoms longer than 10 days (34.8% of exclusions), hospitalization for more than 48 hours at the time of screening (25.1%), and QTc greater than 500 ms (14.0%). The most common reason for eligible patients not to be enrolled was the patient or legally authorized representative declining participation (60.0%). Among enrolled patients, the median age was 57 years (interquartile range [IQR], 44 to 68 years), 44.3% were female, 37.2% were Hispanic/Latinx, and 23.4% were Black. The median duration of symptoms prior to randomization was 5 days (IQR, 3 to 7 days). Among 479 enrolled patients, 242 (50.5%) were randomized to hydroxychloroquine and 237 (49.5%) were randomized to placebo. Baseline characteristics of patients randomized to the hydroxychloroquine group and placebo group are presented in **Table 1** and eTables 6-11 in Supplement 3.

Primary outcome assessment of the COVID Outcomes Scale 14 days after randomization was completed for 433 (90.4%) of 479 randomized patients; 46 patients who were discharged from the hospital before primary outcome assessment, including 25 in the hydroxychloroquine group and 21 in the placebo group, were not successfully contacted for primary outcome evaluation and had values imputed based on a follow-up call on day 7 or were assigned a score of 6 if no call was completed on day 7. Follow-up information on survival through day 28 was completed for 477 (99.6%) of 479 randomized patients; 1 patient in the hydroxychloroquine group and 1 patient in the placebo group were lost to follow-up for vital status.

Receipt of Trial Drug and Cointerventions

In the hydroxychloroquine group, 242 (100%) of 242 patients received at least 1 dose of the trial drug, and 2149 (88.8%) of 2420 scheduled doses of trial drug were received (eTables 12-13 in Supplement 3). In the placebo group, 231 (97.5%) of 237 patients received at least 1 dose of placebo, and 2038 (86.0%) of 2370 scheduled doses of placebo were received. QTc prolongation greater than 500 ms was the reason for 38 (14.0%) of the missed doses in the hydroxychloroquine group and 21 (6.3%) of the missed doses in the placebo group.

Among the 479 patients in the trial, remdesivir, azithromycin, and corticosteroids were received by 104 (21.7%), 91 (19.0%), and 88 (18.4%) patients, respectively, during the same hospitalization in which they were enrolled in the trial (eTables 14-15 in Supplement 3).

Primary Outcome

At 14 days after randomization, there was no significant difference in the COVID Outcomes Scale score between the

Table 2. Outcomes, Systematically Collected Safety Events, and Serious Adverse Events

Outcome	Hydroxychloroquine (n = 242)	Placebo (n = 237)	Unadjusted absolute difference (95% CI)[a]	Adjusted odds ratio or odds ratio (95% CI)[b]
Primary outcome				
COVID Outcomes Scale score at 14 d, median (IQR)[c]	6 (4 to 7)	6 (4 to 7)	0[d]	1.02 (0.73 to 1.42)
Secondary outcomes				
COVID Outcomes Scale score, median (IQR)[c]				
At 2 d	4 (3 to 5)	4 (3 to 5)	0[d]	1.28 (0.90 to 1.81)
At 7 d	5 (4 to 7)	6 (3 to 6)	−1 (−2 to 0)	1.16 (0.84 to 1.61)
At 28 d	6 (6 to 7)	6 (6 to 7)	0 (−1 to 1)	0.97 (0.69 to 1.38)
All-cause, all-location death, No. (%)	n = 241	n = 236		
At 14 d	18 (7.5)	14 (5.9)	1.5 (−2.9 to 6.0)	1.56 (0.68 to 3.57)
At 28 d	25 (10.4)	25 (10.6)	−0.2 (−5.7 to 5.3)	1.07 (0.54 to 2.09)
Time to recovery in days, median (IQR)	5 (1 to 14)	6 (1 to 15)	−1 (−3 to 1)	0.97 (0.69 to 1.35)
Composite of death or ECMO through 28 d, No./total No. (%)	29/241 (12.0)	28/236 (11.9)	0.2 (−5.6 to 6.0)	1.13 (0.60 to 2.14)
Support-free days through day 28, median (IQR)				
Hospital-free days	21 (11 to 24)	20 (10 to 24)	1 (−1 to 3)	1.17 (0.85 to 1.61)
Oxygen-free days	21 (0 to 27)	20 (0 to 27)	1 (−2 to 4)	0.96 (0.68 to 1.34)
ICU-free days	28 (21 to 28)	28 (18 to 28)	0 (0 to 0)	1.26 (0.84 to 1.88)
Ventilator-free days	28 (28 to 28)	28 (28 to 28)	0[d]	1.26 (0.76 to 2.08)
Vasopressor-free days	28 (28 to 28)	28 (28 to 28)	0[d]	1.03 (0.61 to 1.72)
Systematically collected safety events, No. (%)[e]				
Cytopenia[f]	92 (38.0)	87 (36.7)	1.3 (−7.4 to 10.0)	1.06 (0.73 to 1.53)
AST or ALT ≥2 times upper limit of normal	50 (20.7)	65 (27.4)	−6.8 (−14.4 to 0.9)	0.69 (0.45 to 1.05)
Cardiac arrest treated with CPR[g]	10 (4.1)	4 (1.7)	2.5 (−0.8 to 5.6)	2.51 (0.78 to 8.12)
Symptomatic hypoglycemia[h]	10 (4.1)	8 (3.4)	0.8 (−2.8 to 4.3)	1.23 (0.48 to 3.18)
Ventricular tachyarrhythmia[i]	5 (2.1)	6 (2.5)	−0.5 (−3.4 to 2.4)	0.81 (0.24 to 2.70)
Seizure	1 (0.4)	0	0.4 (−1.0 to 1.8)	
Patients with ≥1 SAEs reported[j]	14 (5.8)	11 (4.6)	1.1 (−3.0 to 5.2)	1.26 (0.56 to 2.84)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID, coronavirus disease; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; SAE, serious adverse event.

[a] For multilevel ordinal variables (COVID Outcomes Scale and support-free outcomes), the unadjusted absolute difference was calculated as the median value for the hydroxychloroquine group minus the median value for the placebo group; CIs were computed based on quantile regression using the proc quantreg procedure. For dichotomous variables, the unadjusted absolute difference was calculated as the percentage of participants with the outcome in the hydroxychloroquine group minus the percentage of participants with the outcome in the placebo group; CIs for binomial risk differences were computed using a Wald or Agresti-Coull method.

[b] Models for the primary and secondary outcomes were constructed with trial group assignment (hydroxychloroquine vs placebo) as the independent variable, the outcome as the dependent variable, and the following covariables: age, sex, baseline COVID Outcome Scale category, baseline Sequential Organ Failure Assessment score, and duration of acute respiratory infection symptoms prior to randomization. Multivariable proportional odds models were used for the COVID Outcomes Scale outcomes and support-free outcomes. Multivariable logistic regression models were used for death outcomes. Systematically collected safety events and SAEs were analyzed with simple logistic regression models without covariable adjustment. Odds ratios (ORs) greater than 1.0 indicated more favorable outcomes for patients in the hydroxychloroquine group compared with the placebo group for the following outcomes: COVID Outcomes Scale score (adjusted OR [aOR] >1.0 indicated higher score on the scale) and support-free days (aOR >1.0 indicated more support-free days). ORs greater than 1.0 indicated less favorable outcomes for patients in the hydroxychloroquine group compared with the placebo group for the following outcomes: death (aOR >1.0 indicated more death), systematically collected safety events (OR >1.0 indicated more safety events), and SAEs (OR >1.0 indicated more SAEs).

[c] The COVID Outcomes Scale is a 7-category ordinal scale that classifies a patient's clinical status.[19] The 7 categories are 1: death; 2: hospitalized, receiving ECMO or invasive mechanical ventilation; 3: hospitalized, receiving noninvasive mechanical ventilation or nasal high-flow oxygen therapy; 4: hospitalized, receiving supplemental oxygen; 5: hospitalized, not receiving supplemental oxygen; 6: not hospitalized and unable to perform normal activities; and 7: not hospitalized and able to perform normal activities.

[d] CIs for the absolute difference were not calculated for ordinal variables with identical medians and IQRs in the hydroxychloroquine and placebo groups.

[e] Variables collected based on known potential toxicities of hydroxychloroquine were collected for every participant. Adverse event and serious adverse event reporting was based on the judgement of site investigators.

[f] Defined as any of the following values on a clinically obtained laboratory test between randomization and 28 days later: absolute neutrophil count less than 1000 cells/μL; absolute lymphocyte count less than 1000 cells/μL; hemoglobin less than 12.0 g/dL; and platelet count less than 50 000/μL.

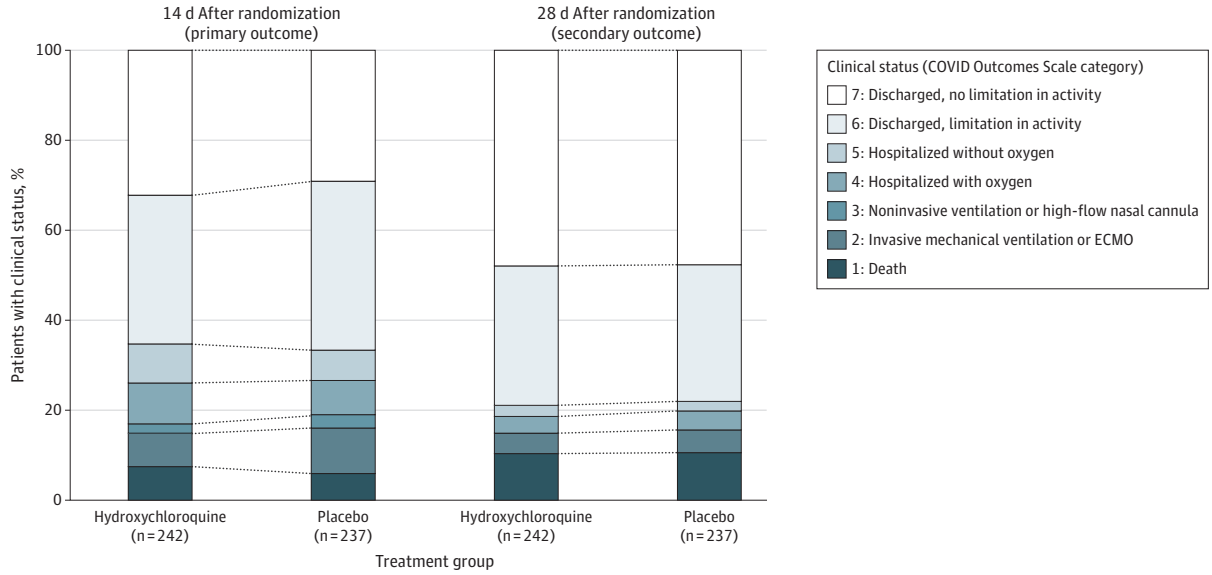
[g] Defined as loss of a palpable pulse treated as a cardiac arrest with resuscitative efforts between randomization and 28 days later. Expected cardiac arrest that occurred as part of the dying process for patients on comfort measures was not classified as cardiac arrest treated with CPR.

[h] Defined as a clinically reported low blood glucose level (no specific threshold provided) that led to treatment for reversal of hypoglycemia between randomization and 28 days later.

[i] Ventricular tachyarrhythmia was defined as ventricular fibrillation or ventricular tachycardia treated with a medication or electrical cardioversion or defibrillation between randomization and 28 days later.

[j] Serious adverse event was defined as an untoward medical event leading to death, a life-threatening experience, prolongation of hospitalization, or persistent or significant disability or incapacity. A detailed report of adverse events and serious adverse events is provided in eTable 24 in Supplement 3.

Figure 2. Clinical Status on the Coronavirus Disease (COVID) Outcomes Scale 14 Days and 28 Days After Randomization



Clinical status (COVID Outcomes Scale category)	14 d After randomization, No. (%)		28 d After randomization, No. (%)	
	Hydroxychloroquine (n = 242)	Placebo (n = 237)	Hydroxychloroquine (n = 242)	Placebo (n = 237)
7: Discharged, no limitation in activity	78 (32.3)	69 (29.1)	116 (47.9)	113 (47.7)
6: Discharged, limitation in activity	80 (33.1)	89 (37.6)	75 (31.0)	72 (30.4)
5: Hospitalized without oxygen	21 (8.7)	16 (6.8)	6 (2.5)	5 (2.1)
4: Hospitalized with oxygen	22 (9.1)	18 (7.6)	9 (3.7)	10 (4.2)
3: Noninvasive ventilation or high-flow nasal cannula	5 (2.1)	7 (3.0)	0	0
2: Invasive mechanical ventilation or ECMO	18 (7.4)	24 (10.1)	11 (4.5)	12 (5.1)
1: Death	18 (7.4)	14 (5.9)	25 (10.3)	25 (10.5)

ECMO indicates extracorporeal membrane oxygenation. There was no significant difference between the hydroxychloroquine group and placebo group in the overall distribution of scores at 14 days (adjusted odds ratio, 1.02 [95% CI, 0.73-1.42]) or 28 days (adjusted odds ratio, 0.97 [95% CI, 0.69-1.38]).

hydroxychloroquine group (median [IQR] score, 6 [4-7]) and placebo group (median [IQR] score, 6 [4-7]) (aOR, 1.02 [95% CI, 0.73-1.42) (**Table 2**; **Figure 2**). Similarly, there were no significant differences in the primary outcome in sensitivity analyses that limited the population to patients with laboratory-confirmed SARS-CoV-2 infection (n = 477), that limited the population to patients who received at least 1 dose of trial drug (n = 473), and that included enrolling site as a random effect (n = 479) (eTable 16 in Supplement 3). There was no significant difference in the primary outcome between the hydroxychloroquine group and placebo group in any prespecified subgroups, including those based on age, sex, race/ethnicity, baseline illness severity, and duration of symptoms (eFigure in Supplement 3). In post hoc analyses among subgroups of patients treated clinically with open-label remdesivir, azithromycin, and corticosteroids, there were no significant differences in the primary outcome between the hydroxychloroquine group and placebo group (eTable 17 in Supplement 3).

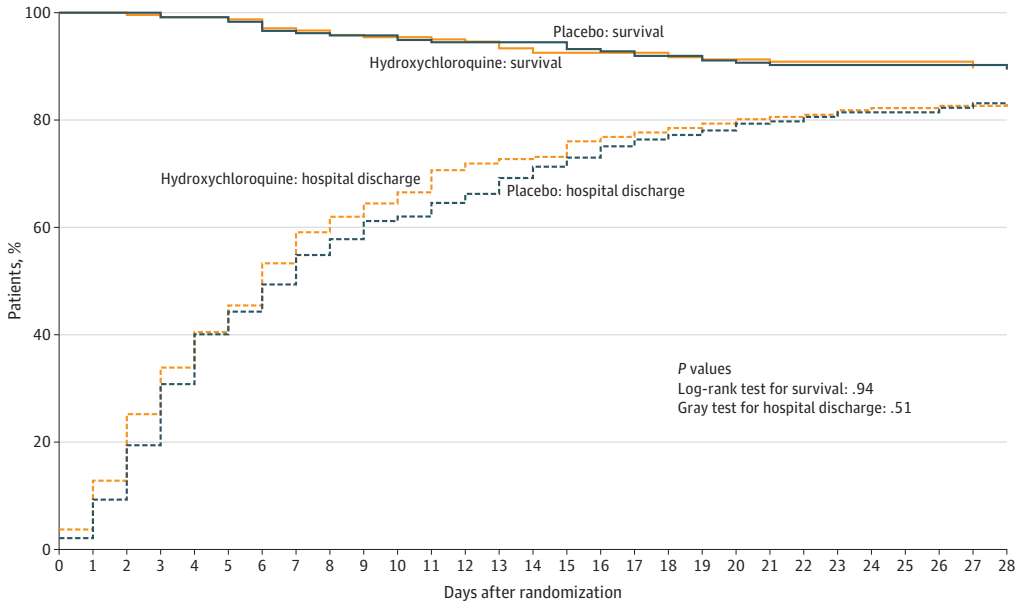
Secondary Outcomes

There was no significant difference in any of the 12 secondary outcomes between the hydroxychloroquine and placebo groups (Table 2; eTables 18-19 in Supplement 3). At 28 days after randomization, 25 (10.4%) of 241 patients with confirmed vital status in the hydroxychloroquine group and 25 (10.6%) of 236 patients with confirmed vital status in the placebo group had died (aOR, 1.07 [95% CI, 0.54-2.09]) (**Figure 3**). In a post hoc analysis, persistent symptoms of COVID-19 were common in both the hydroxychloroquine and placebo groups at 14 days (34.7% vs 32.9%) and 28 days (28.5% vs 30.4%) after randomization (eTable 20 in Supplement 3).

Systematically Collected Safety Events and Adverse Events

Data on systematically collected safety events and adverse events are presented in eTables 21 to 24 in Supplement 3. In the 5 days following randomization, 13 patients (5.9% of 221 patients with QTc assessed) in the hydroxychloroquine group and 7 patients (3.3% of 214 patients with QTc assessed) in the placebo group had a recorded QTc interval greater than 500 ms. A total of 30 serious adverse events were reported, including 18 serious adverse events from 14 patients (5.8%) in the hydroxychloroquine group and 12 serious adverse events from 11 patients (4.6%) in the placebo group.

Figure 3. Survival and Hospital Discharge Through 28 Days Following Randomization



Survival																													
Hydroxychloroquine	241		241	240		239	238	234	233	231		230	229	228	225				223	221		220						219	216
Placebo	236			236		234	232	228	227		226	224				223	220	219		217	215	214							213
Discharge																													
Hydroxychloroquine	242	233	211	180	158	142	129	106	92	84	77	72	61	57	53	50	43	41	39	35	32	30	28	27	25		24	23	21
Placebo	237	232	215	191	162	140	128	113	99	91	83	79	72	68	61	56	50	44	39	37	34	30	28	26			24	22	20

The survival curves are survival function (Kaplan-Meier) curves with a *P* value calculated by the log-rank test. Patients were followed up for death until 28 days following randomization using in-hospital records and telephone follow-up. Two patients had unknown vital status at 28 days and were not included in this analysis. The hospital discharge curves are cumulative incidence curves of hospital discharge accounting for the competing risk of death with a *P* value calculated by Gray test. For hospital discharge, all patients were followed up to discharge or 28 days after randomization. A patient was considered discharged from the hospital once discharged from the index hospitalization; rehospitalizations were not considered in this analysis. There was no difference between the hydroxychloroquine group and placebo group in survival (adjusted hazard ratio, 1.05 [95% CI, 0.60-1.85]) or time to discharge (adjusted hazard ratio, 1.09 [95% CI, 0.89-1.32]).

Discussion

In this multicenter, blinded, placebo-controlled randomized clinical trial conducted at 34 US hospitals, treatment with hydroxychloroquine did not improve or worsen clinical outcomes for adults hospitalized for respiratory illness from COVID-19. These findings were consistent in all subgroups and for all outcomes evaluated, including an ordinal scale of clinical status, mortality, organ failures, duration of oxygen use, and hospital length of stay.

Enthusiasm for hydroxychloroquine as a potential therapy for COVID-19 was sparked by in vitro studies that suggested it limited entry of SARS-CoV-2 into human cells by inhibiting glycosylation of cell receptors targeted by coronaviruses and increasing endosomal pH, thereby reducing endosome-mediated viral entry.[6-8] Additionally, hydroxychloroquine reduces the production of several proinflammatory cytokines involved in the development of acute respiratory distress syndrome, a severe manifestation of COVID-19.[3-5] These factors, combined with broad availability, oral administration, and perceived safety based on historical use in the treatment of malaria and rheumatologic diseases,[4] led to widespread clinical use of hydroxychloroquine for COVID-19.[10,15] On March 28, 2020, the FDA issued an Emergency Use Authorization for hydroxychloroquine to treat adults hospitalized with COVID-19,[29] which was later revoked on June 15, 2020.[30]

The finding of this clinical trial that hydroxychloroquine was not efficacious for the treatment of COVID-19 is consistent with results from recent in vitro studies suggesting no antiviral activity for hydroxychloroquine against SARS-CoV-2[31,32] and open-label pragmatic trials in the United Kingdom[33] and Brazil[34] suggesting no clinical benefit. Interpreted along with these prior studies, the results of this trial provide strong evidence that hydroxychloroquine is not beneficial for adults hospitalized with COVID-19.

Strengths of this trial included its blinded, placebo-controlled design, high adherence to the study protocol, rigorous monitoring for safety events and adverse events, and rapid recruitment from geographically diverse hospitals serving ethnically and racially diverse populations within the US. Additionally, the primary outcome was a patient-centered, clinically meaningful ordinal scale that captured mortality and morbidity related to COVID-19.

Limitations

This trial had several limitations. First, the trial only included hospitalized adults, and findings may not be generalizable to other populations.

Second, patients with respiratory symptoms for up to 10 days prior to randomization were included. Some trials of antiviral medications limit enrollment to patients with symptoms for a shorter duration in an effort to enrich the population for patients most likely to benefit; however, notably, no evidence to suggest efficacy of hydroxychloroquine among patients with shorter duration of symptoms was found in this trial.

Third, outcome ascertainment was limited to 28 days after randomization to accelerate dissemination of findings in the context of an ongoing pandemic; reporting long-term outcomes of trial participants is planned for the future.

Fourth, the minimal clinically important difference in scores on the COVID Outcomes Scale is unknown. While the 95% CI for the aOR for the primary outcome in this trial (0.73-1.42) did not include point estimates that have been considered clinically meaningful in prior trials of COVID-19 therapies,[35,36] moderate sample size in this trial may mean that it had inadequate power to exclude small, yet clinically meaningful, differences between groups.

Fifth, the trial did not include collection of information on serum hydroxychloroquine concentrations, viral shedding, or biomarkers of inflammation.

Sixth, only 1 dosing regimen of hydroxychloroquine was studied in the trial; this regimen was selected based on guidance from the FDA, in vitro studies of hydroxychloroquine lung concentrations,[7] and doses commonly used in US hospitals for COVID-19. Other trials that evaluated higher doses of hydroxychloroquine also demonstrated no clinical benefit.[33,34]

Seventh, this trial evaluated hydroxychloroquine as monotherapy for COVID-19 and did not systematically study coadministration with azithromycin,[9] zinc,[37] remdesivir,[35,36] or other agents.

Conclusions

Among adults hospitalized with respiratory illness from COVID-19, treatment with hydroxychloroquine, compared with placebo, did not significantly improve clinical status at day 14. These findings do not support the use of hydroxychloroquine for treatment of COVID-19 among hospitalized adults.

ARTICLE INFORMATION

Accepted for Publication: October 26, 2020.

Published Online: November 9, 2020. doi:10.1001/jama.2020.22240

Author Affiliations: Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, Tennessee (Self, Collins); Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee (Semler, Casey, Rice); Division of Pulmonary and Critical Care Medicine, Intermountain Medical Center, Murray, Utah (Leither, Brown); University of Utah, Salt Lake City (Leither, Brown); Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Angus); Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland (Brower); Division of Pulmonary and Critical Care Medicine, Department of Medicine, David Geffen School of Medicine at UCLA, Ronald Reagan–UCLA Medical Center, Los Angeles, California (Chang); Department of Surgery, Duke University, Durham, North Carolina (Eppensteiner); Department of Emergency Medicine, Massachusetts General Hospital, Boston (Filbin); Section of Pulmonary, Critical Care, Allergy and Immunologic Disease, Department of Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina (Files, Gibbs); Department of Emergency Medicine, University of Colorado School of Medicine, Aurora (Ginde); Division of Epidemiology and Population Health, Department of Medicine, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York (Gong); Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, Tennessee (Harrell, Lindsell); Department of Medicine, Massachusetts General Hospital, Boston (Hayden, Schoenfeld, Ulysse); Division of Pulmonary and Critical Care Medicine, Department of Medicine, Oregon Health and Science University School of Medicine, Portland (Hough, Khan); Department of Emergency Medicine and Division of Pulmonary, Critical Care, and Sleep Medicine, University of Washington, Seattle (Johnson); Cardiovascular Research Institute, Departments of Medicine and Anesthesia, University of California, San Francisco (Matthay); Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado School of Medicine, Aurora (Moss); Department of Surgery, University of Michigan, Ann Arbor (Park); Department of Surgery, University of Washington, Seattle (Robinson); Department of Emergency Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts (Shapiro); Department of Medicine, University of Massachusetts Medical School-Baystate, Springfield (Steingrub); Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Weissman, Yealy); Division of Pulmonary and Critical Care Medicine, Department of Medicine, Massachusetts General Hospital, Boston (Thompson).

Author Contributions: Drs Schoenfeld and Hayden had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Schoenfeld and Self take responsibility for the trial overall.
Concept and design: Self, Semler, Angus, Casey, Brower, Collins, Eppensteiner, Ginde, Gong, Johnson, Moss, Rice, Robinson, Schoenfeld, Shapiro, Steingrub, Weissman, Yealy, Thompson, Brown.
Acquisition, analysis, or interpretation of data: Self, Semler, Leither, Casey, Angus, Brower, Chang, Collins, Filbin, Files, Gibbs, Ginde, Gong, Harrell, Hayden, Hough, Johnson, Khan, Lindsell, Matthay, Park, Rice, Robinson, Schoenfeld, Steingrub, Ulysse, Weissman, Thompson, Brown.
Drafting of the manuscript: Self, Semler, Casey, Angus, Collins, Johnson, Khan, Matthay, Moss, Robinson, Shapiro, Steingrub, Ulysse, Weissman, Yealy, Thompson, Brown.
Critical revision of the manuscript for important intellectual content: Self, Semler, Leither, Casey, Angus, Brower, Chang, Collins, Eppensteiner, Filbin, Files, Gibbs, Ginde, Gong, Harrell, Hayden, Hough, Johnson, Schoenfeld, Khan, Lindsell, Matthay, Moss, Park, Rice, Robinson, Shapiro, Steingrub, Ulysse, Yealy, Thompson, Brown.
Statistical analysis: Semler, Casey, Angus, Gibbs, Harrell, Hayden, Lindsell, Schoenfeld, Steingrub, Ulysse.
Obtained funding: Self, Collins, Gong, Moss, Shapiro, Thompson.
Administrative, technical, or material support: Self, Semler, Casey, Angus, Ginde, Khan, Rice, Robinson, Shapiro, Thompson.
Supervision: Self, Semler, Casey, Angus, Brower, Chang, Collins, Ginde, Johnson, Moss, Rice, Robinson, Yealy, Thompson, Brown.

Conflict of Interest Disclosures: Dr Self reported receiving grants from the National Heart, Lung, and Blood Institute (NHLBI) during the conduct of the study and personal fees from Aerpio Pharmaceuticals outside the submitted work. Dr Semler reported receiving grants from the NHLBI during the conduct of the study. Dr Leither reported receiving grants from the NHLBI during the conduct of the study. Dr Casey reported receiving grants from the NHLBI during the conduct of the study. Dr Angus reported receiving grants from the NHLBI and National Center for Advancing Translational Sciences (NCATS) during the conduct of the study and personal fees from Ferring Pharmaceuticals, Bristol-Myers Squibb, and Bayer AG and stock from Alung Technologies. Dr Angus has patents pending through Ferring Pharmaceuticals and the University of Pittsburgh. Dr Chang reported receiving grants from the NHLBI during the conduct of the study and personal fees from PureTech Health and LaJolla Pharmaceuticals outside the submitted work. Dr Collins reported receiving grants from the NHLBI and personal fees from Vir Biotechnology outside the submitted

work. Dr Filbin reported receiving grants from the NHLBI during the conduct of the study. Dr Files reported receiving grants from the NIH during the conduct of the study and personal fees from Cytovale and Medpace outside the submitted work. Dr Ginde reported receiving grants from the NIH during the conduct of the study. Dr Gong reported receiving grants from the NHLBI for the submitted work and research funding from the Agency for Healthcare Research and Quality and Regeneron outside the submitted work. Dr Harrell reported receiving grants from the NHLBI and the NCATS during the conduct of this study and personal fees from Adapt Health, Springer, Stanford, University of Texas, ICSB, Duke, Ottawa Hospital, American Statistical Association, Yale, Virginia Commonwealth University, and Arnold Foundation outside the submitted work. Dr Hough reported receiving grants from the NIH during the conduct of the study. Dr Khan reported receiving grants from GlaxoSmithKline, United Therapeutics, Reata Pharmaceuticals, Actelion Pharmaceuticals, and Lung LLC outside the submitted work. Dr Lindsell reported receiving grants from the NHLBI during the conduct of the study and grants from the Department of Defense, NCATS, the NHLBI, the Centers for Disease Control and Prevention, and Marcus Foundation; research contracts from Endpoint Health, Entegrion, and bioMerieux outside the submitted work; in addition, Dr Lindsell has a patent risk stratification in sepsis and septic shock issued. Dr Matthay reported receiving grants from the NHLBI during the conduct of the study and grants from Bayer Pharmaceuticals, Roche-Genentech, the Department of Defense, and the California Institute of Regenerative Medicine and personal fees from GEn1E LifeSciences, Citius Pharma, and Novartis outside the submitted work. Dr Moss reported receiving grants from the NHLBI during the conduct of the study. Dr Park reported receiving grants from NHLBI during the conduct of the study and grants from Eli Lilly and service on Council of the Society of Critical Care Medicine outside the submitted work. Dr Rice reported receiving grants from the NHLBI during the conduct of the study and personal fees from Cumberland Pharmaceuticals Inc, Avisa Pharmaceutical LLC consulting, and Cytovale Inc outside the submitted work. Dr Schoenfeld reported receiving grants from the NIH during the conduct of the study and personal fees from Immunity Pharma and Theravance outside the sumitted work. Dr Shapiro reported receiving grants from the NIH during the conduct of the study. Dr Steingrub reported receiving grants from the NHLBI during the conduct of the study. Dr Yealy reported receiving grants from the NHLBI during the conduct of the study and personal fees from McGraw Hill Inc, Lippincott Williams & Wilkins, Wolters Kluwer Inc, the American College of Emergency Physicians, multiple legal corporations, and UpToDate Inc outside the submitted work. Dr Thompson reported receiving grants from the NHLBI during the conduct of the study and personal fees from Bayer, Novartis, and Thetis outside the submitted work. Dr Brown reported receiving grants from the NHLBI during the conduct of the study and personal fees from Hamilton, Oxford University Press/Brigham Young University, and New York University and grants from Faron Pharmaceuticals, Sedana Pharmaceuticals, Janssen, the NIH, and Department of Defense outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by grants from the NHLBI (3U01HL123009-06S1, U01HL123009, U01HL122998, U01HL123018, U01HL123023, U01HL123008, U01HL123031, U01HL123004, U01HL123027, U01HL123010, U01HL123033, U01HL122989, U01HL123022, and U01HL123020). The REDCap data tools used for this study were supported by a grant from NCATS (5UL1TR002243). The work at Massachusetts General Hospital was supported in part by the Harvard Catalyst/Harvard Clinical and Translational Science Center (NCATS, NIH awards UL1TR001102 and UL1TR002541-01). Sandoz, a Novartis division, supplied the hydroxychloroquine and placebo used in this trial.

Role of the Funders/Sponsor: The NHLBI supported the trial through funding, appointed a protocol review committee and data and safety monitoring board, and reviewed the manuscript prior to submission for publication but did not have the power to veto publication or select a journal. The NHLBI had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; in the preparation of the manuscript; and in the decision to submit the manuscript for publication. Representatives from Sandoz reviewed the manuscript prior to submission for publication but did not have the power to veto publication or select a journal. Sandoz had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; the preparation of the manuscript; and the decision to submit the manuscript for publication.

Disclaimer: Dr Angus is Senior Editor of *JAMA*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Group Information: The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network members are listed in the eAppendix in Supplement 3.

Data Sharing Statement: See Supplement 4.

Additional Information: The data analyses for this trial were conducted at the PETAL Clinical Trials Network Data Coordinating Center at Massachusetts General Hospital by Drs Schoenfeld and Hayden and Ms Ulysse.

REFERENCES

1. Johns Hopkins University. Coronavirus resource center. Accessed July 28, 2020. https://coronavirus.jhu.edu/map.html

2. World Health Organization. WHO coronavirus disease (COVID-19) dashboard. Accessed September 22, 2020. https://covid19.who.int/

3. Zhao M. Cytokine storm and immunomodulatory therapy in COVID-19: role of chloroquine and anti-IL-6 monoclonal antibodies. *Int J Antimicrob Agents*. 2020;55(6):105982. doi:10.1016/j.ijantimicag.2020.105982

4. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol*. 2020;16(3):155-166. doi:10.1038/s41584-020-0372-x

5. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020;323(18):1824-1836. doi:10.1001/jama.2020.6019

6. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. doi:10.1038/s41422-020-0282-0

7. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020;71(15):732-739. doi:10.1093/cid/ciaa237

8. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6:16. doi:10.1038/s41421-020-0156-0

9. 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. doi:10.1016/j.ijantimicag.2020.105949

10. Azoulay E, de Waele J, Ferrer R, et al. International variation in the management of severe COVID-19 patients. *Crit Care*. 2020;24(1):486. doi:10.1186/s13054-020-03194-w

11. Massachusetts General Hospital. Massachusetts General Hospital COVID-19 treatment guidance. Accessed May 8, 2020. https://web.archive.org/web/20200410013441/https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/mass-general-COVID-19-treatment-guidance.pdf

12. Vanderbilt University Medical Center. Clinical recommendations for treatment of COVID-19 adult patients. Accessed March 13, 2020. https://www.vumc.org/coronavirus/sites/default/files/COVID%20Documents/VUMC%20interim%20recommendations%20for%20clinical%20care%20of%20COVID%20patients%203.14.2020%20final.pdf

13. National Institutes of Health (NIH). Coronavirus disease 2019 (COVID-19) treatment guidelines. Accessed June 30, 2020. https://www.covid19treatmentguidelines.nih.gov

14. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis*. Published online April 27, 2020. doi:10.1093/cid/ciaa478

15. Rubin EJ, Harrington DP, Hogan JW, Gatsonis C, Baden LR, Hamel MB. The urgency of care during the COVID-19 pandemic: learning as we go. *N Engl J Med*. 2020;382(25):2461-2462. doi:10.1056/NEJMe2015903

16. Casey JD, Johnson NJ, Semler MW, et al. Rationale and design of ORCHID: a randomized placebo-controlled clinical trial of hydroxychloroquine for adults hospitalized with COVID-19. *Ann Am Thorac Soc*. 2020;17(9):1144-1153. doi:10.1513/AnnalsATS.202005-478SD

17. Roden DM, Harrington RA, Poppas A, Russo AM. Considerations for drug interactions on QTc in exploratory COVID-19 treatment. *Circulation*. 2020;141(24):e906-e907. doi:10.1161/CIRCULATIONAHA.120.047521

18. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19).

JAMA Cardiol. 2020;5(9):1036-1041. doi:10.1001/jamacardio.2020.1834

19. World Health Organization. WHO R&D blueprint: novel coronavirus: COVID-19 therapeutic trial synopsis. Accessed June 28, 2020. https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf

20. EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208. doi:10.1016/0168-8510(90)90421-9

21. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-1736. doi:10.1007/s11136-011-9903-x

22. Yehya N, Harhay MO, Curley MAQ, Schoenfeld DA, Reeder RW. Reappraisal of ventilator-free days in critical care research. *Am J Respir Crit Care Med*. 2019;200(7):828-836. doi:10.1164/rccm.201810-2050CP

23. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

24. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine: reporting of subgroup analyses in clinical trials. *N Engl J Med*. 2007;357(21):2189-2194. doi:10.1056/NEJMsr077003

25. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144

26. RECOVERY Investigators. No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19: statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine, 5 June 2020. Accessed June 28, 2020. https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19

27. Food and Drug Administration (FDA). Fact sheet for healthcare providers: emergency use authorization (EUA) of Veklury (remdesivir) for hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. Accessed October 8, 2020. https://www.fda.gov/media/137566/download

28. Medicines and Healthcare Products Regulatory Agency. MHRA suspends recruitment to COVID-19 hydroxychloroquine trials. Accessed October 10, 2020. https://www.gov.uk/government/news/mhra-suspends-recruitment-to-covid-19-hydroxychloroquine-trials

29. Food and Drug Administration (FDA). Request for emergency use authorization for use of chloroquine phosphate or hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of 2019 coronavirus disease. Accessed July 2, 2020. https://www.fda.gov/media/136534/download

30. Food and Drug Administration (FDA). Letter revoking EUA for chloroquine phosphate and hydroxychloroquine sulfate. Accessed July 2, 2020. https://www.fda.gov/media/138945/download

31. Maisonnasse P, Guedj J, Contreras V, et al. Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. *Nature*. 2020;585(7826):584-587. doi:10.1038/s41586-020-2558-4

32. Hoffmann M, Mösbauer K, Hofmann-Winkler H, et al. Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2. *Nature*. 2020;585(7826):588-590. doi:10.1038/s41586-020-2575-3

33. Horby P, Mafham M, Linsell L, et al; RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2022926

34. Cavalcanti AB, Zampieri FG, Rosa RG, et al; Coalition Covid-19 Brazil I Investigators. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2019014

35. Spinner CD, Gottlieb RL, Criner GJ, et al; GS-US-540-5774 Investigators. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048-1057. doi:10.1001/jama.2020.16349

36. Beigel JH, Tomashek KM, Dodd LE. Remdesivir for the treatment of COVID-19: preliminary report: reply. *N Engl J Med*. 2020;383(10):994. doi:10.1056/NEJMoa2007764

37. Derwand R, Scholz M. Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win today's battle against COVID-19? *Med Hypotheses*. 2020;142:109815. doi:10.1016/j.mehy.2020.109815