HealthCare Partners, IPA
HealthCare Partners, MSO

Medical Advisory Committee Monthly Meeting
Tuesday, February 23, 2021 @6:30 p.m.
❖ AGENDA

Meeting called to order @ 6:30 p.m. — **Joseph Cervia, MD**

Review of Minutes from last meeting (January 26, 2021) — **All Committee Members**

Articles for Review:

1. **Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers** — **Joseph Cervia, MD**

2. **The NEW ENGLAND JOURNAL OF MEDICINE Repurposed Antiviral Drugs for Covid-19-Interim WHO Solidarity Trial Results** — **Joseph Cervia, MD**

3. **Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform Trial Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults** — **Joseph Cervia, MD**

Discussion — **All Committee Members**

Next Meeting: Tuesday, March 23, 2021 @ 6:30 p.m. — **Joseph Cervia, MD**

Adjourned: Meeting will be adjourned at 7:30 p.m. — **Joseph Cervia, MD**

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HealthCare Partners, IPA
HealthCare Partners, Management Services Organization

HealthCare Partner Management Services Organization
Medical Advisory Committee meeting
Tuesday, January 21, 2020

PRESENT: Joseph Cervia, MD; Donald Claxon, MD; Peggy McCoy, Executive Assistant; Lisa Boodram, Pharm.D, VP.; Roger Boykin, MD; Roman Urbanczyk, MD; Edward Zamecki, MD, HNYMPC; Lorraine Marin, MD; Oncology; Kauser Yasmeen, MD; Noel Brown, MD, Senior VP ; Nancy Klotz, MD, HNYMPC, CMO

EXCUSED: Asif Rehman, MD; Robert LoNigro, MD, President; Sandra M. Mitchell, RN, VP Medical Mgmt.; Wesner Moise, MD.; Joseph Padula, MD; James Di Maio, MD;

AGENDA ITEM	FINDINGS / DISCUSSION / CONCLUSIONS / RECOMMENDATIONS	ACTION	RESPONSIBLE PARTY	FOLLOW-UP/ TARGET DATE
Call to Order	The January 26, 2021 Medical Advisory Committee meeting was called to order at 6:40 p.m.	N/A	Joseph Cervia, MD	N/A
Approval of Minutes from last meeting	The Minutes from the December 15, 2020 were reviewed and approved as presented.	Approved as Presented.	Joseph Cervia, MD	N/A
Open Issues	N/A	N/A	Joseph Cervia, MD.	N/A
Articles	1. **Safety and efficacy of the BNT126b2b2mRNA Covid 19 Vaccine – Pfizer** • **Safety:** Vaccine recipients had local reactions (pain, erythema, swelling) and systemic reactions (e.g. fever, headache, myalgias) at higher rates than placebo recipients, with more	Discussion with Committee Members	Joseph Cervia, MD	N/A

AGENDA ITEM	FINDINGS / DISCUSSION / CONCLUSIONS / RECOMMENDATIONS	ACTION	RESPONSIBLE PARTY	FOLLOW-UP/ TARGET DATE
	reactions following the second dose. Most were mild to moderate and resolved rapidly. • **Efficacy:** The vaccine showed some early protection 12 days after the first dose; 7 days after the second dose, 95% efficacy was observed. • **Conclusions:** Two doses of an mRNA-based vaccine were safe over a median of two months and provided 95% protection against symptomatic Covid-19 in persons 16 years of age or older. In this article there was a chart and graph which were discussed as well. 2. **Efficacy and Safety of MRNA-1273 SARS-CoV= Vaccine – Moderna** • **Safety:** Vaccine recipients had higher rates of local reactions (e.g., pain, erythema, swelling) and systemic reactions (e.g., headaches, fatigue, myalgia) than placebo recipients than among placebo recipients. Most reactions were mild to moderate and resolved over 1-3 days. • **Efficacy:** The incidence of Covid-19 was lower among vaccine recipients as early as 14 days after the first dose. Protection in the vaccine group persisted for the period of follow-up. • **Conclusions:** Two doses of a SARS-CoV-2 mRNA-based vaccine were safe and provided 94% efficacy against symptomatic Covid-19 in persons 18 or older.	Discussion with Committee Members	Joseph Cervia, MD	N/A

AGENDA ITEM	FINDINGS / DISCUSSION / CONCLUSIONS / RECOMMENDATIONS	ACTION	RESPONSIBLE PARTY	FOLLOW-UP/ TARGET DATE
Articles – cont'd	In this article there were charts and graphs that were discussed. 3. **Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults** • Therapies to interrupt the progression of early coronavirus disease 2019 (Covid-19) remain elusive. Among them, convalescent plasma administered to hospitalized patients has been unsuccessful, perhaps because antibodies should be administered earlier in the course of illness. • **Methods:** We conducted a randomized, double-blind, placebo-controlled trial of convalescent plasma with high IgG titers against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in older adult patients within 72 hours after the onset of mild Covid-19 symptoms. The primary end point was severe respiratory disease, defined as a respiratory rate of 30 breaths per minute or more, an oxygen saturation of less than 93% while the patient was breathing ambient air, or both. The trial was stopped early at 76% of its projected sample size because cases of Covid-19 in the trial region decreased considerably and steady enrollment of trial patients became virtually impossible. • **Results:** A total of 160 patients underwent randomization. In the intention-to-treat population, severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and 25 of 80 patients (31%) who received placebo (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P = 0.03),	Discussion with Committee Members	Joseph Cervia, MD	N/A

AGENDA ITEM	FINDINGS / DISCUSSION / CONCLUSIONS / RECOMMENDATIONS	ACTION	RESPONSIBLE PARTY	FOLLOW-UP/ TARGET DATE
Presentation	with a relative risk reduction of 48%. A modified intention-to-treat analysis that excluded 6 patients who had a primary end-point event before infusion of convalescent plasma or placebo showed a larger effect size (relative risk, 0.40; 95% CI, 0.20 to 0.81). No solicited adverse events were observed. • **CONCLUSIONS:** Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19. In this article there were charts and graphs which were discussed as well. **Breakthrough of the Year 2020 – Science Magazine** • The Covid 19 vaccine has been recognized as the breakthrough of the year. Very interesting article in Science magazine that Dr. Joseph Cervia highly recommends.	Discussion with Committee Members	Joseph Cervia, MD	N/A
Next Meeting	The next Medical Advisory Committee meeting will be held on Tuesday, February 23, 2020 @6:30 p.m.	N/A	N/A	N/A
Adjournment	The meeting was adjourned at 7:40 p.m.	N/A	Joseph Cervia, MD.	N/A

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Joseph Cervia, MD
Medical Director Reviewer, Medical Advisory Committee Chair

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Date – 02/23/2021

ORIGINAL ARTICLE

Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers

S.F. Lumley, D. O'Donnell, N.E. Stoesser, P.C. Matthews, A. Howarth, S.B. Hatch, B.D. Marsden, S. Cox, T. James, F. Warren, L.J. Peck, T.G. Ritter, Z. de Toledo, L. Warren, D. Axten, R.J. Cornall, E.Y. Jones, D.I. Stuart, G. Screaton, D. Ebner, S. Hoosdally, M. Chand, D.W. Crook, A.-M. O'Donnell, C.P. Conlon, K.B. Pouwels, A.S. Walker, T.E.A. Peto, S. Hopkins, T.M. Walker, K. Jeffery, and D.W. Eyre, for the Oxford University Hospitals Staff Testing Group*

ABSTRACT

BACKGROUND

The relationship between the presence of antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the risk of subsequent reinfection remains unclear.

METHODS

We investigated the incidence of SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) in seropositive and seronegative health care workers attending testing of asymptomatic and symptomatic staff at Oxford University Hospitals in the United Kingdom. Baseline antibody status was determined by anti-spike (primary analysis) and anti-nucleocapsid IgG assays, and staff members were followed for up to 31 weeks. We estimated the relative incidence of PCR-positive test results and new symptomatic infection according to antibody status, adjusting for age, participant-reported gender, and changes in incidence over time.

RESULTS

A total of 12,541 health care workers participated and had anti-spike IgG measured; 11,364 were followed up after negative antibody results and 1265 after positive results, including 88 in whom seroconversion occurred during follow-up. A total of 223 anti-spike–seronegative health care workers had a positive PCR test (1.09 per 10,000 days at risk), 100 during screening while they were asymptomatic and 123 while symptomatic, whereas 2 anti-spike–seropositive health care workers had a positive PCR test (0.13 per 10,000 days at risk), and both workers were asymptomatic when tested (adjusted incidence rate ratio, 0.11; 95% confidence interval, 0.03 to 0.44; P=0.002). There were no symptomatic infections in workers with anti-spike antibodies. Rate ratios were similar when the anti-nucleocapsid IgG assay was used alone or in combination with the anti-spike IgG assay to determine baseline status.

CONCLUSIONS

The presence of anti-spike or anti-nucleocapsid IgG antibodies was associated with a substantially reduced risk of SARS-CoV-2 reinfection in the ensuing 6 months. (Funded by the U.K. Government Department of Health and Social Care and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Eyre at the Microbiology Department, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, United Kingdom, or at david.eyre@bdi.ox.ac.uk.

*A complete list of members of the Oxford University Hospitals Staff Testing Group is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection produces detectable immune responses in most cases reported to date; however, the extent to which previously infected people are protected from a second infection is uncertain. Understanding whether postinfection immunity exists, how long it lasts, and the degree to which it may prevent symptomatic reinfection or reduce its severity has major implications for the SARS-CoV-2 pandemic.

Postinfection immunity may be conferred by humoral and cell-mediated immune responses. Key considerations when investigating postinfection immunity include identifying functional correlates of protection, identifying measurable surrogate markers, and defining end points, such as prevention of disease, hospitalization, death, or onward transmission.[1]

The assay-dependent antibody dynamics of SARS-CoV-2 anti-spike and anti-nucleocapsid antibodies are being defined.[2-6] Neutralizing antibodies against the spike protein receptor-binding domain may provide some postinfection immunity. However, the association between antibody titers and plasma neutralizing activity is assay- and time-dependent.[7-10]

Evidence for postinfection immunity is emerging. Despite more than 76 million people infected worldwide and widespread ongoing transmission, reported reinfections with SARS-CoV-2 have been rare, occurring mostly after mild or asymptomatic primary infection,[11-20] which suggests that SARS-CoV-2 infection provides some immunity against reinfection in most people. In addition, small-scale reports suggest that neutralizing antibodies may be associated with protection against infection.[21] We performed a prospective longitudinal cohort study of health care workers to assess the relative incidence of subsequent positive SARS-CoV-2 polymerase-chain-reaction (PCR) tests and symptomatic infections in health care workers who were seropositive for SARS-CoV-2 antibodies and in those who were seronegative.

METHODS

COHORT

Oxford University Hospitals offer SARS-CoV-2 testing to all symptomatic and asymptomatic staff working at four teaching hospitals in Oxfordshire, United Kingdom. SARS-CoV-2 PCR testing of combined nasal and oropharyngeal swab specimens for symptomatic staff (those with new persistent cough, temperature ≥37.8°C, or anosmia or ageusia) was offered beginning on March 27, 2020. Asymptomatic health care workers were invited to participate in voluntary nasal and oropharyngeal swab PCR testing every 2 weeks and serologic testing every 2 months (with some participating more frequently for related studies) beginning on April 23, 2020, as previously described.[5,22] Staff were followed until November 30, 2020. Deidentified data were obtained from the Infections in Oxfordshire Research Database, which has generic research ethics committee, Health Research Authority, and Confidentiality Advisory Group approvals.

LABORATORY ASSAYS

Serologic investigations were performed with use of an anti-trimeric spike IgG enzyme-linked immunosorbent assay (ELISA), developed by the University of Oxford,[23,24] and an anti-nucleocapsid IgG assay (Abbott). See the Supplementary Appendix, available with the full text of this article at NEJM.org, for details on the assays and PCR tests.

STATISTICAL ANALYSIS

We classified health care workers according to their baseline antibody status. Those with only negative antibody assays were considered to be at risk for infection from their first antibody assay until either the end of the study or their first PCR-positive test, whichever occurred earlier. Those with a positive antibody assay were considered to be at risk for infection (or reinfection) from 60 days after their first positive antibody result to either the end of the study or their next PCR-positive test, whichever occurred earlier, irrespective of subsequent seroreversion (i.e., any negative antibody assay occurring later). The 60-day window was prespecified to exclude persistence of PCR-positive RNA after the index infection that led to seroconversion, on the basis of earlier reports of RNA persistence for 6 weeks or more.[22,25,26] Similarly, we considered only PCR-positive tests occurring at least 60 days after the previous PCR-positive test.

We used Poisson regression to model the incidence of PCR-positive infection per at-risk day according to baseline antibody status, adjusting for incidence over time, age, and participant-reported gender. Primary analyses used anti-spike IgG as-

say results, which were expected before the start of the study to be more closely related to neutralizing activity and protection from infection.[7,10] We also investigated anti-nucleocapsid antibody assay results and a combined model with three baseline antibody statuses (both assays negative, both positive, or only one positive). Sensitivity analyses investigated the effect of different asymptomatic testing rates according to antibody status and different follow-up windows (see the Supplementary Appendix).

RESULTS

BASELINE ANTI-SPIKE IGG ASSAYS AND PCR TESTING RATES

A total of 12,541 health care workers underwent measurement of baseline anti-spike antibodies; 11,364 (90.6%) were seronegative and 1177 (9.4%) seropositive at their first anti-spike IgG assay, and seroconversion occurred in 88 workers during the study (Table 1, and Fig. S1A in the Supplementary Appendix). Of 1265 seropositive health care workers, 864 (68%) recalled having had symptoms consistent with those of coronavirus disease 2019 (Covid-19), including symptoms that preceded the widespread availability of PCR testing for SARS-CoV-2; 466 (37%) had had a previous PCR-confirmed SARS-CoV-2 infection, of which 262 were symptomatic. Fewer seronegative health care workers (2860 [25% of the 11,364 who were seronegative]) reported prebaseline symptoms, and 24 (all symptomatic, 0.2%) were previously PCR-positive. The median age of seronegative and seropositive health care workers was 38 years (interquartile range, 29 to 49). Health care workers were followed for a median of 200 days (interquartile range, 180 to 207) after a negative antibody test and for 139 days at risk (interquartile range, 117 to 147) after a positive antibody test.

Rates of symptomatic PCR testing were similar in seronegative and seropositive health care workers: 8.7 and 8.0 tests per 10,000 days at risk, respectively (rate ratio, 0.92; 95% confidence interval [CI], 0.77 to 1.10). A total of 8850 health care workers had at least one postbaseline asymptomatic screening test; seronegative health care workers attended asymptomatic screening more frequently than seropositive health care workers (141 vs. 108 per 10,000 days at risk, respectively; rate ratio, 0.76; 95% CI, 0.73 to 0.80).

INCIDENCE OF PCR-POSITIVE RESULTS ACCORDING TO BASELINE ANTI-SPIKE IGG STATUS

Positive baseline anti-spike antibody assays were associated with lower rates of PCR-positive tests. Of 11,364 health care workers with a negative anti-spike IgG assay, 223 had a positive PCR test (1.09 per 10,000 days at risk), 100 during asymptomatic screening and 123 while symptomatic. Of 1265 health care workers with a positive anti-spike IgG assay, 2 had a positive PCR test (0.13 per 10,000 days at risk), and both workers were asymptomatic when tested. The incidence rate ratio for positive PCR tests in seropositive workers was 0.12 (95% CI, 0.03 to 0.47; P=0.002). The incidence of PCR-confirmed symptomatic infection in seronegative health care workers was 0.60 per 10,000 days at risk, whereas there were no confirmed symptomatic infections in seropositive health care workers. No PCR-positive results occurred in 24 seronegative, previously PCR-positive health care workers; seroconversion occurred in 5 of these workers during follow-up.

Incidence varied by calendar time (Fig. 1), reflecting the first (March through April) and second (October and November) waves of the pandemic in the United Kingdom, and was consistently higher in seronegative health care workers. After adjustment for age, gender, and month of testing (Table S1) or calendar time as a continuous variable (Fig. S2), the incidence rate ratio in seropositive workers was 0.11 (95% CI, 0.03 to 0.44; P=0.002). Results were similar in analyses in which follow-up of both seronegative and seropositive workers began 60 days after baseline serologic assay; with a 90-day window after positive serologic assay or PCR testing; and after random removal of PCR results for seronegative health care workers to match asymptomatic testing rates in seropositive health care workers (Tables S2 through S4). The incidence of positive PCR tests was inversely associated with anti-spike antibody titers, including titers below the positive threshold (P<0.001 for trend) (Fig. S3A).

ANTI-NUCLEOCAPSID IGG STATUS

With anti-nucleocapsid IgG used as a marker for prior infection in 12,666 health care workers (Fig. S1B and Table S5), 226 of 11,543 (1.10 per 10,000 days at risk) seronegative health care workers tested PCR-positive, as compared with 2 of 1172 (0.13 per 10,000 days at risk) antibody-positive health care workers (incidence rate ratio ad-

Table 1. Demographic Characteristics and SARS-CoV-2 PCR Testing for 12,541 Health Care Workers According to SARS-CoV-2 Anti-Spike IgG Status.*

Characteristic	Anti-Spike Seronegative at Baseline and throughout Follow-Up (N=11,276)	Anti-Spike Seronegative at Baseline, Converting to Seropositive† (N=88)	Anti-Spike Seropositive at Baseline (N=1177)
Age — yr			
Median (IQR)	38 (29–49)	41 (28–49)	38 (29–49)
Range	16–86	21–67	17–69
Gender — no. (%)‡			
Female	8360 (74.1)	68 (77)	835 (70.9)
Male	2900 (25.7)	20 (23)	339 (28.8)
Other	16 (0.1)	0	3 (0.3)
Race or ethnic group — no. (%)§			
White	8313 (73.7)	58 (66)	703 (59.7)
Asian	1719 (15.2)	20 (23)	287 (24.4)
Black	425 (3.8)	4 (5)	81 (6.9)
Chinese	121 (1.1)	0	9 (0.8)
Other	698 (6.2)	6 (7)	97 (8.2)
Role — no. (%)			
Nurse or health care assistant	3930 (34.9)	43 (49)	555 (47.2)
Physician	1671 (14.8)	4 (5)	184 (15.6)
Administrative staff	1452 (12.9)	10 (11)	95 (8.1)
Medical or nursing student	578 (5.1)	6 (7)	36 (3.1)
Laboratory staff	413 (3.7)	3 (3)	36 (3.1)
Physical, occupational or speech therapist	342 (3.0)	7 (8)	37 (3.1)
Porter or domestic worker	319 (2.8)	0	58 (4.9)
Security, estates, or catering staff	245 (2.2)	3 (3)	23 (2.0)
Other	2326 (20.6)	12 (14)	153 (13.0)
Symptoms resembling Covid-19 between February 1, 2020, and baseline serologic assay — no. (%)	2826 (25.1)	34 (39)¶	810 (68.8)
≥1 PCR test for symptoms before baseline — no. (%)	857 (7.6)	10 (11)	358 (30.4)
≥1 Positive PCR test with symptoms before baseline — no. (%)	19 (0.2)	5 (6)	239 (20.3)
Person-days of follow-up	2,036,358	7121 (while seronegative) 5076 (while seropositive)	152,983
Positive PCR during follow-up — no.			
Total	197	26‖	2
Symptomatic	106	17	0
Asymptomatic	91	9	2

* Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, IQR interquartile range, and PCR polymerase chain reaction.

† Those in whom seroconversion occurred were included in the analysis twice, once while they were at risk for infection and antibody-negative and then subsequently while they were antibody-positive and at risk for reinfection.

‡ Gender was reported by the participants. "Other" includes transgender and nondisclosed gender; the categories were combined owing to small numbers.

§ Race and ethnic group were reported by the participants.

¶ Twenty additional health care workers in whom seroconversion occurred reported symptoms between baseline testing and seroconversion.

‖ All PCR-positive results in workers with seroconversion occurred while they were in the seronegative follow-up group. A single health care worker in whom seroconversion occurred first tested PCR-positive while asymptomatic, and is recorded in the asymptomatic category, but also had a further PCR-positive result when symptomatic 8 days later.

justed for calendar time, age, and gender, 0.11; 95% CI, 0.03 to 0.45; P=0.002) (Table S6). The incidence of PCR-positive results fell with increasing anti-nucleocapsid antibody titers (P<0.001 for trend) (Fig. S3B).

A total of 12,479 health care workers had both anti-spike and anti-nucleocapsid baseline results (Fig. S1C and Tables S7 and S8); 218 of 11,182 workers (1.08 per 10,000 days at risk) with both immunoassays negative had subsequent PCR-positive tests, as compared with 1 of 1021 workers (0.07 per 10,000 days at risk) with both baseline assays positive (incidence rate ratio, 0.06; 95% CI, 0.01 to 0.46) and 2 of 344 workers (0.49 per 10,000 days at risk) with mixed antibody assay results (incidence rate ratio, 0.42; 95% CI, 0.10 to 1.69).

SEROPOSITIVE HEALTH CARE WORKERS WITH PCR-POSITIVE RESULTS

Three seropositive health care workers subsequently had PCR-positive tests for SARS-CoV-2 infection (one with anti-spike IgG only, one with anti-nucleocapsid IgG only, and one with both antibodies). The time between initial symptoms or seropositivity and subsequent positive PCR testing ranged from 160 to 199 days. Information on the workers' clinical histories and on PCR and serologic testing results is shown in Table 2 and Figure S4.

Only the health care worker with both antibodies had a history of PCR-confirmed symptomatic infection that preceded serologic testing; after five negative PCR tests, this worker had one positive PCR test (low viral load: cycle number, 21 [approximate equivalent cycle threshold, 31]) at day 190 after infection while the worker was asymptomatic, with subsequent negative PCR tests 2 and 4 days later and no subsequent rise in antibody titers. If this worker's single PCR-positive result was a false positive, the incidence rate ratio for PCR positivity if anti-spike IgG–seropositive would fall to 0.05 (95% CI, 0.01 to 0.39) and if anti-nucleocapsid IgG–seropositive would fall to 0.06 (95% CI, 0.01 to 0.40).

A fourth dual-seropositive health care worker had a PCR-positive test 231 days after the worker's index symptomatic infection, but retesting of the worker's sample was negative twice, which suggests a laboratory error in the original PCR result. Subsequent serologic assays showed waning anti-nucleocapsid and stable anti-spike antibodies.

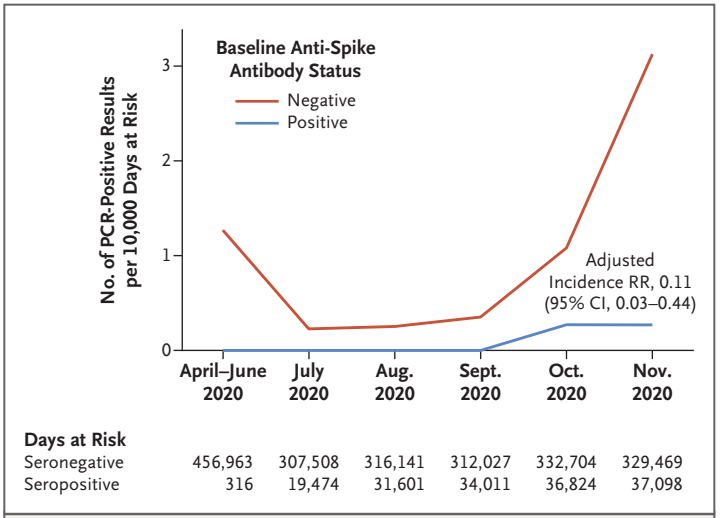

Figure 1. Observed Incidence of SARS-CoV-2–Positive PCR Results According to Baseline Anti-Spike IgG Antibody Status.

The incidence of polymerase-chain-reaction (PCR) tests that were positive for SARS-CoV-2 infection during the period from April through November 2020 is shown per 10,000 days at risk among health care workers according to their antibody status at baseline. In seronegative health care workers, 1775 PCR tests (8.7 per 10,000 days at risk) were undertaken in symptomatic persons and 28,878 (141 per 10,000 days at risk) in asymptomatic persons; in seropositive health care workers, 126 (8.0 per 10,000 days at risk) were undertaken in symptomatic persons and 1704 (108 per 10,000 days at risk) in asymptomatic persons. RR denotes rate ratio.

DISCUSSION

In this longitudinal cohort study, the presence of anti-spike antibodies was associated with a substantially reduced risk of PCR-confirmed SARS-CoV-2 infection over 31 weeks of follow-up. No symptomatic infections and only two PCR-positive results in asymptomatic health care workers were seen in those with anti-spike antibodies, which suggests that previous infection resulting in antibodies to SARS-CoV-2 is associated with protection from reinfection for most people for at least 6 months. Evidence of postinfection immunity was also seen when anti-nucleocapsid IgG or the combination of anti-nucleocapsid and anti-spike IgG was used as a marker of previous infection.

The incidence of SARS-CoV-2 infection was inversely associated with baseline anti-spike and anti-nucleocapsid antibody titers, including titers below the positive threshold for both assays, such that workers with high "negative" titers were relatively protected from infection. In addition to the 24 seronegative health care workers with a previ-

Table 2. Demographic, Clinical, and Laboratory Characteristics of Health Care Workers with Possible SARS-CoV-2 Reinfection.

Health Care Worker	Baseline Serologic Assay	No. of Days between Episodes*	Clinical Characteristics	Timing of PCR, Ct Value, and Assay	Follow-up Serologic Assay
Worker 1: White female physician, 25–29 yr of age	Anti-spike IgG: not detected **Anti-nucleocapsid IgG: detected**	160	1st episode: asymptomatic 2nd episode: symptomatic (mild, febrile illness)	1st episode: not done (before start of asymptomatic testing) 2nd episode: CN 10.6 (Abbott assay), repeat extraction and PCR on same sample Ct 19.0 (Thermo Fisher assay)	Dual antibody seroconversion with a rise in anti-nucleocapsid IgG titer
Worker 2: White female nurse, 55–59 yr of age	**Anti-spike IgG: detected** **Anti-nucleocapsid IgG: detected**	190	1st episode: symptomatic (mild, Covid-19–like symptoms) 2nd episode: asymptomatic	1st episode: Ct 36.0 (PHE assay) 2nd episode: CN 21.2 (Abbott assay), repeat PCR on day 2 and day 4 both negative	No rise in antibody titers
Worker 3: White female administrator with patient contact, 50–54 yr of age	**Anti-spike IgG: detected** Anti-nucleocapsid IgG: not detected	199	1st episode: symptomatic (mild) 2nd episode: asymptomatic when tested (transient myalgia shortly after influenza vaccine 1 week earlier)	1st episode: PCR-negative 2nd episode: CN 12.6 (Abbott assay), repeat PCR on day 2 Ct 24.0 (Altona assay)	Dual antibody seroconversion, with a rise in anti-spike IgG titer

* The number of days between episodes was calculated from the date of symptom onset if the index infection was symptomatic (as it was for health care Workers 2 and 3) or the date of the first clinic attendance if the presumed first episode was asymptomatic with no PCR performed (as it was for Worker 1). Both baseline serologic assays for Worker 1 were repeated and confirmed. A single positive PCR result for Worker 1 was confirmed by repeat nucleic acid extraction. Abbott PCR assay cycle number (CN) values are approximately equivalent to cycle threshold (Ct) values 10 units higher (e.g., CN 21 is approximately equivalent to Ct 31). See Figure S4 for quantitative antibody results. All PCR tests listed were performed at Oxford University Hospitals.

ous positive PCR test, it is likely that other health care workers with baseline titers below assay thresholds, which were set to ensure high specificity,[23] had been previously infected with SARS-CoV-2 and had low peak postinfection titers or rising or waning responses at testing.[5]

Two of the three seropositive health care workers who had subsequent PCR-positive tests had discordant baseline antibody results, a finding that highlights the imperfect nature of antibody assays as markers of previous infection. Neither worker had a PCR-confirmed primary SARS-CoV-2 infection. Subsequent symptomatic infection developed in one worker, and both workers had subsequent dual antibody seroconversion. It is plausible that one or both had false positive baseline antibody results (e.g., from immunoassay interference[27]). The health care worker in whom both anti-spike and anti-nucleocapsid antibodies were detected had previously had PCR-confirmed SARS-CoV-2 infection; the subsequent PCR-positive result with a low viral load was not confirmed on repeat testing and was not associated with a change in IgG response. These results could be consistent with a reexposure to SARS-CoV-2 that did not lead to symptoms but could also plausibly have arisen from undetected laboratory error; although contemporaneous retesting of the PCR-positive sample was not undertaken, samples tested 2 and 4 days later were both negative. If the PCR-positive result is incorrect, the incidence rate ratio for PCR positivity if anti-spike IgG–seropositive would fall to 0.05. We detected and did not include in our analysis a presumed false positive PCR test in a fourth seropositive health care worker.

Owing to the low number of reinfections in seropositive health care workers, we cannot say whether past seroconversion or current antibody levels determine protection from infection or define which characteristics are associated with reinfection. Similarly, we cannot say whether protection is conferred through the antibodies we measured or through T-cell immunity, which we did not assess. It was not possible to use sequencing to compare primary and subsequent infections, since only one of the three seropositive health care workers with a subsequent PCR-positive test had PCR-confirmed primary infection and that worker's original sample was not stored. Our study was relatively short, with up to 31 weeks of follow-up. Ongoing follow-up is needed

in this and other cohorts, including the use of markers of both humoral and cellular immunity to SARS-CoV-2, to assess the magnitude and duration of protection from reinfection, symptomatic disease, and hospitalization or death and the effect of protection on transmission.

Health care workers were enrolled in a voluntary testing program with a flexible follow-up schedule, which led to different attendance frequencies. Although health care workers were offered asymptomatic PCR testing every 2 weeks, the workers attended less frequently than that (mean, once every 10 to 13 weeks). Therefore, asymptomatic infection is likely to have been underascertained. In addition, as staff were told their antibody results, "outcome ascertainment bias" occurred, with seropositive staff attending asymptomatic screening less frequently. However, a sensitivity analysis suggests that the differing attendance rates did not substantially alter our findings. Staff were told to follow guidance on social distancing and use of personal protective equipment and to attend testing if Covid-19 symptoms developed, even if the worker had been previously PCR- or antibody-positive. This is reflected in the similar rates of testing of symptomatic seropositive and seronegative health care workers.

Some health care workers were lost to follow-up after terminating employment at our hospitals; this was likely to have occurred at similar rates in seropositive and seronegative staff. Not all PCR-positive results from government symptomatic testing sites were communicated to the hospital. This is a study of predominantly healthy adult health care workers 65 years of age or younger; further studies are needed to assess postinfection immunity in other populations, including children, older adults, and persons with coexisting conditions, including immunosuppression.

In this study, we found a substantially lower risk of reinfection with SARS-CoV-2 in the short term among health care workers with anti-spike antibodies and those with anti-nucleocapsid antibodies than among those who were seronegative.

The views expressed in this article are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, the Department of Health, or Public Health England.

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APPENDIX

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Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

ABSTRACT

BACKGROUND

World Health Organization expert groups recommended mortality trials of four repurposed antiviral drugs — remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a — in patients hospitalized with coronavirus disease 2019 (Covid-19).

METHODS

We randomly assigned inpatients with Covid-19 equally between one of the trial drug regimens that was locally available and open control (up to five options, four active and the local standard of care). The intention-to-treat primary analyses examined in-hospital mortality in the four pairwise comparisons of each trial drug and its control (drug available but patient assigned to the same care without that drug). Rate ratios for death were calculated with stratification according to age and status regarding mechanical ventilation at trial entry.

RESULTS

At 405 hospitals in 30 countries, 11,330 adults underwent randomization; 2750 were assigned to receive remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir (without interferon), 2063 to interferon (including 651 to interferon plus lopinavir), and 4088 to no trial drug. Adherence was 94 to 96% midway through treatment, with 2 to 6% crossover. In total, 1253 deaths were reported (median day of death, day 8; interquartile range, 4 to 14). The Kaplan–Meier 28-day mortality was 11.8% (39.0% if the patient was already receiving ventilation at randomization and 9.5% otherwise). Death occurred in 301 of 2743 patients receiving remdesivir and in 303 of 2708 receiving its control (rate ratio, 0.95; 95% confidence interval [CI], 0.81 to 1.11; P=0.50), in 104 of 947 patients receiving hydroxychloroquine and in 84 of 906 receiving its control (rate ratio, 1.19; 95% CI, 0.89 to 1.59; P=0.23), in 148 of 1399 patients receiving lopinavir and in 146 of 1372 receiving its control (rate ratio, 1.00; 95% CI, 0.79 to 1.25; P=0.97), and in 243 of 2050 patients receiving interferon and in 216 of 2050 receiving its control (rate ratio, 1.16; 95% CI, 0.96 to 1.39; P=0.11). No drug definitely reduced mortality, overall or in any subgroup, or reduced initiation of ventilation or hospitalization duration.

CONCLUSIONS

These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. (Funded by the World Health Organization; ISRCTN Registry number, ISRCTN83971151; ClinicalTrials.gov number, NCT04315948.)

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*A complete list of the World Health Organization (WHO) Solidarity trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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In February 2020, a World Health Organization (WHO) research forum on coronavirus disease 2019 (Covid-19) recommended evaluation of treatments in large, randomized trials,[1] and other WHO expert groups identified four repurposed antiviral drugs that might have at least a moderate effect on mortality: remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a.[2] In March 2020, the WHO began a large, simple, international, open-label, randomized trial involving hospital inpatients to evaluate the effects of these four drugs on in-hospital mortality. The trial was adaptive; unpromising drugs could be dropped and others added. Hydroxychloroquine, lopinavir, and interferon were eventually dropped from the trial, but others, such as monoclonal antibodies, will be added. We report interim results for the original four drugs.

Methods

Trial Design

The protocol, which was published previously[3] and is available with the full text of this article at NEJM.org, was designed to involve hundreds of hospitals in dozens of countries. Trial procedures were minimal but rigorous, with data entry through a cloud-based Good Clinical Practice–compliant clinical data management system that recorded demographic characteristics, respiratory support, coexisting illnesses, and local availability of trial drugs before generating the treatment assignment. Written informed consent was provided by patients, or if they were unable to do so, by their legal representatives.[3] Consent forms were retained by signatories and encrypted for records. The enrollment of patients who provided consent took just a few minutes. Eligible patients were 18 years of age or older, were hospitalized with a diagnosis of Covid-19, were not known to have received any trial drug, were not expected to be transferred elsewhere within 72 hours, and, in the physician's view, had no contraindication to any trial drug.

The same cloud-based system was used to report any suspected unexpected serious adverse reaction. It was also used to record death in the hospital or discharge alive (with documentation of respiratory support in the hospital, trial-drug timing, use of nontrial drugs, and probable cause of death). National and global monitors raised or resolved queries (or both) and checked progress and completeness.

Treatment Regimens

The trial drugs were remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a (given with lopinavir until July 4). The hydroxychloroquine, lopinavir, and interferon regimens were discontinued for futility on, respectively, June 19, July 4, and October 16, 2020. Participants were randomly assigned in equal proportions to receive no trial drug or one of the trial drug regimens that was locally available (up to five options; all patients were to receive the local standard of care). In this open-label trial, no placebos were used.

The controls for a drug were patients assigned to the standard of care at a time and place in which that drug was locally available (except that when interferon was being given only with lopinavir, its controls were patients given only lopinavir). Assignment to the standard of care at a hospital in which more than one trial drug was available would put that patient into the control group for each of those drugs. Hence, there was partial overlap among the four control groups. Each comparison between a trial drug and its control, however, was evenly randomized (in a 1:1 ratio) and unbiased, because both groups were affected equally by differences between countries or hospitals and by time trends in patient characteristics or the standard of care.

Daily doses were those already used for other diseases, but to maximize any efficacy without undue cardiac risk, the hydroxychloroquine dose was based on that for amoebic liver abscess rather than the lower dose for malaria.[4] (Hydroxychloroquine slightly prolongs the QT interval, and an unduly high dose or rapid administration might cause arrhythmias or hypotension.) Treatments stopped at discharge.

The regimen for remdesivir (intravenous) was 200 mg on day 0 and 100 mg on days 1 through 9. The regimen for hydroxychloroquine (oral) was four tablets at hour 0, four tablets at hour 6, and, starting at hour 12, two tablets twice daily for 10 days. Each tablet contained 200 mg of hydroxychloroquine sulfate (155 mg of hydroxychloroquine base per tablet; a little-used alternative involved 155 mg of chloroquine base per tablet). The regimen for lopinavir (oral) was two tablets twice daily for 14 days. Each tablet contained 200 mg of lopinavir (plus 50 mg of ritonavir, to slow hepatic lopinavir clearance). Other formulations were not provided, so patients who were receiving mechanical ventilation received

no trial lopinavir while they were unable to swallow. The regimen for interferon (mainly subcutaneous) was three doses over a period of 6 days (the day of randomization and days 3 and 6) of 44 μg of subcutaneous interferon beta-1a; where intravenous interferon was available, patients receiving high-flow oxygen, ventilation, or extracorporeal membrane oxygenation (ECMO) were instead to be given 10 μg intravenously daily for 6 days.

OUTCOMES

The protocol-specified primary objective was to assess effects on in-hospital mortality (i.e., death during the original hospitalization; follow-up ceased at discharge), regardless of whether death occurred before or after day 28. The only protocol-specified secondary outcomes were the initiation of mechanical ventilation and hospitalization duration. Although no placebos were used, appropriate analyses of these secondary outcomes can still be informative. Add-on studies that were led from Canada, France, India, and Norway recorded other outcomes (not reported here).

OVERSIGHT AND FUNDING

The trial was registered at the ISRCTN Registry and ClinicalTrials.gov, with the core protocol approved by the WHO ethics review committee and local protocols approved by national ethics committees and regulatory authorities. Trial conduct was in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The only exclusions from the intention-to-treat analyses were the few patients with no, or uncertain, consent to follow-up. All other randomly assigned patients were included. The WHO was the global cosponsor and governments the national cosponsors, with trial governance by the executive group of the international steering committee. External statistical analyses for the independent data and safety monitoring committee were unseen by the executive group or the WHO, with two exceptions. After outside evidence of the futility of hydroxychloroquine and lopinavir became available, the executive group requested unblinded analyses of the findings just for these two drugs. In addition, after deciding in a blinded fashion to report all interim results, the executive group revised this manuscript, which has been drafted only by the WHO trial team and external statisticians. Remdesivir was donated by Gilead Sciences, hydroxychloroquine by Mylan, lopinavir by AbbVie, Cipla, and Mylan, and interferon beta-1a by Merck (subcutaneous) and Faron Pharmaceuticals (intravenous).

SAMPLE SIZE

The protocol stated, "The larger the number entered the more accurate the results will be, but numbers entered will depend on how the epidemic develops. . . . it may be possible to enter several thousand hospitalised patients with relatively mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the trial." The executive group, whose members were unaware of the findings, made the decision to release the interim results.

STATISTICAL ANALYSIS

The intention-to-treat analyses related outcome to assigned treatment. The primary analyses were of in-hospital mortality among all randomly assigned patients (each drug vs. its control). The only protocol-specified subgroup analyses involved patients who already had severe disease at entry and those who did not. Severity was not protocol-defined, but separate analyses are provided regarding those receiving some supplemental oxygen or none and for those already receiving ventilation at entry or not. Rate ratios for death (or, equivalently, hazard ratios) and P values are from log-rank analyses stratified according to six strata of age and ventilation status at entry. Graphs of mortality according to time are from unstratified Kaplan–Meier methods, with denominators chosen to yield in-hospital mortality. (For example, if 99 of 100 patients were discharged alive before the last one died, the in-hospital mortality would be 1% and at the time of that death the probability of not having died in the hospital was multiplied by 99/100; this denominator included those already discharged.)

The risk on day *N* was calculated by first excluding patients with an outcome not reported or an entry fewer than *N* days before data-set closure (or transferred elsewhere before day *N*); then, the number of in-hospital deaths on day *N* was divided by the total number of patients in the hospital on day *N* or discharged alive before day *N*. This denominator (or "risk set"), which includes those discharged before day *N*, was also used to calculate the contribution of day *N* to log-rank

analysis and Cox analysis of in-hospital mortality. Denominators for the few deaths on day 0, but not on later days, included patients with no follow-up reported (because if any patient died on the day of randomization, this would probably have been reported).

If the stratified log-rank observed minus expected number of deaths is O−E with variance V, the $\log_e$ rate ratio is calculated as (O−E)/V with variance 1/V and a normal distribution. If event times are accurate and b is the log hazard ratio and L(b) the Cox log-likelihood, the first and second derivatives of L(b) at b=0 are (O−E) and −V.[5] Forest plots (with 95% confidence intervals only for overall trial results; otherwise, with 99% confidence intervals to allow for subgroup multiplicity) and chi-square statistics (sum of $[O-E]^2/V$, without any P value) help interpret any heterogeneity of rate ratios between subgroups. All rate ratios describe proportional risk reductions; absolute risk reductions would also depend on background risks. Analyses were performed with the use of SAS software, version 9.4, and R software, version 4.02.

Meta-analyses of the major trial results are based on the inverse-variance–weighted average of $b=\log_e$ rate ratio from each stratum of each trial, with the use of odds ratios when hazard ratios or rate ratios for death were unavailable. (This weighted average is derived from the sums of [O−E] and of V over strata.[5]) In general, the more deaths in a stratum the larger V is and, correspondingly, the smaller is the variance of the $\log_e$ rate ratio, so the more weight that stratum gets. The variance that is attributed to the result in each stratum and to the overall weighted average reflects only the play of chance at randomization. Homogeneity of different rate ratios is not needed for such a weighted average to be informative.

RESULTS

PATIENT CHARACTERISTICS AND ADHERENCE

From March 22 to October 4, 2020, a total of 11,330 patients were entered in the trial from 405 hospitals in 30 countries in all six WHO regions. Of these patients, 64 (0.6%) had no, or uncertain, consent to follow-up, which left 11,266 in the intention-to-treat analyses. A total of 2750 patients were assigned to receive remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir (without interferon), 2063 to interferon (including 651 to interferon plus lopinavir), and 4088 to no trial drug (Fig. 1); reporting is 97% complete for those who were entered more than 1 month earlier and 99.7% complete for those who were entered more than 3 months earlier. All 3 patients for whom the diagnosis of Covid-19 was later ruled out were included in the analyses and survived. Table 1 shows patient characteristics: 9120 (81%) were younger than 70 years of age, 6985 (62%) were male, 2768 (25%) had diabetes, 916 (8%) were already receiving ventilation, and 7002 (62%) underwent randomization on days 0 or 1. For each drug, patient characteristics were well balanced by the unstratified 1:1 randomization between it and its control. Deaths were at a median of day 8 (interquartile range, 4 to 14), and discharges were at a median of day 8 (interquartile range, 5 to 12).

There were 1253 in-hospital deaths (the primary outcome, including those before and after day 28). The Kaplan–Meier risk of in-hospital death to day 28 was 11.8%; a few in-hospital deaths occurred later. This risk depended on several factors, particularly age (20.4% if ≥70 years and 6.2% if <50 years) and ventilation status (39.0% if the patient was already receiving ventilation and 9.5% otherwise).

Table 1 also shows adherence. For remdesivir, the scheduled treatment duration was 10 days (or to death or discharge). Of those assigned to remdesivir, 98% began treatment. Midway through this period, 96% of the patients were still taking it (as compared with only 2% of those in the relevant group). Similarly, for other drugs adherence midway was 94% to 95%, and crossover was 2 to 6%. Trial treatments ceased on schedule (if the patient was still in the hospital). Absolute differences (active vs. control) in the use of glucocorticoids (i.e., corticosteroids) and other nontrial drugs were 0.2 to 3.5 percentage points (Table S2 in the Supplementary Appendix, available at NEJM.org).

PRIMARY OUTCOME

For each pairwise comparison of a drug and its control, Figure 2 and Figures S1 through S5 show the results of unstratified Kaplan–Meier analyses of in-hospital mortality (with numbers of patients who underwent randomization, in-hospital deaths each week and after day 28, and weekly denominators), along with rate ratios for death stratified according to age and ventilation

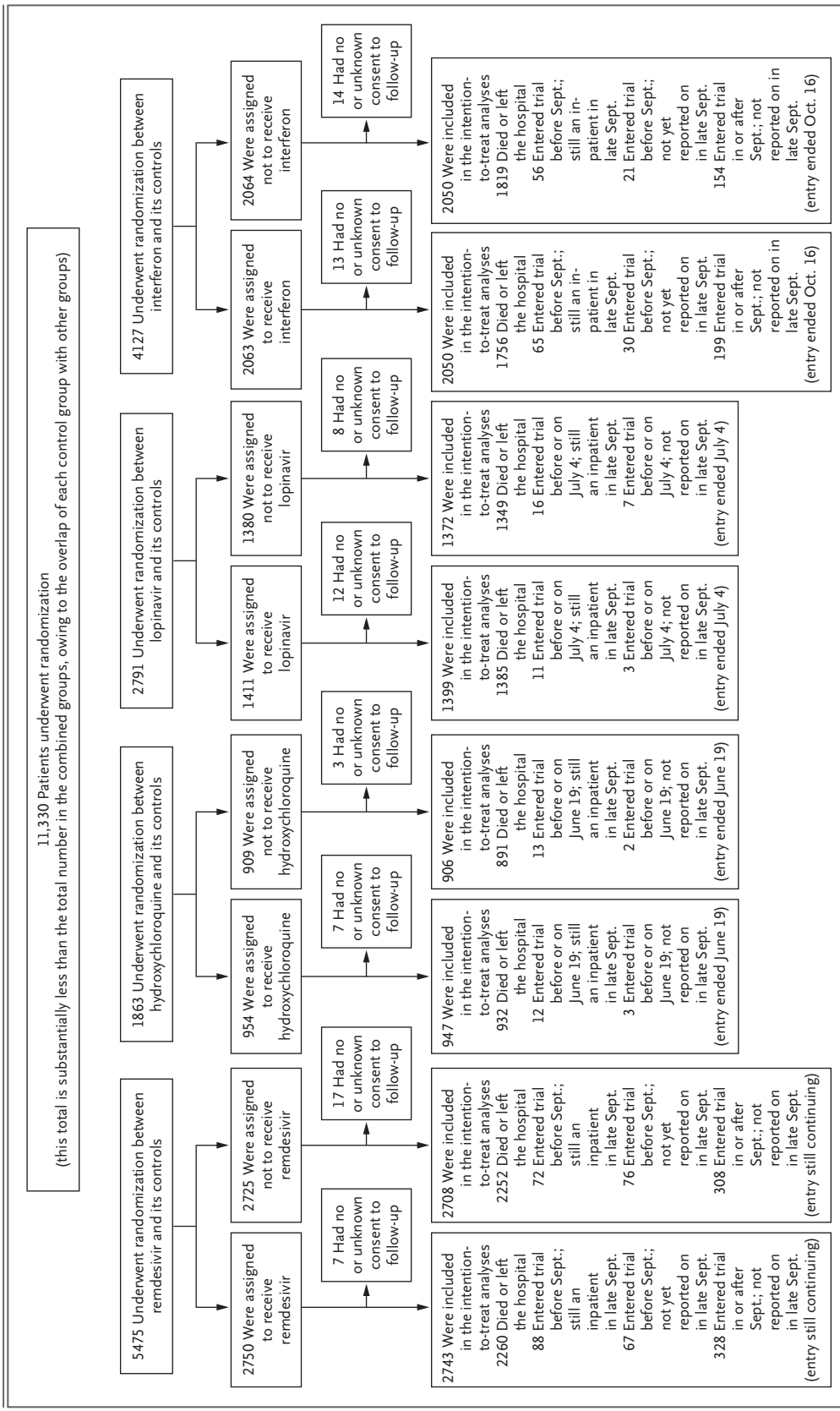

Figure 1. Information to October 4, 2020, on Trial Entry, Follow-up, and Intention-to-Treat Analyses.

After it was determined which treatments were locally available, random assignment (with equal probability) was between the local standard of care and the available treatments. After the exclusion of 64 of 11,330 patients (0.6%) who had provided either no or uncertain consent regarding follow-up, 11,266 remained in the intention-to-treat analyses. Each pairwise intention-to-treat analysis was between a particular trial drug and its control (i.e., patients who could have been assigned to a particular trial drug but were concurrently assigned to the same care without it). There is partial overlap of each control group with other groups.

Table 1. Entry Characteristics According to Random Assignment, and Adherence to That Assignment.*

Variable	Any Intention-to-Treat Analysis (N=11,266)			Remdesivir vs. Its Control		Hydroxychloroquine vs. Its Control		Lopinavir vs. Its Control		Interferon vs. Its Control†	
	Entered Trial	Died in Hospital‡	28-Day Mortality§	Active (N=2743)	Control (N=2708)	Active (N=947)	Control (N=906)	Active (N=1399)	Control (N=1372)	Active (N=2050)	Control (N=2050)
	no. (%)	*no.*	*%*	*no. of patients*							
Entry characteristics											
Age											
<50 yr	3995 (35)	237	6.2	961	952	335	317	511	501	720	697
50–69 yr	5125 (45)	618	12.8	1282	1287	410	396	597	596	934	973
≥70 yr	2146 (19)	398	20.4	500	469	202	193	291	275	396	380
Respiratory support											
No supplemental oxygen at entry	3204 (28)	78	2.5	661	664	345	341	528	539	482	490
Supplemental oxygen at entry	7146 (63)	844	12.8	1828	1811	517	483	759	719	1429	1430
Already receiving ventilation	916 (8)	331	39.0	254	233	85	82	112	114	139	130
Lesions in both lungs											
No	1266 (11)	49	3.7	287	259	154	170	235	256	162	155
Yes	8832 (78)	1043	12.7	2175	2153	656	618	985	945	1723	1718
Not imaged at entry	1168 (10)	161	14.9	281	296	137	118	179	171	165	177
Previous days in the hospital											
0	3289 (29)	319	9.8	724	712	296	281	423	403	678	677
1	3713 (33)	384	10.8	917	938	317	312	442	445	681	662
≥2	4264 (38)	550	14.6	1102	1058	334	313	534	524	691	711
Geographic region											
Europe and Canada¶	2488 (22)	188	7.8	715	698	286	267	349	350	254	244
Latin America‖	1941 (17)	400	22.7	470	514	97	96	145	148	474	478
Asia and Africa**	6837 (61)	665	10.3	1558	1496	564	543	905	874	1322	1328
Other characteristics											
Male sex	6985 (62)	852	13.0	1706	1725	574	535	851	802	1303	1278
Current smoker	830 (7)	93	11.8	178	161	92	82	141	124	136	138

Coexisting conditions											
Diabetes	2768 (25)	379	14.7	707	666	199	205	341	324	489	537
Heart disease	2337 (21)	319	14.7	571	567	193	194	289	290	427	456
Chronic lung disease	635 (6)	102	17.2	151	145	62	66	95	87	114	109
Asthma	529 (5)	56	11.5	139	139	41	46	65	56	75	97
Chronic liver disease	135 (1)	21	17.2	36	41	15	14	15	23	11	22
Adherence to assigned treatment											
Percent taking trial drug midway through scheduled duration†††‡‡				96	2	95	6	94	2	94	2
Percent ever reported as discharged who were still in the hospital at various times††											
On day 7				69	59	64	54	68	59	55	51
On day 14				22	19	23	20	31	22	19	18
On day 21				9	8	11	10	12	11	8	7

* A total of 64 patients who did not provide clear informed consent regarding follow-up were excluded. Comparisons are of each trial drug with concurrent assignment to the same treatment without it. Because the control groups overlap, the total number (11,266) is less than the sum of the numbers in the pairwise comparisons. The few patients (always <0.4%) with a particular characteristic not yet known were merged with the largest category of that characteristic: 33 were merged with male sex, 40 were merged with an age of 50 to 69, and 45 were merged with previous days in the hospital of 2 or more.

† Interferon randomization was interferon plus lopinavir as compared with lopinavir until July 4, 2020, then it was interferon as compared with the local standard of care.

‡‡ Shown are any in-hospital deaths, regardless of whether they occurred before or after day 28 (total, 1253 deaths).

§§ Shown is the Kaplan–Meier 28-day risk of in-hospital death, expressed as a percentage (overall value, 11.8%). Percentages may not total 100 because of rounding.

¶¶ Countries in Europe were Albania, Austria, Belgium, Finland, France, Ireland, Italy, Lithuania, Luxembourg, North Macedonia, Norway, Spain, and Switzerland.

‖‖ Countries included Argentina, Brazil, Colombia, Honduras, and Peru.

** Countries included Egypt, India, Indonesia, Iran, Kuwait, Lebanon, Malaysia, Pakistan, the Philippines, Saudi Arabia, and South Africa.

†† Percentage of patients (rather than number of patients) is shown for this variable.

‡‡ Adherence was calculated only among patients who died or were discharged alive and was defined as the percentage of patients who were taking the trial drug midway through its scheduled duration (or midway through the time from entry to death or discharge, if this was shorter).

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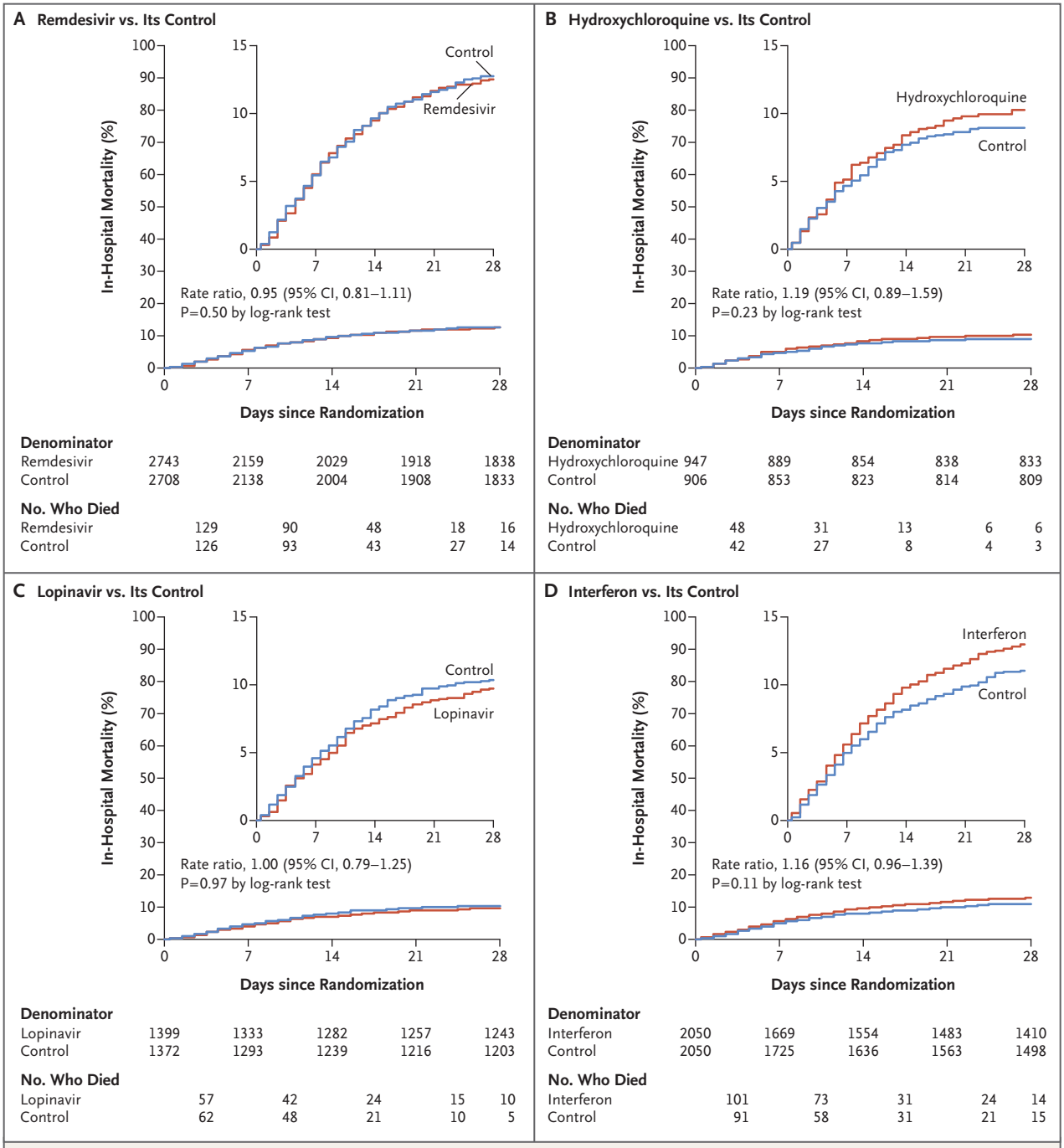

Figure 2. Effects of Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon on In-Hospital Mortality.

Shown are Kaplan–Meier graphs of in-hospital mortality at any time (the primary outcome), comparing each treatment with its control without standardization for any initial patient characteristics. Insets show the same data on an expanded y axis. The rate ratios for death were standardized for age and for ventilation status at entry. Denominators for the few events on day 0, but not thereafter, include patients with no follow-up. Numbers of deaths are by week, and then deaths after day 28. CI denotes confidence interval.

status; Figure 3 shows the stratified rate ratios according to age and according to ventilation status. No trial drug had any definite effect on mortality, either overall (each P>0.10) or in any subgroup defined according to age, ventilation status at entry, other entry characteristics, geographic region, or glucocorticoid use (Figs. S6 through S9).

Death occurred in 301 of 2743 patients receiv-

Subgroup	Active Treatment	Control	Log-Rank Statistics for No. of Deaths in Active-Treatment Group O−E	Variance	Rate Ratio for Death (99% CI; 95% CI for total)
	no. of deaths reported/no. of patients (%)				
Remdesivir					
Age at entry					
<50 yr	61/961 (6.9)	59/952 (6.8)	2.3	29.8	1.08 (0.67–1.73)
50–69 yr	154/1282 (13.8)	161/1287 (14.2)	−7.6	77.5	0.91 (0.68–1.21)
≥70 yr	86/500 (20.5)	83/469 (21.6)	−2.9	41.5	0.93 (0.63–1.39)
Respiratory support at entry					
No mechanical ventilation	203/2489 (9.4)	232/2475 (10.6)	−15.8	108.0	0.86 (0.67–1.11)
Mechanical ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Total	**301/2743 (12.5)**	**303/2708 (12.7)**	**−8.3**	**148.8**	**0.95 (0.81–1.11)**
Heterogeneity around total: χ^2_3=3.9					P=0.50
Hydroxychloroquine					
Age at entry					
<50 yr	19/335 (5.7)	19/317 (5.8)	0.9	9.2	1.10 (0.47–2.57)
50–69 yr	55/410 (12.1)	31/396 (7.1)	10.8	21.2	1.66 (0.95–2.91)
≥70 yr	30/202 (14.0)	34/193 (17.8)	−3.5	15.8	0.80 (0.42–1.53)
Respiratory support at entry					
No mechanical ventilation	69/862 (7.4)	57/824 (6.6)	4.7	31.4	1.16 (0.73–1.84)
Mechanical ventilation	35/85 (39.2)	27/82 (32.3)	3.4	14.8	1.26 (0.65–2.46)
Total	**104/947 (10.2)**	**84/906 (8.9)**	**8.1**	**46.2**	**1.19 (0.89–1.59)**
Heterogeneity around total: χ^2_3=5.0					P=0.23
Lopinavir					
Age at entry					
<50 yr	20/511 (3.6)	27/501 (4.9)	−3.0	11.7	0.77 (0.36–1.64)
50–69 yr	66/597 (9.8)	57/596 (9.1)	2.7	30.4	1.09 (0.68–1.74)
≥70 yr	62/291 (20.4)	62/275 (22.7)	0.0	30.2	1.00 (0.63–1.60)
Respiratory support at entry					
No mechanical ventilation	113/1287 (8.1)	111/1258 (8.7)	−1.6	55.6	0.97 (0.69–1.37)
Mechanical ventilation	35/112 (28.1)	35/114 (28.7)	1.3	16.7	1.08 (0.57–2.03)
Total	**148/1399 (9.7)**	**146/1372 (10.3)**	**−0.4**	**72.3**	**1.00 (0.79–1.25)**
Heterogeneity around total: χ^2_3=1.2					P=0.97
Interferon					
Age at entry					
<50 yr	48/720 (7.5)	35/697 (5.3)	7.5	20.6	1.44 (0.82–2.54)
50–69 yr	122/934 (14.3)	108/973 (11.4)	13.3	56.9	1.26 (0.90–1.78)
≥70 yr	73/396 (19.9)	73/380 (20.9)	−4.0	35.8	0.89 (0.58–1.38)
Respiratory support at entry					
No mechanical ventilation	188/1911 (10.9)	176/1920 (9.5)	9.1	90.3	1.11 (0.84–1.45)
Mechanical ventilation	55/139 (42.4)	40/130 (33.8)	7.7	23.0	1.40 (0.82–2.40)
Total	**243/2050 (12.9)**	**216/2050 (11.0)**	**16.8**	**113.3**	**1.16 (0.96–1.39)**
Heterogeneity around total: χ^2_3=4.8					P=0.11

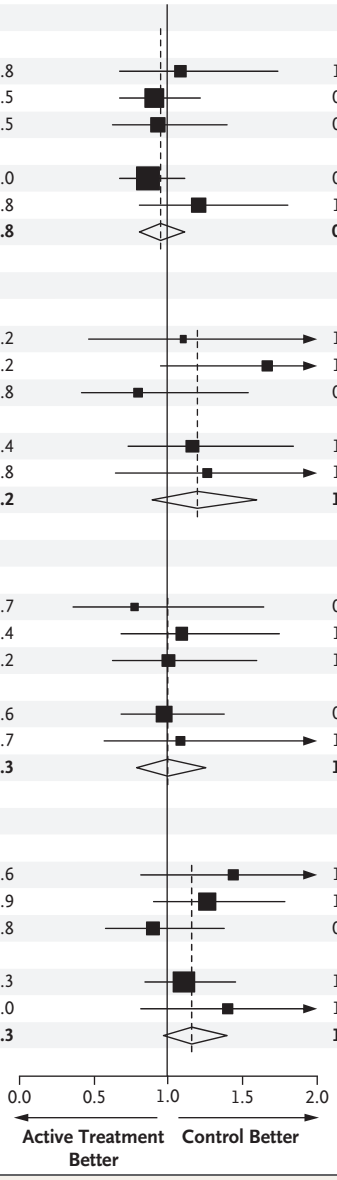

Figure 3. Rate Ratios for In-Hospital Death, Subdivided by Age and Respiratory Support at Trial Entry.

Analyses in subgroups of age are stratified according to respiratory status at trial entry and vice versa, so each total is stratified for both factors. The percentages show Kaplan–Meier 28-day mortality. O−E denotes the observed minus expected number of deaths in patients assigned to active treatment. Diamonds show 95% confidence intervals for treatment effects. Squares and horizontal lines show treatment effects in particular subgroups and their 99% confidence intervals, with an arrow if the upper 99% confidence limit is outside the range shown. The area of each square is proportional to the variance of O−E in the subgroup it describes.

ing remdesivir and in 303 of 2708 receiving its control (rate ratio, 0.95; 95% confidence interval [CI], 0.81 to 1.11; P=0.50), in 104 of 947 patients receiving hydroxychloroquine and in 84 of 906 receiving its control (rate ratio, 1.19; 95% CI, 0.89 to 1.59; P=0.23), in 148 of 1399 patients receiving lopinavir and in 146 of 1372 receiving its control (rate ratio, 1.00; 95% CI, 0.79 to 1.25; P=0.97), and in 243 of 2050 patients receiving interferon and in 216 of 2050 receiving its control (rate ratio,

1.16; 95% CI, 0.96 to 1.39; P=0.11). Unstratified comparisons yielded similarly null findings (Fig. 2), as did analyses that excluded patients receiving glucocorticoids and multivariable sensitivity analyses that estimated trial drug effects simultaneously (Table S3). If mechanical ventilation prevented oral administration of lopinavir or other trial drugs, then this could have reduced any effects on mortality of assignment to those drugs, but prespecified analyses of mortality among patients not already receiving ventilation at entry also indicated no definite protective effect of any trial drug (Fig. 3).

SECONDARY OUTCOMES

The prespecified secondary outcomes were ventilation and time to discharge. No trial drug reduced the initiation of ventilation among patients not already receiving ventilation. Ventilation was initiated after randomization in 295 patients receiving remdesivir and in 284 receiving its control, in 75 patients receiving hydroxychloroquine and in 66 receiving its control, in 126 patients receiving lopinavir and in 121 receiving its control, and in 209 patients receiving interferon and in 210 receiving its control (Table S1). Figure S10 shows the results for the combined outcome of in-hospital death or ventilation initiation.

In this open-label trial, patients who would be considered fit for discharge might be kept in the hospital somewhat longer just because they were being given a trial drug, but information on time to recovery can be obtained by comparing the effects of different drugs on time to discharge. Each of the three trial treatments that were scheduled to last more than 7 days increased the percentage of patients remaining in the hospital at day 7 (Table 1). If one of these three drugs had appreciably accelerated recovery, then the sizes of these effects should have differed, but they did not. Figures S11 through S16 plot time to discharge for all patients, those receiving supplemental oxygen, those not receiving supplemental oxygen, those receiving ventilation, those not receiving ventilation, and those receiving any respiratory support. Each drug delayed discharge by approximately 1 to 3 days while it was being given. Directly randomized comparisons of one trial drug with another (Fig. S17) likewise showed no appreciable differences in discharge rates while both drug regimens continued or after both had ended.

The supplementary analyses (Tables S2 and S3) tabulate co-medication (only small absolute differences were found between each trial drug and its control) and provide a multivariable Cox regression fitting all four treatment effects simultaneously (rate ratios for death were similar to those in Fig. 3). The analyses also (in Figs. S1 through S9) subdivide 28-day mortality graphs according to ventilation status at entry and give subgroup analyses of rate ratios for death according to other characteristics and according to glucocorticoid use (with no noteworthy subgroup-specific or geographic variation).

All active treatment ended within 14 days, and the numbers of deaths during this 14-day period with any cardiac cause mentioned on the electronic death record were seven with remdesivir and eight with its control, four with hydroxychloroquine and two with its control, six with lopinavir and three with its control, and six with interferon and eight with its control (Fig. S18). Many deaths from Covid-19 involve multiorgan failure, but no death in a patient assigned to a trial drug was attributed specifically by the doctor reporting the death to renal or hepatic disease.

META-ANALYSES

There are four trials that have compared remdesivir with control: the Solidarity trial (604 deaths in 5451 randomly assigned patients), the Adaptive Covid-19 Treatment Trial (ACTT-1) (136 deaths in 1062 patients; mortality was a secondary outcome), and two smaller trials (41 deaths).[6-9] Figure 4 shows the mortality results from each trial, stratified according to initial respiratory support. Within each trial, summation of the observed minus expected numbers of deaths with remdesivir in each stratum led to the stratified rate ratio for death in that trial. Summation of these trial-specific observed-minus-expected subtotals then led to an appropriately weighted average of the results from all trials, which yielded a rate ratio for death (remdesivir vs. control) of 0.91 (95% CI, 0.79 to 1.05).[5] Figures S19 and S20 show the mortality results in the trials of hydroxychloroquine (rate ratio, 1.09; 95% CI, 0.98 to 1.21) and of lopinavir (rate ratio, 1.01; 95% CI, 0.91 to 1.13).

DISCUSSION

The main outcomes of mortality, initiation of ventilation, and hospitalization duration were not definitely reduced by any trial drug, either overall

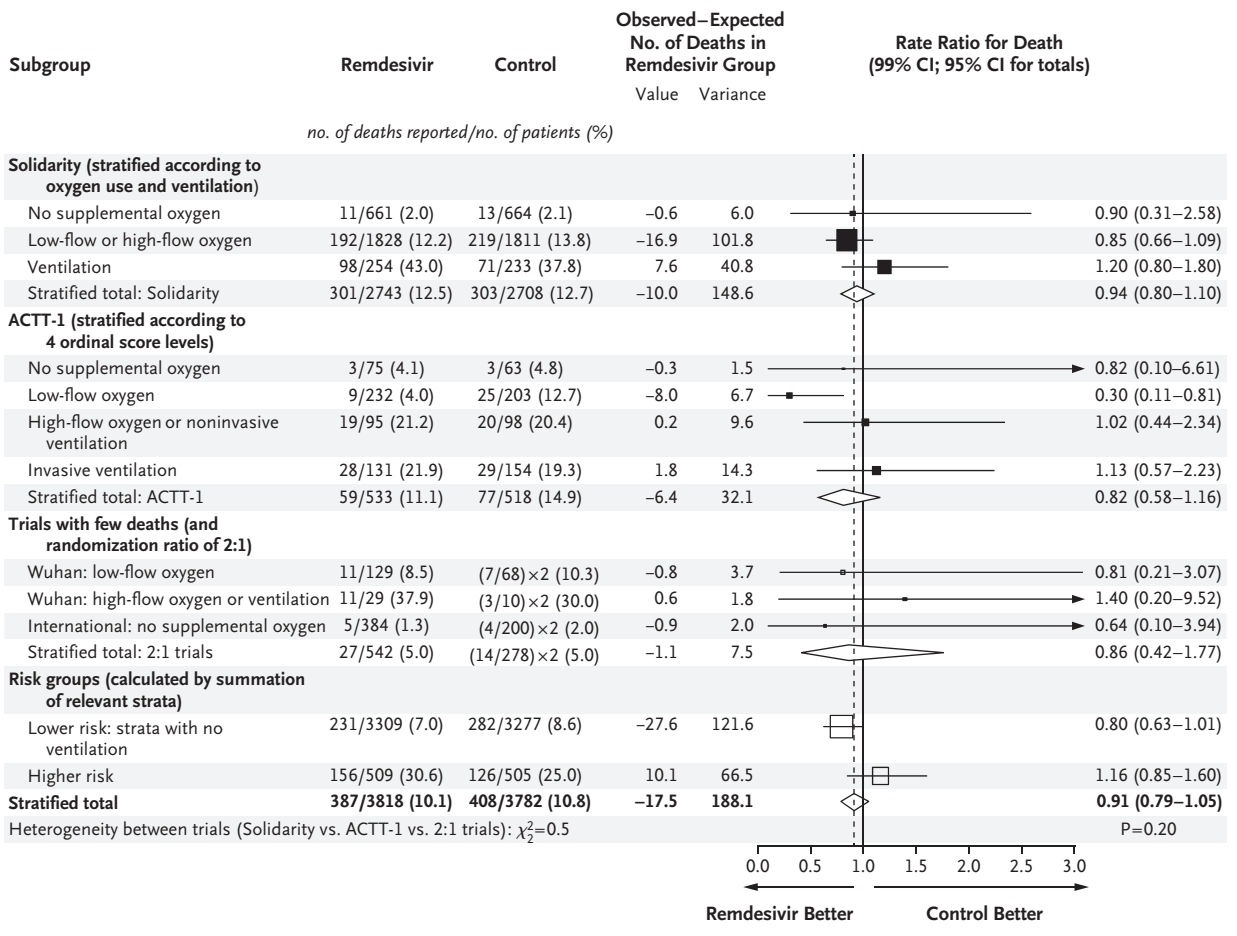

Figure 4. Meta-Analysis of Mortality in Trials of Random Assignment of Remdesivir or Its Control to Hospitalized Patients with Covid-19.

Percentages show Kaplan–Meier 28-day mortality. Values for observed minus expected number of deaths (O – E) are log-rank O – E for the Solidarity trial, O – E from 2-by-2 tables for the Wuhan[7] and international[8] trials, and w.log$_e$ hazard ratio for each stratum in the Adaptive Covid-19 Treatment Trial (ACTT-1)[6] (with the weight w being the inverse of the variance of the log$_e$ hazard ratio, which was calculated from the confidence interval of the hazard ratio). Rate ratios were calculated by taking the log$_e$ rate ratio to be (O – E)/V with a Normal distribution and variance 1/V. Subtotals or totals of (O – E) and of V yield inverse-variance–weighted averages of the log$_e$ rate ratios. For balance, controls in the 2:1 trials were counted twice in the control totals and subtotals. Diamonds show 95% confidence intervals for treatment effects. Squares and horizontal lines show treatment effects in particular subgroups and their 99% confidence intervals, with an arrow if the upper 99% confidence limit is outside the range shown. The area of each square is proportional to the variance of O – E in the subgroup it describes.

or in any particular subgroup. The findings for mortality and for initiation of ventilation cannot have been appreciably biased by the open-label design without placebos, or by variation in local care or patient characteristics, and were little affected when homogeneity was increased by stratification according to geographic region, age, or use of ventilation at entry. No trial drug reduced the initiation of mechanical ventilation. The similarity of this null effect for all four drugs is further evidence that none has any material effect on major disease progression, a conclusion supported by analyses of the combined outcome of death or ventilation initiation.

Although assignment to any of the active trial treatments in this open-label trial somewhat delayed discharge from the hospital, this could have been because some recovered patients otherwise fit for discharge were kept in the hospital merely to continue their trial treatment. In all patients and in those not receiving ventilation, assignment to each active trial drug increased

the time to discharge by approximately 1 to 3 days while treatment continued. Because no treatment had much effect on death or progression to ventilation, the similarity of these four moderate delays of discharge suggests that none of the four treatments had a pharmacologic effect that substantially reduced time to recovery (i.e., fitness for discharge). In particular, it suggests at most only a small effect of remdesivir on time to recovery, a conclusion supported by the directly randomized comparisons between remdesivir and the other three trial drugs.

ACTT-1, which examined remdesivir, was placebo-controlled,[6] which avoids any bias in time to discharge. In that trial, however, the proportion of lower-risk patients (i.e., those not already receiving high-flow oxygen or ventilation) happened to be appreciably greater in the remdesivir group than in the placebo group. This chance imbalance might account for some of the differences in time to recovery between ACTT-1 and the Solidarity trial.

The chief aim of the Solidarity trial was to help determine whether any of four repurposed antivirals could at least moderately affect in-hospital mortality. Its results should be considered in the context of the evidence on mortality from all trials, but for remdesivir and for interferon it provides more than three fourths of that evidence (Fig. 4). Stratification of the findings according to initial respiratory support again facilitates allowance for the remdesivir group in ACTT-1 having, by chance, started with a greater proportion of low-risk patients and a smaller proportion of high-risk patients than the placebo group. The stratified rate ratios for death in the Solidarity trial and ACTT-1 are compatible with each other, and either singly or together they are compatible with there being little or no effect of remdesivir on mortality.

With an appropriately weighted average of the stratified results from each of the four trials,[5] the rate ratio for death with remdesivir as compared with control was 0.91 (95% CI, 0.79 to 1.05). Interpretation of this should chiefly reflect not the P value (P=0.20) or point estimate (rate ratio, 0.91) but the confidence interval (0.79 to 1.05), which shows the range of rate ratios for death that are compatible with the weighted average of the findings from all trials. This does not support the suggestion that remdesivir can prevent a substantial fraction of all deaths. The confidence interval is compatible with prevention of a small fraction of all deaths, but it is also compatible with prevention of no deaths.

Statistical uncertainties are magnified if attention is restricted to particular subgroups or time periods.[10] If remdesivir has no effect on mortality, then chance could well produce somewhat favorable findings in a subgroup of the results for all trials or striking findings in a selected subgroup of a particular trial (as in the unplanned subgroup of ACTT-1 in which the rate ratio for death was 0.30) (Fig. 4). Although both the Solidarity trial and ACTT-1 envisaged separate analyses involving lower-risk and higher-risk patients, they did not define how this subdivision would apply to mortality analyses. The ACTT-1 protocol prespecified separate analyses of time to recovery among those with mild-to-moderate disease not receiving supplemental oxygen, as did the recent Food and Drug Administration reanalyses,[11] which categorized anyone receiving even low-flow supplemental oxygen as having severe disease. This subdivision, however, leaves few deaths in the no-supplemental-oxygen category (death in 3 of 75 patients with remdesivir and in 3 of 63 with placebo in ACTT-1, in 11 of 661 patients with remdesivir and in 13 of 664 with its control in the Solidarity trial, and in 5 of 384 patients with remdesivir and in 4 of 200 with the standard of care in an international trial with a 2:1 randomization ratio[8]).

To augment these small numbers of deaths, the subtotals in Figure 4 include low-flow oxygen with no supplemental oxygen, which yields a large lower-risk subgroup and a small higher-risk subgroup. With this nonprespecified subgrouping, there appears to be an absolute reduction of approximately 1 to 2 percentage points in mortality among lower-risk inpatients and an absolute increase of approximately 5 to 6 percentage points among higher-risk inpatients. These absolute differences in the meta-analysis of all four trials are similar to the absolute differences seen when the Solidarity trial is subdivided according to ventilation status at entry. Neither subgroup should, however, be considered in isolation from the other or from the confidence interval for overall mortality.

For hydroxychloroquine and lopinavir, the Solidarity trial showed no definite effect on mortality in any subgroup. The only other substantial trial is the Randomized Evaluation of Covid-19

Therapy (RECOVERY) trial,[12,13] which for these two drugs was larger than the Solidarity trial and also showed no benefit. Combination of both trials reinforces these null findings (Figs. S19 and S20).

For hydroxychloroquine, the joint rate ratio for death (combining the Solidarity and RECOVERY trials) was 1.10 (95% CI, 0.98 to 1.23), with no apparent benefit whether the patient was receiving ventilation or not. This confidence interval rules out any material benefit from this hydroxychloroquine regimen in hospitalized patients with Covid-19. It is compatible with some adverse effect but is not good evidence for any adverse effect and is not a safety signal. Despite concerns that the loading dose could be temporarily cardiotoxic,[4] in neither trial was there any excess mortality during the first few days, and cardiac deaths were too few to be reliably informative. A recent meta-analysis identified 15 small, randomized trials with nonzero mortality[14]; combining all 17 hydroxychloroquine trials yields a rate ratio of 1.09 (95% CI, 0.98 to 1.21), which still rules out any material benefit.

For lopinavir, which was always administered with ritonavir, the joint rate ratio for death (combining the Solidarity and RECOVERY trials and the only informative smaller trial[15]) was 1.01 (95% CI, 0.91 to 1.13). Although lopinavir tablets could not be swallowed by patients receiving ventilation, there was no apparent benefit in analyses that involved only those not already receiving ventilation at entry. This confidence interval suggests no material effect on mortality and rules out a 10% proportional reduction. An add-on study within the Solidarity trial, Discovery, recorded many clinical variables and identified an unexpected increase in the creatinine level (perhaps because blood lopinavir levels are higher than in patients with human immunodeficiency virus infection receiving similar doses[16,17]), but the Solidarity and RECOVERY trials recorded no specifically renal or hepatic deaths with lopinavir.

For interferon beta-1a, no other large trials exist. With 4000 patients, the rate ratio for death in the Solidarity trial was 1.16 (95% CI, 0.96 to 1.39), or 1.12 (95% CI, 0.83 to 1.51) without lopinavir co-administration; these findings suggest no mortality reduction. Subcutaneous and intravenous interferon have different pharmacokinetic characteristics,[18,19] and glucocorticoids could affect interferon signaling,[20,21] but the clinical relevance of both issues is unclear. Most interferon was administered subcutaneously, because intravenous interferon was used only in patients receiving high-flow oxygen or ventilation, and distribution of it began only in late May, just before strong evidence emerged of glucocorticoid efficacy in such patients.[22,23] Hence, few patients received intravenous interferon without a glucocorticoid. Approximately half the patients who were assigned to interferon (and half their controls) received glucocorticoids, but the rate ratio for death with interferon as compared with its control seemed unaffected by glucocorticoid use. Randomization to interferon was discontinued on October 16, but other trials continue. A report that nebulized interferon beta-1a might be effective involved only approximately 100 patients with Covid-19 (ClinicalTrials.gov number, NCT04385095), but the ongoing placebo-controlled ACTT-3 of subcutaneous interferon beta-1a aims to involve 1000 patients (NCT04492475), with examination of time to recovery.

For each of these four repurposed nonspecific antivirals, several thousand patients have now undergone randomization in various trials. The unpromising overall findings from the regimens tested suffice to refute early hopes, based on smaller or nonrandomized studies, that any of these regimens will substantially reduce inpatient mortality, the initiation of mechanical ventilation, or hospitalization duration. Narrower confidence intervals would be helpful (particularly for remdesivir), but the main need is for better treatments. The Solidarity trial has been recruiting approximately 2000 patients per month, and efficient factorial designs may allow it to assess further treatments, such as immune modulators or anti–SARS-Cov-2 monoclonal antibodies.

Manuscript preparation, revision, and submission were controlled by the World Health Organization (WHO) trial team and writing committee. Any views expressed are those of the writing committee, not necessarily of the WHO. No funder or donor unduly influenced analyses, manuscript preparation, or submission; their comments merely clarified methods, not changing analyses or conclusions. Donors of trial drugs were shown the main results for their drug in the last week of September.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org..

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Castor EDC donated and managed Castor's cloud-based clinical data capture and management system, with blinding to trial findings. Anonymized data handling or analysis was performed at the Universities of Bern, Bristol, and Oxford. Nicholas J. White and colleagues provided unpublished data on the pharmacokinetic characteristics of hydroxychloroquine to help the WHO select the regimen, the members of the Discovery data and safety monitoring committee shared clinical variables, the investigators of the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial shared log-rank statistics, the investigators of the Adaptive Covid-19 Treatment Trial (ACTT-1) shared subgroup hazard ratios, and Bin Cao shared details of the Wuhan trial. Collaborators, committee members, data analysts, and data management systems charged no costs.

APPENDIX

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Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

*RECOVERY Collaborative Group**

Summary

Background Azithromycin has been proposed as a treatment for COVID-19 on the basis of its immunomodulatory actions. We aimed to evaluate the safety and efficacy of azithromycin in patients admitted to hospital with COVID-19.

Methods In this randomised, controlled, open-label, adaptive platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]), several possible treatments were compared with usual care in patients admitted to hospital with COVID-19 in the UK. The trial is underway at 176 hospitals in the UK. Eligible and consenting patients were randomly allocated to either usual standard of care alone or usual standard of care plus azithromycin 500 mg once per day by mouth or intravenously for 10 days or until discharge (or allocation to one of the other RECOVERY treatment groups). Patients were assigned via web-based simple (unstratified) randomisation with allocation concealment and were twice as likely to be randomly assigned to usual care than to any of the active treatment groups. Participants and local study staff were not masked to the allocated treatment, but all others involved in the trial were masked to the outcome data during the trial. The primary outcome was 28-day all-cause mortality, assessed in the intention-to-treat population. The trial is registered with ISRCTN, 50189673, and ClinicalTrials.gov, NCT04381936.

Findings Between April 7 and Nov 27, 2020, of 16 442 patients enrolled in the RECOVERY trial, 9433 (57%) were eligible and 7763 were included in the assessment of azithromycin. The mean age of these study participants was 65·3 years (SD 15·7) and approximately a third were women (2944 [38%] of 7763). 2582 patients were randomly allocated to receive azithromycin and 5181 patients were randomly allocated to usual care alone. Overall, 561 (22%) patients allocated to azithromycin and 1162 (22%) patients allocated to usual care died within 28 days (rate ratio 0·97, 95% CI 0·87–1·07; p=0·50). No significant difference was seen in duration of hospital stay (median 10 days [IQR 5 to >28] *vs* 11 days [5 to >28]) or the proportion of patients discharged from hospital alive within 28 days (rate ratio 1·04, 95% CI 0·98–1·10; p=0·19). Among those not on invasive mechanical ventilation at baseline, no significant difference was seen in the proportion meeting the composite endpoint of invasive mechanical ventilation or death (risk ratio 0·95, 95% CI 0·87–1·03; p=0·24).

Interpretation In patients admitted to hospital with COVID-19, azithromycin did not improve survival or other prespecified clinical outcomes. Azithromycin use in patients admitted to hospital with COVID-19 should be restricted to patients in whom there is a clear antimicrobial indication.

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*The writing committee and trial steering committee are listed at the end of this manuscript and a complete list of collaborators in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is provided in the appendix (pp 2–22)

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See Online for appendix

Introduction

A substantial proportion of individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) develop a respiratory illness requiring hospital care, which can progress to critical illness with hypoxic respiratory failure requiring prolonged ventilatory support. Among patients with COVID-19 admitted to UK hospitals in the first wave of the epidemic, the case fatality rate was greater than 26%, and in excess of 37% in patients requiring invasive mechanical ventilation.[1]

In patients with severe COVID-19, the host immune response is thought to play a key role in driving an acute pneumonic process with diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis.[2] The beneficial effects of dexamethasone and other corticosteroids in patients with hypoxic lung damage suggest that other drugs that suppress or modulate the immune system might provide additional improvements in clinical outcomes.[3,4]

Macrolide antibiotics, such as azithromycin, clarithromycin, and erythromycin, are widely available and their safety is well established. In addition to antibacterial properties, they are known to have immunomodulatory activity, decreasing production of pro-inflammatory cytokines and inhibiting neutrophil activation.[5–7] They are widely used both in bacterial pneumonia due to their antimicrobial activity and in chronic inflammatory lung disease due to their immunomodulatory effects.[8–10] In

Research in context

Evidence before this study

Azithromycin is commonly used in patients with COVID-19 for either its antimicrobial, anti-inflammatory, or purported antiviral activity. We searched MEDLINE, Embase, bioRxiv, medRxiv, and the WHO International Clinical Trials Registry Platform, from Sept 1, 2019, up to Nov 12, 2020, for completed clinical trials published in any language evaluating the effect of azithromycin or other macrolide antibiotics in patients with COVID-19. We used the search terms ("COVID.mp." OR "COVID-19.mp." OR "SARS-CoV-2.mp." OR "2019-nCoV.mp." OR "coronavirus/" or "CORONAVIRUS.mp.") AND ("azithromycin.mp." OR "macrolide.mp."), filtered by randomised controlled trials according to validated filters. We identified three published randomised clinical trials (two at low risk of bias and one with some concerns due to limited information on the randomisation process) that compared the effect of azithromycin (500 mg once a day) to usual care in patients admitted to hospital with COVID-19. In all three studies, all patients also received hydroxychloroquine. None of the three studies, which in combination included 1223 patients, found differences in mortality or odds of clinical improvement; however, all were underpowered to exclude moderate but clinically relevant treatment effects.

Added value of this study

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is a large, randomised trial evaluating the effect of azithromycin monotherapy on mortality in patients admitted to hospital with COVID-19. We found no significant difference between the azithromycin group and the usual care group in 28-day all-cause mortality, the probability of discharge alive within 28 days, or, among the patients who were not receiving invasive mechanical ventilation at randomisation, the probability of progressing to the composite outcome of invasive mechanical ventilation or death. We saw no evidence of clinical benefit of azithromycin in any patient subgroup.

Implications of all the available evidence

Azithromycin should not be used to treat patients admitted to hospital with COVID-19 unless there is a clear antimicrobial indication.

addition, azithromycin has in-vitro antiviral activity against a range of viruses and has been reported to inhibit SARS-CoV-2 replication in Vero cells and human epithelial cells at concentrations (50% effective concentration 2·12 μM) that are achieved in lung tissue with a dose of 500 mg once per day.[11–13]

The use of macrolides in influenza-associated pneumonia has been associated with a faster reduction in inflammatory cytokines and, in combination with naproxen, decreased mortality.[14–16] However, randomised trials have so far not shown convincing clinical benefit of macrolides in COVID-19.[17–19] Here, we report the results of a randomised controlled trial of azithromycin in which we aimed to assess whether azithromycin improves clinical outcomes in patients admitted to hospital with COVID-19.

For the **protocol, statistical analysis plan, and additional information** see https://www.recoverytrial.net

Methods

Study design and participants

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients admitted to hospital with COVID-19. Details of the trial design and results for other possible treatments (dexamethasone, hydroxychloroquine, and lopinavir–ritonavir) have been published previously.[3,20,21] The trial is underway at 176 hospitals in the UK (appendix pp 2–22), supported by the National Institute for Health Research (NIHR) Clinical Research Network. The trial is coordinated by the Nuffield Department of Population Health at the University of Oxford (Oxford, UK), the trial sponsor. The trial is done in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines and approved by the UK Medicines and Healthcare products Regulatory Agency and the Cambridge East Research Ethics Committee (20/EE/0101). The protocol, statistical analysis plan, and additional information are available on the study website. Although the azithromycin, dexamethasone, hydroxychloroquine, lopinavir–ritonavir, convalescent plasma, and tocilizumab groups have now been stopped, the trial continues to study the effects of REGN-COV2 (a combination of two monoclonal antibodies directed against SARS-CoV-2 spike glycoprotein), aspirin, and colchicine. Other treatments might be studied in future.

Patients admitted to hospital were eligible for the study if they had clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial. Initially, recruitment was limited to patients aged at least 18 years, but from May 9, 2020, the age limit was removed. Patients with known prolonged QTc interval or hypersensitivity to a macrolide antibiotic and those already receiving chloroquine or hydroxychloroquine were excluded from random assignment between azithromycin and usual care.

Written informed consent was obtained from all patients, or a legal representative if they were too unwell or unable to provide consent.

Randomisation and masking

Baseline data were collected using a web-based case report form that included demographics, amount of respiratory support, major comorbidities, suitability of the study

treatment for a particular patient, and treatment availability at the study site (appendix pp 23–25). Eligible and consenting patients were assigned to either usual standard of care or usual standard of care plus azithromycin or one of the other available RECOVERY treatment groups using web-based simple (unstratified) randomisation with allocation concealed until after randomisation (appendix pp 23–25). Randomisation to usual care was twice that of any of the active treatment groups the patient was eligible for (eg, 2:1 in favour of usual care if the patient was eligible for only one active group, 2:1:1 if the patient was eligible for two active groups). For some patients, azithromycin was unavailable at the hospital at the time of enrolment or a macrolide antibiotic was considered by the managing physician to be either definitely indicated or definitely contraindicated. These patients were excluded from the randomised comparison between azithromycin and usual care. Patients allocated to azithromycin were to receive azithromycin 500 mg by mouth, nasogastric tube, or intravenous injection once a day for 10 days or until discharge, if sooner. Allocated treatment was prescribed by the managing doctor. Azithromycin was supplied from routine National Health Service (NHS) stocks.

For eligible participants, factorial randomisations were introduced such that participants could simultaneously be randomly assigned to convalescent plasma versus REGN-COV2 versus usual care and to aspirin versus usual care (appendix pp 23–25). Within 21 days of initial random assignment, participants with evidence of hypoxia and inflammation could be additionally randomly assigned to tocilizumab versus usual care alone. Participants and local study staff were not masked to the allocated treatment. The steering committee, investigators, and all others involved in the trial were masked to the outcome data during the trial.

Procedures

A single online follow-up form was completed when participants were discharged from hospital, died, or at 28 days after randomisation, whichever occurred earliest (appendix pp 29–35). Information was recorded on adherence to allocated study treatment, receipt of other COVID-19 treatments, duration of admission, receipt of respiratory or renal support, and vital status (including cause of death). In addition, routine health-care and registry data were obtained, including information on vital status (with date and cause of death), discharge from hospital, receipt of respiratory support, or renal replacement therapy. Details of how this information was used to derive baseline characteristics and clinical outcomes are provided in the appendix (pp 112–31).

Outcomes

Outcomes were assessed at 28 days after randomisation, with further analyses specified at 6 months. The primary outcome was 28-day all-cause mortality. Secondary outcomes were time to discharge from hospital and, among patients not on invasive mechanical ventilation at randomisation, invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death. Prespecified subsidiary clinical outcomes were cause-specific mortality, use of haemodialysis or haemofiltration, major cardiac arrhythmia (recorded in a subset), and receipt and duration of ventilation. Among those on invasive mechanical ventilation at randomisation, a subsidiary clinical outcome of successful cessation of invasive mechanical ventilation was defined as cessation within (and survival to) 28 days. Information on suspected serious adverse reactions was collected in an expedited manner to comply with regulatory requirements.

Statistical analysis

An intention-to-treat comparison was made between patients randomly assigned to azithromycin and those

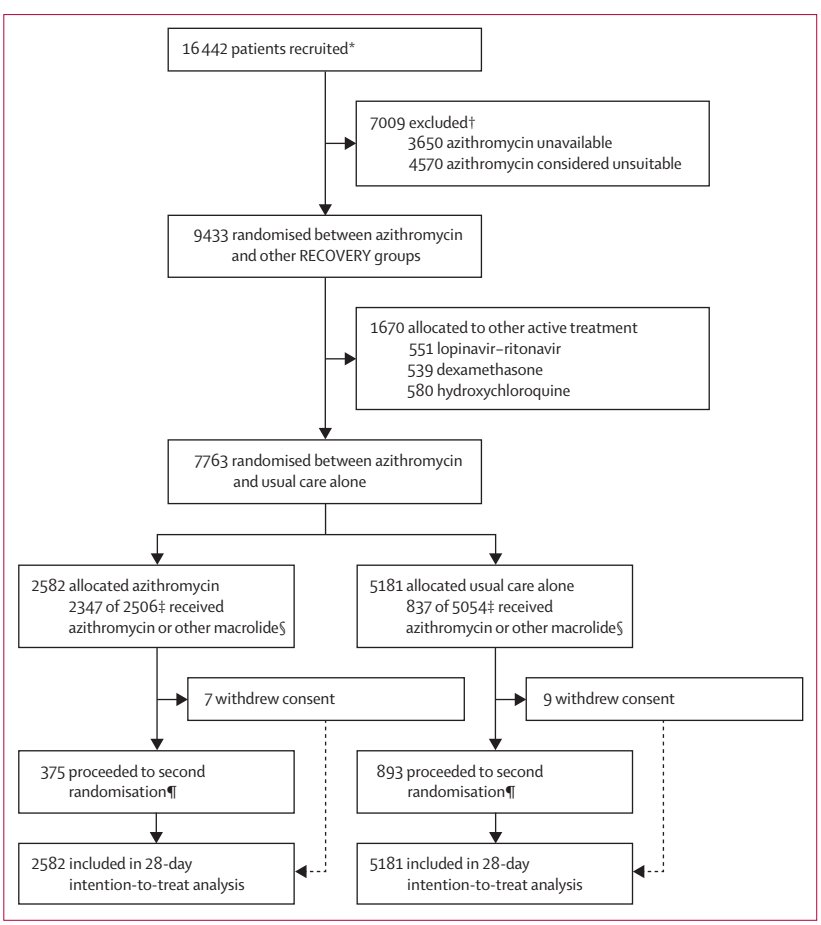

Figure 1: **Trial profile**

*Number recruited overall during the period that participants could be recruited into the azithromycin comparison. †Some patients were included in both of the below groups. ‡2506 (97%) of those allocated to azithromycin and 5054 (98%) of those allocated to usual care had a complete follow-up at time of analysis. §3993 patients were additionally randomly assigned to convalescent plasma versus REGN-COV2 versus control (1320 [51·1%] patients allocated to azithromycin versus 2673 [51·6%] patients allocated usual care) and 975 patients were additionally randomly assigned to aspirin versus usual care (323 [12·5%] patients allocated to azithromycin versus 652 [12·6%] patients allocated usual care). ¶Includes 198 (7·7%) of 2582 patients in the azithromycin group and 450 (8·7%) of 5181 patients in the usual care group allocated to tocilizumab.

randomly assigned to usual care but for whom azithromycin was both available and suitable as a treatment. For the primary outcome of 28-day mortality, the log-rank observed minus expected statistic and its variance were used to both test the null hypothesis of equal survival curves (ie, the log-rank test) and to calculate the one-step estimate of the mortality rate ratio. We constructed Kaplan-Meier survival curves to display cumulative mortality over the 28-day period. We used similar methods to analyse time to hospital discharge and successful cessation of invasive mechanical ventilation, with patients who died in hospital right-censored on day 29. Median time to discharge was derived from Kaplan-Meier estimates. For the prespecified composite secondary outcome of invasive mechanical ventilation or death within 28 days (among those not receiving invasive mechanical ventilation at randomisation) and the subsidiary clinical outcomes of receipt of ventilation and use of haemodialysis or haemofiltration, the precise dates were not available and so the risk ratio was estimated instead.

Prespecified analyses of the primary outcome were done separately in six subgroups defined by characteristics at the time of random assignment: age, sex, ethnicity, days since symptom onset, level of respiratory support, and use of corticosteroids (appendix p 105). Observed effects within subgroup categories were compared using a χ^2 test for heterogeneity or trend, in accordance with the prespecified analysis plan.

Estimates of rate and risk ratios are shown with 95% CIs. All p values are two-sided and are shown without adjustment for multiple testing. The full database is held by the study team who collected the data from study sites and did the analyses at the Nuffield Department of Population Health (University of Oxford, Oxford, UK).

As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned at the start of the COVID-19 pandemic as it was unknown how large the epidemic would become (appendix p 26). As the trial progressed, the trial steering committee, whose members were unaware of the results of the trial comparisons, determined that sufficient patients should be enrolled to provide at least 90% power at a two-sided p value of 0·01 to detect a clinically relevant proportional reduction in the primary outcome of 20% between the two groups. Consequently, on Nov 27, 2020, the steering committee, masked to the results, closed recruitment to

	Azithromycin (n=2582)	Usual care (n=5181)
Age, years	65·4 (15·6)	65·2 (15·7)
<70*	1508 (58%)	3014 (58%)
≥70 to <80	615 (24%)	1167 (23%)
≥80	459 (18%)	1000 (19%)
Sex		
Men	1604 (62%)	3215 (62%)
Women†	978 (38%)	1966 (38%)
Ethnicity		
White	1961 (76%)	3978 (77%)
Black, Asian, and minority ethnic	372 (14%)	737 (14%)
Unknown	249 (10%)	466 (9%)
Number of days since symptom onset	8 (5–11)	8 (5–11)
Number of days since admission to hospital	2 (1–4)	2 (1–4)
Respiratory support received		
No oxygen received	490 (19%)	918 (18%)
Oxygen only‡	1940 (75%)	3963 (76%)
Invasive mechanical ventilation	152 (6%)	300 (6%)
Previous diseases		
Diabetes	700 (27%)	1433 (28%)
Heart disease	693 (27%)	1350 (26%)
Chronic lung disease	621 (24%)	1313 (25%)
Tuberculosis	3 (<1%)	16 (<1%)
HIV	7 (<1%)	22 (<1%)
Severe liver disease§	45 (2%)	65 (1%)
Severe kidney impairment¶	155 (6%)	334 (6%)
Any of the above	1507 (58%)	3013 (58%)
Use of corticosteroids		
Yes	1567 (61%)	3171 (61%)
No	182 (7%)	397 (8%)
Not asked or missing‖	833 (32%)	1613 (31%)
SARS-CoV-2 test result		
Positive	2350 (91%)	4743 (92%)
Negative	202 (8%)	386 (7%)
Unknown	30 (1%)	52 (1%)

Data are mean (SD), n (%), or median (IQR). SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Includes 26 children (<18 years). †Includes 25 pregnant women. ‡Includes non-invasive ventilation. §Defined as requiring ongoing specialist care. ¶Defined as estimated glomerular filtration rate <30 mL/min per 1·73 m². ‖Information on use of corticosteroids was collected from June 18, 2020, onwards, following announcement of the results of the dexamethasone comparison from the RECOVERY trial.

Table 1: **Baseline characteristics**

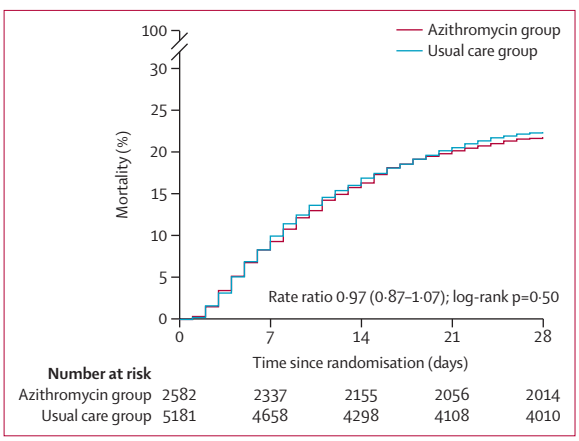

Figure 2: **Effect of allocation to azithromycin on 28-day mortality**

the azithromycin comparison as sufficient patients had been enrolled.

Analyses were done using SAS, version 9.4, and R, version 3.4.0. This trial is registered with ISRCTN, 50189673, and ClinicalTrials.gov, NCT04381936.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 7 and Nov 27, 2020, 9433 (57%) of 16442 patients enrolled in the RECOVERY trial were eligible to be randomly allocated to azithromycin (ie, azithromycin was available in the hospital at the time and the attending clinician was of the opinion that the patient had no known indication for or contraindication to azithromycin, figure 1, appendix p 38). 2582 patients were randomly allocated to azithromycin and 5181 were randomly allocated to usual care, with the remainder being randomly allocated to one of the other treatment groups. The mean age of study participants in this comparison was 65·3 years (SD 15·7) and the median time since symptom onset was 8 days (IQR 5–11; table 1; appendix p 38).

The follow-up form was completed for 2506 (97%) patients in the azithromycin group and 5054 (98%) patients in the usual care group. Among patients with a completed follow-up form, 2269 (91%) allocated to azithromycin versus 68 (1%) allocated to usual care received at least one dose, and 2347 (94%) versus 837 (17%) received any macrolide antibiotic (appendix p 39). The median duration of treatment with azithromycin was 6 days (IQR 3–10). Use of other treatments for COVID-19 was similar among patients allocated azithromycin and among those allocated usual care, with more than half receiving a corticosteroid, about a quarter receiving remdesivir, about a fifth receiving convalescent plasma, and about a twelfth receiving tocilizumab or sarilumab (appendix p 39).

We observed no significant difference in the proportion of patients who met the primary outcome of 28-day mortality between the two randomised groups (561 [22%] of 2582 patients in the azithromycin group *vs* 1162 [22%] of 5181 patients in the usual care group; rate ratio 0·97, 95% CI 0·87–1·07; p=0·50; figure 2). We observed similar results across all prespecified subgroups (figure 3). In an exploratory analysis restricted to the 7093 (91%) of 7763 patients with a positive SARS-CoV-2 test result, the result was similar (rate ratio 0·95, 95% CI 0·86–1·06; p=0·38).

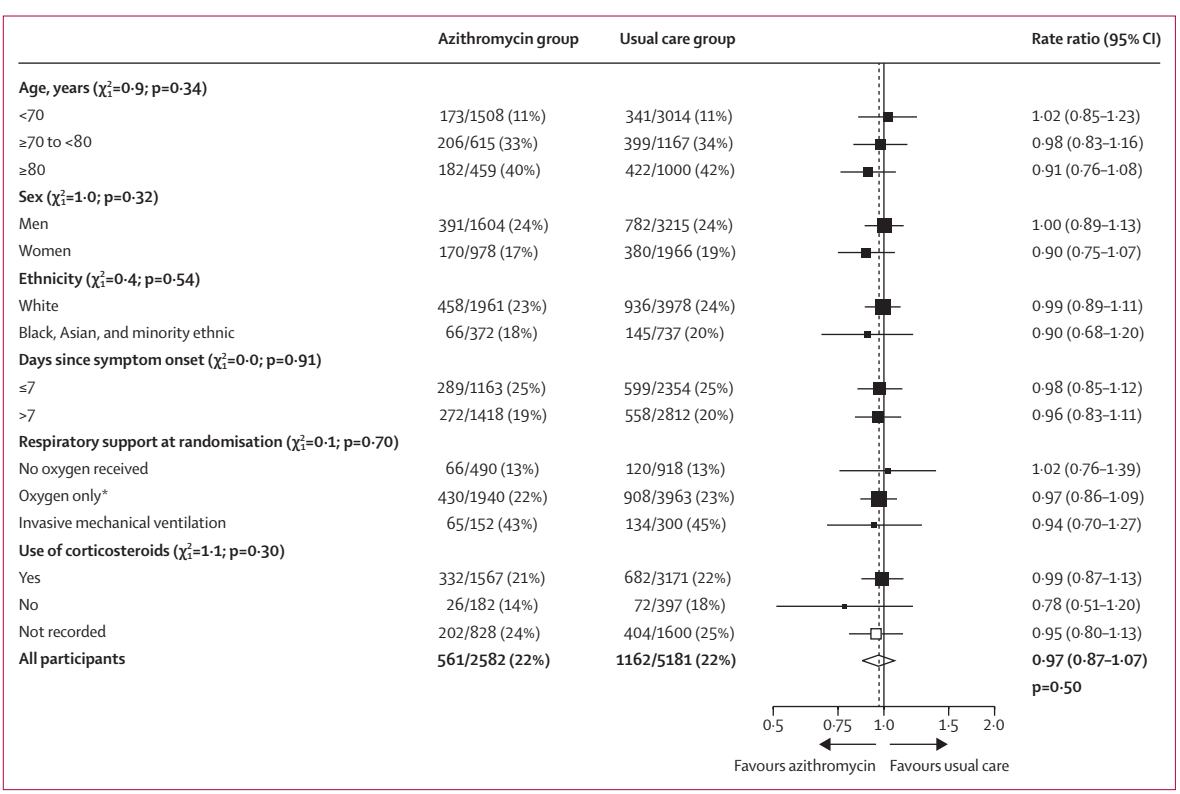

Figure 3: **Effect of allocation to azithromycin on 28-day mortality by baseline characteristics**

Subgroup-specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to 95% CIs. The ethnicity, days since onset, and use of corticosteroids subgroups exclude those with missing data, but these patients are included in the overall summary diamond. Information on use of corticosteroids was collected from June 18, 2020, onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. *Includes patients receiving non-invasive ventilation.

	Azithromycin (n=2582)	Usual care (n=5181)	RR (95% CI)	p value
Primary outcome				
28-day mortality	561 (22%)	1162 (22%)	0·97 (0·87–1·07)	0·50
Secondary outcomes				
Time to being discharged alive, days	10 (5 to >28)	11 (5 to >28)	NA	NA
Discharged from hospital within 28 days	1788 (69%)	3525 (68%)	1·04 (0·98–1·10)	0·19
Receipt of invasive mechanical ventilation or death*	603/2430 (25%)	1273/4881 (26%)	0·95 (0·87–1·03)	0·24
Invasive mechanical ventilation	211/2430 (9%)	461/4881 (9%)	0·92 (0·79–1·07)	0·29
Death	496/2430 (20%)	1028/4881 (21%)	0·97 (0·88–1·07)	0·52
Subsidiary clinical outcomes				
Receipt of ventilation†	226/1368 (17%)	491/2705 (18%)	0·91 (0·79–1·05)	0·20
Non-invasive ventilation	214/1368 (16%)	467/2705 (17%)	0·91 (0·78–1·05)	0·19
Invasive mechanical ventilation	57/1368 (4%)	115/2705 (4%)	0·98 (0·72–1·34)	0·90
Successful cessation of invasive mechanical ventilation‡	54/152 (36%)	96/300 (32%)	1·15 (0·82–1·62)	0·42
Use of haemodialysis or haemofiltration§	105/2539 (4%)	224/5102 (4%)	0·94 (0·75–1·18)	0·61

Data are n (%), median (IQR), or n/N (%), unless otherwise indicated. RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. NA=not applicable. *Analyses exclude those on invasive mechanical ventilation at randomisation. †Analyses exclude those on any form of ventilation at randomisation. ‡Analyses restricted to those on invasive mechanical ventilation at randomisation. §Analyses exclude those on haemodialysis or haemofiltration at randomisation.

Table 2: **Effect of allocation to azithromycin on key study outcomes**

Allocation to azithromycin was associated with a similar time until discharge from hospital alive as usual care (median 10 days [IQR 5 to >28] *vs* 11 days [5 to >28]) and a similar probability of discharge alive within 28 days (69% *vs* 68%, rate ratio 1·04, 95% CI 0·98–1·10; p=0·19; table 2). Among those not on invasive mechanical ventilation at baseline, the number of patients progressing to the prespecified composite secondary outcome of invasive mechanical ventilation or death among those allocated to azithromycin was similar to that among those allocated to usual care (25% *vs* 26%, risk ratio 0·95, 95% CI 0·87–1·03; p=0·24; table 2). Allowing for multiple testing in interpretation of the results, there was no evidence that the effect of allocation to azithromycin versus usual care on time until discharge from hospital alive or on invasive mechanical ventilation or death differed between prespecified subgroups of patients (appendix pp 43–44).

We found no significant differences in the prespecified subsidiary clinical outcomes of cause-specific mortality (appendix p 40), use of ventilation, successful cessation of invasive mechanical ventilation, or need for renal dialysis or haemofiltration (table 2). We observed no significant differences in the frequency of new cardiac arrhythmias (appendix p 41). There was one report of a serious adverse reaction believed to be related to azithromycin: a case of pseudomembranous colitis from which the patient recovered with standard treatment.

Discussion

The results of this large, randomised trial show that azithromycin is not an effective treatment for patients admitted to hospital with COVID-19. Allocation to azithromycin was not associated with reductions in mortality, duration of hospital stay, or the risk of being ventilated or dying for those not on ventilation at baseline. These results were consistent across the prespecified subgroups of age, sex, ethnicity, duration of symptoms before randomisation, level of respiratory support at randomisation, or use of corticosteroids at randomisation.

Azithromycin was proposed as a treatment for COVID-19 on the basis of its immunomodulatory activity.[7] Although no major organisation or professional society has recommended the routine use of azithromycin in COVID-19 unless there is evidence of bacterial superinfection, it has nevertheless been used widely in patients with COVID-19, particularly in combination with hydroxychloroquine.[22–24] Macrolides have long been suggested as potential therapies for inflammatory viral pneumonias but this hypothesis has been based on in-vitro, animal, and observational data, with very little evidence of benefit in clinical trials.[13–15] The benefit of dexamethasone in patients with COVID-19 requiring respiratory support suggests that inflammation has a causal role in mortality.[3] Noting that the absence of meaningful effect of azithromycin was consistent regardless of whether patients were also being given a corticosteroid or not, we conclude that the immunomodulatory properties of azithromycin are either insufficient in COVID-19.

Macrolides are commonly used to treat bacterial infections of the lower respiratory tract because of their activity against Gram-positive bacteria and atypical pathogens such as *Mycoplasma pneumoniae* and *Legionella* spp, as well as their excellent tissue penetration. More than 75% of patients with COVID-19 who were admitted to hospital in the UK during 2020 were prescribed antibiotics and the widespread clinical use of macrolides in COVID-19 is likely to be driven largely by concerns of bacterial superinfection rather than purported immunomodulatory activity.[25] It is therefore important to highlight that in patients with moderate or severe COVID-19, who might be expected to have some burden of secondary bacterial lung infection, there was no observed clinical benefit of azithromycin use. This absence of meaningful effect could either reflect the relatively low rate of secondary bacterial infection in COVID-19 or the widespread use of β-lactam or other antibiotics, which might have abrogated any antibacterial benefit of allocation to azithromycin in this trial.[26,27] Our results showed that the addition of azithromycin to routine clinical care of patients admitted to hospital with COVID-19 confers no clinical benefit, whether that be anti-inflammatory or antimicrobial. Although we detected no harm to individual patients given azithromycin, there is a risk of harm at a societal level from widespread use of

antimicrobial agents. Azithromycin is classified within the WHO Watch Group of Antibiotics (ie, antibiotics that have higher resistance potential and should be prioritised as key targets of antimicrobial stewardship programmes).[28] In light of the new evidence from the RECOVERY trial, the widespread use of macrolides in particular and antibiotics in general in patients with COVID-19 should be questioned.[29]

Strengths of this trial included that it was randomised, had a large sample size, broad eligibility criteria, and more than 98% of patients were followed up for the primary outcome. The trial also had some limitations. Detailed information on laboratory markers of viral load, inflammatory status, immune response, coexistent bacterial infection, or use of non-macrolide antibiotics was not collected, nor was information on radiological or physiological outcomes. Following random assignment, 17% of patients in the usual care group were given azithromycin or another macrolide antibiotic. Although this randomised trial is open label (ie, participants and local hospital staff are aware of the assigned treatment), the outcomes are unambiguous and were ascertained through linkage to routine health data systems (regardless of treatment allocation).

Three other randomised controlled trials have assessed the efficacy of azithromycin for the treatment of COVID-19 in patients admitted to hospital, all of which additionally treated patients with hydroxychloroquine.[17–19] The COALITION I and COALITION II trials found that for patients with COVID-19 who had been admitted to hospital, treatment with azithromycin and hydroxychloroquine was not associated with any improvement in mortality, duration of hospital stay, or clinical status as assessed using an ordinal outcome scale.[17,18] A small trial in Iran that randomly assigned patients to hydroxychloroquine and lopinavir–ritonavir with or without azithromycin also found no significant difference in mortality or intensive care unit admission, but suggested a reduction in duration of hospital stay.[19] The total number of patients in all three previous trials combined was 1223, with 130 deaths. The RECOVERY trial, with 7763 participants and 1723 deaths in this assessment of azithromycin, is well powered to detect modest treatment benefits; however, none were observed.

At the time of writing, 24 trials evaluating the use of macrolides in patients with COVID-19 were registered in the WHO International Clinical Trials Registry Platform, of which three (COALITION I and COALITION II, and Q-PROTECT, a study in patients who had not been admitted to hospital) have published results.[17,18,30] Of the remaining 21, 16 are studying macrolides in inpatients either alone or in combination with other putative treatments, while five are studying macrolides in patients who had not been admitted to hospital with suspected or confirmed COVID-19.

Although our findings do not address the use of macrolides for the treatment of patients with COVID-19 who had not been admitted to hospital with early, mild disease, the results do show that azithromycin is not an effective treatment for patients admitted to hospital with COVID-19.

Contributors

This manuscript was initially drafted by PWH and MJL, further developed by the writing committee, and approved by all members of the trial steering committee. PWH and MJL vouch for the data and analyses, and for the fidelity of this report to the study protocol and data analysis plan. PWH, MM, JKB, LCC, SNF, TJ, KJ, WSL, AMo, KR, EJ, RH, and MJL designed the trial and study protocol. MM, AR, GP-A, CB, BP, DC, AU, AA, ST, BY, RB, SS, DM, RH, the data linkage team at the RECOVERY coordinating centre, and the health records and local clinical centre staff listed in the appendix collected the data. ES, NS, and JRE verified the data and did the statistical analysis. All authors contributed to data interpretation and critical review and revision of the manuscript. PWH and MJL had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Declaration of interests

We declare no competing interests.

Data sharing

The protocol, consent form, statistical analysis plan, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, and other relevant study materials are available online. As described in the protocol, the trial steering committee will facilitate the use of the study data and approval will not be unreasonably withheld. De-identified participant data will be made available to bona fide researchers registered with an appropriate institution within 3 months of publication. However, the steering committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (eg, relating to data protection and privacy). The steering committee will have the right to review and comment on any draft manuscripts before publication. Data will be made available in line with the policy and procedures described on the Nuffield Department of Population Health website Those wishing to request access should complete the online form and e-mail data.access@ndph.ox.ac.uk.

For **trial details** see https://www.recoverytrial.net

For **data access details** see https://www.ndph.ox.ac.uk/data-access

For **online form** see https://www.ndph.ox.ac.uk/files/about/data_access_enquiry_form_13_6_2019.docx

For the **WHO International Clinical Trials Registry Platform** see https://www.who.int/clinical-trials-registry-platform

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For more on the **Nuffield Department of Population Health staff policy** see https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-20.pdf

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