Hydroxychloroquine versus Azithromycin for Hospitalized Patients with Suspected or Confirmed COVID-19 (HAHPS)

Protocol for a Pragmatic, Open-Label, Active Comparator Trial

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Abstract

Coronavirus disease (COVID-19) is a potentially fatal illness with no proven therapy beyond excellent supportive care. Treatments are urgently sought. Adaptations to traditional trial logistics and design to allow rapid implementation, evaluation of trials within a global trials context, flexible interim monitoring, and access outside traditional research hospitals (even in settings where formal placebos are unavailable) may be helpful. Thoughtful adaptations to traditional trial designs, especially within the global context of related studies, may also foster collaborative relationships among government, community, and the research enterprise. Here, we describe the protocol for a pragmatic, active comparator trial in as many as 300 patients comparing two current "off-label" treatments for COVID-19—hydroxychloroquine and azithromycin—in academic and nonacademic hospitals in Utah. We developed the trial in response to local pressures for widespread, indiscriminate off-label use of these medications. We used a hybrid Bayesian-frequentist design for interim monitoring to allow rapid, contextual assessment of the available evidence. We also developed an inference grid for interpreting the range of possible results from this trial within the context of parallel trials and prepared for a network meta-analysis of the resulting data. This trial was prospectively registered (ClinicalTrials.gov Identifier: NCT04329832) before enrollment of the first patient.

Clinical trial registered with www.clinicaltrials.gov (NCT04329832).

Keywords: COVID-19; clinical trial; hydroxychloroquine

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In late 2019, a novel coronavirus, subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) based on a genetic similarity to the SARS coronavirus, was first observed to cause human illness (1). The illness caused by SARS-CoV-2 was named coronavirus disease (COVID-19). The clinical course of COVID-19 is highly variable. A majority of infected patients experience a relatively benign course. However, in a significant number of individuals, a viral pneumonia may occur, with high rates of hospitalization, acute respiratory distress syndrome (ARDS), mechanical ventilation, and death (2).

To date, there is no reliable evidence regarding efficacy in COVID-19 for any therapy beyond appropriate supportive care (3). Controlled trials of many proposed therapies are underway or imminently launching, although many early trials in China were unable to accrue to target given delays in launch combined with early efforts to control the epidemic there. These issues, as well as previous disappointing experiences with Ebola, underscore the need for nimble, timely, rigorous controlled trials in a pandemic setting (4, 5). However, active community interest in such trials and their results may affect the range of trial designs available, requiring both rigor and flexibility from trialists.

Among many novel or repurposed medications proposed for the treatment of COVID-19, two agents marketed in the United States have been prescribed hundreds of thousands or even millions of times for other conditions: (hydroxy) chloroquine and azithromycin. Chloroquine and hydroxychloroquine have been proposed as treatments for a broad range of microorganisms, including viruses (6). We review the mechanisms of hydroxychloroquine and clinical results regarding its efficacy in the online supplement. Briefly, hydroxychloroquine has *in vitro* efficacy against multiple viruses but has never demonstrated clinical efficacy. Well-publicized case series have been taken in public discussions to indicate clear evidence of clinical efficacy. Public attention to hydroxychloroquine has been associated with subsequent shortages and sometimes fatal overdoses (7–10).

Governments have explored the possibility of widespread off-label use of (hydroxy)chloroquine for treatment of COVID-19. However, the ubiquitous off-label use of untested treatments blocks our ability to know whether they have efficacy, and may lack adequate safety monitoring or informed consent. Academic, regulatory, and health authorities have affirmed the need to avoid the use of hydroxychloroquine outside clinical trials whenever possible (11–14).

On the basis of data available at the time of trial launch, we believe that there are compelling arguments for a randomized trial to evaluate the efficacy of hydroxychloroquine in COVID-19. Given specific social and scientific circumstances, we confronted the question of what kind of randomized trial to perform in the state of Utah. Although placebo-controlled trials of proposed therapies for COVID-19 are in various phases of planning or execution, such trials generally exclude patients treated outside academic medical centers and may take weeks or months to launch, which may be too late to enroll many patients during this pandemic, especially during its first major wave. As large placebo-controlled trials of hydroxychloroquine and other agents in academic centers (including our own) were preparing to launch, the investigators leading the trial, representing the two major health systems in the state of Utah, were faced with a dilemma. Some citizens and government officials in Utah sought immediate, widespread administration of hydroxychloroquine without a physician's prescription (15). The pressure to "do something" was intense, and a meaningful response from local trialists was exquisitely time sensitive.

In addition to two quaternary referral centers, we are responsible for a large number of other hospitals ($n = 22$), in most of which the traditional research infrastructure is limited and patients may not have access to placebo. Based on our urgent discussions with community members and local leaders, we concluded that the state of Utah had little appetite for placebo or "usual care" control arms among hospitalized patients. Practitioners were under considerable pressure from patients and from the community to embrace off-label use of agents viewed as potentially beneficial. Furthermore, we estimated (using current drug par levels, projections, and external reports [7–9]) that drug supplies were already or would soon be depleted by off-label use. We sought to offer patients treatment as quickly as possible in a way that would prevent overuse of untested medications with possible adverse effects while protecting the drug supply for patients who depend on those drugs for their indicated conditions.

In our response, we sought to be rigorous without being rigid. We designed a pragmatic comparison of two common treatments for COVID-19 in a real-world setting, without the timely availability of an identical placebo or blinding, and in a context where a "usual care" or "standard of care" arm would be shifting constantly and would be at high risk for contamination. We thus designed a pragmatic, randomized, active comparator trial focused on nonacademic hospitals.

As the active comparator, we chose azithromycin, a macrolide antibiotic with antiinflammatory properties (and possibly some indirect antiviral effects [16, 17]) and a longstanding, well-established safety record in a variety of conditions. Although azithromycin is commonly recommended in combination with a β-lactam for community-acquired pneumonia (which can be occasionally confused with COVID-19 during the pandemic), evidence from a randomized trial suggests that omitting the macrolide is in fact noninferior (18). Azithromycin's pleiotropic antiinflammatory effects have been proposed to provide benefit in both chronic and acute lung disease. In a secondary analysis of one ARDS trial ($N = 235$), azithromycin was associated with higher survival (19), and a retrospective study (with propensity matching) of 125 patients with sepsis-associated ARDS also suggested lower 60-day mortality (20). A secondary analysis of a prospective observational cohort of patients with ARDS ($N = 873$) suggested higher survival with azithromycin (21). In the AMAZES (Asthma and Macrolides: the Azithromycin Efficacy and Safety) trial ($N = 420$, 213 with azithromycin), chronic treatment with azithromycin was associated with improvement in asthma symptoms. In that study, gastrointestinal symptoms were the primary side effect (the only other adverse event that may have differed from placebo was a 2% higher incidence of long QT, with no report of cardiac arrhythmias) (22). The WIZARD (Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders) trial attempted to prevent secondary cardiovascular events in 7,747 patients (3,879 randomized to azithromycin) with coronary disease (a group at high risk for complications) but showed no efficacy. The safety profile was excellent overall: other than a lower rate of bacterial infections, only symptoms from the known gastrointestinal promotility effects were observed. Although there was no significant decrease in mortality or coronary events overall, the time-to-event curves may have favored azithromycin slightly (23). Population-level retrospective studies have provided conflicting evidence regarding an increase in the risk of sudden cardiac death (vs. amoxicillin); however, the effect has not been observed in randomized trials, suggesting that it may reflect indication bias rather than harm attributable to azithromycin itself (24–26). Therefore, we believed that azithromycin was potentially efficacious, with a very low likelihood of harm, and thus was an appropriate comparator for hydroxychloroquine.

Table 1. Eligibility criteria to define the target population of the trial

Criteria	Rationales
Inclusion criteria	
Age ⩾18 yr	Children have much lower rates of severe COVID-19
Scheduled for admission or already admitted to an inpatient bed	Hospitalized patients have higher disease severity and may be most likely to benefit from hydroxychloroquine
Confirmed or suspected COVID-19 Confirmed: positive assay for COVID-19 within the last 10 d Suspected: pending assay for COVID-19 with high clinical suspicion	The treatments are intended to improve outcomes from COVID-19; occasional delays in turnaround time for testing might impede timely treatment of patients with COVID-19
Exclusion criteria	
Allergy to hydroxychloroquine or azithromycin	High risk of adverse events
History of bone marrow transplant	The study team believed that bone marrow transplant clinicians would not allow randomization of their patients in this trial, and that immunity in his population is distinctive
Known G6PD deficiency	Theoretical concern about hemolysis
Chronic hemodialysis or glomerular filtration rate <20 ml/min	Package insert advises increased risk of adverse effects
Psoriasis	May cause worsening of psoriasis
Porphyria	May cause porphyria crisis
Concomitant use of digitalis, flecainide, amiodarone, procainamide, propafenone, cimetidine, dofetilide, phenobarbital, phenytoin, or sotalol	Both agents may prolong QT interval
History of long QT syndrome	Both agents may prolong QT interval
Current known QTc >500 ms	Both agents may prolong QT interval
Seizure disorder	Hydroxychloroquine may interfere with the function of antiepilepsy drugs or lower the seizure threshold
Severe liver disease	Both drugs are hepatically cleared
Outpatient use of hydroxychloroquine or azithromycin for a chronic condition or received more than 2 d of hydroxychloroquine or azithromycin for suspected or confirmed COVID-19	Inappropriate to randomize away from the indicated use of drugs or to give overlapping courses of hydroxychloroquine or azithromycin for COVID-19
Patient has recovered from COVID-19 and/or is being discharged from the hospital on the day of enrollment	A physiological rationale in this population is lacking; the probability of benefit substantially decreased
Pregnant or nursing	Risk to fetus/infant. Low numbers of potential participants of this profile would limit investigators' ability to understand efficacy and safety in pregnant or nursing patients
Prisoner	Concern to avoid violation of autonomy
Weight <35 kg	Package insert advises increased risk of adverse effects

Definition of abbreviation: COVID-19 = coronavirus disease.

In this paper, we provide details beyond the normal methodology for a study protocol, given the complexity of operating nimbly and flexibly during a pandemic in a normally inflexible regulatory environment and in collaboration with a state government. The exponential spread of COVID-19 across the globe and the high rate of contagion, especially in healthcare environments, make it necessary to have flexibility regarding certain logistical details while maintaining the appropriate ethical and methodological standards for clinical research. We began work on this trial on March 20, 2020, received institutional review board approval on March 25, and enrolled the first patient on April 3.

Methods

We designed a prospective, randomized, open-label, active comparator trial of hydroxychloroquine versus azithromycin among hospitalized patients with confirmed or suspected COVID-19.

Target Population

The eligibility criteria are displayed in Table 1. Conceptually, we seek to study adult patients who are sick enough to require hospitalization and who are either confirmed to have COVID-19 or are suspected to have COVID-19 with high clinical probability. Details regarding the suspected COVID-19 criterion (including plans to suspend it when testing results are quickly available) are presented in the online supplement.

Study Procedures

After informed consent is obtained (using the "no-touch" techniques outlined in the online supplement), patients will be randomized to one of two drug regimens in an open-label, randomized, active comparator design. For enrolled patients whose laboratory test returns negative for SARS-CoV-2, if the clinical team believes that another cause of the patient's presentation is more likely than COVID-19 in light of the negative laboratory test, the clinical team will stop the study drug. Such discontinuation will be recorded. Because the fundamental clinical question is whether to start treatment in patients with confirmed or suspected COVID-19, these patients will remain in the primary analytic cohort for efficacy and safety. A secondary analytic cohort will include only those who test positive for COVID-19.

Study Drug

Patients in the hydroxychloroquine arm will receive hydroxychloroquine 400 mg by mouth twice a day for 1 day, and then 200 mg by mouth twice a day for 4 days (27) (with dose reductions for weight <45 kg or glomerular filtration rate <50 ml/min). The drug dose chosen falls at the lower end of doses proposed in various international trials, but it has proven *in vitro* efficacy, with a ratio of lung tissue trough concentrations to the effective concentration to suppress 50% of viral activity of >20 (27). Given *in vitro* confirmation of the adequacy of the dose and the likely superior safety profile at the lower dose, we chose the total dose of 2.4 g over 5 days for pragmatic reasons.

Patients in the azithromycin arm will receive azithromycin 500 mg on Day 1 plus 250 mg daily on Days 2–5 (administered orally or intravenously per the clinician's preference). Note: if the clinical attending physician believes that bacterial pneumonia is likely and requires a second antibacterial agent for "atypical" infection (an uncommon occurrence in COVID-19), patients may receive another agent (e.g., doxycycline or levofloxacin) as appropriate at the clinician's discretion.

For patients who received hydroxychloroquine or azithromycin immediately before randomization (no more than 2 d before), prior doses will count toward the total randomized dose.

Adverse Event Monitoring and Medication Monitoring

While patients are receiving the study medication, they will be monitored remotely on a daily basis for *1*) the development of adverse events and *2*) attempted introduction of medications that may increase the risk of QT prolongation among study patients (*see* the list in the online supplement). We are monitoring daily for other medications that may prolong the QTc and will perform an electrocardiogram (if one is not performed clinically) on study Day 2, after the loading dose is administered. Treating teams will monitor electrolytes according to standard clinical practice.

Study Endpoints

The primary endpoint is the World Health Organization (WHO) COVID Ordinal Outcomes Scale at Day 14. The details of the endpoint are displayed in Table 2.

Secondary endpoints include hospital-free, ventilator-free, and intensive care unit–free days, all at 28 days and all calculated as a worst-rank ordinal, in which death is scored as −1 and the lowest score possible for survivors is 0 (to limit survivorship bias [28, 29]). We will use the last-off method (only the time after the last liberation from, e.g., ventilation counts toward the total number of -free days). We will also evaluate time to a one-point decrease in the WHO COVID Ordinal Outcomes scale and the shape of the WHO COVID Ordinal Outcomes scale over time.

Ethical Considerations

This protocol was reviewed and approved by the institutional review board before the first patient was enrolled. A Data and Safety Monitoring Board (DSMB) was formed, with the charter finalized and the initial meeting held before study launch. Given the risk to research personnel, and in the absence of guidance from the U.S. Food and Drug Administration or Office for Human Research Protections regarding modifications to the Common Rule or guidance for trialists, we developed a no-touch consenting approach (reproduced in the online supplement) that allowed consent without direct physical contact between patients (or their legally authorized representatives) and research staff. (Our approach is consistent with subsequent guidance issued by the Food and Drug Administration on March 27, 2020.)

Rationale for an Active Comparator

We anticipate that the absence of a placebo or "usual care" control arm will be the most controversial design element of this trial. In terms of actual placebo, we had no capacity to manufacture or source a matching placebo in the time frame required for timely trial launch, nor would many of our nonacademic hospitals have been able to store or administer a placebo (lacking an investigational pharmacy). Furthermore, we had a brief window of time in which to launch a trial that would monitor patients closely and provide meaningful evidence to guide clinical care and also be responsive to a community context in which state officials and even some physicians felt an overriding imperative to provide hydroxychloroquine to all patients.

We also considered a "usual care" control arm. Even outside of a pandemic setting, usual care control arms are known to be problematic given the risk of variability, contamination, and decreases in trial efficiency (30–33). In the context of a pandemic, we anticipated that usual care would shift frequently and that we would encounter substantial rates of contamination (whether by one of the investigated agents or by differential use of other untested therapies). Our decisions were also affected by conversations about trial design with operational leaders and clinicians.

We were also mindful of the global context of clinical trials during a pandemic in which a rapid launch and simultaneous evaluation of multiple therapies are high priorities (34). Aware that placebo-controlled trials of hydroxychloroquine were being performed or about to be launched in academic centers (in addition to a global pragmatic trial led by WHO), we anticipated that a trial comparing hydroxychloroquine with another treatment commonly being administered would be of use to the global community. This technique—the use of active comparators rather than placebo control in a pandemic setting—has been used to good effect in Ebola. The PALM (Pamoja Tulinde Maisha) Consortium trial allowed efficient prioritization of novel monoclonal antibodies over an earlier antibody combination and antiviral medication (35). We note that a similar approach is being used in COVID-19 for remdesivir: some trials (e.g., NCT04280705) use placebo controls, whereas others use two active arms (e.g., NCT04292899: 5 vs. 10 d of remdesivir). Importantly, the techniques of a network meta-analysis provide the opportunity to integrate the results of our trial with other trials in similar target populations, and we expect to use them (36–38).

Table 2. World Health Organization COVID Ordinal Outcomes Scale*

Patient State	Descriptor	Score
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized, mild disease	No oxygen therapy	3
	Oxygen by mask or nasal cannulae	4
Hospitalized, severe disease	Noninvasive ventilation or high-flow oxygen	5
	Invasive mechanical ventilation without other organ support	6
	Invasive mechanical ventilation with other organ support (e.g., ECLS, CRRT, and vasopressors)	7
Death	Dead	8

Definition of abbreviations: COVID = coronavirus disease; CRRT = continuous renal replacement therapy; ECLS = extracorporeal life support.
*The score for the day reflects the worst status for the given calendar day.

Other precedents are also relevant to our design decisions in the present trial. Although comparative effectiveness research is often used to evaluate two treatments that are widely known to be efficacious, more broadly it is a framework for segmenting observed clinical care into units that can be compared with each other. This technique has been used to compare targets for optimal oxygen therapy (39, 40), targets for tidal volume in ARDS (41), positive end-expiratory pressure targets in ARDS (42, 43), blood pressure targets for hypotension (44) or hypertension (45), balanced crystalloids versus normal saline (46, 47), and fluids versus vasopressors early in the course of sepsis-associated hypotension (48). In each of these trials, several of which have appropriately changed clinical practice, no "usual care" arm was included. Instead, two (or more) common treatment strategies and/or medications were compared against each other. Fundamentally, we pursued a similar pragmatic question: in the case of two generally well tolerated treatments with considerable current clinical use (off-label use that is depleting supplies of the drug for clinical use), is one better than the other?

We outline the anticipated interpretation of our trial, including three different results from ongoing or imminently launching trials of hydroxychloroquine versus placebo. We include an inference grid (Table 3) to describe our anticipated response to the possible outcomes of the present trial, assuming that enrollment targets are met. We highlight the fact that under most (but admittedly not all) circumstances, our trial will offer a straightforwardly interpretable result. We also anticipate a network meta-analysis in which our trial data are merged with trials that include placebo arms in similar target populations.

We emphasize that the probability of both treatments being efficacious, when scores of treatments for viral pneumonia and similar syndromes have been tested and found to lack clinical efficacy, is low. If, for example, we estimate that hydroxychloroquine is a promising treatment, on the basis of prior trials of promising treatments, it may have a 10% likelihood of a positive result for clinical efficacy (which is probably high for the expected success rate in similar clinical trials [49]). Even if azithromycin were similarly promising, the probability that both will be efficacious (assuming independence) is 1%. We note that our intention is not to use an occult placebo, even if there currently is greater interest in hydroxychloroquine than in azithromycin. Azithromycin's extensive historic use in respiratory infections, and excellent safety record, provides a reliable benchmark for hydroxychloroquine, a novel proposed therapeutic in COVID-19 (a viral pneumonia).

Statistical Considerations

A formal statistical analysis plan (SAP) will be written before the initial formal interim analysis is conducted. In the setting of rapidly evolving knowledge concerning the COVID-19 pandemic, new information may come to light that will necessitate subsequent modifications to the study protocol and analyses; any such modifications will be documented and time stamped. The principles of the SAP are outlined here, and an expanded version of this summary is provided in the online supplement.

General. Descriptive summaries will be produced for relevant variables. The primary analysis and analyses of secondary efficacy outcomes will be performed in the intention-to-treat (ITT) population, which consists of all randomized patients. Summaries of safety outcomes will be obtained from a safety population consisting of all patients who receive at least one dose of the study medication. We will also perform secondary analyses of efficacy and safety within subsets of the intention-to-treat population (especially those with positive COVID tests) and safety populations restricted to patients who are confirmed to have COVID-19 (this

Table 3. Inference grid for interpretation of possible study outcomes in the context of other trials

Study Outcome	Outcomes in Other Trials of Hydroxychloroquine versus Placebo	Expected Inference
No significant difference	Unknown	Neither agent is likely to be efficacious; explore other options.
	Hydroxychloroquine not efficacious	Neither agent is efficacious; explore other options.
	Hydroxychloroquine efficacious	Both agents are likely efficacious; trials of combination therapy indicated.
Hydroxychloroquine is significantly better than azithromycin	Unknown	Hydroxychloroquine should be preferred to azithromycin and is likely efficacious.
	Hydroxychloroquine not efficacious	Azithromycin may have unanticipated toxicities.
	Hydroxychloroquine efficacious	Hydroxychloroquine is superior to azithromycin and is efficacious.
Azithromycin is significantly better than hydroxychloroquine	Unknown	Hydroxychloroquine is likely toxic and should not be recommended; azithromycin may merit additional investigation.
	Hydroxychloroquine not efficacious	Hydroxychloroquine is likely toxic and should not be recommended; azithromycin may merit additional investigation.
	Hydroxychloroquine efficacious	Both hydroxychloroquine and azithromycin are likely efficacious; combination therapy should be investigated.

approach has been used in other trials, such as the VIOLET (Vitamin D to Improve Outcomes by Leveraging Early Treatment) trial [50]).

Primary analysis. The prespecified primary analysis will compare the Day 14 assessment of the eight-level COVID Ordinal Outcomes Scale between the randomized hydroxychloroquine and azithromycin groups. This analysis will be performed using a proportional odds logistic regression model (51), with the randomized treatment group as the independent variable and patient age, comorbidities, and the baseline level of the COVID Ordinal Outcomes Scale as covariates. The proportional odds model is closely linked to the Wilcoxon rank-sums test (52) and is thus expected to provide approximately valid inference even if the proportional odds assumption is violated.

In accordance with a structure proposed by Harrell and Lindsell (53), the primary analysis will be performed using a Bayesian framework, with a somewhat conservative normal prior distribution assumed for the log-transformed odds ratio. The prior distributions for the intercept parameters and covariate regression coefficients in the proportional odds model will be defined in the SAP. The same Bayesian proportional odds model will be applied to the secondary endpoints. Our primary analyses will be restricted to nonmissing observations, without imputation, with sensitivity analyses using multiple imputation if required by missingness.

Safety. The safety of both the hydroxychloroquine and azithromycin treatments being evaluated in this study has been well established in studies of thousands of patients and in postmarketing surveillance. Nevertheless, we will evaluate the safety of these drugs in the context of COVID-19 by providing counts (proportions) of adverse events, with special attention to those listed in the package insert for hydroxychloroquine and azithromycin, and careful investigation of any serious and unexpected adverse events.

Interim monitoring. More details regarding interim monitoring are provided in the online supplement. Under the Bayesian design, the posterior distribution describing the accumulating evidence provided by the data for treatment benefit or harm will be updated in successive interim analyses as the trial proceeds (54). Modifying slightly the approach of Harrell and Lindsell, we will evaluate through simulation the implications of given decision thresholds (55). Final details on the interim monitoring plan will be established in the DSMB charter before the first interim analysis.

The general strategy would allow the trial to stop early for efficacy (in either direction), but not for futility. Given the nature of the COVID-19 pandemic (with sudden and transient increases in patient volume in a given location), it may be difficult for any single trial to answer a question definitively on its own. We will also include feasibility evaluations to allow us to determine when the first wave of COVID-19 has resolved, such that further enrollment in the trial is unlikely. Given the potentially cyclic nature of COVID-19, the DSMB, principal investigator, and trial statistician may make a determination, given the totality of the evidence, whether to suspend the trial if there is clear evidence that the first wave is over in Utah, and secondarily whether to consider recurrent enrollment (without release of results to investigators) in subsequent waves of disease.

Sample size and power. Details regarding the power calculation are provided in the online supplement. The target sample size of this trial is 300 randomized subjects, with a maximum detectable odds ratio (<1, suggesting efficacy of hydroxychloroquine over azithromycin) of 0.55, which corresponds to a detectable risk ratio of 0.702. In any case, we anticipate that the data from this study will meaningfully contribute to network meta-analyses of therapeutics for COVID-19.

Conclusions

Faced with the prospect of massive statewide expansions of clinical use of untested therapies with unknown risk/benefit profiles in COVID-19, and operating within the context of global placebo-controlled trials being launched in parallel, we initiated a pragmatic trial intended to both provide treatment options in a structured environment, with informed consent and formal safety monitoring, and contribute to knowledge about which treatment strategies may be of use in subsequent waves of COVID-19 activity. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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