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Hazan

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(54) **METHODS OF TREATING COVID-19 INFECTION**

(71) Applicant: **Sabine Hazan**, Ventura, CA (US)

(72) Inventor: **Sabine Hazan**, Ventura, CA (US)

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A61K 31/4706	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/7052*** (2013.01); ***A61K 31/375*** (2013.01); ***A61K 31/4706*** (2013.01); ***A61K 31/593*** (2013.01); ***A61K 33/30*** (2013.01); ***A61P 31/14*** (2018.01)

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CPC A61K 31/4706; A61K 31/7052; A61K 31/375; A61K 31/593; A61K 33/30; A61P 31/14

See application file for complete search history.

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Primary Examiner — Michael B. Pallay

(74) *Attorney, Agent, or Firm* — Cislo & Thomas, LLP

(57) **ABSTRACT**

A method of treating an individual infected with COVID-19, the method comprising the steps of: providing an individual infected with COVID-19; administering five antimicrobials to the individual, wherein the antimicrobials comprise: hydroxychloroquine; azithromycin; vitamin C; vitamin D; and zinc; and monitoring the individuals condition over a pre-determined period of time to determine whether the individual is no longer infected with COVID-19.

3 Claims, 6 Drawing Sheets

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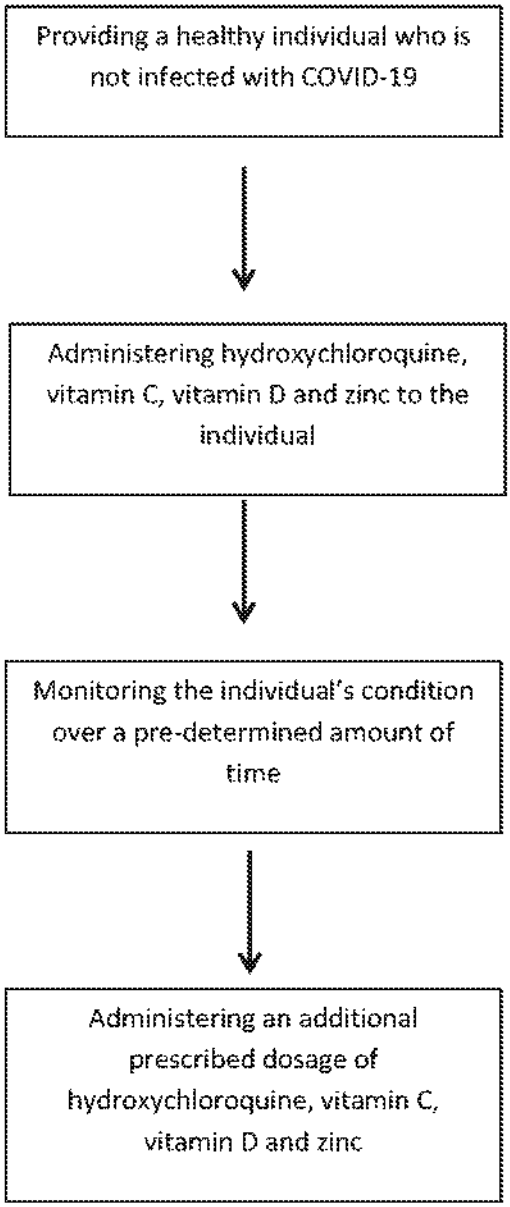

Providing a healthy individual who is not infected with COVID-19
Administering hydroxychloroquine, vitamin C, vitamin D and zinc to the individual
Monitoring the individual's condition over a pre-determined amount of time
Administering an additional prescribed dosage of hydroxychloroquine, vitamin C, vitamin D and zinc

Figure 1

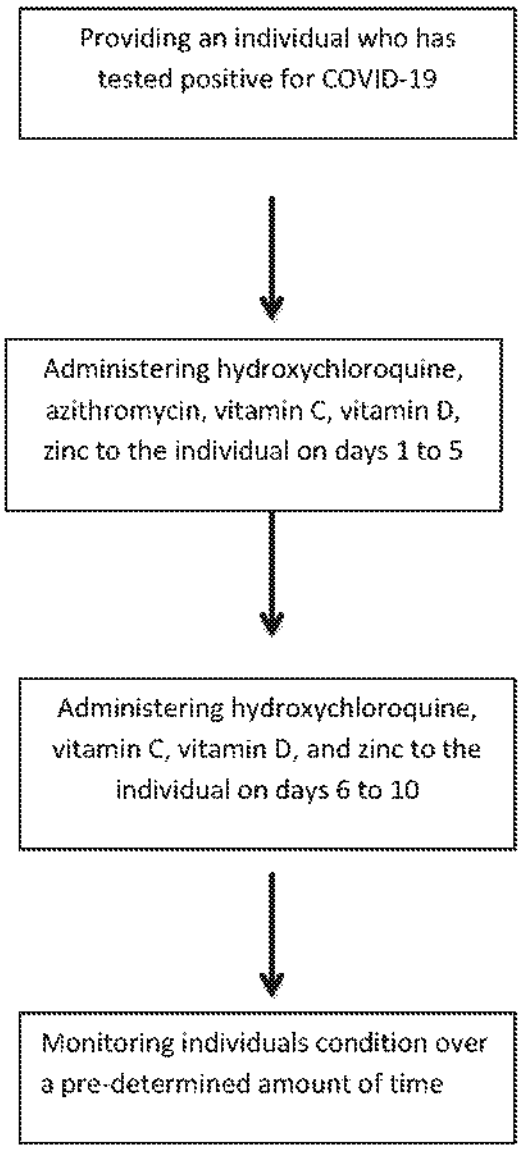

Providing an individual who has tested positive for COVID-19
Administering hydroxychloroquine, azithromycin, vitamin C, vitamin D, zinc to the individual on days 1 to 5
Administering hydroxychloroquine, vitamin C, vitamin D, and zinc to the individual on days 6 to 10
Monitoring individuals condition over a pre-determined amount of time

Figure 2

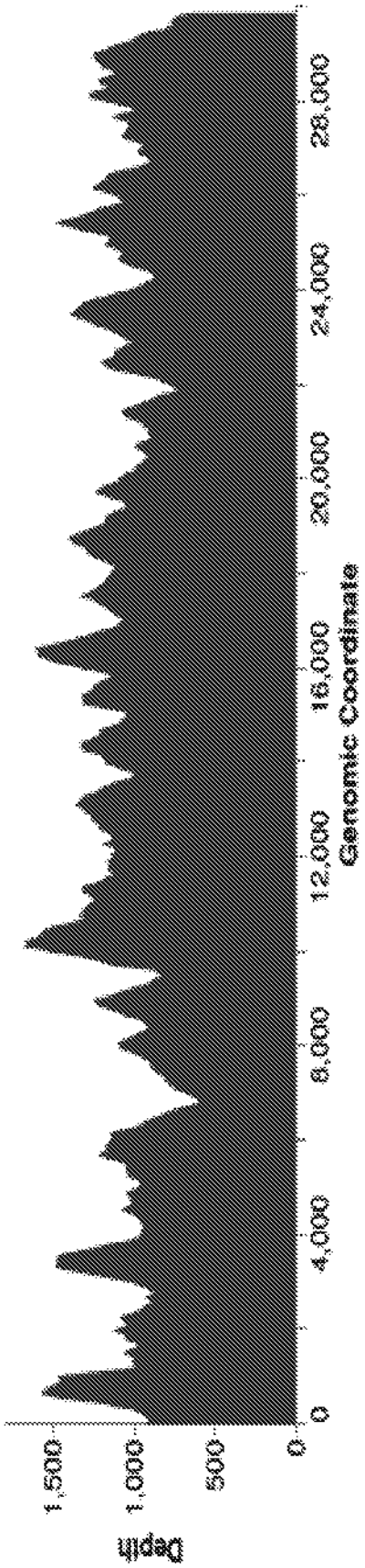


Figure 3A

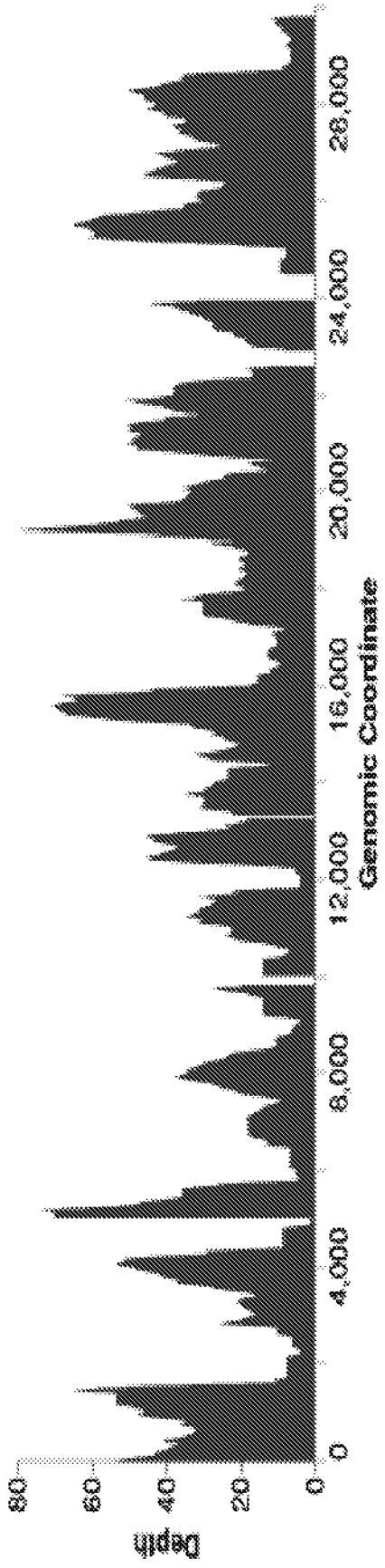


Figure 3B

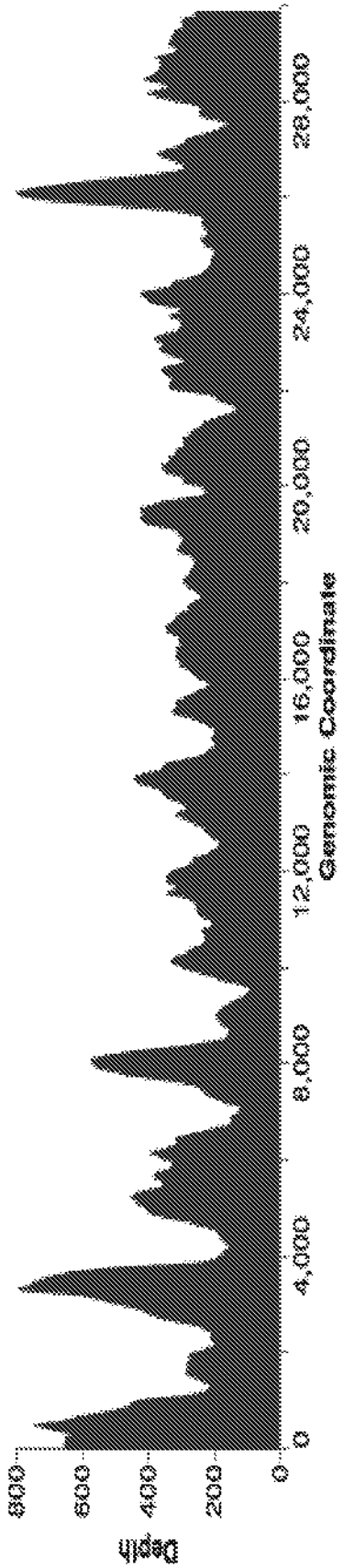


Figure 3C

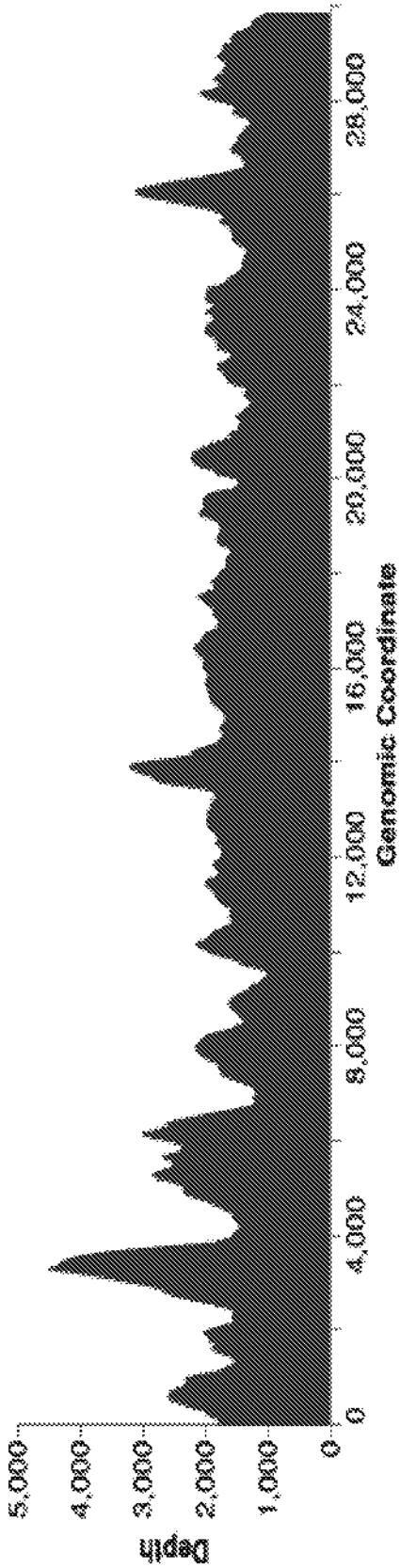


Figure 3D

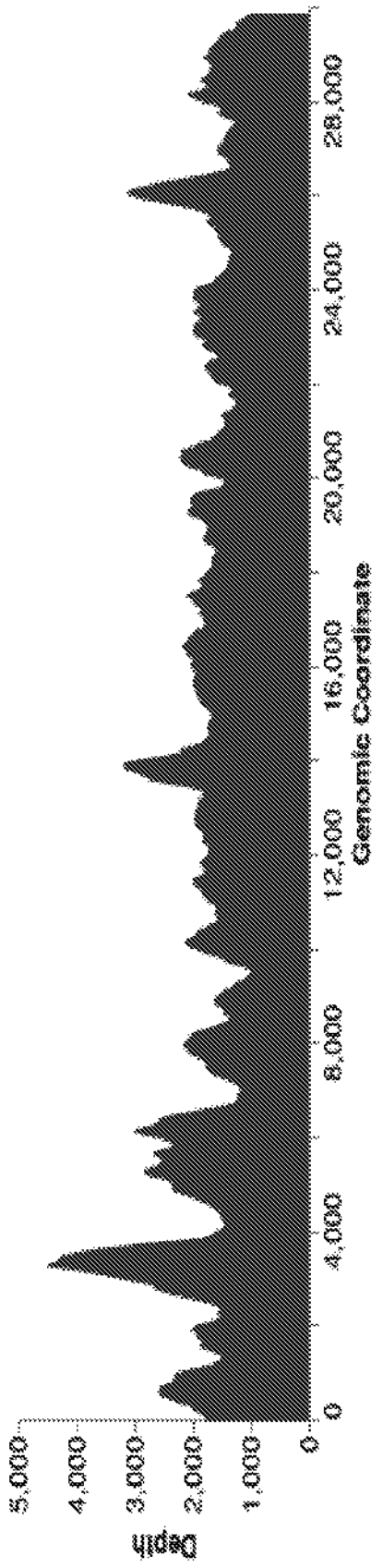
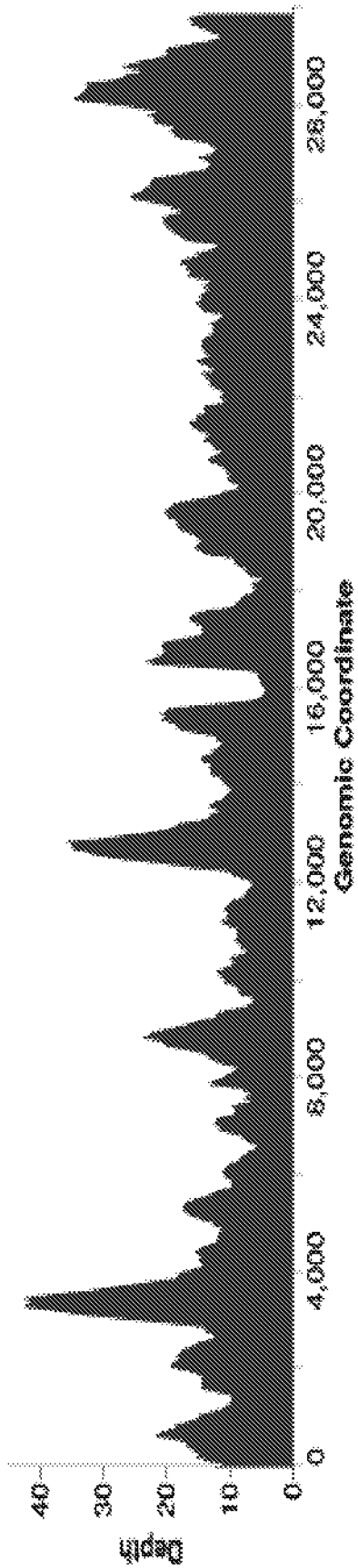


Figure 3E



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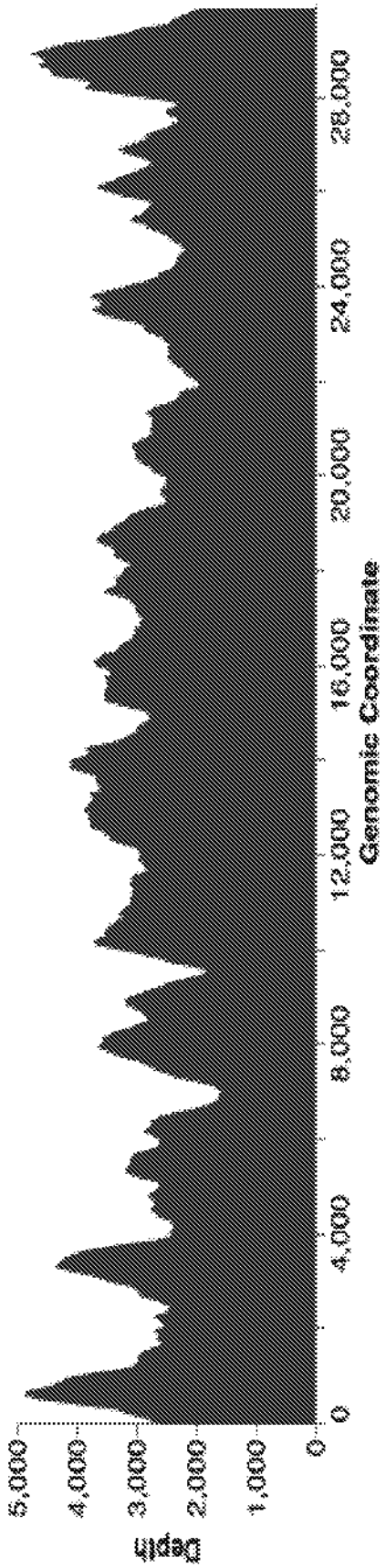

Figure 3G

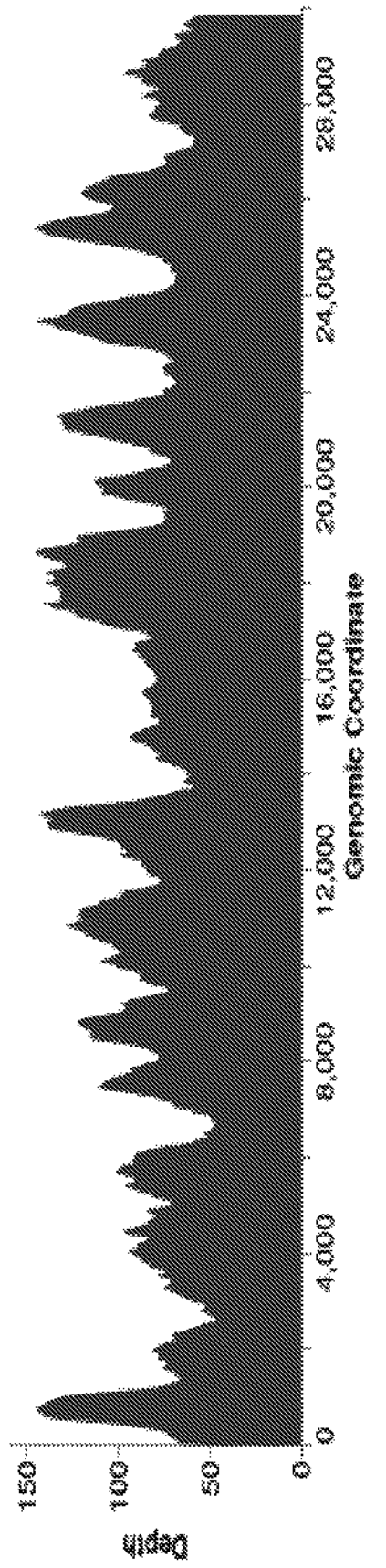

Figure 3H

METHODS OF TREATING COVID-19 INFECTION

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional application of U.S. patent application Ser. No. 17/026,051, titled "Method of Preventing and Treating COVID-19 Infection, filed Sep. 18, 2020, which claims priority to U.S. Provisional Patent Application No. 62/993,345, titled "Method of Treating and Preventing COVID-19 Infection," filed Mar. 23, 2020, U.S. Provisional Patent Application No. 63/022,371, titled "Method of Treating and Preventing COVID-19 Infection," filed May 8, 2020, U.S. Provisional Patent Application No. 63/002,494, titled "Method of Using Vitamin C, Vitamin D, Zinc, and Optionally Hydroxychloroquine, to Prevent COVID-19 Infection," filed Mar. 31, 2020, U.S. Provisional Patent Application No. 63/022,368, titled "Method of Using Vitamin C, Vitamin D, Zinc, and Optionally Hydroxychloroquine, to Prevent COVID-19 Infection," filed May 8, 2020, and U.S. Provisional Patent Application No. 63/001,161, titled "Method of Using Aerosolized Hydroxychloroquine, Vitamin C, and Zinc to Treat Covid-19 Infection," filed Mar. 27, 2020, the contents of which are incorporated by reference in their entirety.

BACKGROUND

COVID-19 is a novel betacoronavirus that originated in bats in the city of Wuhan, China. This disease has rapidly spread to become a worldwide pandemic, as declared by the World Health Organization (WHO). Symptoms of COVID-19, including fever, myalgia, coughing and shortness of breath, may appear from 2 and 14 days after exposure. Approximately 20% of patients progress to severe illness, including pneumonia, respiratory distress, and even death. Cases in the US have increased five-fold over the last week, alone. The disease is spreading rapidly, and a cure is desperately needed.

Nucleotide analogues, protease inhibitors and altered cellular bonding due to pH change will maximize host protection by: optimizing levels of gamma interferon and reducing the level of pathogenic microbes in the airways, especially in 'at risk' patients.

It is known that single anti-viral agents work poorly when used alone in other chronic viral infections such as Hepatitis C or HIV infection. Therefore, the greater the number of anti-viral agents used in combination, the greater the cure rate.

Thus, there is a significant unmet need for preventing and treating this viral infection. The present invention addresses this need.

SUMMARY

The invention herein is directed to my method of treating an individual infected with COVID-19. The method of treatment comprises the steps of: providing an individual infected with COVID-19; administering five antimicrobials to the individual, wherein the antimicrobials comprise: chloroquine or hydroxychloroquine; azithromycin; vitamin C; vitamin D; and zinc; and monitoring the individuals condition over a pre-determined period of time to determine whether the individual is no longer infected with COVID-19.

Optionally, the method of treatment comprises administering hydroxychloroquine in daily dosage range of 20 mg to 2,000 mg; administering azithromycin in a daily dosage range of 250 mg to 500 mg; administering vitamin C in a daily dosage range of 250 mg to 10,000 mg; administering vitamin D in a daily dosage range of 1,000 mg to 100,000 mg; and administering zinc in a daily dosage range of 5 mg to 100 mg.

Optionally, the method of treatment comprises the steps of: administering, on day 1: two doses of 200 mg of hydroxychloroquine; one dose of 500 mg of azithromycin; one dose of 3,000 mg of vitamin C; one dose of 3,000 mg of vitamin D; and one dose of 50 mg of zinc; administering daily, on days 2 to 5: two doses of 200 mg of hydroxychloroquine; one dose of 250 mg of azithromycin; one dose of 3,000 mg of vitamin C; one dose of 3,000 mg of vitamin D; and one dose of 50 mg of zinc; and administering daily, on days 6 to 10: two doses of 200 mg of hydroxychloroquine; one dose of 3,000 mg of vitamin C; one dose of 3,000 mg of vitamin D; and one dose of 50 mg of zinc.

The antimicrobials can be administered orally in the form of an aerosolized spray.

The two doses of hydroxychloroquine can be administered as a single daily dose.

The method of treatment can further comprise administering daily, on days 6 to 10, administering one dose of 250 mg of azithromycin.

BRIEF DESCRIPTION OF THE DRAWINGS

Further advantages of the present invention may become apparent to those skilled in the art with the benefit of the following detailed description of the preferred embodiments and upon reference to the accompanying drawings in which:

FIG. **1** is a flow chart depicting the steps of a method of preventing infection of an individual with COVID-19;

FIG. **2** is a flow chart depicting the steps of a method of treating an individual infected with COVID-19;

FIG. **3**A a graphical representation of whole genome alignment of SARS-CoV-2 in patient 1 of Example 6;

FIG. **3**B a graphical representation of whole genome alignment of SARS-CoV-2 in patient 3 of Example 6;

FIG. **3**C a graphical representation of whole genome alignment of SARS-CoV-2 in patient 4 of Example 6;

FIG. **3**D a graphical representation of whole genome alignment of SARS-CoV-2 in patient 6 of Example 6;

FIG. **3**E a graphical representation of whole genome alignment of SARS-CoV-2 in patient 8 of Example 6;

FIG. **3**F a graphical representation of whole genome alignment of SARS-CoV-2 in patient 10 of Example 6;

FIG. **3**G a graphical representation of whole genome alignment of SARS-CoV-2 in patient 11 of Example 6; and

FIG. **3**H a graphical representation of whole genome alignment of SARS-CoV-2 in patient 12 of Example 6.

DETAILED DESCRIPTION

As used herein, the following terms and variations thereof have the meanings given below, unless a different meaning is clearly intended by the context in which such term is used.

The terms "a," "an," and "the" and similar referents used herein are to be construed to cover both the singular and the plural unless their usage in context indicates otherwise.

As used in this disclosure, the term "comprise" and variations of the term, such as "comprising" and "comprises," are not intended to exclude other additives, components, integers ingredients or steps.

Referring now to the drawings, wherein like reference numerals designate identical or corresponding features throughout the several views. Further, described herein are certain non-limiting embodiments of my pipeline filter assembly for pool filtering and maintenance.

The following discussion describes in detail multiple embodiments of the invention with several variations of those embodiments. This discussion should not be construed, however, as limiting the invention to those particular embodiments. Practitioners skilled in the art will recognize numerous other embodiments as well.

In a first embodiment, the present invention is directed to a method of preventing COVID-19 infection in an individual. The method involves administration of chloroquine or hydroxychloroquine, Vitamin C, Vitamin D, and Zinc. Both methods are discussed in greater detail below.

Referring now to FIG. **1**, there is shown the method of prevention. The method of prevention comprises administering four different antimicrobials. The four antimicrobials comprise: chloroquine or hydroxychloroquine, vitamin C, vitamin D, and zinc.

Day 1 the individual takes the following, ideal, regimen outlined in Table 1:

TABLE 1

Drug	AM Dose	PM Dose
Hydroxychloroquine	200 mg	200 mg
Vitamin C	3000 mg	—
Vitamin D	3000 mg	—
Zinc	50 mg	—

Optionally, the method of prevention can comprise administering on day 2: 3,000 mg of vitamin C; 3,000 mg of vitamin D; and 50 mg of zinc.

Hydroxychloroquine is administered only on day 1. The half-life of hydroxychloroquine is up to 32 days, thus treatment with this drug for one day should be sufficient. However, should the need to prevent the infection or disease last longer than 32 days, repeat dosing can be considered. Accordingly, if necessary, the cycle of day 1 followed by day 2 can be repeated weekly, 2nd-weekly, every 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, or 8 weeks.

Vitamin C is administered at 3,000 mg per day ongoing. This 3,000 mg can be broken up into two 1500 mg doses, one taken in the morning and one taken at night.

Vitamin D is administered at 3,000 mg per day ongoing. This 3,000 mg can be broken up into two 1500 mg doses, one taken in the morning and one taken at night.

Zinc is administered at 50 mg per day ongoing. This 50 mg can be broken up into two 25 mg doses, one taken in the morning and one taken at night.

Chloroquine or hydroxychloroquine can be administered in a daily dosage range of 20 mg to 2,000 mg. The above amounts recited in the tables are not limiting.

Vitamin C can be administered in a daily dosage range of 250 mg to 10,000 mg. The above amounts recited in the tables are not limiting.

Vitamin D can be administered in a daily dosage rage of 1,000 mg to 100,000 mg. The above amounts recited in the tables are not limiting.

Zinc can be administered in a daily dosage of 5 mg to 100 mg. The amount of Zinc can be reduced to 25 mg per day if gastrointestinal upset occurs.

Zinc, Vitamin C and D help in numerous aspects of viral protection through cellular metabolism, including catalytic activity of enzymes, and play roles in immune function, protein synthesis.

The chloroquine or hydroxychloroquine can come in various forms: as a pill, liquid solution, lozenges, topical treatment such as a cream or oil, or any other means of delivery. Hydroxychloroquine prevents cytokine release, and cytokine release is what causes anaphylactic flush. Optionally, the hydroxychloroquine is sprayed directly on the users tongue.

In the method of prevention described above, all, or any combination of, the four antimicrobials disclosed above can be administered in the form of a single small atomizer. The patient sprays the atomizer towards the back of their throat. The spray is administered at least once a day, but preferably twice a day when coughing starts. Use of the atomizer continues as directed by the supervising physician.

In a second embodiment, the present invention is directed to a method of treating an individual with infection or disease with five different antimicrobials. The five antimicrobials comprise: hydroxychloroquine, azithromycin, vitamin C, vitamin D and zinc. Referring now to FIG. **2**, there is shown the method of treatment.

Day 1 following positive test (isolation), the individual takes the following regimen outlined in Table 2:

TABLE 2

Drug	AM Dose	PM Dose
Hydroxychloroquine	200 mg	200 mg
Azithromycin	500 mg	—
Vitamin C	3000 mg	—
Vitamin D	3000 mg	—
Zinc	50 mg	—

On Day 2-Day 5 the individual takes the following regimen outlined in Table 3:

TABLE 3

Drug	AM Dose	PM Dose
Hydroxychloroquine	200 mg	200 mg
Azithromycin	250 mg	—
Vitamin C	3000 mg	—
Vitamin D	3000 mg	—
Zinc	50 mg	—

On Day 6-Day 10, the individual takes the following regimen outlined in Table 4:

TABLE 4

Drug	AM Dose	PM Dose
Hydroxychloroquine	200 mg	200 mg
Vitamin C	3000 mg	—
Vitamin D	3000 mg	—
Zinc	50 mg	—

Hydroxychloroquine is administered daily, at 200 mg twice daily for days 1-10.

Azithromycin is administered daily, at 500 mg on day 1, and 250 mg days 2-5. Optionally, azithromycin can be administered at 250 mg per day for 5-10 days with a loading dose of 500 mg×day 1 or simply 250 mg on day 1. Azithromycin may be substituted with doxycycline at a daily dosage range of 25 mg to 800 mg, for those unable to take azithromycin.

Vitamin C is administered at 3,000 mg per day ongoing. This 3,000 mg can be broken up into two 1500 mg doses, one taken in the morning and one taken at night.

Vitamin D is administered at 3,000 mg per day ongoing. This 3,000 mg can be broken up into two 1500 mg doses, one taken in the morning and one taken at night.

Zinc is administered at 50 mg per day ongoing. This 50 mg can be broken up into two 25 mg doses, one taken in the morning and one taken at night.

Chloroquine or hydroxychloroquine can be administered in a daily dosage range of 20 mg to 2,000 mg. The above amounts recited in the tables are not limiting.

Vitamin C can be administered in a daily dosage range of 250 mg to 10,000 mg. The above amounts recited in the tables are not limiting.

Vitamin D can be administered in a daily dosage rage of 1,000 mg to 100,000 mg. The above amounts recited in the tables are not limiting.

Zinc can be administered in a daily dosage of 5 mg to 100 mg. The amount of Zinc can be reduced to 25 mg per day if gastrointestinal upset occurs.

Concurrently with the above treatment, the individual is self-quarantined per CDC recommendations.

Optionally, for the method of treatment noted above, as the dosages of the hydroxychloroquine, vitamin C, vitamin D and zinc remain the same throughout treatment, all four of those antimicrobials can be administered in the form of a single small atomizer. The patient sprays the atomizer towards the back of their throat. The spray is administered at least once a day, but preferably twice a day when coughing starts. Use of the atomizer continues as directed by the supervising physician.

For all protocols provided in this application, vitamin C dosage can range from 250 mg to 10,000 mg per day, vitamin D dosage can range from 1000 IU (mg) to 100,000 IU (mg) per day, zinc (which can be any form or type of zinc) dosage can range from 5 mg to 100 mg per day, and hydroxychloroquine dosage can range from 50 mg to 2,000 mg per day for a treatment period of 1 to 10 days treatment. Optionally, hydroxychloroquine can be administered once as single dose. For all protocols provided in this application, when a dosage range is provided, any dosage amount that is included in that range can be administered. Accordingly, the invention is not limited to the dosage ranges disclosed, and includes all dosage amounts contained in those ranges.

Optionally, the above protocols can include selenium, copper and other vitamins that are deemed acceptable supplements for vitamin C, vitamin D or zinc or to counteract the negative depletion of certain vitamins, which is why copper or selenium are typically used.

Treatment can be for one day or consecutive or repeated in 2 weeks, 1 month, 6 months or 1 year, or weekly for 6 months.

The above protocols can be used to treat other viruses (not just COVID-19), including other flu and various respiratory viruses, including more benign coronaviruses and rhinoviruses.

The above protocols can also be used to treat Autism, Parkinson's, Alzheimer's and other neurological diseases.

EXAMPLES

Example 1: Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for Prevention of COVID-19 Infection

Objective: To determine whether treatment with hydroxychloroquine, vitamin C, vitamin D, and zinc in combination will prevent infection with COVID-19 and to assess the safety and tolerability of hydroxychloroquine, vitamin C, vitamin D, and zinc in healthy, high-risk individuals without hypertension, and no evidence of COVID-19 infection.

Procedure: Day 1: Prescription of study drugs and home health monitoring equipment. The study drugs are hydroxychloroquine 200 mg twice a day for 1 day only, vitamin C 3000 mg per day ongoing, vitamin D 3000 mg per day ongoing, and zinc 50 mg per day ongoing per day. The home health monitoring equipment is an electrocardiogram (EKG) which synchs up with a smartphone

Days 2-7: Patient collects the EKG once during this week using the home health equipment

Weeks 1-23: Patient provides an assessment of any COVID-19 symptoms and continues to collect EKG weekly throughout the remainder of the trial

Week 24: Patient undergoes confirmatory COVID-19 testing which consists of nasopharyngeal (NP) and oropharyngeal (OP) swabs collected according to CDC (Center for Disease Control) protocol. The swabs consist of synthetic fiber swabs with plastic shafts. NP swabs are collected by insertion of a swab into the nostril parallel to the palate. The swab is left in place a few seconds to allow it to absorb secretions. OP swabs are inserted into the oropharynx parallel to the palate, avoiding the tongue. The swab is left in place a few seconds to allow it to absorb secretions. The swabs are then immediately placed in sterile tubes with 2-3 mL of viral transport media. The tubes are placed in biohazard bags then boxes and couriered to the local Public Health Lab.

Table 5 provides a schedule of events for Example 1.

TABLE 5

Assessment	Screening (Day 1)	Day 3	Weeks 1-23	Week 24
Informed consent and demographics	X			
Review of prior and concomitant medications	X			
EKG at home		X	X	
Prescription of Hydroxychloroquine, vitamin C, vitamin D, and zinc	X			
Provision of home health EKG and pulse oximeter	X			
Update list of prior and concomitant medications	X		X	X
Ask about any adverse events and any serious adverse events		X	X	X
Evaluation of COVID-19 symptoms			X	X
COVID-19 testing				X
Blood draw for future testing				X
Vitals in-clinic				X
Physical exam				X

Regarding Table 5: Vitals at home to include EKG and O2Sat, future testing will require separate informed consent and could possibly include antibody or cytokine testing, and vitals in-clinic to include height, weight, blood pressure (following 5 minutes sitting) pulse, respiratory rate, temperature, and oxygen saturation.

Example 2: Randomized, Double-Blind, Placebo-Controlled Phase IIA Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection

Objectives: Prevention of COVID-19, Lack of COVID-19 symptoms, and assessment of safety and tolerability

Procedure: Screening Period (Days −5 to −1): Prescription of home health monitoring equipment that includes a

thermometer, a pregnancy test if applicable, and a daily diary. There are two groups being studied: Arm 1 and Arm 2.

Arm 1 is prescribed the following antimicrobials: hydroxychloroquine 200 mg twice a day for 1 day only, vitamin C 3000 IU per day for 12 weeks, vitamin D 3000 IU per day for 12 weeks, and zinc 50 mg per day for 12 weeks. The zinc can be reduced to 25 mg if GI upset occurs.

Arm 2 is prescribed the following antimicrobials: Placebo twice a day for 1 day only, vitamin C 3000 IU per day for 12 weeks, vitamin D 3000 IU per day for 12 weeks, and zinc 50 mg per day for 12 weeks. The zinc can be reduced to 25 mg if GI upset occurs.

Day 1: Patient is called to teach them how to use the diary in the EDC, discuss the medication regimen, and answer any questions they may have. Patient takes pregnancy test if applicable, collects a temperature reading, completes their diary, and takes the prescribed treatment regimen. Table 6 outlines the prescribed treatment regimen for Day 1.

TABLE 6

Drug	AM Dose	PM Dose
Hydroxychloroquine (or placebo)	200 mg	200 mg
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 2: Patient collects a temperature reading, completes their diary, and is called on the phone for assessment of any adverse events or serious adverse events, assessment of any COVID-19 symptoms, the list of prior and concomitant medications is updated, any questions the patient has are answered, and the patient takes their prescribed treatment regimen. Table 7 outlines the prescribed treatment regimen for Day 2.

TABLE 7

Drug	AM Dose	PM Dose
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Days 3-10: Patient collects a temperature reading, completes their diary, and takes their prescribed treatment regimen. Table 8 outlines the prescribed treatment regimen for Days 3-10.

TABLE 8

Drug	AM Dose	PM Dose
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 14: The patient is called for instruction on how to collect a nasal swab and package for shipping, assessment COVID-19 symptoms, updating their list of prior and concomitant medications, and answering any questions they may have.

Weeks 3-11: The patient is called weekly for assessment of any adverse events or serious adverse events, assessment of any COVID-19 symptoms, updating their list of prior and concomitant medications, and answering any questions they may have. The patient takes weekly temperature readings, completes their diary, and takes the prescribed treatment regimen. During Week 4 the patient is reminded to collect a nasal swab. The prescribed treatment regimen for Weeks 3-11 is shown in Table 9.

TABLE 9

Drug	AM Dose	PM Dose
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Week 12: The patient presents to the clinic for evaluation that includes assessment for adverse events and serious adverse events, updating their list of prior and concomitant medications, a physical exam, nasal swab collection and COVID-19 sample collection.

Samples for COVID-19 testing are collected using synthetic swabs with plastic shafts. Nasal swabs are collected and immediately placed into a sterile vial with 2-3 mL of viral transport media. The vials are placed into biohazard bags, boxed up, the box sterilized, and picked up for shipment to the central laboratory. Samples are tested by RT-PCR.

Table 10 presents the schedule of events for Example 2.

TABLE 10

Assessment	Screening	Day 1	Day 2	Day 3-10	Day 14	Weeks 3-12	Month 1	Month 2	Month 3
Informed Consent & Demographics	X								
Initial Review of Prior and Concomitant	X								
Medications	X								
Medical Records review,	X								
including baseline EKG									
Randomization	X								
Prescription of Hydroxychloroquine or	X								
placebo, vitamin C, vitamin D, and zinc									
Provision of daily diary, thermometer	X								
and pregnancy test									
Pregnancy Test if applicable		X							
Temperature at home		X	X	X	X	X	X	X	X
Complete daily diary		X	X	X	X	X	X	X	X
Hydroxychloroquine 200 mg		X							
Vitamin C 3000 mg		X	X	X	X	X	X	X	X
Vitamin D 3000 IU		X	X	X	X	X	X	X	X
Zinc 50 mg[a]		X	X	X	X	X	X	X	X
Phone/video call to patient[b]	X	X	X		X	X	X	X	
Update list of prior and concomitant		X	X	X	X	X	X	X	X
medications									
Ask about AE and SAE		X	X	X	X	X	X	X	X
Assessment of COV1D-19 symptoms		X	X	X	X	X	X	X	X

TABLE 10-continued

Assessment	Screening	Day 1	Day 2	Day 3-10	Day 14	Weeks 3-12	Month 1	Month 2	Month 3
Swabs for RT-PCR					X		X		X
Vitals in-clinic[e]									X
Physical Exam									X

Regarding Table 10: The Zinc may be reduced to 25 mg if GI upset occurs, phone/video calls to the patient occur weekly during Weeks 2-11, and vitals in-clinic include height, weight, blood pressure (following 5 minutes sitting) pulse, respiratory rate, temperature, and oxygen saturation.

Statistical Analysis: The treated patients in this study are compared to the placebo group. Measurements include PCR test results, presence or absence of symptoms, and symptom severity.

The change of these measurements from the end to the baseline (post-pre) are used as the primary outcome, for example, $\mu e=\mu e1-\mu e0$, where $\mu e1$ and $\mu e0$ are the outcome of patients from the treatment group at the end and at baseline, respectively.

H_0: $\Delta \leq \delta_0$ against H_α: $\Delta > \delta_0$ where $\delta 0$ is a clinically meaningful threshold to measure the disease symptoms. In this study, that meaningful threshold is calculated as mean change in clinical symptoms as recorded in the diary, from baseline through week 12. Each category in the diary is assigned a number, 0 for None, 1 for Mild, 2 for Moderate and 3 for severe. Each category is analyzed independently and as a group.

Categorical variables are summarized by presenting the number (n) and percent (%) of subjects in each category. All Statistical tests for the analysis are performed using the $p<0.05$ level of significance. All confidence intervals are one-sided.

Since these are healthcare workers who are exposed to COVID-19 at every shift, efficacy is determined by RT-PCR testing, as well as the presence or absence of symptoms as recorded in the patient diary via EDC.

Example 3: Use of Hydroxychloroquine, Azithromycin, Vitamin C, Vitamin D, and Zinc to Treat COVID-19 Infection

Objectives: test the efficacy of hydroxychloroquine, azithromycin, vitamin C, vitamin D, and zinc in the treatment of patients with COVID-19 infection and to assess the safety and tolerability of this treatment in patients with COVID-19 infection.

Procedure: First, the patient is determined to have COVID-19.

Day 1 following positive test (isolation): The patient takes prescribed regimen outlined in Table 11.

TABLE 11

Drug	AM Dose	PM Dose
Hydroxychloroquine	200 mg	200 mg
Azithromycin	500 mg	—
Vitamin C	3000 mg	—
Vitamin D	3000 mg	—
Zinc	50 mg	—

Day 2-Day 5: The patient takes the prescribed regimen outlined in Table 12.

TABLE 12

Drug	AM Dose	PM Dose
Hydroxychloroquine	200 mg	200 mg
Azithromycin	250 mg	—
Vitamin C	3000 mg	—
Vitamin D	3000 mg	—
Zinc	50 mg	—

Day 6-Day 10: The patient takes the prescribed regimen outlined in Table 13.

TABLE 13

Drug	AM Dose	PM Dose
Hydroxychloroquine	200 mg	200 mg
Vitamin C	3000 mg	—
Vitamin D	3000 mg	—
Zinc	50 mg	—

Follow-Up Period: Month 1 (outpatient only AFTER negative test): vital signs are taken that include blood pressure, heart rate, respiratory rate, oxygen saturation, temperature), the patient is assessed for adverse events and serious adverse events, and swabs for PCR are taken.

Month 3 (outpatient): vital signs are taken that include blood pressure, heart rate, respiratory rate, oxygen saturation, temperature), the patient is assessed for adverse events and serious adverse events, and swabs for PCR are taken.

Month 6 (outpatient) vital signs are taken that include blood pressure, heart rate, respiratory rate, oxygen saturation, temperature), the patient is assessed for adverse events and serious adverse events, and swabs for PCR are taken.

Month 9 (outpatient) vital signs are taken that include blood pressure, heart rate, respiratory rate, oxygen saturation, temperature), the patient is assessed for adverse events and serious adverse events, and swabs for PCR are taken.

Month 12 (outpatient) vital signs are taken that include blood pressure, heart rate, respiratory rate, oxygen saturation, temperature), the patient is assessed for adverse events and serious adverse events, and swabs for PCR are taken.

COVID-19 sample collection procedure is as follows: nasopharyngeal (NP) and oropharyngeal (OP) swabs are collected according to CDC protocol. The swabs comprise synthetic fiber swabs with plastic shafts. NP swabs are collected by insertion of a swab into the nostril parallel to the palate. The swab is left in place a few seconds to allow it to absorb secretions. OP swabs are inserted into the oropharynx parallel to the palate, avoiding the tongue. The swab is left in place a few seconds to allow it to absorb secretions. NP and OP swabs are immediately placed in sterile tubes with 2-3 mL of viral transport media. The tubes are placed in biohazard bags then boxes and couriered to the local Public Health Lab. Table 14 outlines the schedule of events for Example 3.

TABLE 14

Assessment	Diagnosis and Rx (Day 1)	Day 1 → 7	Month 1 (±4 d)	Month 3 (±4 d)	Month 6 (±4 d)	Month 9 (±4 d)	Month 12 (±4 d)
Informed Consent & Demographics	X						
Confirmation of Positive PCR for COVID-19	X						
Review of Medical Records	X						
Vitals[a]			X	X	X	X	X
Prescription of Antimicrobials[b]	X						
Ask about AE and SAE		X	X	X	X	X	X

Regarding Table 14: Vitals to include height (only at first visit), weight, blood pressure (following 5 minutes sitting) pulse, respiratory rate, temperature, and oxygen saturation. Dosage to be given as in section 8, below

Table 15 provides a summary of the antimicrobial dosage of Example 3.

TABLE 15

Treatment Method	Medication	Dose	Frequency
Quintuple Therapy	Hydroxychloroquine	200 mg	BID
	Azithromycin	500 mg\Day 1→ 250 mg Day 2-5	Daily
	Vitamin C	3000 mg	Daily
	Vitamin D	5000 mg	Daily
	Zinc	50 mg	Daily

Example 4: Randomized, Double-Blind, Placebo-Controlled Phase IIA Study of Hydroxychloroquine, Azithromycin, Vitamin C, Vitamin D, and Zinc to Treat COVID-19 Infection

Objectives: Test the efficacy of hydroxychloroquine, azithromycin, vitamin C, vitamin D, and zinc in the treatment of patients with COVID-19 infection and to assess the safety and tolerability of this treatment in patients with COVID-19 infection.

Procedure: First, the patient's diagnosis of COVID-19 infection is confirmed.

Screening Period (Days −3 to −1): Prescription of home health monitoring equipment that includes a thermometer, a pulse oximeter, a pregnancy test if applicable, and a daily diary. There are two groups being studied: Arm 1 and Arm 2.

Arm 1 is prescribed the following antimicrobials: Hydroxychloroquine 200 MG BID for 10 days; Azithromycin 500 mg on day 1, 250 mg day 2-5; Vitamin C 3000 mg for 10 days, then 1500 mg for 20 days; Vitamin D 3000 for 10 days, then 1500 IU for 20 days; and Zinc 50 mg for 10 days, then 25 mg for 20 days.

Arm 2 is prescribed the following antimicrobials: Placebo for Hydroxychloroquine BID for 10 days; Placebo for Azithromycin to be taken 2 the on Day 1, then 1 on Days 2-5, Vitamin C 3000 mg for 10 days, then 1500 mg for 20 days; Vitamin D 3000 IU for 10 days, then 1500 IU for 20 days; and Zinc 50 mg for 10 days, then 25 mg for 20 days. Table 16 outlines the prescribed antimicrobials discussed above.

TABLE 16

Treatment Method	Medication	Dose	Frequency
Quintuple Therapy	Hydroxychloroquine	200 mg	BID
	Azithromycin	500 mg\Day 1→ 250 mg Day 2-5	Daily
	Vitamin C	3000 mg	Daily
	Vitamin D	5000 mg	Daily
	Zinc	50 mg	Daily
Placebo	Placebo	1 tablet	BID
	Placebo	2 tablets day 1, then 1 tablet day 2-5	Daily
	Vitamin C	3000 mg	Daily
	Vitamin D	3000 IU	Daily
	Zinc	50 mg	Daily

Treatment Period: Day 1 following positive test (isolation), the patient is video called to ensure they have all study materials and the following is discussed: Use of home health equipment, Subject will take baseline measurements at this time and record it in the diary, Diary and how to transmit its contents, Medication dosing, Subject will take pregnancy test if applicable, Subject will use provided equipment to measure vital signs such as EKG, Oxygen Saturation, and Temperature. The patient takes prescribed regimen outlined in Table 17.

TABLE 17

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200 mg	200 mg
Azithromycin (or Placebo)	500 mg	—
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 2: The patient completes the AM and PM diary entries, the patient uses the provided equipment to measure vital signs such as EKG, Oxygen saturation, and temperature, and the patient takes the prescribed regimen outlined in Table 18.

TABLE 18

Drug	AM Dose	PM Dose
Hydroxychloroquine (for Placebo)	200 mg	200 mg
Azithromycin (or Placebo)	250 mg	—
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 3: The patient is called and asked if they are experiencing any difficulties with swab collection, whether there have been any adverse events and/or serious adverse events, the list of prior and concomitant medications is

updated, the patient is asked about symptom resolution or progression, the patient is instructed on how to collect nasal swabs, and the patient then collects the first nasal swab. The patient completes their AM and PM diary entries, and collects their vital signs such as EKG, oxygen saturation and temperature. The patient takes the prescribed regimen outlined in Table 19.

TABLE 19

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200 mg	200 mg
Azithromycin (or Placebo)	250 mg	—
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 4: The patient completes their AM and PM diary entries, collects their vital signs, and takes the prescribed regimen outlined in Table 20.

TABLE 20

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200 mg	200 mg
Azithromycin (for Placebo)	250 mg	—
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 5: The patient completes their AM and PM diary entries, collects their vital signs, collects a nasal swab, and takes the prescribed regimen outlined in Table 21.

TABLE 21

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200 mg	200 mg
Azithromycin (or Placebo)	250 mg	—
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 6: The patient completes their AM and PM diary entries, collects their vital signs, and takes the prescribed regimen outlined in Table 22.

TABLE 22

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200 mg	200 mg
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 7: The patient is called and asked whether there have been any adverse events and/or serious adverse events, the list of prior and concomitant medications is updated, the patient is asked about symptom resolution or progression, and the patient then collects a nasal swab. The patient also completes their AM and PM diary entries and collects their vital signs. The patient takes the prescribed regimen outlined in Table 23.

TABLE 23

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200 mg	200 mg
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 8: The patient completes their AM and PM diary entries, collects their vital signs, and takes the prescribed regimen outlined in Table 24.

TABLE 24

Drug	AM Dose	PM Dose
Hydroxychloroquin (or Placebo)	200 mg	200 mg
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 9: The patient completes their AM and PM diary entries, collects their vital signs, and takes the prescribed regimen outlined in Table 25.

TABLE 25

Drug	AM Dose	PM Dose
Hydroxychloroquine (or Placebo)	200 mg	200 mg
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 10: The patient is called reminded to decrease dosage of vitamins C, vitamin D, and zinc tomorrow. The patient is asked whether there have been any adverse events and/or serious adverse events, the list of prior and concomitant medications is updated, and the patient is asked about symptom resolution or progression. The patient also completes their AM and PM diary entries and collects their vital signs. The patient takes the prescribed regimen outlined in Table 26.

TABLE 26

Drug	AM Dose	PM Dose
Hydroxychloroquine or Placebo)	200 mg	200 mg
Vitamin C	3000 mg	—
Vitamin D	3000 IU	—
Zinc	50 mg	—

Day 11 to Day 13: The patient completes their AM and PM diary entries and takes the prescribed regimen outlined in Table 27.

TABLE 27

Drug	AM Dose	PM Dose
Vitamin C	1500 mg	—
Vitamin D	1500 IU	—
Zinc	25 mg	—

Day 14: The patient is called and asked whether there have been any adverse events and/or serious adverse events, the patient is asked about symptom resolution or progression, and the patient then collects a nasal swab. The patient

also completes their AM and PM diary entries and collects their vital signs. The patient takes the prescribed regimen outlined in Table 28.

TABLE 28

Drug	AM Dose	PM Dose
Vitamin C	1500 mg	—
Vitamin D	I500 IU	—
Zinc	25 mg	—

Day 15 to Day 30: The patient completes their AM and PM diary entries and takes the prescribed regimen outlined in Table 29.

TABLE 29

Drug	AM Dose	PM Dose
Vitamin C	1500 mg	—
Vitamin D	1500 IU	—
Zinc	25 mg	—

Follow-Up Period: Month 1 (outpatient only AFTER negative test): Vital signs are taken (BP, HR, RR, oxygen saturation, temperature), the patient is assessed for adverse events and/or serious adverse events, and EKG is administered as well as physical exam and a blood draw for CBC/Complete metabolic panel/C-Reactive Protein. The list of prior and concomitant medications is updated and a nasal swab is collected.

Month 2 (outpatient): Vital signs are collected (BP, HR, RR, oxygen saturation, temperature) the patient is assessed for adverse events and/or serious adverse events, and EKG is administered as well as physical exam and a blood draw for CBC/Complete metabolic panel/C-Reactive Protein. The list of prior and concomitant medications is updated.

Month 3 (outpatient): Vital signs are taken (BP, HR, RR, oxygen saturation, temperature), the patient is assessed for adverse events and/or serious adverse events, and EKG is administered as well as physical exam and a blood draw for CBC/Complete metabolic panel/C-Reactive Protein. The list of prior and concomitant medications is updated and a nasal swab is collected.

COVID-19 Sample Collection Procedure is the same as that outlined above in prior Examples. Table 30 outlines the schedule of events for Example 4.

TABLE 30

Assessment	Screening (Da-3 to Day-1)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Days 15-30	Month 1	Month 2	Month 3
Informed Consent & Demographics	X																		
Make list of prior and concomitant medications	X			X				X			X				X		X	X	X
Confirmation of Positive PCR for COVID-19	X																		
Review of Medical Records	X																		
Prescription of Antimicrobials[a]	X																		
Provide home health equipment[b]	X																		
Pregnancy test[c]		X																	
Call Subject at home[d]		X		X				X			X				X				
Vitals at home[e]		X	X	X	X	X	X	X	X	X	X								
Subject will complete AM/PM diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hydroxychloroquine 200 mg BID (or placebo		X	X	X	X	X	X	X	X	X	X								
Azithromycin 500 mg (2 tablets) once daily (or placebo)		X																	
Azithromycin 250 mg (1 tablet) once daily (or placebo)			X	X	X	X													
Vitamin C 3000 mg (4 capsules) once daily			X	X	X	X	X	X	X	X	X								
Vitamin D 3000 IU (4 capsules) once daily			X	X	X	X	X	X	X	X	X								
Zinc 50 mg (4 capsules) once daily			X	X	X	X	X	X	X	X	X								
Vitamin C 1500 mg (2 capsules) once daily												X	X	X	X	X			
Vitamin D 1500 IU (2 capsules) once daily												X	X	X	X	X			
Zinc 25 mg (2 capsules) once daily												X	X	X	X	X			
Ask about AE and SAE				X				X			X				X		X	X	X
Vitals in-clinic[f]																	X	X	X
Physical exam																	X	X	X
EKG in-clinic																	X	X	X
Swabs for RT-PCR				X		X		X							X		X		X
Bloodwork[g]																	X	X	X
Review list of prior and concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Regarding Table 30: The antimicrobials include hydroxychloroquine 200 mg tablets (#20), azithromycin 250 mg tablets (#6), vitamin C 750 mg capsules (#80), vitamin D 750 IU capsules (#80), zinc 12.5 mg capsules (#80): the home health equipment includes an EKG (worn continuously), pulse oximeter, and thermometer; the pregnancy test is administered if the patient is a woman of childbearing potential; the patients are called at home to remind them to collect swabs for RT-PCT, ask about AE/SAE, ask about symptoms, and answer any questions; the vitals taken at home include an EKG, oxygen saturation, and temperature; the vitals in-clinic include height (only at first visit), weight, blood pressure (following 5 minutes sitting) pulse, respiratory rate, temperature, and oxygen saturation; and the bloodwork includes CBC, Complete Metabolic Panel, and CRP (details in section 9 Sample Collection).

Statistical Analysis: The treated patients in this study are compared to the placebo group. Measurements include PCR test results, presence or absence of symptoms, and symptom severity. PCR results will be compared between the groups as positive or negative

In this study, the meaningful threshold is calculated as mean change in clinical symptoms as recorded in the diary, from Day 1 through week 12. Each category in the diary is assigned a number, 0 for None, 1 for Mild, 2 for Moderate and 3 for severe. Each category is analyzed independently and as a group. Ultimately, efficacy is determined based upon reduction and/or progression of symptomatic days, reduction of symptom severity, as well as analysis of the subject's RT-PCR testing per protocol. These data are compared to an existing database of de-identified Subject data.

The change of these measurements from the end to the baseline (post-pre) are used as the primary outcome, for example, $\mu e=\mu_{e1}-\mu_{e0}$, where μ_{e1} and μ_{e0} are the outcome of Subjects from the treatment group at the end and at baseline, respectively.

Categorical variables are summarized by presenting the number (n) and percent (%) of subjects in each category. All Statistical tests for the analysis are performed using the $p<0.05$ level of significance. All confidence intervals will be one-sided

Sample size was calculated as follows:

$$n=\log \beta$$

$$\log \rho$$

Where β=the probability of a Type II error

ρ=the proportion of the population NOT affected

The proportion of the population affected by COVID-19 is 0.005 percent, thus 0.995 percent aren't affected

The probability of a type II error is 0.05

Thus:

$$n=\log 0.050$$

$$\log 0.995$$

n=597.647

A sample size of 600 was used.

Example 5: Successful Treatment of COVID-19 Infected Outpatients and Prophylaxis of Immediate Associates

Objective: to successfully treat COVID-19 infected outpatients and prophylaxis of immediate associates.

Procedure: Prospective COVID-19 infected individuals were diagnosed using a Pangea DNA/RNA Shield™ Collection Tube to obtain a nasopharyngeal swab and PCR +ve patients were entered into the study. They were immediately commenced on a 10 day course of Hydroxychloroquine (200 mg, twice a day, for 10 days), Azithromycin extended release (500 mg on day 1, then 250 mg a day for days 9-10), zinc (50 mg a day for days 1-10), Vitamin D (3000 IU a day for days 1-10) and Vitamin C (3000 mg a day for days 1-10). Some individuals lived alone, otherwise immediate partners and family deemed to be most exposed were given a prophylactic which comprised hydroxychloroquine 200 mg twice a day on day 1 only with Zinc, Vitamin C and Vitamin D for given at the same doses as above for days 1-10.

Results: In 11 families a total of 21 family members were identified to be PCR COVID-19 positive index cases and were treated with the above treatment protocol while 22 exposed associates with negative PCR were given the above prophylaxis protocol. This is shown below in Table 31. All 21 index cases were cured of COVID-19 infection as judged by the repeat swab PCR on day 10 and accompanying symptom resolution. None of the 22 highly exposed associates developed COVID-19 infection when retested on day 10 (day 14 in Family 10) in spite of close co-habitation with the infected index cases. TABLE 31: Results from families received 10-day course of daily HCQ (200 mg bd), AZ extended release (500 mg day 1, then 250 mg), zinc (50 mg), Vitamin D (3000 IU) and Vitamin C (3000 mg)

TABLE 31

Family	Patientls treated	Age (years)-sex of the patient	Comorbidities of the patients	After treating with HAZDPAC Cured/ PCR test positive/negative/ other symptoms	After treating ZINCD+H family member prophylaxed
#1	1	23-male	Asthma	Negative PCR-day 10	Parents overweight, diabetes, father with heart disease never got the disease
#2	3	60-male (father) 18-male (son) 16-female (daughter)	Asthma	All 3 patients cured	Mother didn't get the virus
#3	1	40-female	Arvoided intubation by leaving hospital	Sever multiple symptoms resolved at home	Husband did not turn positive
#4	2	78-male 77-female	BCG + COPD, diabetes, heart	Both cured	Daughter, son-in-law and 2 grandkids

TABLE 31-continued

Family	Patientls treated	Age (years)-sex of the patient	Comorbidities of the patients	After treating with HAZDPAC Cured/ PCR test positive/negative/ other symptoms	After treating ZINCD+H family member prophylaxed
			disease (heart surgery month prior Pacemaker, BCG		didn't catch the virus
#5	3	56-male 27-male 24-female	Unable to eat or drink Asthma	Started treatment on day 10, Sever symptoms resolved Cured	Wife never got the disease
#6	1	56-female		Admitted to hospital-sent home, as two kids were sick with fever. All recovered with vitamins	Husband never got the disease
#7	1	44-female		Cured, autoimmune issues started	Husband and 4 kids never got the disease
#8	3	52-female 53-male 19-male	Lupus Severe asthma	Cured Cured Cured	Boyfriend (54 y) with Diabetes, son (18) and daughter (16) never got the disease
#9	2	45-female 16-male		Both cured from severe symptoms of cough and fever	Husband and daughter never got the disease
#10	2	44-male 25-female 21-female		Cured from loss of smell, fever, cough Cured Partially treated with HAZDPAC-slowly turned-ve	Mother (50 y) never got the disease
#11	1	33-female	No	ICU nurse recovered	Boyfriend never got the disease

Apart from the families a further 11 single infected individuals found to be swab PCR positive were treated with the above treatment protocol. This is shown below in Table 32. All were also successfully cured of the infection.

TABLE 32

Patient	Age (years)-sex of the patient	Comorbidities/symptoms of the patients	After treating with HAZDPAC Cured/not
#1	44-female (no BCG in childhood)	Asthma	Cured
#2	81-male	Diarrhea	Cured
#3	52-female	Fever	Cured
#4	66-male	Valve surgery	Cured
#5	29-female (no BCG in childhood)	Asthma	Cured

TABLE 32-continued

Patient	Age (years)-sex of the patient	Comorbidities/symptoms of the patients	After treating with HAZDPAC Cured/not
#6	50-female	Auto immune thyroiditis, sever cough and fever	Cured
#7	43-male	Cough, desaturation of oxygen	Cured
#8	53-male	Diarrhea, cough, fever, desaturation of oxygen	Cured
#9	44-female	Autoimmune history, fever, increase heart rate	Cured
#10	44-female	Pneumothorax discharged from ICU with COVID-19	Cured
#11	43-male	Fever +ve Covid-19 PCR	Cured

A further 9 individuals recently closely exposed to Covid-19 infected persons were given the prophylaxis protocol outlined above. The prophylactic worked very well with no exposed person acquiring the infection. This is shown in Table 33.

TABLE 33

Individual	Age (years) & details of the individual	After treating with ZINCD+H
#1	Mother of 16 year old child who had COVID-19	Prophylaxed and never got the disease
#2	24-female, ICU nurse-multiple exposures	Prophylaxed and never got the disease
#3	47-male, cardiologist exposed to +ve patients	Prophylaxed and never got the disease
#4	70-male medical director of a hospital (exposed to numerous doctors with COVID-19)	Prophylaxed and never got the disease
#5	55-male anaesthesiologist (intubates COVID-19 patients)	Prophylaxed and never got the disease

TABLE 33-continued

Individual	Age (years) & details of the individual	After treating with ZINCD+H
#6	55-ICU nurse(worked on Covid-19 floor)	Prophylaxed and never got the disease
#7	40-ICU nurse many Covid-19 patients	Prophylaxed and never got the disease
#8	53-Doctor with pancreatitis	Prophylaxed and never got the disease
#9	28-Paramedic-healthy	Prophylaxed and never got the disease

Discussion: It was demonstrated that a 10 day combination of hydroxychloroquine, azithromycin (for 5 days only), zinc with vitamin D and vitamin C, can result in uniform cure of COVID-19 infection when used in an outpatient population. The prophylaxis treatment noted above for those closely exposed to proven, infected patients can completely prevent spread of COVID-19. This combination of test-and-treat permits abolishing of new outbreaks of infection such as a 'next wave'—by avoiding quarantine to treat the infected and give prophylactics to surrounding staff and family.

In conclusion, this is an effective anti-Covid-19 therapy as well as an effective prophylactic combination capable of arresting the spread of coronavirus infection throughout the community. This is achieved by treating the index case and the surrounding associates of the patient as early as possible after infection is identified and then treating the people they live with and close associates.

Example 6: Presence of the SARS-CoV-2 by NGS of Fecal Samples

Objective: In view of the large percentage of SARS-CoV-2 detectible by RT-PCR in stools of infected patients, the objective was to identify the presence of the SARS-CoV-2 by NGS of fecal samples from symptomatic study participants positive for SARS-CoV-2 by nasopharyngeal sample RT-PCR, in addition to asymptomatic individuals (with or without prior nasopharyngeal sample RT-PCR). The objective was also to execute whole genome analysis to characterize SARS-CoV-2 mutational variations to identify potentially significant nucleotide changes.

Procedure: Study participants (n=14) underwent testing for SARS-CoV-2 from fecal samples by whole genome enrichment NGS. Following fecal collection (Zymo Research Shield Fecal Collection Tubes), RNA was extracted (Qiagen Allprep Power Viral Kit), reverse transcribed (New England Biolabs NEBNext 1st and 2nd Strand Synthesis Modules), library prepped (Illumina Nextera Flex for Enrichment), enriched (Illumina Respiratory Virus Oligo Panel), and sequenced on Illumina's NextSeq 550 System. Sequences were then mapped to the SARS-CoV-2 Wuhan-Hu-1 (MN90847.3) complete genome utilizing One Codex's SARS-CoV-2 bioinformatics analysis pipeline. SARS-CoV-2 positive samples were further analyzed for mutational variants that differed from the reference genome. Of the 14 study participants, 12 also had their nasopharyngeal swabs tested for SARS-CoV-2 by RT-PCR.

Results: The results from patients that had their stool samples tested by whole genome enrichment NGS, and their nasopharyngeal swabs tested by RT-PCR for the presence of SARS-CoV-2 were evaluated. Of the 14 study participants, ten were symptomatic and tested positive for SARS-CoV-2 by RT-PCR, two asymptomatic individuals tested negative, and two other asymptomatic individuals did not undergo RT-PCR testing (Table 34). Patients 5 and 7, which tested positive by RT-PCR from nasopharyngeal swabs, were treated with the protocol from Example 5 above (Hydroxychloroquine, Azithromycin, vitamin C, vitamin D, and zinc for 10 days prior to fecal collection). Similarly, after positive nasopharyngeal swab, patient 13 was treated with vitamin C, vitamin D, and zinc for 10 days (the same protocol as noted above in Example 5) before fecal collection. The concordance of SARS-CoV-2 detection by enrichment NGS from stools among positive non-treated patients tested by RT-PCR nasopharyngeal analysis was 100% (7/7). Patient 8, who did not undergo nasopharyngeal analysis, tested positive for SARS-CoV-2 by NGS. The three patients (5, 7, 13) that received treatment prior to providing fecal samples, all tested negative by NGS. Asymptomatic patients 2 and 9, who tested negative by nasopharyngeal swab, were also negative by NGS, as was asymptomatic patient 14. Table34 outlines the symptoms and SARS-CoV-2 testing results.

TABLE 34

Sample ID	Symptoms	Nasopharyngeal Swab (RT-PCR)	Treated	Fecal (NGS)	Patient Location
Patient 1	febrile, diarrhea, anosmia, O2 sat. <90%	+	no	+	PA
Patient 3	febrile, diarrhea, O2 sat. <90%	+	no	+	CA
Patient 4	febrile, diarrhea, anosmia, O2 sat. <90%	+	no	+	AZ
Patient 6	febrile, cough, anosmia	+	no	+	AZ
Patient 8	none	n/a	no	+	CA
Patient 10	febrile, cough, headache	+	no	+	GA
Patient 11	febrile, cough, headache	+	no	+	GA
Patient 12	febrile, cough	+	no	+	GA
Patient 5	febrile, cough	+	yes	–	CA
Patient 7	febrile, cough	+	yes	–	GA
Patient 13	febrile, cough	–	yes	–	GA
Patient 2	none	–	no	–	CA
Patient 9	none	+	no	–	CA
Patient 14	none	n/a	no	–	CA

All fecal samples analyzed by enrichment NGS from positive patients by RT-PCR, achieved 100% genome coverage of SARS-CoV-2 except for patient 3 which had 45%, and patient 10 which had 93% coverage. Table 35 outlines the enrichment NGS metrics.

TABLE 35

Sample ID	Genome Coverage	#Variants (over 10x)	Mapped Reads	Mean Depth
Patient 1	100%	11	465645	1129.8x
Patient 3	45%	11	5984	31.7x
Patient 4	100%	9	131582	318.6x
Patient 6	100%	10	793603	11924.6x
Patient 8	100%	10	496852	1206.7
Patient 10	93%	9	5929	15.6x
Patient 11	100%	10	1270734	3075.3x
Patient 12	100%	10	38256	92.7x

The total number of SARS-CoV-2 mapped reads for patients 1, 3, 4, 6, 8, 10, 11, and 12 were 465645, 5984, 131582, 793603, 496852, 5929, 1270734, and 38256 respectively. The mean read depths of SARS-CoV-2 for patients 1, 3, 4, 6, 8, 10, 11, and 12 were 1129.8×, 31.7×, 318.6×, 1924.6×, 1206.7×, 15.5×, 3075.3×, and 92.7×, and respectively. The read depths at specific coordinates along the SARS-CoV-2 genome for each patient are captured in FIGS. 3A-3H. Whole genome alignment of SARS-CoV-2 in patients 1, 3, 4, 6, 8, 10, 11, and 12 (respectively) as identified by One Codex's SARS-CoV-2 analysis pipeline. The x-axis depicts the genomic coordinates as aligned to the MN908947.3 reference genome, and the y-axis represents the read depth at specific loci.

Following alignment and mapping of SARS-CoV-2, patient genomes were compared to the Wuhan-Hu-1 (MN90847.3) SARS-CoV-2 reference genome via One Codex's bioinformatics pipeline to identify mutational variations. This analysis identified nucleotide variants at positions nt241 (C→T) and nt23403 (A→G) across all positive patients, and variants at positions nt3037 (C→T) and nt25563 (G→T) in seven of the eight patients (Table 3). Interestingly, patients 8, 11, and 12 harbored the same set of variants, as did patients 4 and 6 (who were kindred). Unique variants not identified in any of the other individuals were detected in patients 1, 3, 6, and 10, with patient 3 harboring the most distinct SARS-CoV-2 genome with eight unique variants, followed by patient 1 with seven. Collectively, there were thirty-three different mutations among the patients in which SARS-CoV-2 was detected by whole genome enrichment NGS. Table 36 outlines the SARS-CoV-2 genomic positions, variant changes, and frequencies across the positive patient cohort.

TABLE 36

Region (ORF)	Position	Variant	Patient 1	Patient 3	Patient 4	Patient 6	Patient 8	Patient 10	Patient 11	Patient 12
5'-UTR	241	C → T	100%	100%	100%	100%	100%	100%	100%	100%
1a	833	T → C	x	x	x	x	100%	x	100%	100%
1a	1059	C → T	x	x	100%	100%	99%	100%	100%	100%
1a	1758	C → T	x	x	100%	100%	x	x	x	x
1a	1973	C → T	x	x	x	87%	x	x	x	x
1a	3037	C → T	100%	x	100%	100%	100%	100%	100%	100%
1a	3078	C → T	x	89%	x	x	x	x	x	x
1a	4866	G → T	75%	x	x	x	x	x	x	x
1a	6720	C → T	93%	x	x	x	x	x	x	x
1a	8102	G → T	x	100%	x	x	x	x	x	x
1a	9401	T → C	x	x	x	x	x	64%	x	x
1a	9403	T → A	x	x	x	x	x	64%	x	x
1a	10870	G → T	x	x	100%	100%	x	x	x	x
1a	11123	G → A	x	x	100%	100%	x	x	x	x
1b	14408	C → T	100%	x	100%	100%	100%	x	100%	100%
1b	14877	C → T	x	100%	x	x	x	x	x	x
1b	16616	C → T	x	x	x	x	100%	x	100%	100%
1b	16848	C → T	100%	x	x	x	x	x	x	x
1b	18652	C → A	x	x	x	x	x	83%	x	x
1b	19989	T → G	x	100%	x	x	x	x	x	x
Spike	21576	T → G	x	83%	x	x	x	x	x	x
Spike	23264	G → A	x	75%	x	x	x	x	x	x
Spike	23403	A → G	100%	100%	100%	100%	100%	100%	100%	100%
Spike	23603	C → T	82%	x	x	x	x	x	x	x
3a	25563	G → T	x	100%	100%	100%	100%	100%	100%	100%
3a	25976	C → A	x	x	x	x	100%	x	100%	100%
8	27964	C → T	x	x	x	x	100%	x	100%	100%
Nucleoprotein	28881	G → A	100%	x	x	x	x	x	x	x
Nucleoprotein	28882	G → A	100%	x	x	x	x	x	x	x
Nucleoprotein	28883	G → C	100%	x	x	x	x	x	x	x
Nucleoprotein	28997	C → T	x	100%	x	x	x	x	x	x
Nucleoprotein	29019	A → T	x	100%	x	x	x	x	x	x
Nucleoprotein	29364	C → G	x	x	x	x	x	85%	x	x

Discussion: Although previous studies have identified SARS-CoV-2 in fecal collections by RT-PCR, this study was able to report whole genome sequencing (WGS) of SARS-CoV-2 from stool samples. SARS-CoV-2 was identified in patients that tested positive by nasopharyngeal swab RT-PCR analysis and unique genomes in 62.5% of the NGS positive patients was observed. The overall homology among the genomes was high (99.97%), with variations identified in the ORF regions 1a, 1b, S, 3a, 8, and N. Of particular interest, was the adenine to guanine change in the S protein at position nt23403 which converts aspartic acid to glycine (D→G).

Conclusion: Next generation sequencing identified the SARS-CoV-2 whole genome sequence in 100% of patients with positive nasopharyngeal RT-PCR and did not detect it in treated patients, or those with negative rt-PCR. These results highlight the importance of metagenomic analysis of the SARS-CoV-2 viral genome.

Example 7: Randomized, Double-Blind, Placebo-Controlled Phase IIA Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection

Objectives: Prevention of COVID-19, Lack of COVID-19 symptoms, and assessment of safety and tolerability

Procedure: Screening Period (Days −7 to −1): Prescription of home health monitoring equipment that includes a thermometer, a pregnancy test if applicable, and a daily diary. There are two groups being studied: Arm 1 and Arm 2.

Arm 1 is prescribed the following antimicrobials: hydroxychloroquine 200 mg twice a day for 1 day only, vitamin C 3000 IU per day for 12 weeks, vitamin D 3000 IU per day for 12 weeks, and zinc 50 mg per day for 12 weeks. The zinc can be reduced to 25 mg if GI upset occurs. The hydroxychloroquine is to be taken first thing in the morning as soon as subject has eaten and again right before bed, and must be separated from vitamin dose by at least 2 hours.

Arm 2 is prescribed the following antimicrobials: Placebo twice a day for 1 day only, vitamin C 3000 IU per day for 12 weeks, vitamin D 3000 IU per day for 12 weeks, and zinc 50 mg per day for 12 weeks. The zinc can be reduced to 25 mg if GI upset occurs.

Day 1: Patient is called to teach them how to use the diary in the EDC, discuss the medication regimen, and answer any questions they may have. Patient takes pregnancy test if applicable, collects a temperature reading, completes their diary, and takes the prescribed treatment regimen. Table 37 outlines the prescribed treatment regimen for Day 1.

TABLE 37

Drug	AM Dose	PM Dose
Hydroxychloroquine (or placebo)	200 mg	200 mg
Vitamin C	1500 mg	1500 mg
Vitamin D	1500 IU	1500 IU
Zinc	25 mg	25 mg

Day 2: Patient collects a temperature reading, completes their diary, and is called on the phone for assessment of any adverse events or serious adverse events, assessment of any COVID-19 symptoms, the list of prior and concomitant medications is updated, any questions the patient has are answered, and the patient takes their prescribed treatment regimen. Table 38 outlines the prescribed treatment regimen for Day 2.

TABLE 38

Drug	AM Dose	PM Dose
Vitamin C	1500 mg	1500 mg
Vitamin D	1500 IU	1500 IU
Zinc	25 mg	25 mg

Days 3-10: Patient collects a temperature reading, completes their diary, and takes their prescribed treatment regimen. Table 8 outlines the prescribed treatment regimen for Days 3-10.

TABLE 8

Drug	AM Dose	PM Dose
Vitamin C	1500 mg	1500 mg
Vitamin D	1500 IU	1500 IU
Zinc	25 mg	25 mg

Day 14: The patient is called for instruction on how to collect a nasal swab and package for shipping, assessment COVID-19 symptoms, updating their list of prior and concomitant medications, and answering any questions they may have.

Week 3: The patient is called for assessment of any adverse events or serious adverse events, assessment of any COVID-19 symptoms, updating their list of prior and concomitant medications, and answering any questions they may have. The patient takes a temperature reading, completes their diary, and takes the prescribed treatment regimen.

Table 39 outlines the treatment regime for week 3.

TABLE 39

Drug	AM Dose	PM Dose
Vitamin C	1500 mg	1500 mg
Vitamin D	1500 IU	1500 IU
Zinc	25 mg	25 mg

Week 4: The patient is called for assessment of any adverse events or serious adverse events, assessment of any COVID-19 symptoms, updating their list of prior and concomitant medications, and answering any questions they may have. The patient takes a temperature reading, completes their diary, and takes the prescribed treatment regimen. The patient also collects a nasal swab.

Table 40 outlines the treatment regime for week 4.

TABLE 40

Drug	AM Dose	PM Dose
Vitamin C	1500 mg	1500 mg
Vitamin D	1500 IU	1500 IU
Zinc	25 mg	25 mg

Weeks 5-11: The patient is called weekly for assessment of any adverse events or serious adverse events, assessment of any COVID-19 symptoms, updating their list of prior and concomitant medications, and answering any questions they may have. The patient takes a weekly temperature reading, completes their diary, and takes the prescribed treatment regimen.

Table 41 outlines the treatment regime for weeks 5-11.

TABLE 41

Drug	AM Dose	PM Dose
Vitamin C	1500 mg	1500 mg
Vitamin D	1500 IU	1500 IU
Zinc	25 mg	25 mg

Week 12: The patient presents to the clinic (or video conference) for evaluation that includes assessment for adverse events and serious adverse events, updating their list of prior and concomitant medications, a physical exam, nasal swab collection and COVID-19 sample collection.

Samples for COVID-19 testing are collected using synthetic swabs with plastic shafts. Nasal swabs are collected and immediately placed into a sterile vial with 2-3 mL of viral transport media. The vials are placed into biohazard bags, boxed up, the box sterilized, and picked up for shipment to the central laboratory. Samples are tested by RT-PCR.

Table 42 present the schedule of events for Example 7.

TABLE 42

Assessment	Screening (Day-7 to Day 1)	Day 1	Day 2	Day 3-10	Day 14	Week 3	Week 4/ Month 1	Week 5	Week 6	Week 7	Week 8/ Month 2	Week 9	Week 10	Week 11	Week 12/ Month 3
Informed Consent & Demographics	X														
Initial Review of Prior and Concomitant Medications	X														
Medical Records review, including baseline EKG	X														
Randomization	X														
Prescription of Hydroxy - chloroquine or placebo, vitamin C, vitamin D, and zinc	X														
Provision of daily diary, thermometer and pregnancy test	X														
Pregnancy Test if applicable		X													
Temperature at home		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete daily diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hydroxychloroquine 200 mg		X													
Vitamin C 3000 mg		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitamin D 3000 IU		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Zinc 50 mg[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone/video call to patient[b]	X	X	X		X	X	X	X	X	X	X	X	X	X	
Update list of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ask about AE and SAE		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of COVID-19 symptoms		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Swabs for RT-PCR		X			X		X								X
Vitals in-clinic[c]															X
Physical Exam															X

Regarding Table 42: The Zinc may be reduced to 25 mg if GI upset occurs, phone/video calls to the patient occur weekly during Weeks 2-11, and vitals in-clinic include height, weight, blood pressure (following 5 minutes sitting) pulse, respiratory rate, temperature, and oxygen saturation.

Statistical Analysis: The treated patients in this study are compared to the placebo group. Measurements include PCR test results, presence or absence of symptoms, and symptom severity.

The change of these measurements from the end to the baseline (post-pre) are used as the primary outcome, for example, $\mu e=\mu e1-\mu e0$, where $\mu e1$ and $\mu e0$ are the outcome of patients from the treatment group at the end and at baseline, respectively.

H_0: $\Delta \leq \delta_0$ against H_α: $\Delta > \delta_0$ where 0 is a clinically meaningful threshold to measure the disease symptoms. In this study, that meaningful threshold is calculated as mean change in clinical symptoms as recorded in the diary, from baseline through week 12. Each category in the diary is assigned a number, 0 for None, 1 for Mild, 2 for Moderate and 3 for severe. Each category is analyzed independently and as a group.

Categorical variables are summarized by presenting the number (n) and percent (%) of subjects in each category. All Statistical tests for the analysis are performed using the $p<0.05$ level of significance. All confidence intervals are one-sided.

Since these are healthcare workers who are exposed to COVID-19 at every shift, efficacy is determined by RT-PCR testing, as well as the presence or absence of symptoms as recorded in the patient diary via EDC.

Having thus described the invention, it should be apparent that numerous structural modifications and adaptations may be resorted to without departing from the scope and fair meaning of the instant invention as set forth herein above and described herein below by the claims.

While particular forms of the invention have been illustrated and described, it will also be apparent to those skilled in the art that various modifications can be made without departing from the spirit and scope of the invention.

Although the present invention has been described in considerable detail with reference to certain preferred embodiments, other embodiments are possible. The forgoing description is not intended to be exhaustive or to limit the invention to the precise form disclosed. Many modifications and variations are possible in light of the above teaching. The steps disclosed for the present methods, for example, are not intended to be limiting nor are they intended to indicate that each step is necessarily essential to the method, but instead are exemplary steps only. Therefore, the scope of the appended claims should not be limited to the description of preferred embodiments/methods contained in this disclosure. All references cited herein are incorporated by reference. Insofar as the description above and the accompanying drawings disclose any additional subject matter that is not within the scope of the claims below, the inventions are not dedicated to the public and the right to file one or more applications to claim such additional inventions is reserved.

What is claimed is:

1. A method of treating an individual infected with COVID-19, the method comprising the steps of:

a) providing an individual infected with COVID-19;

b) administering to the individual, on day 1:

i) two doses of 200 mg of hydroxychloroquine;

ii) one dose of 500 mg of azithromycin;

iii) one dose of 3,000 mg of vitamin C;

iv) one dose of 3,000 IU of vitamin D; and

v) one dose of 50 mg of zinc;

c) administering daily to the individual, on days 2 to 5:

i) two doses of 200 mg of hydroxychloroquine;

ii) one dose of 250 mg of azithromycin;

iii) one dose of 3,000 mg of vitamin C;

iv) one dose of 3,000 IU of vitamin D; and

v) one dose of 50 mg of zinc; and

d) administering daily to the individual, on days 6 to 10:

i) two doses of 200 mg of hydroxychloroquine;

ii) one dose of 3,000 mg of vitamin C;

iii) one dose of 3,000 IU of vitamin D; and

iv) one dose of 50 mg of zinc; and

e) monitoring the individuals condition over a pre-determined period of time to determine whether the individual is no longer infected with COVID-19.

2. The method of claim 1, wherein step d) of administering on days 6 to 10 further comprises administering one dose of 250 mg of azithromycin.

3. The method of claim 1, wherein the two doses of hydroxychloroquine in step b), step c), and step d) are administered as a single daily dose.

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