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Review Article

Review of Formulations and Methods for Prevention and Treatment of COVID-19 and other Viral Infections

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Abstract

While the number of COVID-19 cases keeps increasing with more and more data suggesting spread by asymptomatic carriers (especially as quarantine is lifted or eased in many locations), there is an urgent need for prophylactic formulations and methods that can be easily available to the public. The goal of the prophylactic formulations and methods is to reduce disease rate among the exposed population and severity of symptoms among the symptomatic cases and to facilitate development of community herd immunity, without overloading hospital systems and depleting medications, ICU beds and other resources.

This is an extensive case review analysis of use of over the counter formulations and methods for prevention and treatment of COVID-19. The analysis shows a strong statistical significance in favor of the use of the formulations and methods in a large patient sample even with the assumption that only 10% percent of the exposed patients get infected, which is an extremely conservative underestimate in light of the current virus spread pattern. The conservative infection rate and exposure model compensates for the lack of complete randomization of the sample.

Background

From early March to mid-May 2020, I took the call for about 600 patients in the Columbus and Cleveland areas, Ohio regions most heavily affected by COVID-19, and did consults for several friends and colleagues in the NYC area. Over that period, we dealt with dozens of clinical and/or confirmed cases of COVID-19.

Since accurate testing and effective medications were at best scarce, we developed and implemented over-the-counter formulations and methods for prevention and treatment of the potentially deadly viral pandemic. Even prior to confirmation through our quantitative analyses presented herein of data of about 100 patients and their contacts on results of using the formulations and methods, the qualitative outcomes were overwhelmingly positive as to the effectiveness of the over-the-counter formulations and methods for prevention and treatment of early-stage COVID-19.

Our approach provides an economical and safe over-the-counter option for prevention and treatment, freeing such prescribed medications as hydroxychloroquine and remdesivir for treatment of moderate to severe COVID-19 cases. Our approach to prevention and treatment of early-stage COVID-19 may also decrease the number of cases with moderate to severe symptoms requiring powerful drugs and/or hospitalization. In addition, the formulations and methods may prevent virus spread from asymptomatic carriers and address "second wave infection" threats.

We review below the background for the formulations and methods used:

Role of the Cinchona bark, quinine and similar products

Native to the Andes, Quina (Cinchona calisaya) is a Peruvian evergreen shrub with large glossy leaves and fragrant yellow/green or red flowers. Quina is the source for the malaria treatment quinine, of which the highest concentration exists primarily in the bark of the shrub.

For example, Nutramedix, the U.S. manufacturer of **Quina™**, utilizes a proprietary extraction and enhancement process that claims as features:

- Efficient full spectrum extract
- Clinically appears to cross the blood/brain barrier within 2 min.
- Water/Alcohol extract that does not damage protein
- Easy to use for all ages

- Cost effective

Practitioners are now using Quina to treat Lyme borrelisosis. Lyme borreliosis has been linked to hundreds of medical conditions; many researchers and physicians believe that Lyme borreliosis may be a factor in many prevalent chronic conditions. Quina's antibiotic affect can help to prevent secondary infection.

Since the limited availability of hydroxychloroquine (which cannot be easily obtained even by prescription in numerous locations and, even if prescribed, can be used for usually 5 days only (Table 1), the Quina extracts and other quinine-preparations given below (under Formulations) as components of our formulations provide an economical and safe prophylaxis modality. Since the quinine and other components of the extract may have a shorter pharmacokinetic half-life than hydroxychloroquine, we suggest daily use of the formulations for prevention and treatment.

In addition, on many occasions hydroxychloroquine is not well tolerated (in contrast to the formulations disclosed herein) and can cause serious side effects, especially in older patient.

For centuries, Cinchona bark alkaloids (Cinchona calisaya) were the primary treatment of malaria [1]. Quinine, one of the components of the extract and the prototype of hydroxychloroquine, was shown to have an independent anti-viral activity [2].

Role of Quercetin as Zn Ionophore

Quercetin is a bioflavonoid supplement that has been shown [3] to act as a zinc ionophore, enhancing entrance of zinc into cells to inhibit virus replication (e.g., [4]). Increasing the intracellular Zn^{2+} concentration with zinc-ionophores like pyrithione (PT) can efficiently impair the intracellular replication of a variety of RNA viruses, including poliovirus and influenza virus [4]. Quercetin is similar in this respect to hydroxychloroquine which also is a zinc ionophore [4]. It is also believed to block viruses from entering cells in the first place, lowering the 'viral load'. A study published by the University of Tennessee and Oak Ridge National Labs used the most powerful IBM supercomputer to model which FDA-approved compounds or supplements might interfere with the COVID-19-causing coronavirus binding to cells. Quercetin was listed as fifth most effective of almost twenty (Table 3 herein, from [5]). This study has also suggested Quercetin's beneficial effect on the ACE2 receptors used by the COVID-19 virus to bind to the outside of potential host cells as an essential step before entering those cells. Additionally, a study [6] showed that Quercetin has anti-inflammatory properties, which could help limit the inflammatory response of the cytokine storm caused by COVID-19.

Dr. Michel Chrétien and Dr. Qiu are well known Canadian researchers who have been researching the effects of Quercetin for decades and have found it to inhibit various bacteria and viruses. They have seen positive results in mice with its use against Ebola and Zika [7]. It has also been tested against influenza [8] and SARS [9]. As reported March 2020, they are in the process of testing it against COVID-19 [10,11].

There is evidence of the anti-TNF alpha effect of quinine [12] that contributes to the assumed protective effect for COVID-19 patients. For example, research on IBD patients shows possible protective effects of anti-TNF alpha antibodies and other treatments in Crohn's patients [13]. Interestingly, Quercetin also shows a significant anti-TNF alpha activity *in vitro* [14,15] and in animal models [16].

Name (Obtained from the SWEETLEAD)	Vina Score	ZincID
pemirolast	-7.4	ZINC5783214
benserazide	-7.4	ZINC3830273
Natural Product: luteolin-monoarabinoside	-7.4	ZINC18185774
pyruvic acid calcium isoniazid	-7.3	ZINC4974291
Natural Product: quercetol;quercitin	-7.3	ZINC3869685
protirelin	-7.3	ZINC4096261
carbazochrome	-7.2	ZINC100029428
nitrofurantoin	-7.2	ZINC3875368
benserazide	-7.2	ZINC3830273
carbazochrome	-7.1	ZINC100045148
sapropterin	-7.1	ZINC13585233
Vidarabine	-7.1	ZINC970363
Natural Product: eriodictyol	-7.1	ZINC58117
tazobactum	-7.1	ZINC3787060
phenformin hcl	-7	ZINC5851063
carbazochrome	-7	ZINC100045148
carbazochrome	-7	ZINC100045148
vildagliptin	-7	ZINC100003507
Natural product: demethyl-coclaurine	-7	ZINC896041

Table 3: Top scoring ligands for S-protein:ACE2 receptor interface that have undergone regulatory review in the USA or elsewhere [5].

Use of Ivermectin for COVID-19

Ivermectin has been researched in Australia for use for COVID-19 prophylaxis and treatment.

Ivermectin has been used as an anti-parasitic in more than 6 million people globally for a variety of indications which includes treatment and sometimes elimination of scabies, river blindness, a variety of worm infections, and filariasis. It can be used orally, with well-established dose schedules effective for those common conditions, at modest costs, and with minimal toxicity.

Ivermectin also has some effects on a variety of RNA and DNA viruses, and is being evaluated for malaria. A manuscript published in Antiviral Therapy on April 3, 2020, by Caly, Druce, Catton, Jans and Wagstaff from the Monash BioMedicine Discovery Institute and the Doherty Institute in Melbourne, Australia, describes complete destruction of COVID-19 causing virus in cell culture after incubation for 48 hours with Ivermectin [17-19].

With research proceeding on optimal doses for efficacy and likely safety, the WHO is directing additional focus to Ivermectin, and the Bill and Melinda Gates Foundation is supporting redirection of US$19 million of its grant funds to repurposing Ivermectin for COVID-19 management [17-19].

Trials with Ivermectin are not yet listed among the COVID-19 clinical trials dashboard [17-19]. We advocate that Ivermectin be evaluated for management of COVID-19 in three contexts: treatment of hospitalized patients with serious manifestations of COVID-19; management of COVID-19 positive symptomatic patients at home or in other forms of social isolation; and prophylaxis for close contacts of people symptomatic with, or diagnosed to have, COVID-19.

Controlled trials could be implemented immediately of oral Invermectin at current therapeutic doses (often two single doses a week apart), generally deemed safe, to assess its efficacy in both treatment and prophylaxis of COVID-19 infections

Case studies

Case report series analysis. Since the availability of testing and treatment was limited in Ohio, we monitored clinical cases of COVID-19, patients with documented exposure to COVID-19 (essential workers, family members and other patients exposed to documented cases of COVID-19) and documented cases in those areas where testing was available. Many of the documented patients started on a regimen of our formulations and methods after having had a course of hydroxychloroquine and Zithromax or as an alternative in cases of poor tolerance of hydroxychloroquine. Results of administration of the recommended core formulations (below) were followed as described in the statistical analysis sections below. In addition to the core formulations according to their recommended administration protocols, patients were encouraged to implement one or more additional/ancillary methods herein described. The additional/ancillary components and methods are suggested based on the available literature analysis.

Formulations

The formulations consist of the following components and substances that have been demonstrated to have beneficial effect both outside of and within clinical settings in the prevention of COVID-19 and other viral infections and also in the treatment of early stages of such diseases**:**

A mixture of Quercetin together with drops of Quina (NutroMedix Cinchona Calisaya extract; all similar plant extracts including, but not limited, to Quina Raja, Cinchona extracts, Quinine tinctures, extracts or other preparations, teas or powders can be used) with Zn.

The mixture, additionally, contains Vitamin C, Vitamin E, L-Lysine and Vitamin D3.

These components and substances been demonstrated to have beneficial effect (see Background and References below).

Additional components and substances that these formulations for prevention and treatment of viral disease may comprise:

Parts, extracts and/or derivatives of one or more of the following: Amla fruit, Lianhuaqingwenjiaonang, Ginger, Lemon, Licorice (*Glycyrrhiza glabra*), Red Reishi mushroom, Oregano oil, Garlic, Olive leaf, Guduchi (*Tinospora cordifolia*), other such natural products.

Representative other natural products that may be ancillary components and substances that these formulations for treatment of viral disease may comprise:

Parts, extracts and/or derivatives of one or more of the following: Bee propolis (Apismellifica; e.g., extract 5:1), Red Marine Algae (whole plant; e.g., extract 10:1), Self-Heal (Prunella vulgaris fruit; e.g., extract 10:1), *Lomatium dissectum* (including *Lomatium* "Immune support" tincture), Holy Basil (*Ocimum sanctum*), *Terminalia bellerica, Adhatoda vasica, Piper nigrum* (fruit), *Zingiber officinale* (rhizome), *Piper longum* (fruit) (e.g., "Trikatu," a blend of equal parts of the last three listed items).

Copper (e.g., copper orotate) may also be an ancillary component that these formulations for treatment of viral disease may comprise.

Methods of administration

Oral administration (self-administration and/or as supervised by caregiver) of the formulations via capsule, powder, softgel, tablet, mixture in such liquids as water or juice, or other forms of administration.

For prevention of disease (implemented and monitored in the group of 54 individuals discussed below in the statistical analysis):

One dose/day (as, for example, one capsule), the dose containing: 400 mg of Quercetin together with 10 drops of Quina (we used NutroMedix Cinchona Calisaya extract to good effect, but all similar plant extracts including, but not limited to, Quina Raja, Cinchona extracts, Quinine tinctures extracts or other preparations, teas or powders may be used) with 25 mg of Zn, 1000 mg of Vitamin C, 400 IU of Vitamin E, 500 mg of L-Lysine, and 1000 units of Vitamin D3. Other amounts and proportions of these substances and components may be used. None, one or more than one of the additional/ancillary substances and components presented above have been used.

Prevention-dosing may be continued prophylactically over any period of concern of contracting COVID-19 or other viral diseases.

For treatment of mild to moderate symptoms in early-stage disease:

Multiples of the prevention-dose daily. We have used two prevention-doses per day, administered separately or together; on the second day of administration, with an additional 50 mg of Zn (titrated up to 200 mg of Zn for 5 days over 2-3 days as tolerated). Patient and/or caregiver may consider adding 500 mg daily Azithromycin (Zithromax) for 5 days (as prescribed by a treating physician), as well as none, one or more of the additional/ancillary components and substances.

Treatment dosing can be administered for 1, 2, 3, 4 or 5 days or until symptoms are alleviated. After symptoms are alleviated, prevention-dosing may be maintained.

We suggest a daily dose of 400mg of Quercetin together with 10 drops of Quina (Cinchona Calisaya extract) with 25 mg of Zn for prevention; and 800 mg of Quercetin together with 20 drops of Quina plus 50 mg of Zn for symptomatic patients. (Zn can be titrated up to 200 mg for 5 days.)

With the exception of the readily available Azithromycin to be considered in treating mild to moderate symptoms of early-stage disease, none of the components and substances of the formulations used in these methods of administration requires prescription by physician. Thus, these formulations and methods provide options that are economical and almost completely Over-The-Counter (OTC; completely OTC for prevention, and mostly OTC even for the treatment outlined above for relieving early-stage symptoms). Through use of our formulations and methods, prescribed medications such as hydroxychloroquine can be reserved for moderate to severe cases. We note that use of these formulations and methods can also decrease the number of moderate or severe cases that require such prescribed medications and/or hospitalization. In addition, use of these formulations and methods may prevent virus spread from asymptomatic carriers and, thus, help address threats of "second wave infections."

Methods specification, route of administration

Oral administration, when possible, of the formulations via capsule, powder, soft gel, tablet, mixture in such liquids as water or juice, or other forms of administration.

Formulation ingredients may be divided among various modes of administration, such as: IV or other parenteral routes for vitamins C and E, extracts containing quinine-analogs/derivatives, and/or zinc; and PEG administration for vitamin D3, L-Lysine, and/or other components and substances of the formulations.

For treatment of moderate to severe disease, administration of two doses per day, each dose containing:

400 mg of Quercetin together 10 drops of Quina (we used to anticipate and advocate use of NutroMedix Cinchona Calisaya extract for good effect. However, all similar plant extracts including, but not limited to Quina Raja, Cinchona extracts, Quinine tinctures, extracts or other preparations, teas or powders may be used) with 25 mg of Zn, 1000 mg of Vitamin C, 400 IU of Vitamin E, 500 mg of L- Lysine, and 1000 units of Vitamin D3.

Other amounts and proportions of these substances and components may be used.

After the first day of administration of the formulations, we recommend, in addition to the two doses/day indicated above, also another 50 mg of Zn the second day, titrated up to 200 mg of Zn over 2-3 days for 5 days as tolerated.

We anticipate and advocate considering supplementing the above regimen with one or more antibiotics and/or anti-parasitic agents (each by prescription by the treating physician), for instance: Azithromycin (Zithromax) 500 mg daily for 5 days; Ivermectin [17-19], with possible dosing being 3 mg, typically orally or by PEG, if possible titrating to up 15 mg (or as indicated and as tolerated) for a single dose, with a single dose repeat in 7 days (or as indicated and as tolerated); Isoniazide, Nitrofurantoin, Doxycycline and/or Levaquin (for secondary infection prevention) or other medications (dosing per PDR) (See Table 3).

We anticipate and advocate considering supplementing the above regimen with one or more antibiotics and/or anti-parasitic agents (each by prescription by the treating physician), for instance: Azithromycin (Zithromax) 500 mg daily for 5 days; Ivermectin (references 22-24), with possible dosing being 3 mg, typically orally or by PEG, if possible titrating to up 15 mg (or as indicated and as tolerated) for a single dose, with a single dose repeat in 7 days (or as indicated and as tolerated); Isoniazide, Nitrofurantoin, Doxycycline and/or Levoquin (for secondary infection prevention) or other medications (dosing per PDR) (See Table 3).

We note that the formulations without prescription-necessary supplementation (i.e., entirely OTC), have been demonstrated effective in preventing COVID-19 at 1 dose/day; and, at 2 doses/day with no or only minimal prescription-necessary supplementation (e.g., only Azithromycin, Doxycycline or other medications, as above), are considered effective in treating the mild to moderate symptoms of early-stage COVID-19. Thus, prophylactic use of our OTC formulations and early use of the OTC formulations plus minimal antibiotic supplementation may significantly reduce the incidence of the moderate to severe symptoms of later-stage COVID-19 that may require expensive, scarce or potentially risk-bearing prescribed medications and/or in-hospital procedures. As noted, use of our OTC formulations and methods may prevent virus spread from asymptomatic carriers and, thus, help address threats of "second wave infections."

In addition, our formulations and methods may have beneficial effects on weight reduction, blood pressure control [20], diabetes [21], cardiovascular health [22], mood and memory [23].

Additional methods

Combination of the formulations and methods with anti-TNF and interleukin-modulating substances; with antibiotic and anti-viral substances

We anticipate and advocate for treatment of COVID-19 any combinations of the above formulations and methods with use of existing medications, both chemical compounds and or antibodies with known anti-TNF alpha activity (e.g., Remicade (infliximab) and other compounds), substances known and/or that become accepted as effective modulators of interleukins such as IL-6 and of other cytokines (e.g., Acterma (tocilizumab) [24] and other compounds).

We anticipate and advocate any combinations of the above formulations and methods with use of macrolide and other antibiotics, including but not limited to the aforementioned Zithromax, Isoniazide, Nitrofurantoin, Doxycycline and/or Levaquin, and/or with retroviral therapy (ribavirine, leronlimab, remdesivir or any other retroviral medication; see Tables 1 and 2). In a hospital setting, the above formulations and methods can also be combined with use of dipyridamole and/or steroids. Such enhanced formulations (i.e., the formulations and methods presented above in the Formulations and Methods sections, plus any of the additional chemical and/or biological components of this section and/or following sections of the disclosure) can generally be used even in circumstances of mechanical ventilation if administered via PEG or other feeding tube or, with adjustments addressing solution state, by IV.

MEDICAMENT NAME	DESCRIPTION	Studies/Comments
Hydroxychloroquine Sulfate	Hydroxychloroquine Sulfate is an antimalarial agent used for the treatment of systemic lupus erythematosus, rheumatoid arthritis and other autoimmune, inflammatory and dermatologic conditions. Also acts as an inhibitor of autophagy and toll-like receptor (TLR) 7/9.	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial
Carfilzomib (PR-171)	Carfilzomib (PR-171) is an irreversible proteasome inhibitor with IC50 of <5 nM in ANBL-6 cells, displayed preferential in vitro inhibitory potency against the ChT-L activity in the β5 subunit, but little or no effect on the PGPH and T-L activities.	Fast Identification of Possible Drug Treatment of Coronavirus Disease -19 (COVID-19) Through Computational Drug Repurposing Study
Favipiravir (T-705)	Favipiravir (T-705) is a potent and selective RNA-dependent RNA polymerase inhibitor, used to treat influenza virus infections.	Discovering drugs to treat coronavirus disease 2019 (COVID-19)
Azithromycin	Azithromycin is an antibiotic by inhibiting protein synthesis, used for the treatment of bacterial infections.	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial
Darunavir Ethanolate	DarunavirEthanolate (DRV) is a nonpeptidic HIV protease inhibitor, used to treat HIV infection.	Many drugs already approved by FDA may have promise against COVID-19
Ciclesonide	Ciclesonide is a glucocorticoid used to treat obstructive airway diseases.	Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia: Report of three cases
Daunorubicin HCl	DaunorubicinHCl inhibits both DNA and RNA synthesis and inhibits DNA synthesis with K_i of 0.02 μM in a cell-free assay.	Many drugs already approved by FDA may have promise against COVID-19
Chloroquine diphosphate	Chloroquine diphosphate is a 4-aminoquinoline anti-malarial and anti-rheumatoid agent, also acting as an ATM activator.	Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

Tideglusib	Tideglusib is an irreversible, non ATP-competitive GSK-3β inhibitor with IC50 of 60 nM in a cell-free assay; fails to inhibit kinases with a Cys homologous to Cys-199 located in the active site. Phase 2.	Structure of M pro From COVID-19 Virus and Discovery of Its Inhibitors
Camostat Mesilate	Camostat is a trypsin-like protease inhibitor, inhibits airway epithelial sodium channel (ENaC) function with IC50 of 50 nM, less potent to trypsin, prostasin and matriptase.	The Impact of Camostat Mesilate on COVID-19 Infection (CamoCO-19)
Remdesivir (GS-5734)	Remdesivir,amonophosphoramidate prodrug of an adenosine analog, is an investigational broad-spectrum antiviral agent with in vitro activity against multiple RNA viruses, including Ebola and CoV.	Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro
Bictegravir	Bictegravir is a novel, potent, once-daily, unboosted inhibitor of HIV-1 integrase.	Potential COVID-2019 3C-like Protease Inhibitors Designed Using Generative Deep Learning Approaches
Pitavastatin Calcium	Pitavastatin calcium, a novel member of the medication class of statins, is a calcium salt formulation of pitavastatin which is a highly effective HMG-CoA reductase inhibitor.	Potential COVID-2019 3C-like Protease Inhibitors Designed Using Generative Deep Learning Approaches
Disulfiram	Disulfiram is a specific inhibitor of aldehyde-dehydrogenase (ALDH1), used for the treatment of chronic alcoholism by producing an acute sensitivity to alcohol.	Structure of M pro From COVID-19 Virus and Discovery of Its Inhibitors
Nafamostat Mesylate	Nafamostat mesilate is a synthetic serine protease inhibitor, used as an anticoagulant during hemodialysis.	Nafamostat inhibits SARS-CoV-2 infection, preventing COVID-19 transmission
Lamivudine	Lamivudine is a potent nucleoside analog reverse transcriptase inhibitor, used for treatment of chronic HBV and HIV/AIDS. It works by blocking the HIV reverse transcriptase and hepatitis B virus polymerase.	
Shikonin	Shikonin, a potent and specific Pyruvate kinase M2 (PKM2) inhibitor, is a major component of zicao (purple gromwell, the dried root of Lithospermumerythrorhizon), a Chinese herbal medicine with various biological activities. It is also an inhibitor of TMEM16A chloride channel activity using cell-based fluorescent-quenching assay.	
Lopinavir	Lopinavir is a potent HIV protease inhibitor with K_i of 1.3 pM in a cell-free assay.	Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicin
Mitoxantrone 2HCl	Mitoxantrone is a type II topoisomerase inhibitor with IC50 of 2.0 μM, 0.42 mM for HepG2 and MCF-7/wt cells, respectively.	Many drugs already approved by FDA may have promise against COVID-19
Nelfinavir Mesylate	Nelfinavir Mesylate is a potent HIV protease inhibitor with K_i of 2 nM.	Potential COVID-2019 3C-like Protease Inhibitors Designed Using Generative Deep Learning Approaches

Ritonavir	Ritonavir is a Cytochrome P450 3A and Protease Inhibitor; Also inhibits Cytochrome P450 2D6, P-Glycoprotein and induces Cytochrome P450 2C19, Cytochrome P450 1A2, Cytochrome P450 2C9, Cytochrome P450 2B6 and UDP Glucuronosyltransferases.	Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine
Ivermectin	Ivermectin is a glutamate-gated chloride channel (GluCls) activator, used as a broad-spectrum antiparasitic drug.	
Tenofovir	Tenofovir blocks reverse transcriptase and hepatitis B virus infections.	
Rosuvastatin	Rosuvastatin is an inhibitor of HMG-CoA reductase, an enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis, with Ki value (inhibition constant) of approximately 0.1 nM.	Many drugs already approved by FDA may have promise against COVID-19
Darunavir	Darunavir is a nonpeptidic HIV protease inhibitor, used to treat HIV infection.	Many drugs already approved by FDA may have promise against COVID-19
Ledipasvir (GS5885)	Ledipasvir (GS5885) is a HCV NS5A polymerase inhibitor, used for the treatment of hepatitis C virus infection.	Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CL pro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates
Telaprevir (VX-950)	Telaprevir (VX-950) is an HCV NS3-4A serine protease inhibitor with IC50 of 0.35 μM.	α-Ketoamides as Broad-Spectrum Inhibitors of Coronavirus and Enterovirus Replication: Structure-Based Design, Synthesis, and Activity Assessment
Danoprevir (ITMN-191)	Danoprevir(ITMN-191) is a peptidomimetic inhibitor of the NS3/4A protease of hepatitis C virus (HCV) with IC50 of 0.2-3.5 nM, inhibition effect for HCV genotypes 1A/1B/4/5/6 is ~10-fold higher than 2B/3A. Phase 2.	First Clinical Study Using HCV Protease Inhibitor Danoprevir to Treat Naive and Experienced COVID-19 Patients
Rosuvastatin Calcium	Rosuvastatin Calcium is a competitive inhibitor of HMG-CoA reductase with IC50 of 11 nM in a cell-free assay.	Many drugs already approved by FDA may have promise against COVID-19
Carmofur	Carmofur is a highly potent acid ceramidase inhibitor, used in the treatment of breast and colorectal cancer.	
PX-12	PX-12 is a potent thioredoxin-1 (Trx-1) inhibitor by irreversibly thioalkylation of Cys73 of Trx-1. Phase 2.	Structure of M pro From COVID-19 Virus and Discovery of Its Inhibitors
Atovaquone	Atovaquone is a medication used to treat or prevent for pneumocystis pneumonia, toxoplasmosis, malaria, and babesia.	Many drugs already approved by FDA may have promise against COVID-19
TDZD-8	TDZD-8 is a non-ATP competitive GSK-3β inhibitor with IC50 of 2 μM; minimal inhibitory effect observed on CDK1, casein kinase II, PKA and PKC.	Structure of M pro From COVID-19 Virus and Discovery of Its Inhibitors

Praziquantel	Praziquantel is an anthelmintic effective against flatworms.	Potential COVID-2019 3C-like Protease Inhibitors Designed Using Generative Deep Learning Approaches
Boceprevir	Boceprevir is an oral, direct acting hepatitis C virus (HCV) protease inhibitor with Ki value of 14 nM for NS3. It is used in combination with other antiviral agents in the treatment of chronic hepatitis C, genotype 1.	α-Ketoamides as Broad-Spectrum Inhibitors of Coronavirus and Enterovirus Replication: Structure-Based Design, Synthesis, and Activity Assessment
Velpatasvir	Velpatasvir is a second-generation NS5A inhibitor that inhibits hepatitis C viral replication through acting on the crucial "membranous web" that facilitates RNA replication.	Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CL pro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates
Prulifloxacin (NM441)	Prulifloxacin, the prodrug of ulifloxacin, is a broad-spectrum oral fluoroquinolone antibacterial agent.	Potential COVID-2019 3C-like Protease Inhibitors Designed Using Generative Deep Learning Approaches
Indinavir Sulfate	Indinavir sulfate is a specific and potent inhibitor of HIV-1 protease and is widely used in the treatment of AIDS.	Potential Therapeutic Agents for COVID-19 Based on the Analysis of Protease and RNA Polymerase Docking
Moexipril HCl	MoexiprilHCl is a potent orally active nonsulfhydryl angiotensin converting enzyme (ACE) inhibitor, used for the treatment of hypertension and congestive heart failure.	Many drugs already approved by FDA may have promise against COVID-19
Bepotastine Besilate	Bepotastine is a non-sedating, selective antagonist of histamine 1 (H1) receptor with pIC50 of 5.7.	Many drugs already approved by FDA may have promise against COVID-19
Bepotastine	Bepotastine is a non-sedating, selective antagonist of the histamine 1 (H1) receptor that is indicated in allergic rhinitis, urticaria, and pruritus associated with skin disease.	Many drugs already approved by FDA may have promise against COVID-19
Ebselen	Ebselen is a small-molecule capsid inhibitor of HIV-1 Replication with IC50 of 46.1 nM in TR-FRET assay.	

Table 1: List of additional agents; description, with suggested mechanism of action; studies/comments.

Name	Information	Reference
Tocilizumab (anti-IL-6R)	Tocilizumab (anti-IL-6R) is a humanized monoclonal antibody that binds to the interleukin-6 receptor, MW: 148 KD.	Tocilizumab treatment in COVID‐19: A single center experience
Serum antibody, with or without modifications, for conferring passive immunity	Harvested through plasmapheresis from convalesced COVID-19 patients presenting sufficiently high antibody titers	Numerous programs underway worldwide for titer testing, harvesting, therapeutic use

Table 2: COVID-19 Related Antibodies.

Combination of the formulations and methods with ultraviolet light (UVC and/or UVA) disinfection

A factor contributing to infection by the pathogens that cause COVID-19, other viral diseases and other microbial illnesses, is contact with surfaces upon which the pathogens have been deposited and remain infectious, invisible to the eye. Even freshly washed or gloved hands can readily pick up infectious agents from such surfaces, and then spread the agents.

Current evidence suggests that novel coronavirus may remain viable for hours to days on surfaces of a variety of materials. Cleaning of visibly dirty surfaces followed by disinfection of the cleaned surfaces is a best practice measure for prevention of COVID-19 and other viral respiratory illnesses in households and community settings.

Ultraviolet light (UVC and/or UVA) has been shown to be effective in disinfection of surfaces against coronavirus and other viruses and bacteria [25-27]. As an important step in prevention of infection by such pathogens, household surfaces and the outer packaging of products and groceries should be made free of infectious agents. This is certainly true of surfaces that are used as preparation areas for the formulations and of products that are components of the formulations.

We anticipate and advocate any combinations of the above formulations and methods with ultraviolet light (UVC/UVA) surface disinfection using standard LED, fluorescent lamps or other light emitting devices, and even a simple timer (see below) set for times people are not in the room being treated (e.g. 3-4 am). We anticipate and advocate use of our device system of light source and timer. As illustrated in Figures 1, 1a, 2, 2a, 2b and 2c, the lamps of this additional system and method can be installed in ceiling fixtures or on mounts and used to disinfect surfaces, purchases and groceries. Since the suggested time for UVC viral disinfection is 30 minutes in vacuum studies [27], we suggest using our system of lamps with timers (or of lamps without timers in vacant and preferably closed rooms or other enclosures such as closets) for a one hour time period within the regular air environment. With adequate precautions and eye-protection, the same lamps can be used hand-held to disinfect surfaces, purchases and groceries.

Figure 1: Portable ultraviolet light (UVC/UVA) lamp mounted on stand and set via timer for surface disinfection. Timer below kitchen counter is illustrative of the type shown here.

Figures 1a and 1b: UVC/UVA (black light) stand for office waiting room after-hours disinfection.

Figure 2: Use of existing fixture of mudroom (or any other closed room) for ultraviolet light disinfection.

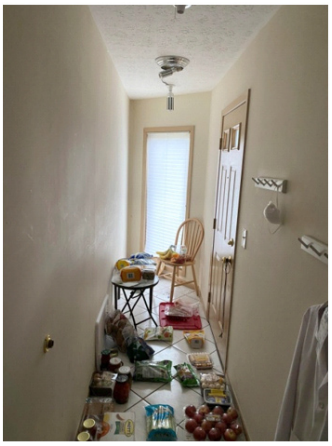
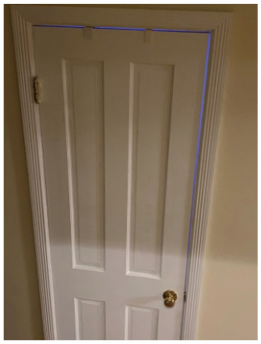
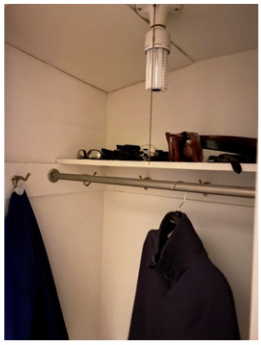


Figure 2a: Mail, clothes, mask, utensils and food set for ultraviolet light disinfection in UVC/UVA-equipped room.





Figures 2b and 2c: Using closeable clothing closet for UVC/UVA disinfection of personal items and clothing (for emergency/essential workers and general public).

Combination of the formulations and methods with chemical surface disinfection

We anticipate and advocate any combinations of the above formulations and methods with surface disinfection using germicidal disinfectants, such as Mediclean germicidal cleaner concentrate or spray, alcohol-based (e.g., 70% or higher alcohol) cleaners, 70% isopropyl alcohol.

Combination of the formulations and methods with local heat for patients with pulmonary symptoms

Local heating of the throat, chest, sides and back of the thorax can be achieved with local wet wraps (based on Zalmanov techniques or methods [28]), heating patches (e.g., mustard patch (*Sinapis charta*, or "gorchichnik"), capsicum patch or any type of heating patch), by applying vessels to the skin filled with hot air ("banki"), or any other local heating method. Such heating has been used to good effect to alleviate symptoms. We anticipate and advocate any combinations of the above formulations and methods with such local heating.

Combination of the formulations and methods with probiotics

Probiotics have been shown to modulate and enhance the mammalian immune system [29]. We anticipate and advocate any combinations of the above formulations and methods with probiotic treatments (e.g., Florastor *Saccharomyces boulardii* CNCM **I-**745 **(***S. boulardii***)** or other yeast or bacteria species and/or other probiotic and prebiotic substances).

Combination of the formulations and methods with hot fluid hydration

We anticipate and advocate any combinations of the above formulations and methods with use of hot fluid hydration to prevent or alleviate dehydration, which can compound a patient's discomfort. While plain hot water suffices to this end, tastier brews increase compliance with a hydration regimen. Addition of some of the abovementioned ancillary components may enhance therapeutic effect. Thus, a suggested recipe: Cut fresh, preferably organic ginger and lemon into an empty pot, kettle or thermos cup. Pour freshly fully boiled water, steep for 5-10 min; serve with honey and optionally add one or more the following (as plant piece extract and/or derivative): Licorice, Lianhua Qingwen Jiao Nang**,** Weeping Forsythia Capsule, Japanese or other brands of Honeysuckle Flower, Ephedra Herb (honey-fried), Bitter Apricot Seed (stir-baked), Isatis Root, Male Fern Rhizome, Heartleaf Houttuynia Herb, Cablin Patchouli Herb, Rhubarb, Big flower Rhodiola Root or other herbs.

Combination of the formulations and methods with modalities for stress control and reduction

We anticipate and advocate any combinations of the above formulations and methods with modalities for stress control and reduction. Patients and others (e.g., patients' relatives, neighbors, coworkers, caregivers, etc.) often experience high stress during the course of a potentially life-threatening medical condition. This is true all the more so in the case of COVID-19, with its characteristics of global pandemic, high infection rate and demonstrated fatality, all exacerbated by endless media coverage, lengthy societal lockdown and the uncertainties generated by the suddenness, novelty and unknowns of the disease.

Studies have established long-term high stress as a suppressor of the immune response, rendering patients and others more susceptible to disease effects, with negative health outcomes ensuing. Additionally, distressed patients and others are often less likely to properly follow through on hygiene and medicament protocols that may be key elements of prevention and treatment of disease.

A modality for patients and others stress control and reduction includes adding to our dosing formulations (presented above in the Formulations and Methods sections) (or for a patient or other taking in conjunction with our dosing formulations) one or

more of extracts, compounds, parts or derivatives: Valerian Root (e.g., 0.8% Varleric acid), Ashwagandha (e.g., root extract, 1.5% Withanolides), Chamomile (*Matricarcia recutita* flower), Lemon Balm Leaf (*Melissa officinalis*), Passion Fruit (*Passiflora edulis*), L-Tryptophan, Gamma-Aminobutyric acid (GABA) (e.g., 200 mg), Jujube Seed Extract (e.g., 2% Jujubosides), Inositol (e.g., 600 mg), Niacin (e.g., 10 mg), Calcium (e.g., 200 mg), Magnesium (e.g., 200 mg), Vitamin B-6 (e.g. pyridoxine hydrochloride, 20 mg), Taurine (e.g., free form, 600 mg), Glycine (e.g., free form, 400 mg).

Another modality for patients' and others' stress control and reduction includes hot fluid relaxation therapy. In this modality for stress control and reduction, use is made of hot tea infusions based on any of Valerian Root, Ashwagandha, Chamomile (*Matricarcia recutita flower*), Lemon Balm Leaf (*Melissa officinalis*), Passion Fruit (*Passiflora edulis*) or other herbs.

Combination of the formulations and methods with isometric exercise

Isometric exercise, in which static positions are maintained without movement for specific time periods, has shown to decrease stress and boost immune response. Such exercise can be readily performed even under COVID-19 quarantine conditions without special equipment or accommodations even by individuals with deconditioning, medical problems or disability. We anticipate and advocate any combinations of the above formulations and methods with isometric exercise.

Exemplary isometric exercises are illustrated in Figure 3. Recommendations often include starting with exercises number 1, 5 and 7 illustrated below, beginning with one minute for each exercise, twice a day, and then increasing as tolerated to at least 20 minutes a day total of those and other exercises.

Figure 3: Exemplary isometric exercises.

Combination of the formulations and methods with low sugar anti-inflammatory diet

We anticipate and advocate any combinations of the above formulations and methods with low sugar anti-inflammatory diets. Such diets generally call for elimination from one's diet of junk food and most commercial carbonated drinks (exceptions: seltzer and similar drinks); for decrease or elimination of processed carbohydrates; and for increase of complex, slowly digested carbohydrates, of organic vegetables (including green leafy vegetables) and of fruits and nuts. Such diets may replace the minimized sugar with zero calorie or low calorie substitutes such as those derived from the Stevia leaf or from Monk fruit or with tolerated sugar-alcohols. Such diets often allow a once-weekly serving of red meat, with a strong recommendation for organic or free-range meat. Additional recommendations include a daily input of fish oil and/or turmeric (2-4gm daily).

Combination of the formulations and methods with immune-response boosting supplementation:

We anticipate and advocate any combinations of the above formulations and methods with products, substances and/or extracts clinically accepted as enhancing the human immune response, such as the extracts/derivatives of the above-mentioned Amla fruit and Red Reishi mushrooms. These also include low-concentration coffee bean supplements, and extracts and/or derivatives of Maitake mushroom (*Grifola frondosa*) and Turkey Tail mushroom (*Trametes versicolor*). Echinacea (*purpurea, angustifolia* and *pallida*) may be recommended, particularly for early and short-term use. (Until clarifying research is available, Elderberry would not be recommended.)

Combination of the formulations and methods with essential oil use

We anticipate and advocate any combinations of the above formulations and methods with essential oil use, for both external and internal use of any type of essential oil (e.g., formulas branded "Thieves", "Immune Boost", and others).

Combination of the formulations and methods with mindful meditation

We anticipate and advocate any combinations of the above formulations and methods with mindful meditation. Mindful meditation is widely thought to reduce stress and anxiety, and to boost immune system performance. We have used the protocol available in the link below to good effect. We recommend starting with track 1 daily for one week, then track 2 for one week, etc. In addition, on each day, track 5 and/or track 6 and/or track 7 can be added:

https://www.penguinrandomhouse.com/mindfulness-meditation-downloads/

Combination of the formulations and methods with pulmonary hygiene exercises

We anticipate and advocate any combinations of the above formulations and methods with exercises for maintenance of pulmonary hygiene.

Exemplary breathing exercises for pulmonary hygiene, instructions for which are presented in stages addressed to the patient (preferably, all the following three stages should be included in a personal regimen cycle of pulmonary hygiene breathing exercises):

- **RELAXATION:** Inhale through your nose for a count of four; then hold your breath for a count of seven; and then exhale through your mouth for a count of eight. (Repeat RELAXATION stage 2-3 times).
- **FOCUS:** Inhale through your nose for a count of five; then hold your breath for a count of five; then exhale through your mouth for a count of five; then pause for a count of five. (Repeat FOCUS stage 2-3 times.)
- **PULMONARY CAPACITY:** (Requires equipment: "Blow-bottle" as supplied by hospital; or, an upright water bottle ~2/3 full, with narrow plastic tubing inserted fully into the water to the bottle bottom and secured to the bottle's exterior, with the tube length such that the free end is readily available to the patient; see Figure 4, below. Both the tubing diameter and the bottle size may be chosen based on availability and, as the patient will be exhaling against the water, also the patient's tolerance/capacity). Take 6 deep breaths; then cough (covering mouth/face); then, lying down on your belly, take shallow breaths for 5-10 minutes; then, remaining on your belly, breath for another 5-10 minutes, but now exhaling by mouth into the tubing connected with the bottle, raising the ball within the hospital-supplied blow-bottle or, in a DIY device as given in Figure 4., causing bubbles to rise through the water of the open bottle.

We recommend repeating the personal regimen cycle of breathing exercises 2-3 times a day. (In a hospital setting, typically only the PULMONARY CAPACITY stage's blow-bottle activities are conducted. We recommend a full personal regimen including all stages.)

Figure 4: A person wishing to incorporate PULMONARY CAPACITY with a device such as that depicted, would inhale through the nose and exhale by mouth into the free end of the tube, forcing bubbles through the water. The duration of the exercise can be set based on the patient's tolerance/capacity and may be increased accordingly. Our recommendation for duration is at least 15 minutes daily.

Combination of the formulations and methods with anticoagulation medication

We anticipate and advocate any combinations of the above formulations and methods with oral (or other route) regimens of anti-coagulant medication, both in the clinical setting and on an out-patient basis. It has become increasingly clear that a large percentage of COVID-19 patients, particularly those that become critically ill, develop a pro-thrombotic state which places them at a significantly increased risk of thrombosis. Thrombotic events include autopsy-proven microvascular thrombosis in a variety of vascular beds (pulmonary, hepatic, renal), likely contributory to end-organ-function deterioration. Also clinically established is the increased risk of large vessel thrombosis such as extensive DVTs, as well as life- and/or limb-threatening arterial thromboses, even in otherwise low risk patients [30,31].

We recommend oral (or other route) anticoagulant regimens that may include physician-recommended selection from ASA (aspirin) and Plavix, as well as Lovenox (low molecular weight heparin), warfarin, rivaroxaban, apixaban, dabixaban or other anti-coagulation medicines. A diet or supplementation regimen rich in Omega-3 fish oils and/or Vitamin E may also or alternatively be beneficial for its blood thinning effect.

Combination of the formulations and methods with use of angiotensin receptor blockers

We anticipate and advocate any combinations of the above formulations and methods with use of angiotensin receptor blockers (ACE receptor blockers) and of other medicaments that interfere with viral binding. As a first step in mounting its viral attack, the coronavirus that causes COVID-19 binds to ACE2 receptor molecules on the exterior of lung lining cells. Thus, blocking the receptors with specific medicinal molecules may render the receptors completely or partly inaccessible to virus binding, preventing or at least partly inhibiting the COVID-19 virus from latching onto and then entering the potential host cells. Preparations that include such medicinal molecules would include Moexipril HCl or other medications and agents with ACE inhibitory actions.

The virus binds to the ACE2 receptor by means of a spike (S) protein of the viral coat. To bind, the S protein needs to first be primed by an enzyme. Inhibiting that enzyme prevents priming and, thus, prevents binding. There are specific medicinal molecules that inhibit the enzyme. Preparations that include such medicinal molecules would include Camostat mesilate or other medications and agents with such selective protease action.

Combination of the formulations and methods with other medications/agents

We anticipate and advocate any combinations of the above formulations and methods with other medications or agents (such

as antibodies) that contribute to the prevention of COVID-19, to alleviation of its symptoms and/or to cure of the disease. Such medications and agents include those presented in Tables 1 and 2.

Patient groups monitoring

Since our office was open for essential procedures and treatments, 94 patients were followed for up to an 8 week period during the COVID-19 pandemic in Ohio, with all CDC and state rules and guidelines carefully observed. The same 94 patients usually had to follow up with other medical facilities and had other potential exposures to the virus.

Since testing and the conventional medications were not readily available and access to personal protective equipment was limited, we suggested to participants to voluntarily use our over-the-counter formulations and methods for prevention and treatment. 54 participants (Group 1) implemented the over-the-counter regimen (mostly the core formulations and some or all the methods), while 60 (Group 2) chose to decline the regimen of formulations and methods out of concerns ranging from cost, education and socio-economic barriers or other reasons. Patients typically reported use of the recommended Vitamin C, Zinc and Vitamin E, as described above, over the observation time, with some use of Quercetin as above (based on the availability and cost) and of Quina, and implementation of methods described above (usually life style modifications, exercises and relaxation). All individuals in a high exposure group (exposed 6 times or more) were sure to use Quercetin. The individuals in this group included members of our staff who were in close contact with the high risk patients providing them our office's essential procedures and treatments.

Six patients out of 60 (of Group 2) who refused the formulations and methods described above developed clinical COVID-19 infection and were quarantined (but, prior to development of symptoms, they were seen in our office, creating exposure for other participants). Only three out of six had access to testing and, upon being tested, were positive for COVID-19.

Since the exact infection rate after an exposure to COVID-19 is not known, we assumed two models of 30% infection and of 10% infection after an exposure. Lack of complete randomization (some of the 54 patients implemented most of the core formulations and only part of the methods; compliance was based on patient self-reporting), is compensated by the very conservative assumptions about the rate of infection (30% and 10%) and exposure rate (for six symptomatic patients, we can assume four times more asymptomatic carriers than six symptomatic patients based on the CDC model, according to which 80% of infected individuals remain asymptomatic and 20% develop symptoms).

Statistical analysis

30% of patients who are exposed get infected

Probability of getting sick once exposed =20% (after each exposure; this is constant for each exposure)

54 patient's in-group that used the formulations and methods.

Analysis

Expected number of patients getting infected =16.2 (30% of 54)

To simplify model, round this number and assume 16 patients are infected.

Group A

8 exposed 6 times;

Apply binomial model

Probability individual stays well after 1 exposure =.8

Probability any individual stays well after 6 exposures =.8^6 =.2621

Probability all 8 patients stay well = .2612^8 =.00002.

Group B

8 exposed 3 times

Apply binomial model

Probability any individual stays well after 3 exposures = .8^3 =.512

Probability all 8 patients stay well = .512^8 =.0047

Probability all individuals in both groups stay well =product of above probabilities = .000002 This is statistically significant at the .05 level (also well below .01).

Result

Probability that all individuals stay well is .0000001

This would be considered statistically significant at the .05 level (also well below the .01 level)

This model is statistically significant even with the assumption that only 10% percent of the exposed patients get infected (an extremely conservative underestimate in light of the current virus spread pattern):

10% of patients who are exposed get infected

Probability of getting sick once exposed =20% (after each exposure; this is constant for each exposure)

54 patients in experiment

Expected number of patients getting infected =5.4 (10% of 54)

To simplify the model, round this number and assume 5 patients are infected

(To gauge the effect of rounding to 5, we separately, below, run a case where we round to 6.)

Group C

4 exposed 6 times;

Apply binomial model

Probability any individual stays well after 6 exposures = .8^6 =.2621

Probability all 4 patients stay well = .2621^4 =.0047

Group D

1 exposed 3 times

Apply binomial model

Probability any individual stays well = 0.8^3 =.512

Probability all individuals in both groups stay well =product of above probabilities = .0024

Case where we round to 6:

Group 1

4 exposed 6 times;

Apply binomial model

Probability any individual stays well after 6 exposures= .8^6 =.2621

Probability all 4 patients stay well = .2621^4 =.0047

Group 2

2 exposed 3 times

Apply binomial model

Probability any individual stays well after 3 exposures= .8^3 =.512

Probability all 2 patients stay well = .512^2 =.2621
Probability all individuals in both groups stay well =product of above probabilities = .0012

Result: Probability that all individuals stay well is between .0012 and .0024

Group 1 vs. Group 2 analysis

54 patients take supplements; 0 of these develop symptoms.

60 patients do not take supplements; 7 of these develop symptoms. Using this information to estimate the probability

of an individual developing symptoms, we conclude that:

The probability of an individual developing symptoms = 7/60 = .1167

Binomial probability calculation

The probability of an individual not developing symptoms = 1-.1167=.8833

Result: Probability that none of the 54 patients develop symptoms -.8833^54 = .0012. This is statistically significant at the .05 level (also significant at the .01 level).

Conclusion

This is an extensive case review analysis of use of over the counter formulations and methods for prevention and treatment of COVID-19. The analysis shows a strong statistical significance in favor of the use of the formulations and methods in a large patient sample even with the assumption that only 10% percent of the exposed patients get infected (which is an extremely conservative underestimate in light of the current virus spread pattern). The conservative infection rate and exposure model compensates for the lack of complete randomization of the sample described above.

While the pandemic is unfolding and disrupting lives of hundreds of millions of people and causing millions of infected cases and hundreds of thousands of death, the scientific debate is still continuing as to whether COVID-19 will follow the pattern of the 2003 SARS outbreak or the 2012 MERS outbreak (which is still developing in waxing and waning fashion over 8 years). Some epidemiologists expect "COVID-19 activity" over the next 18-24 months [32]. While the studies are ongoing, there is still a dearth of clear data on the effectiveness of the prescribed medications and also substantial uncertainty regarding schedules of vaccine production and availability (Tables 1 and 2).

Debate is ongoing over efficacy of testing protocols and over efficacy and duration of antibody immunity. In this environment, the over-the-counter formulations and methods described above can provide an economical and effective alternative available to the public and healthcare workers.

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