Randomized Double-Blind, Placebo-Controlled Feasibility Study, Evaluating the Efficacy of Homeopathic Medicines in the Prevention of COVID-19 in a Quarantined Population

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Homeopathy

Abstract

Introduction Exploring preventive therapeutic measures has been among the biggest challenges during the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We explored the feasibility and methods of recruitment, retention, and potential signal of efficacy, of selected homeopathic medicines as preventive measure for developing COVID-19 in a multi-group study.

Materials and Methods A six-group, randomized, double-blind, placebo-controlled prophylaxis study was conducted in a COVID-19 exposed population in a quarantine facility in Mumbai, India. Each group received one of the following: *Arsenicum album* 30c, *Bryonia alba* 30c, a combination (*Arsenicum album* 30c, *Bryonia alba* 30c, *Gelsemium sempervirens* 30c, and *Influenzinum* 30c), coronavirus nosode CVN01 30c, *Camphora* 1M, or placebo. Six pills twice a day were administered for 3 days. The primary outcome measure used was testing recruitment and retention in this quarantined setting. Secondary outcomes were numbers testing positive for COVID-19 after developing symptoms of illness, number of subjects hospitalized, and days to recovery.

Results Good rates of recruitment and retention were achieved. Of 4,497 quarantined individuals, 2,343 sought enrollment, with 2,294 enrolled and 2,233 completing the trial (49.7% recruitment, 97.3% retention). Subjects who were randomized to either *Bryonia alba* or to the CVN01 nosode signaled ($p < 0.10$) a lower incidence of laboratory-confirmed COVID-19 and a shorter period of illness, with evidence of fewer hospitalizations, than those taking placebo. The three other groups did not show signals of efficacy.

Conclusion This pilot study supports the feasibility of a larger randomized, double-blind, placebo-controlled trial. *Bryonia alba* 30c and CVN01 30c should both be explored in disease prevention or shortening the course of disease symptomatology in a COVID-19-exposed population.

Keywords
- coronavirus
- SARS-Cov-2
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Introduction

Exploring preventive therapeutic measures has been among the biggest challenges during the coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. As per the WHO,[1] a total of 158,551,526 confirmed cases of COVID-19, including 3,296,855 deaths, had been reported by May 10, 2021. Although highly effective vaccines have been recently made available, there remains continued need for novel methods of prophylaxis, should the current vaccination programs decline in efficacy, or as needed alternatives potentially for those individuals who cannot be vaccinated by the currently available vaccines.[2]

In addition, and complementary to conventional vaccines, homeopathic medicines have been discussed extensively as potentially preventive in epidemics of dengue,[3] and have been tested to various degrees in the prevention of leptospirosis[4] and influenza.[5] Some homeopathic nosodes have shown specific anti-infective potential in *in vitro*,[6] animal,[7,8] and human models.[9,10] The COVID-19 pandemic offered another opportunity to examine homeopathy's potential through controlled trials. Previously, the Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) has recommended the use of *Arsenicum album* 30c as preventive for at-risk groups.[11]

Commonly used homeopathic medicines used as preventives against influenza-like illnesses include *Bryonia alba*, *Arsenicum album*, *Gelsemium sempervirens*, *Influenzinum*, *Camphora*, and *Eupatorium perfoliatum*. During the SARS-CoV-2 pandemic there were numerous reports that several of these remedies, including *Bryonia alba*, were frequently indicated.[12] The use of a combination of homeopathic medicines is a common technique that many practitioners follow. Many such combinations of medicines are sold over the counter or as supplements by pharmaceutical companies in many countries. In the present study, we have therefore used *Arsenicum album* 30c, *Bryonia alba* 30c, a combination remedy (*Arsenicum album* 30c with *Bryonia alba* 30c, *Gelsemium sempervirens* 30c, and *Influenzinum* 30c), coronavirus nosode CVN01 30c, and *Camphora* 1M. Prescribing a chronic or constitutional remedy is also common practice, but this was not explored in this trial.[13]

We designed this trial with multiple groups as the virus was novel and there was a need to evaluate if any homeopathic medicine might show a potential beneficial effect. In early drug discovery, it is not unusual to test several molecules in a multi-group trial to see if any show a signal of efficacy. In this way, one may completely discard some molecules, while continuing with further, more robust, studies using a molecule that elicited a potential signal.[14] Further, the benefit of design allows for economies of scale, a smaller pool of needed subjects, as well as cost savings.

The city of Mumbai reported the highest number of COVID-19 infected patients in India from April 2020 onwards.[15] During the first 6 months, Mumbai had more than 20% of all COVID-19 cases in India, having 115,346 cases and 6,395 deaths from the start of the epidemic until the end of July, 2020.[16] In Mumbai, there are 24 regional administrative wards under Brihanmumbai Municipal Corporation (BMC).[17] The present study was conducted by Life Force Foundation Trust in cooperation with the BMC, ward "S", one administrative region in Mumbai. BMC ward "S" strategically quarantined all high-risk individuals who were exposed to confirmed cases of COVID-19, patients from UN-defined "slum" areas, and heavily crowded residential locations, to be housed in one of two distant quarantine facilities for 2 weeks. The present study took place in one of these facilities, housing 4,497 exposed persons. "S" ward medical staff managed the accommodation, lodging, food, sanitization, medical supervision, and all needs for the subjects, while Life Force Center managed the study and collected relevant data. All quarantined populations were medically monitored. Those developing clinical symptoms were tested for COVID-19 and were moved to COVID-19 hospitals if tested positive. From March 2020 to August 2020, due to the shortage of diagnostic kits, diagnostic tests were performed only if the patients presented with clinical symptoms.

Objective

The primary aim of the study was to evaluate the feasibility and methods of recruitment and retention of a sample of subjects within in a multiple-group randomized design. Secondary aims were to assess any potential signal of efficacy of commonly recommended homeopathic medicines for the prevention of COVID-19 in a high-risk population at a government-run quarantine facility for a COVID-19 exposed population, as well as assessing the number of subjects hospitalized and days to recovery. Secondary outcome measures would be used to develop efficacy trials with fewer treatment groups.

Materials and Methods

Study Design

This was a six-group randomized, double-blind, placebo-controlled study designed to evaluate feasibility for a follow-on trial, testing potential efficacy of homeopathic preparations in quarantined populations having exposure to at least one case of COVID-19 in their building, chawl (thickly populated "slum" area where several people live in small rooms), community, or workplace (for example, hospitals, BMC workers, or similar risk groups). Participant data were gathered in the quarantined facility for 14 days. Once released from quarantine and allowed to return home, due to the lockdown restrictions the participants were all contacted telephonically and not physically present at the time of their 30-day scheduled visit.

Approval

The trial protocol was reviewed by the Life Force Foundation Trust Scientific Advisory Board and approved by an Institutional Ethics Committee constituted by Homeopathy India Private Limited. The trial was registered at the Clinical Trial Registry of India (CTRI), trial registration number: CTRI/2020/05/025491. Telephone consent was obtained from every

subject and a waiver for the written informed consent forms was obtained from the Ethics Committee due to the stringent safety measures in place during the lockdown period.

Interventions

Group 1: *Arsenicum album* 30c. Group 2: *Bryonia alba* 30c. Group 3: a combination of *Arsenicum album* 30c with *Bryonia alba* 30c, *Gelsemium sempervirens* 30c and *Influenzinum* 30c. Group 4: coronavirus nosode CVN01 30c. Group 5: *Camphora* 1M. Group 6: matching placebo pills were used.

Coronavirus nosode CVN01 is a variant of nosode, prepared from a clinical sample,[18] which has undergone a Phase 1 study[19] and a homeopathic pathogenetic trial.[20]

The homeopathic medicines used in the present study were prepared as per the directives of the Homoeopathy Pharmacopoeia of India, under the Ministry of AYUSH, Government of India. The medicines are essentially free from toxic effects as they undergo the process of potentization using 90% alcohol as vehicle.

Dose: Six pills (size 30) twice a day for 3 consecutive days.

Study Population

Recruitment occurred within the government-run high-risk quarantine facility. Subjects satisfying pre-specified criteria were included in the study. A total of 2,343 subjects were assessed for eligibility, with 2,294 enrolled and randomized in the study from June 4, 2020 to July 27, 2020.

Subjects meeting the following criteria were included in the study:

1. Age between 5 and 100 years.
2. Male- and female-bodied individuals.
3. Quarantined individuals.
4. COVID-19 risk groups (for example, police or hospital staff) exposed to reverse transcription polymerase chain reaction (RT-PCR)-confirmed case/s of COVID-19.
5. The participant and/or the caregiver is willing and able to provide informed consent for participation in the study.
6. Subjects agree to consume homeopathic medication.
7. Subjects agree not to self-medicate with potential antiviral agents.

Subjects meeting the following criteria were excluded from the study:

1. Subjects who were detected as SARS-CoV-2 positive at baseline (as per data provided by the BMC team).
2. Inability to be followed up for the trial period.
3. Subjects who had taken any homeopathic preventive medicine immediately before their enrollment.
4. Subjects scheduled to receive any other investigational drug during the study.

Study End Points and Assessments

The primary outcome measure used was percent of recruitment and retention in a quarantined setting. Secondary outcome measures included a comparative study of different groups and the placebo group with respect to the number of subjects testing positive on RT-PCR to COVID-19. Other secondary outcomes were number of subjects hospitalized and days to recovery. Recovery was judged based on the reply to a questionnaire (on days 15 and 30—see below), time interval to turn asymptomatic, and the duration of hospital stay.

Study Method

Demographic characteristics were recorded from the source notes by the coordinator at the facility. Enrolled subjects in the study were given coded bottles of homeopathic medicine and were advised to consume medication twice a day for three consecutive days. The study coordinator had handed over the homeopathic medicine bottle to the quarantined individual while maintaining physical distancing at the study site. All individuals were advised to take the first dose in front of the study coordinator. For compliance, bilingual instructions (Marathi and English) on printed stickers, on medicine bottles as well as videos, were sent to almost all the subjects on their mobile phones. Every medicinal bottle had a printed label, linked to a webpage offering more information and emergency reporting.

While in quarantine, all subjects were under the care of a physician trained in COVID-19 diagnosis. If experiencing COVID-19 symptoms, the subjects were instructed to report to the center coordinator. Subjects experiencing symptoms were tested for SARS-CoV-2, and positive cases were sent for further treatment as per the standard protocol of the BMC. Data of those subjects were captured by the study coordinator, and subjects who were positive were followed telephonically on day 15 and day 30. As a part of a questionnaire, the subjects were asked questions about symptom severity, well-being, and duration of hospital stay. Subjects were advised to report (telephonically or in person) to the quarantine center coordinator if they were experiencing any COVID-19 symptoms or potentially untoward side effects during the month of the study period.

Subjects who were asymptomatic or did not test positive for COVID-19, and who took the homeopathic medicines, stayed at the BMC-run quarantined facility for 14 days and were monitored closely by their medical team. On the 15th day, the subjects who were asymptomatic, and were not exposed to positive cases during these 15 days, were discharged from the quarantine facility. Due to the lockdown restrictions, and thus avoiding the need to be physically present, the participants were contacted telephonically at the time of the 30-day scheduled visit.

Randomization

Randomization was performed using a computer-generated random number table, and concealment was achieved by strict adherence to a single sequential numbered list that was sealed and kept in controlled access. The subject, the doctor, and the site coordinator were each unaware of the preventive medicine they were given. The blinded design allowed for an unbiased evaluation of the intervention and became the basis for the use of statistical methods while analyzing the data. Identical pills (size 30) and bottles were provided to all the treatment groups, which involved five different medicines and one placebo group. A total of 2,400

bottles were prepared for distribution and sent to the facility for distribution. The subjects at the quarantine center were from all localities of the city of Mumbai. The decoding was conducted by the investigator.

Statistics and Data Analysis

Data captured from the quarantine center and data collected by the study coordinator telephonically were entered in a pre-specified form and analyzed.

Statistical analyses were performed using the SPSS version 1.0.0.1447. All available data were presented in a patient's data listing, which was sorted by a unique patient identifier. Demographic characteristics were presented as data listings and summary statistics from the 2,233 subjects who completed the trial. Whilst intention-to-treat (ITT) analysis that comprised all patients randomized into the study would have been the best approach, it was impractical as subjects might be moved in and out of the facility due to crowding issues, controlled by government regulations, and we would lose contact with them. We pre-designed the study instead to use the Efficacy Evaluable analysis set, comprising all patients in the ITT analysis who had been enrolled according to the protocol and who completed the clinical trial plus observation period of 30 days, or were withdrawn from the study due to an adverse event.

In this study, at each analysis, there were two independent comparison groups, and the outcome of interest was dichotomous (i.e., the patient tested positive by the end of day 30 [=1] or not [=0]). Two-sample proportion tests (two-proportion *Z*-test) were used to determine whether the proportions of the two groups were the same or different. The goal of the analysis was to compare proportions of positive cases after day 30 between two groups. As a secondary analysis of two samples, we explored the same data using a Fisher Exact test, to be presented as an odds ratio. As this feasibility study was to explore a *signal* of efficacy, and not to prove efficacy, we considered a one-sided alternative and the level of significance $p < 0.05$ as a positive signal.

For days to recover, since the sample sizes were small, we explored using the non-parametric Mann-Whitney U test.

Whilst multi-group trials carry many benefits by testing multiple hypotheses within one trial, they increase the potential for type-1 error, or false positives. Many times, very early exploratory trials do not use multiple-testing correction, and if they find a signal then either they pare down the groups of a trial or they use some form of multiple-testing correction.[21] As this is a feasibility and exploratory trial, no correction was applied.

Results

A total of 4,497 individuals were quarantined during the time of the study, of which 2,343 volunteered to be assessed for eligibility (52.1%). Of the 2,343 subjects, 37 were under age 5, which did not satisfy the inclusion criteria, and 12 participants had already consumed the homeopathy medication *Arsenicum album* recommended by the government. Of the remaining 2,294 randomized subjects, 58 enrolled in the study and who were asymptomatic were considered dropouts as they were shifted to another quarantine center by the BMC, out of our study site. Three other subjects (two in the combination group and one in the *Camphora* group) had completed the day 15 visit and were asymptomatic, but they did not complete the day 30 telephonic visit after being discharged from the quarantine center: they were therefore not counted. Retention of randomized individuals to completion was 97.3%. Of the 2,233 retained analyzed subjects, 1,077 were female and 1,156 were male, having a mean age of 32.66 years. The lowest age of the subjects was 5 years and the highest age was 91 years. The first subject enrollment date was June 4, 2020, and the last subject enrollment was conducted on July 27, 2020. Subjects' disposition is represented as per the flowchart (►**Fig. 1**) and demographic details (►**Table 1**). The group receiving the combination of *Arsenicum album*, *Bryonia alba*, *Gelsemium* and *Influenzinum* contained twice the number of participants: we had hypothesized that the combination might have provided better results during this dynamic situation of changing symptom complexes.

The numbers of individuals per group who tested positive for COVID-19 were as follows: *Bryonia alba* 30c, four out of 310 (1.29%); Coronavirus nosode CVN01 30c, five out of 312 (1.60%); *Arsenicum album* 30c, seven out of 311 (2.25%);

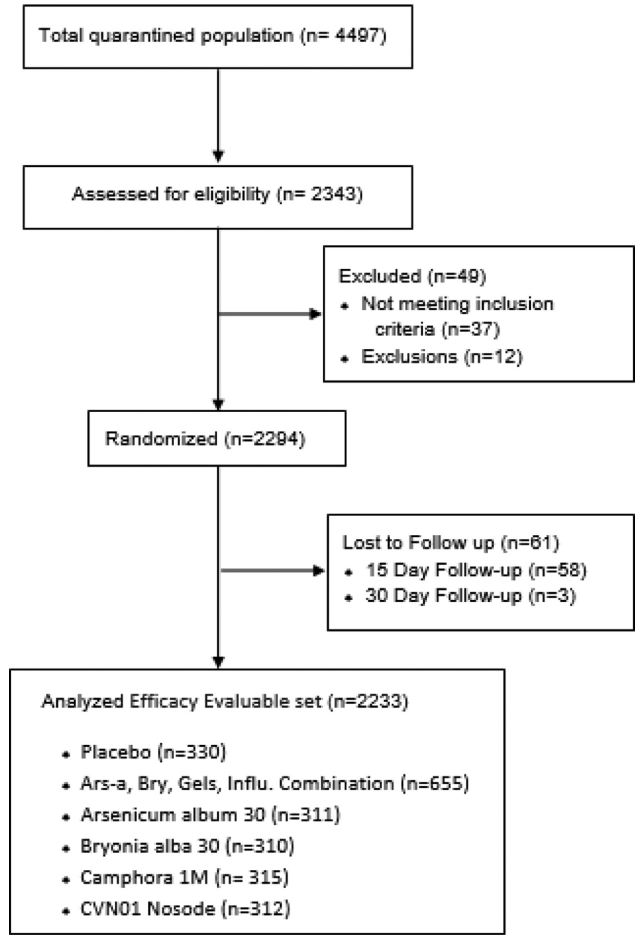

Fig. 1 Flowchart for randomized double-blind, placebo-controlled feasibility study evaluating the efficacy of homeopathic medicines in the prevention of COVID-19 in a quarantined population.

Table 1 Demographic characteristics (gender and age) by treatment arm

Group (*n*)	Age		Gender	
	Mean	Range	Male	Female
CVN01 nosode (312)	32.6	5–82	161	151
Bryonia (310)	31.5	6–87	157	153
Arsenicum (311)	32.7	5–91	150	161
Combination (655)	31.4	5–80	361	294
Camphora (315)	33.5	5–78	165	150
Placebo (330)	35.2	5–85	162	168

combination, 18 out of 655 (2.75%); *Camphora* 1M, 12 out of 315 (3.81%); placebo, 13 out of 330 (3.94%) (►**Table 2**).

Using the two-proportion *Z*-test, the *Bryonia alba* 30c and CVN01 30c groups each had a lower number of positive cases on Day 30 as compared with the placebo group ($p < 0.05$; ►**Table 2**). Exploring the same data using the Fisher Exact test, and presenting the results as odds ratios, we identified *Bryonia alba* 30c as signaling statistical significance ($p = 0.04$), with CVN01 30c approaching significance ($p = 0.09$; ►**Table 3**).

A total of 18 individuals required hospitalization. The number of hospitalized individuals was least in each of the *Bryonia alba* and CVN01 groups, though these numbers were very small for all groups (►**Fig. 2**).

Lastly, we looked at days to recover (►**Table 4**). Since the distribution could not be assessed due to sample size, we used the non-parametric Mann-Whitney U test. Here, the CVN01 nosode signaled significantly different from placebo ($p = 0.03$).

Discussion

The city of Mumbai has faced one of the worst spreads of COVID-19 infection in the world, as it topped India's lists for months in terms of total COVID-19 positive cases. In congested chawls, with shared toilets, viral spread increased exponentially. Limited availability of diagnostic kits hindered early detection and isolation of infected individuals. The COVID-19 pandemic created the need for research in drug discovery for novel treatment, as well as various methods in prevention, including accelerated vaccine programs that have led to 14 approved vaccines to date.[22,23]

Within this background we assessed the homeopathic method of prophylaxis by testing the hypothesis that taking a homeopathic medicine while healthy may prevent either transmission or severity of illness caused by an infectious agent. For measuring prophylaxis, we selected the end point as symptomatic illness that led to a positive COVID-19 test. This is the same primary end point chosen for regulatory approval in most vaccine studies.[24,25]

The need for a variety of preventive solutions is imperative since we do not yet have substantive experience with the SARS-CoV-2 virus or related vaccines. The current vaccines are approximately 90% effective in the short term. We do not know how long this efficacy will last, and if the current vaccines will continue to work. More importantly, we do not

Table 2 Probability of laboratory-confirmed COVID-19 cases in treatment groups, as compared with placebo by day 30 of the study (*Z*-test)

		COVID-19 positive	COVID-19 negative	*p*-Values *Z*-test
CVN01 nosode	%	1.60	98.40	0.036
	n/*N*	*5*/*312*	*307*/*312*	
Bryonia	%	1.29	98.71	0.018
	n/*N*	*4*/*310*	*306*/*310*	
Arsenicum	%	2.25	97.75	0.100
	n/*N*	*7*/*311*	*304*/*311*	
Combination	%	2.75	97.25	0.150
	n/*N*	*18*/*655*	*637*/*655*	
Camphora	%	3.81	96.19	0.464
	n/*N*	*12*/*315*	*303*/*315*	
Placebo	%	3.94	96.06	
	n/*N*	*13*/*330*	*317*/*330*	

Table 3 Odds ratio of laboratory confirmed COVID-19 cases in treatment groups, as compared with placebo by day 30 of the study (Fisher Exact test)

	OR	95% CI	*p*-Values
CVN01 nosode	0.397	0.15–1.05	*0.09*
Bryonia	0.318	0.11–0.94	*0.04*
Arsenicum	0.561	0.21–1.46	*0.25*
Combination	0.689	0.32–1.39	*0.33*
Camphora	0.965	0.40–2.10	*0.99*

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 4 Median days to recovery for RT-PCR-confirmed cases of COVID-19, comparing different treatment arms with the placebo group

	N	Median	IQR	*p*-Values
CVN01 nosode	5	5	2	0.03
Bryonia	4	7.5	2.5	>0.05
Arsenicum	7	10	1.5	>0.05
Combination	18	9.5	4.75	>0.05
Camphora	12	13	4.25	>0.05
Placebo	13	12	7.25	–

Abbreviations: IQR, interquartile range; RT-PCR, reverse transcription polymerase chain reaction.

yet know if people will be able to tolerate repeated booster or annual vaccines. Other options are thus both necessary and desirable. Furthermore, there are some individuals that are unable to tolerate these vaccines, as for example those who have had a severe allergic reaction to ingredients of the vaccine or who developed vaccine-induced immune thrombotic thrombocytopenia, as well as those who are severely immune compromised. As one specific example, recent reports indicate that some individuals who are currently under immunosuppressive treatment may gain little benefit from the vaccines.[26,27] These people need an alternative pathway. Lastly, as the vaccine production and rollout stalls, with difficulties in procurement in developing countries due to internal local infrastructure challenges, as well as being bedeviled by unpredictable and continual viral mutations, an effective alternative is vital.

Use of therapies that currently fall into the category of integrative medicine, such as homeopathy, is limited by insufficient high-quality studies, of which there is a need in general and for COVID-19 in particular.[28] Regarding randomized controlled trials of homeopathy, a 2003 review

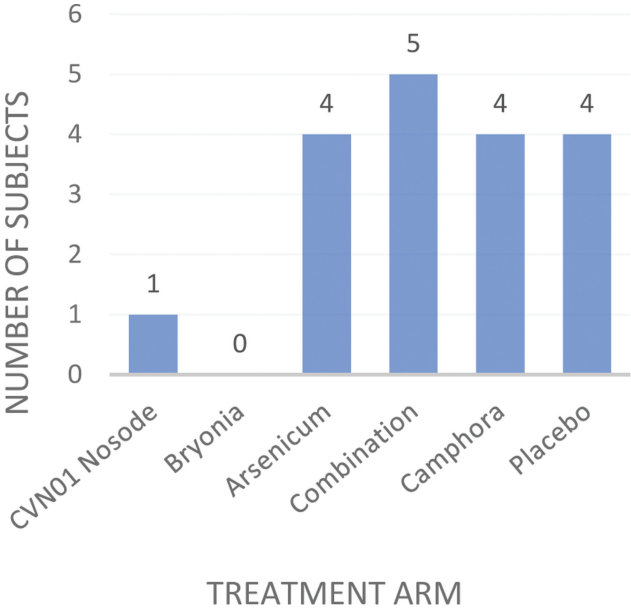

Fig. 2 RT-PCR-confirmed case/s of COVID-19 who were hospitalized, by treatment arm. RT-PCR, reverse transcription polymerase chain reaction.

identified upper respiratory tract infection as the most frequently researched topic of disease.[29] With the possibility that the vaccination program does not lead to a long-term complete solution, it becomes important to test potential strategies, especially those that may have a long history in the field, such as homeopathy.[30] To build a more robust evidence base of trials, it may be appropriate to build upon prior *treatment* research to examine if it might be extended to selected *preventive* intervention. Having a focus on the prevention of upper respiratory tract infection may therefore be an appropriate area of exploration.

There are several methods of prescribing homeopathy for the prevention of infections during epidemics, including genus epidemicus (based on the most commonly indicated acute medicine in the current pandemic), nosodes such as *Influenzinum*, and a combination of commonly prescribed medicines. Prescribing an individualized chronic remedy is also useful in epidemics, though not tested here. We decided to compare several homeopathic medicines to refine options to test for efficacy in a more robust follow-on trial.

The *Bryonia alba* and COVID-19 nosode (CVN01) groups showed fewer people developing symptomatic COVID-19 than did so in the placebo group. In addition, the CVN01 group signaled fewer symptomatic days when compared with the placebo group. The symptom complex described for *Arsenicum album* and *Bryonia alba* matched with that of COVID-19 disease, though *Arsenicum album* showed no differentiation from placebo. A combination of the common homeopathic medicines has shown non-significant results, which might be explained by some inhibitory effects of one of the medicines in the combination. *Camphora's* symptom complex does not match well with acute infection symptoms of the disease, which may explain its inferior results as compared with the placebo group.

When comparing the *Bryonia alba* group with the placebo group, the former had 67% fewer diagnosed subjects than did the latter. Were this to be the result in a larger efficacy trial, it could have great significance for public health. Interestingly, this finding matches previous results from other diseases. For example, in a study on tularemia, Jonas presented results that were significantly better than placebo (22%), but not as effective as vaccinations (100%).[31] If there is *some* level of

protection afforded by homeopathic prophylaxis, it may be useful for those who are unable to tolerate vaccines or do not have access to them.

This feasibility study has yielded a comparative stratification of commonly used homeopathic medicines and a new coronavirus nosode. The potential for homeopathic medicines as prophylactic should be further explored on a larger scale. Our study points us to a larger trial comprising only two to three groups, investigating *Bryonia alba* and/or COVID-19 nosode (CVN01) and placebo, with the evaluation of immunological biomarkers as indicated based on the present results. With data from this current trial, we estimate that the next trial with a dichotomous end point, and with $\alpha = 0.05$, $\beta = 0.2$, power = 0.8, and incidence for placebo = 3.94%, for two independent samples, would need 1,136 subjects if testing *Bryonia alba* (incidence, 1.29%) or 1,542 subjects if testing CVN01 nosode (incidence, 1.6%) against placebo.

Challenges in the trial included the facts that individual contacts with the subjects and close monitoring was difficult due to the regulatory restrictions and that a limited number of volunteers were collecting the data during the countrywide lockdown. Other limitations of the study include the impossibility of physical examination of every participant due to the social distancing recommendations, as well as the lack of some laboratory investigations because testing was rationed by the government during the time of the trial. Another limitation might be the disposition of the study participants, who were quarantined at a controlled facility. It may be that results would vary if the subjects had been free to move about the city. In a follow-on trial, to test transmission rates as well, all subjects would be tested for coronavirus before, during, and at the end of the trial. These data were not captured during the vaccination development trials, but measuring transmission rates might help us understand benefits of this form of potential protection. In a related comment, 10% of the subjects were under 15 years of age and were equally distributed amongst the groups. Young people are less susceptible to the SARS-CoV-2 virus and do not become symptomatic as easily as older age groups.[32] Testing all subjects in a forthcoming trial would capture a potentially latent sub-set.

This was a multi-group trial, and testing multiple hypotheses within one trial increases the potential for type-1 error, a false positive. As such, the *p*-values presented here only show a potential signal of efficacy, and should be more extensively explored. In an upcoming trial, one could remedy this situation by testing only one homeopathic medicine versus placebo, as for example examining the COVID-19 nosode (CVN01) or *Bryonia alba* versus placebo. Alternatively, one could design a study with three groups: COVID-19 nosode (CVN01), *Bryonia alba*, and placebo. In this last design, to adjust *p*-values, one would use a multiple-testing correction, not appropriate in the current study.

Conclusion

A good proportion of potential subjects were recruited and retained in this feasibility study. COVID-19-exposed subjects who were randomized to either *Bryonia alba* or to the COVID-19 nosode signaled a lower incidence of symptomatic illness with COVID-19, and were ill for a shorter period of time with fewer hospitalizations, than those taking placebo. A larger efficacy study is warranted and feasible, and should be limited to two or three groups, using *Bryonia alba* and/or the COVID-19 nosode (CVN01), plus placebo.

Highlights

- A six-group, randomized, double-blind, placebo-controlled prophylaxis study was conducted in a COVID-19 exposed population in a quarantine facility in Mumbai.
- The study elicited initial signals of efficacy for two homeopathic medicines in reducing the incidence of symptomatic illness and in shortening the course of disease.
- The study supports the feasibility of a larger randomized controlled trial.
- *Bryonia alba* 30c and the coronavirus nosode CVN01 30c should both be explored for their potential in disease prevention.

Authors' Contributions

Gitanjali Talele of Life Force Foundation Trust assisted in research coordination and manuscript writing. Dr. Shashikant Vaidya and Dr. Abhay Chowdhary contributed toward nosode development, the study protocol, and manuscript review. Paul Herscu assisted in manuscript writing and statistical analysis. Rajesh Shah was the principal investigator and contributed toward the nosode development and manuscript writing.

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None.

Conflict of Interest

Dr Rajesh Shah holds patent pending for one of the preparations used in the experiment.

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References

1 WHO Coronavirus Disease (COVID-19) Dashboard. 2021. Available at: https://covid19.who.int/
2 Bartsch SM, O'Shea KJ, Ferguson MC, et al. Vaccine efficacy needed for a COVID-19 coronavirus vaccine to prevent or stop an epidemic as the sole intervention. Am J Prev Med 2020;59:493–503
3 Manchanda RK. Dengue epidemic: what can we offer? Indian J Res Homoeopathy 2015;9:137–140
4 Bracho G, Varela E, Fernández R, et al. Large-scale application of highly-diluted bacteria for Leptospirosis epidemic control. Homeopathy 2010;99:156–166

5 Siqueira CM, Homsani F, da Veiga VF, et al. Homeopathic medicines for prevention of influenza and acute respiratory tract infections in children: blind, randomized, placebo-controlled clinical trial. Homeopathy 2016;105:71–77

6 Joshi S, Munshi R, Talele G, et al. An experimental in vitro study to evaluate the antimalarial activity of select homeopathy preparations. International Journal of Medical and Health Research 2017;7:65–68

7 Bagai U, Walter NS. Antiplasmodial potential of homeopathic drugs Chelidonium and nosode against *Plasmodium berghei* infection. J Complement Integr Med 2014;11:195–201

8 Camerlink I, Ellinger L, Bakker EJ, Lantinga EA. Homeopathy as replacement to antibiotics in the case of *Escherichia coli* diarrhoea in neonatal piglets. Homeopathy 2010;99:57–62

9 Shah R. Clinical trial for the evaluation of a human immunodeficiency virus nosode in the treatment for human immunodeficiency virus-infected individuals. Indian J Res Homoeopathy. 2015;9:25–33

10 Shah R. Hepatitis C nosode: the preparation and homeopathic pathogenetic trial. Homeopathy 2013;102:207–214

11 Press Information Bureau, Government of India. Advisory for coronavirus. Available at: https://pib.gov.in/pressreleasepage.aspx?prid=1600895

12 Herscu P. Thoughts on Epidemics from a Clinical Physician Written March 11, 2020. Accessed March 25, 2021 at: http://nesh.com/thoughts-on-epidemics-from-a-clinical-physician-march-11-2020/

13 Herscu P. Winter 2017-2018 Epidemic Updates. Accessed March 25, 2021 at: https://nesh.com/articles-on-homeopathy/-winter-2017-epidemic-updates/

14 Brown MJ, Chuang-Stein C, Kirby S. Designing studies to find early signals of efficacy. J Biopharm Stat 2012;22:1097–1108

15 Coronavirus LIVE. Maharashtra reports 328 new positive cases, 3648 total cases. Accessed September 25, 2020 at: https://www.nationalheraldindia.com/india/coronavirus-live-updates-covid-19-india-wuhan-us-italy-who-alert-novel-coronavirus-latest-news-18th-april

16 Kaushal J, Mahajan P. Asia's largest urban slum–Dharavi: a global model for management of COVID-19. Cities 2021;111:103097

17 Municipal Corporation of Greater Mumbai (Disaster Management Department). Accessed March 25, 2021 at: https://dm.mcgm.gov.in/ward-maps

18 Mukherjee S, Talele G, Chowdhary A, et al. Preparation of coronavirus nosodes sourced from a clinical sample of SARS-Cov-2 positive patient, inactivated strain, and spike glycoprotein. Int J High Dilution Res. 2020;19:2–9

19 Talele G, Vaidya S, Shah R. An open-label, homeopathic pathogenetic trial for safety and evaluation of immune response of Coronavirus nosode in healthy volunteers. (Manuscript under review)

20 Talele G, Shah R. An open-label, exploratory documentation of proving-symptoms of CVN01 (Coronavirus nosode from the clinical sample) in healthy volunteers. (Manuscript accepted)

21 Wason JMS, Stecher L, Mander AP. Correcting for multiple-testing in multi-arm trials: is it necessary and is it done? Trials 2014;15:364

22 The COVID-19 candidate vaccine landscape and tracker. Accessed May 2, 2021 at: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

23 COVID-19 Vaccine Tracker. Accessed May 2, 2021 at: https://covid19.trackvaccines.org/vaccines/

24 Voysey M, Costa Clemens SA, Madhi SA, et al; Oxford COVID Vaccine Trial Group. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet 2021;397:881–891

25 Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383:2603–2615

26 Rincon-Arevalo H, Choi M, Stefanski AL. Impaired antigen-specific memory B cell and plasma cell responses including lack of specific IgG upon SARS-CoV-2 BNT162b2 vaccination among kidney transplant and dialysis patients. MedRχiv 2021.04.15.21255550; doi: https://doi.org/10.1101/2021.04.15.21255550

27 Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. JAMA 2021;325:1784–1786

28 Kirkby R, Calabrese C, Kaltman L, Monnier J, Herscu P. Methodological considerations for future controlled influenza treatment trials in complementary and alternative medicine. J Altern Complement Med 2010;16:275–283

29 Mathie RT. The research evidence base for homeopathy: a fresh assessment of the literature. Homeopathy 2003;92:84–91

30 Kirkby R, Herscu P. Homeopathic trial design in influenza treatment. Homeopathy 2010;99:69–75

31 Jonas WB. Do homeopathic nosodes protect against infection? An experimental test. Altern Ther Health Med 1999;5:36–40

32 Viner RM, Mytton OT, Bonell C, et al. Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis. JAMA Pediatr 2021;175:143–156