REVIEW ARTICLE

Prophylaxis for COVID-19: Mission I'm-possible?

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Abstract

Aim and objective: To review the status of various approaches for prophylaxis of coronavirus disease-2019 (COVID-19).

Background: The extensive spread of the novel COVID-19 has seen tremendous success over the span of few months. In comparison, our progress in developing an adequate treatment or preventive modality has been sluggish, at most.

Results: Many observational studies and clinical trials are published evaluating chloroquine and hydroxychloroquine as prophylactic measures for COVID-19. Some question its safety, some refute its use while some uphold its beneficial effect. Although some scientific bodies advocated its routine use in some population without adequate evidence, current consensus proposes its prophylactic use in the context of clinical research only. Apart from chemotherapeutic drugs, several vaccines are under various phases of clinical development. Innovative vaccine development faces many hurdles as do the new drugs—from the inception of concept and establishing manufacturing process to time-consuming preclinical and clinical development, regulatory processes, large scale production, and then marketing. There is a lot of hopes and expectations from AstraZeneca's candidate vaccine, ChAdOx1-S, and Serum Institute of India's recombinant bacille Calmette–Guerin that are currently in phase III clinical trial. In order to expedite vaccine development, controlled human infection models are also being explored. Some research bodies also suggest using complementary and alternative medicine to supplement the existing and novel prophylactic therapies in preventing the infection.

Conclusion and clinical significance: The increase in literature on the management of COVID-19 reflects the demand to address the current pandemic. At the same time, it becomes critical that research community works toward providing best evidence for guiding the clinicians' practice and that clinicians and regulators emphasize on appraising the existing evidence before prescribing and making policies, respectively.

Keywords: Chloroquine, Clinical trials, Complementary and alternative medicine, Controlled human infection model, Corona, Human challenge model, Hydroxychloroquine, SARS-CoV-2, Vaccine.

Journal of Postgraduate Medicine, Education and Research (2020): 10.5005/jp-journals-10028-1382

Introduction

The novel coronavirus disease-2019 (COVID-19) pandemic is perhaps the most profound medical, social, and economic crisis, which we, as a population today, have witnessed in our lifetimes. As reported on July 6, 2020, the world has seen more than 11.4 million confirmed cases of COVID-19 with 534,000 deaths attributable to the disease.[1] In their article, Baud et al. estimate a mortality rate of 5.7% (5.5–5.9%).[2] This figure could well be an overestimate of the real situation as the denominators could be lower than reality due to underreporting.[3] In March 2020, *The Lancet* highlighted in an editorial, the burden of the disease to the healthcare system, not just with respect to increasing patient load, but as the high infection risk it posed among the healthcare workers.[4] Indeed, healthcare workers are not the only vulnerable population. As the number of asymptomatic cases becomes more apparent, it seems prevention is not as easy a task as it once seemed. As the patient load increases, prophylaxis seems more and more like a viable option to be explored.[4]

Coronaviruses (CoV) are a family of viruses that cause common cold and respiratory syndromes—severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). With the growth of technology, structure and genome identification of the virus causing current pandemic was very swift. Scientists could easily relate the structure of the virus with SARS virus and hence named it as SARS-CoV-2. This also paved way to identify potential targets for drug and vaccine development. Coronaviruses have spike-like structure on their surface and studies on these viruses have showed that the S (spike) protein is an ideal target. This protein interacts with the angiotensin convertase enzyme 2 (ACE_2) receptor and antibodies targeting the spike can interfere with the binding, thereby prevent replication of the virus. Besides the spike protein, there are other structural components that are identified as either target for chemoprophylaxis or for generating protective immunological responses.[5]

Chemotherapeutic agents, such as hydroxychloroquine (HCQ), emtricitabine/tenofovir, and chloroquine (CQ), are being evaluated for preventing COVID-19 (ClinicalTrials.gov[6]). The prophylactic strategies probe both preexposure and postexposure approaches.

Lessons from HIV preexposure prophylaxis (data collected from randomized control trials (RCTs) and systematic reviews on tenofovir disoproxil fumarate/emtricitabine or tenofovir disoproxil fumarate monotherapy) have shown favorable results in adherent individuals ranging from 75 to 90% protection which was proportional to the

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How to cite this article: Gamad N, Kumar MP, Panditrao A, *et al.* Prophylaxis for COVID-19: Mission I'm-possible? J Postgrad Med Edu Res 2020;54(3):126–133.

Source of support: Nil

Conflict of interest: None

adherence to the prophylactic agent(s).[7,8] On March 9, 2020, Yao et al. first described the preexposure prophylactic potential of HCQ[9] and as the authors are writing this article, there are 12 clinical trials registered with ClinicalTrials.gov to evaluate this strategy (9 of which contain HCQ as prophylactic agent).[6]

Postexposure prophylaxis refers to regular intake of agents for the prevention of development of disease after exposure to the disease-causing agent, in all exposed individuals within the recommended timelines after exposure. Building up on the example of HIV, efficacy of postexposure prophylaxis too depended on the adherence to regimen and offered up to 80% protection.[10–12] Although CQ was shown to be effective *in vitro* against the previous SARS-CoV back in 2005,[13] it was a study by Wang et al. in early February 2020 that sparked interest in CQ, and later HCQ, as a potential prophylactic and therapeutic modality for SARS-CoV-2.[14] At the time of writing this article, there were 20 trials registered with ClinicalTrials.gov studying postexposure prophylaxis for COVID-19 (15 of which contained HCQ as prophylactic agent).[6] These strategies will be discussed in further detail later in the article.

The various preventive and treatment modalities being studied are all, ultimately, directed to the natural life cycle of the virus and the changes it induces in the host body.[3,15] While chemoprophylaxis is an attractive area of research for COVID-19, an increasing body of scientists is working toward developing or repurposing a safe and effective vaccine against SARS-CoV-2. Despite the prediction for the long trial period for these vaccines, the research is steadily moving forward with 57 trials studying vaccines for SARS-CoV-2/COVID-19 being registered with ClinicalTrials.gov [including bacille Calmette–Guerin (BCG) vaccine, artificial antigen-presenting cells (aAPC) vaccine, ChAdOx1 vaccine, mRNA-1273 vaccine, Ad5-nCoV, among others] at the time of writing this article.[6,16] Among these, 13 studies are reportedly in the phase III stage, while the rest are the phase I/II stage.[6]

Largely in southeast Asia, but also in some other countries, a lot of complementary and alternative medicines (CAM) are being touted as effective prophylactic agents by virtue of their immunomodulating properties. The evaluation of their usefulness is also a matter of close scrutiny. In the present article, we review the status of various approaches for prophylaxis of COVID-19 (Table 1).

Chemoprophylaxis: HCQ/CQ

Chloroquine and HCQ, both being quinine derivatives were originally marketed as antimalarial agents, but have gathered attention for other indications as well. Both the drugs are orally administered with rapid absorption and good bioavailability (~90% for CQ and ~70% for HCQ), have wide tissue distribution and hepatic metabolism and excretion in urine. The peak blood concentration of CQ is reached with 3–5 hours while that of HCQ is 3–12 hours. The terminal half-life of CQ is 30–60 days while that of HCQ is 40–50 days. While the adverse profile of HCQ is slightly more favorable than CQ, both the drugs may cause cardiovascular issues including (but not limited to) prolonged QT interval, *torsade de pointes*, other arrhythmias, cardiomyopathy; dermatological adverse events like alopecia, dermatitis, Steven–Johnson syndrome, toxic epidermal necrolysis; central nervous system (CNS) disturbances like ataxia, dizziness, vertigo, seizure, psychosis, nightmares, irritability, suicidal tendency, myopathy, deafness, tinnitus; ophthalmic problems like accommodation disturbances, blurred vision, corneal opacity, maculopathy, visual field defect, retinal pigment changes (bull's eye appearance), transient scotomata among others on protracted use of the drug. Single eye is a contraindication while pregnancy and lactation are not a contraindication for its use.[18–21] Keeping side effects and contraindications in mind, it is recommended to have baseline workup before administering and also follow regular follow-up to identify any adverse events at the earliest.

Chloroquine is available in both sulfate and phosphate salts, while HCQ as a sulfate salt. Table 2 shows equivalence between the different formulations.

Hydroxychloroquine is one of the few drugs which has been evaluated in the context of both therapeutic and prophylactic benefits. It was advocated by some scientific bodies without adequate evidence in the era of evidence-based medicine. Owing to these reasons, HCQ was able to garner huge political and media attention.[22–26] In this article, we will be restricting our discussion on the prophylactic role of HCQ in COVID-19.

Table2: Chloroquine and hydroxychloroquine formulations

Drug	*Base*	*Sulphate*	*Phosphate*
Chloroquine	150 mg	200 mg	250 mg
Hydroxychloroquine	155 mg	200 mg	–

Table 1: Trials registered in ctri.nic.in (RCTs only) as on 06.07.2020[17]

S. no	*Agent*	*Sponsor*	*Design*	*Target population*	*Status*
1	HCQ	Aster Malabar Institute of Medical Sciences, Kozhikode, Kerala (CTRI/2020/03/024402)	Phase III, open-label, randomized, parallel group, active-controlled trial	(1) Moderate to high risk of exposure to infected patients during the study period. (2) Healthy at the time of enrolment without any symptoms suggestive of any viral infection.	Not yet recruiting
2	Recombinant BCG VPM1002	Serum Institute of India Pvt. Ltd., Pune (CTRI/2020/04/024749)	Phase III, multicenter, double-blind, randomized, parallel group, placebo-controlled trial	Adult subjects at high risk of SARS-CoV-2/COVID-19 infection	Open to recruitment
3	HCQ	The George Institute for Global Health, New Delhi, India (CTRI/2020/05/025067)	Open-label, randomized, parallel group trial	All healthcare workers directly exposed to confirmed COVID-19 patients	Not yet recruiting

Contd…

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S. no	*Agent*	*Sponsor*	*Design*	*Target population*	*Status*
4	BCG-Denmark	Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER), Puducherry (CTRI/2020/04/024833)	Phase III, double-blind, randomized, parallel group, placebo-controlled trial	Healthcare workers likely to come into contact with COVID-19 positive or suspected cases or samples of such cases	Not yet recruiting
5	*Mycobacterium* w	Cadila Pharmaceuticals Limited, Ahmedabad, Gujarat (CTRI/2020/05/025277)	Randomized, double-blind, two-arm, placebo-controlled clinical trial	Individuals at high risk of contracting COVID-19 infection	Not yet recruiting
6	Dabur Chyawanprash	National Institute of Ayurveda, Jaipur (CTRI/2020/05/024981)	Phase III, open-labelled, multicentric, randomized, parallel group trial	Healthy male and female individuals aged between 5 and 70 years	Open to recruitment
7	Bryonia alba 30C	Principal Aarogya Homoeopathic Medical College and Hospital, Jaipur (CTRI/2020/06/025558)	Double-blind, randomized, parallel group, placebo-controlled trial	Persons in quarantine centers with history of exposure	Not yet recruiting
8	Samshamani Vati + Anu taila	All India Institute of Ayurveda, New Delhi (CTRI/2020/05/025171)	Open-label, randomized, parallel group trial	Delhi police personnel having risk of exposure to COVID-19 infection	Not yet recruiting
9	Ashwagandha	Ministry of AYUSH, Government of India, New Delhi (CTRI/2020/05/02516)	Open-label, randomized, controlled, prospective, interventional, community-based clinical study	All heathy male and female individuals	Not yet recruiting
10	Guduchi	Central Council for Research in Ayurvedic Sciences, New Delhi (CTRI/2020/05/025088)	Open-label, randomized, controlled, prospective, interventional, community-based clinical study	All healthy male and female individuals	Not yet recruiting
11	Ashwagandha	Ministry of AYUSH, New Delhi (CTRI/2020/05/025178)	Open-label, randomized, parallel group, active-controlled trial	Healthcare provider at risk for contracting COVID-19	Not yet recruiting
12	Arsenicum Album 30c	Central Council for Research in Homoeopathy, New Delhi (CTRI/2020/05/025205)	Cluster-randomized trial	High-risk contacts of cases COVID-19 infection	Not yet recruiting
13	Samshamani Vati + Nishamalaki Churna + Yoga Therapy	All India Institute of Medical Sciences New Delhi (CTRI/2020/06/026147)	Phase II/III, randomized, controlled, parallel group, open-label study	Quarantine individuals with a history of close contact or exposure to COVID-19 patients in the same household	Not yet recruiting
14	Ivermectin	R D Gardi Medical College, Ujjain (CTRI/2020/05/025333)	Phase II, open-label, randomized, parallel group trial	Healthcare workers and contacts of COVID-19 cases	Not yet recruiting
15	Chyawanprash	CCRAS New Delhi	Phase III, open-label, randomized-controlled parallel group study	All healthcare professionals and staff	Open to recruitment
16	Guduchi Ghana Vati	National Institute of Ayurveda, Jaipur (CTRI/2020/05/025488)	Phase II/III, open-label, multicentric, randomized, comparative, parallel group trial	Healthy, male or female subjects	Not yet recruiting
17	Arsenic album 30c + Bryonia alba 30c + Camphora 1M + Coronavirus-related nosodes (30c potency)	Life Force Foundation Trust, Mumbai (CTRI/2020/05/025491)	Double-blind, placebo-controlled, multicentric, cluster-randomized study	Quarantined or exposed individuals	Open to recruitment
18	Melatonin	All India Institute of Medical Science Rishikesh (CTRI/2020/06/025613)	Phase IV, randomized, parallel group, placebo-controlled trial	Individuals at high risk for COVID-19-related disease Elderly: age >60 years Diabetes Obesity Heart failure Immunosuppressed patients	Not yet recruiting

The earliest shreds of evidence of CQ and HCQ against SARS-CoV-2 arrive from the *in vitro* studies which evaluated the prophylactic role of HCQ (in addition to the therapeutic role), evaluating the addition of HCQ before or the introduction of the virus into the cell line. They did find that the HCQ was efficacious in preventing viral growth.[9,22] One of the *in vitro* studies also evaluated the postentry benefit of HCQ and found it to be efficacious up to 72 hours postexposure.[27]

The proposed mechanism by which HCQ acts as prophylaxis is as follows. Hydroxychloroquine in an unionized state traverses through the cell membrane and then into the lysosomes and gets ionized inside the lysosomes due to the presence of acidic pH. In this ionized state, it gets trapped and changes the pH of the lysosomes from acidic to basic in nature. The acidic nature is essential for the uncoating of the SARS-CoV-2 virus; in the absence of which, the cycle of SARS-CoV-2 infecting the cell, stops as it fails to get transferred from early lysosomes to late endolysosomes.[27] In addition to the above-mentioned mechanism, the glycosylation of the ACE_2 receptor which plays a crucial role in the binding of the envelope protein of SARS-CoV-2 has also been proposed as a mechanism of prophylaxis.

On March 18, 2020, World Health Organization (WHO) announced the multinational phase III/IV solidarity trial for treatments, which would study the efficacy of different treatment modalities in COVID-19 positive cases, HCQ/CQ being one of the treatment modalities. However, after a series of safety concerns, following which the HCQ arm was temporarily halted only to be reinstated, and then withdrawn again, in June 2020 WHO completely suspended the HCQ arm when an interim analysis showed that HCQ provided no benefit to hospitalized people severely infected with COVID-19.[28] The National Health Service (NHS)-sponsored RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial, on June 4, 2020, discontinued the HCQ arm following interim analysis which showed no benefit of this treatment.[29] Both these studies were evaluating HCQ for treatment and for prophylaxis, the answer remains open. However, since the mechanisms for therapeutic benefit and prophylaxis were similar, it will be prudent to be cautious about prophylactic benefit emerging out of studies which are directed toward assessing prophylaxis.

In the Indian context, HCQ usage as prophylactic agent gained momentum after an advisory issued by Indian Council of Medical Research (ICMR) on March 22, 2020. Hydroxychloroquine was recommended by ICMR to be administered as prophylaxis to the high-risk healthcare workers, and the close contacts of COVID-19 patients in a dose of 400 mg twice 12 hours apart on day 1, followed by 400 mg weekly for next 7 weeks for healthcare workers and for next 3 weeks for contacts.[23] Following this, a second advisory was released by ICMR on May 22, 2020, in which it continued its recommendation and also advised HCQ to be given beyond a period of 8 weeks, but under medical supervision.[30] In addition, ICMR extended the scope of administration to asymptomatic healthcare workers working in on non-COVID areas and field workers involved in the COVID-19 duties.

The ICMR's decision as mentioned in the advisory was on the basis of an *in vitro* study conducted at the National Institute of Virology, Pune, the safety data from the pharmacovigilance program of India, and observational data based on five studies, though the references for these data were not mentioned. Nausea and abdominal pain were the common adverse events noted. Serious adverse events were noted in seven participants, out of which three individuals had prolongation of QT interval. The committee also recommended performing the electrocardiography at the baseline, before extending the administration beyond 8 weeks, in the event of any cardiovascular events or any random time point in-between administration. A case–control study by Chatterjee et al. reported that consumption of four or more maintenance doses of HCQ significantly reduced the chances of acquiring SARS-CoV-2 and they elucidated a dose–response relationship between frequency of exposure to HCQ and such reductions.[31] However, this study has some issues—being an observational study performed by telephonic conversation, there could be recall bias; there could be a selection bias for those healthcare workers who were prescribed HCQ; the use of personal protective equipment was more in the HCQ arm which could have affected the results to name a few.

There are very few well-powered clinical studies which have evaluated the prophylactic role of HCQ, but methodological flaws preventing generalization have been noted in these studies. Boulware et al. assessed the efficacy of HCQ as postexposure prophylaxis administered within 4 days of exposure in a double-blind RCT with a pragmatic approach in 821 participants.[20] The trial showed that the risk of development of COVID-19 is not significantly different between the HCQ group and the placebo-controlled group. In spite of being a double-blind RCT with a sample size powered to detect the effect, there have been many limitations or pitfalls in the study as follows:[32]

- It is uncertain whether the exposure has definitely occurred, as the history was subjective.
- The outcome is based on the symptom of COVID-19 rather than the confirmation by the gold standard reverse transcriptase-polymerase (RT-PCR) test for SARS-CoV-2 virus in the nasopharyngeal swab.
- The entire data are provided by the participant themselves and their comprehension of the trial understanding is questionable.
- The compliance of the patients to the drug administered is also a significant concern.
- Also, in the inclusion criteria, the time duration from exposure to drug initiation was allowed up to 4 days.
- Moreover, the study basically evaluated the question of efficacy with respect to postexposure prophylaxis rather than preexposure prophylaxis.

With the media hype, in addition to COVID-19, the advocacy of HCQ as prophylaxis affected non-COVID-19 patients. Hydroxychloroquine is the primary pharmacotherapy for some rheumatological illnesses.[33–35] At the start of the pandemic, when the HCQ demand shot up in the market, there occurred an acute shortage in the supply of HCQ, compelling rheumatology patients on HCQ to look for alternative solutions and rheumatology societies to issue prompt guidelines for the management of rheumatological diseases. Gradually, this situation settled down with an increase in the manufacturing of the drug by the pharmaceutical industry. Multiple opinions have hence surfaced which are for or against the move of advocating HCQ as prophylaxis or to COVID-19 patients.[36,37] The consensus among these opinions was to advocate HCQ only under the umbrella of clinical trial (outside India) and issued a stern warning against self-administration.[36,37]

In addition to the studies which have already been published, there are currently a number of studies that are in progress evaluating the role of HCQ as a prophylactic agent in COVID-19. A search in the ClinicalTrials.gov registry with the search term

hydroxychloroquine COVID-19 yielded 230 results as of June 29, 2020. Out of these, more than 50 studies were dealing with the question of prophylactic benefit of HCQ in COVID-19 with studies evaluating both preexposure and postexposure benefits. The outcome which was used for evaluation varied from the incidence of COVID-19 in participants as confirmed by symptoms, RT-PCR, or both, time for the occurrence of COVID-19, the 21-day incidence of COVID-19 in participants, evaluation of safety. The largest study among these evaluating studies is CROWN-Corona (55,000 participants, study design: international, multisite, randomized, double-blind, placebo-controlled).[38] In this study, besides the other things, the contentious issue of appropriate dose is also being addressed.

There was a press release of one of the studies—HCQ4COV19 (2,250 participants, study design: randomized, parallel, two-arm, standard of precaution second arm, an open-label study) suggesting no benefit of HCQ, the scientific paper is yet to follow.[39] The heterogeneity among these studies is well recognized, and recently reviewed extensively, thereby requiring clinical acumen and scientific judgment in the overall interpretation about the efficacy of HCQ in COVID-19 prophylaxis.[40]

Besides, lack of evidence for efficacy with HCQ, the dose and duration of HCQ prophylaxis also remains a matter of debate.

Immunization Strategies for COVID-19

On June 26, 2020, WHO's chief scientist Dr Soumya Swaminathan announced that we may get vaccine for COVID-19 much ahead of the schedule due to diligent progress made in the trials.[41] Recently, Bharat Biotech and Zydus Cadila, two Indian companies announced Indian regulatory approval for phase I/II clinical trials on COVID-19 vaccine.[42] As per WHO's updated list, as on July 6, 2020, there are 19 specific candidate vaccines in clinical evaluation and more than 100 are in preclinical evaluation.[43] The candidate vaccine developed by AstraZeneca in collaboration with University of Oxford, ChAdOx1-S and another candidate, recombinant bacille Calmette–Guerin (rBCG)-BCG VPM1002, developed by University of Oxford and Serum Institute of India (SII) are leading the race for corona vaccines by starting phase III trials and interim results are expected within 2–3 months.[44,45]

COVID-19 Vaccine Research

Approaches to Develop COVID-19 Vaccine

Broadly, there are five categories of vaccine technologies or platforms against SARS-CoV-2, which rely on distinctive viruses or bacteria or viral parts.

Whole Virus as a Tool

Inactivated and live attenuated virus: In this conventional platform, SARS-CoV-2 is either inactivated by treating with formaldehyde or heat or weakened (live-attenuated) by passing through animal or human cells until the virus attains mutations and becomes less capable of producing disease. In both the cases, virus retains the capacity of eliciting immune response. This technology is well established, procedures underneath is known and hence, it may consume less time for the four vaccines that are using this conventional technology to come to market, if successful in clinical trials.[45]

Bharat Biotech's Covaxin is an inactivated virus vaccine, the strain of which was isolated by National Institute of Virology, Pune and transferred to Bharat Biotech. This has entered phase I/II trial.[42] Sinovac, a Chinese developer, has also registered phase I/II trial to evaluate an alum potentiated inactivated SARS-CoV-2 to prevent COVID-19. As of now, no live-attenuated viral vaccines are in clinical development but in addition to many companies, two Indian companies — SII in collaboration with US-based Codagenix and Indian Immunologicals Ltd. with Griffith University — are evaluating live-attenuated SARS-CoV-2 at preclinical stage.[43]

Vaccines with Viral Vectors as Backbones

This is a new approach and only one vaccine has come to the market till now. However, many companies have shown interest in this technology owing to its safety and stronger immunogenicity and more than 30 candidate vaccines are being evaluated in this platform. Adenovirus, influenza, and weakened measles virus are genetically engineered to be non-infectious and used as backbone viruses to carry gene of interest, e.g., gene encoding spike protein. Measles virus acts as replicating vector, while other two are viruses are non-replicating vectors.[45]

The leading vaccine candidate, ChAdOx1-S by AstraZeneca/University of Oxford is using adenovirus as a backbone in this approach. India's Zydus Cadila has developed measles vector-based vaccine and it is still in preclinical development.[43] Existing immunity against viral vectors can blunt the vaccine's effectiveness. Hence, population who have received measles or influenza vaccines during their infancy or childhood are not the ideal candidates for vector-based vaccination.

The Oxford group has successful experience with ChAdOx-MERS. Its sister candidate ChAdOx1-S has also undergone a successful preclinical test for efficacy and safety. A single dose of this adenovirus-vectored vaccine encoding spike protein, has shown to be immunogenic in mice via both cell- and humoral immunity. van Doremalen et al. (in preprint) have observed significant reduction in viral load in lung tissues and no pneumonia in vaccinated rhesus macaques.[46] Following this, the vaccine has undergone safety testing in phase I, the results of which are not published yet. However, entry into phase III indicates that this candidate had successful phase I and II trials.

Nucleic Acid Vaccines

In this technology, part of SARS-CoV-2 virus's RNA or recombinant DNA is harnessed as vaccine. The genetic material will be injected into the cell in lipid coat (for RNA vaccines) or via electroporation (for DNA vaccines) that will produce copies of proteins, mostly spike protein which itself cannot produce infection or viral replication but will elicit immune response. Such genetic vaccines are safe and easy to develop but the success rate is not known as no such vaccine is marketed for any disease.[45] American biotech company, Moderna has completed phase II trial for its lipid nanoparticle-encapsulated mRNA vaccine. This is one of the first vaccines in this class to enter phase III trial.[43,47]

Protein-based Vaccines

Proteins or fragments of proteins of the virus are injected directly into the body to generate immunity. Such vaccines are the safest as they do not produce any threat of infection. However, they require adjuvants as well as multiple doses to elicit desired response. Spike protein and its fragments are the most exploited proteins for this purpose. Empty virus shells that lack genetic material (virus-like particle) are also constructed and evaluated.[45] Clover Biopharmaceuticals has initiated phase I/II trials using

native-like trimeric subunit spike protein while another company Novavax is using full-length recombinant SARS-CoV-2 glycoprotein nanoparticle adjuvanted with matrix M in its early phase clinical trials.[43]

Heterologous Vaccines

Bacille Calmette–Guerin, an attenuated strain of *Mycobacterium bovis*, is in use since 1921 for the prevention of tuberculosis. Experimental studies in mice have shown that BCG has protective activity against viral infections, such as herpes and influenza. This activity is brought about by induction of innate immunity and heterologous lymphocyte activation.[48] This was confirmed in a small human trial against yellow fever vaccine virus.[49] IL-1beta, a heterologous cytokine, is considered as a cause for decrease in viremia. Based on this evidence, it is hypothesized that BCG might have potential activity against SARS-CoV-2. In preclinical studies, an experimental BCG-VPM1002 (rBCG), developed by SII and University of Oxford, has been far more efficacious, safer, and can produce increased immune induction compared to classical or conventional BCG.[50–52] Data from four clinical studies on rBCG suggest safe and effective alternative to conventional BCG for the prevention of tuberculosis. Since we do not have any vaccine at hand and the development of new vaccines consume lot of time, and BCG produces proven heterologous immunity, its alternative, rBCG is being tested in phase III trial against COVID-19. Another strain, a heat-killed Mycobacterium w (Mw), originally developed as an adjunct to multidrug therapy for leprosy, is also being evaluated for COVID-19. This acts through toll-like receptor pathway and enhancing host T-cell response to virus. Based on the preliminary evidence, such vaccines are believed to be safe and effective. However, the efficacy needs to be evaluated in confirmatory clinical trials to derive a conclusion.[53]

Recently, controlled human infection models (CHIMs) are proposed as one of the strategies to fast-track SARS-CoV-2 vaccine development. In these studies, healthy human volunteers are deliberately infected with the virus to study the immune response to proposed vaccines, the disease pathogenesis, and benefit of new therapies. Inherently, CHIMs involve microorganisms that cause less chances of severe diseases and should have effective therapy existing. Although such strategies have been receiving negative remarks since the beginning of inception, typhoid and cholera models lead the way. Vaxchora is the only vaccine that has received regulatory approval for cholera. The approval came after it showed efficacy in a randomized, placebo-controlled CHIM study. Many clinical trials which preceded and followed upheld the results of CHIM study.[54] Similar success is seen in typhoid-CHIM model. Data generated from CHIM model using wild-type Quailes strain of *Salmonella typhi* coupled with data from previous vaccine trials have accelerated the advancement of Typbar TCV.[55] Such challenge models also exist for malaria, schistosomiasis, leishmaniasis, and tuberculosis. Coronavirus challenge models were constructed and worked upon between 1960s and 1990s, which instigated with the current pandemic.[56] Ethical considerations weigh between public health benefits, potential direct benefit to participants with mild infection and subsequent immunity, and risk to participants with the challenge infection. Nevertheless, it is important to note that CHIMs provide robust data and accelerate drug development and hence commentaries are focused on policies that are scientifically sound, ethical, and practical.[57]

CAM

Complementary and alternative medicines have gained substantial attention among the public and scientific community. CAM involves ayurveda, Unani, siddha, homeopathy, osteopathy, and traditional Chinese medicine. The Ministry of AYUSH has asserted the role of some foods and herbs in COVID-19 for their immunomodulatory and antiviral action. Aqueous extracts of *Tinospora cordifolia* (Samshamani Vati), *Andrographis paniculata* (Nilavembu kudineer), *Cydonia oblonga* (Behidana Unnab), and Arsenicum album 30 are recommended for prophylactic management, while AYUSH-64, Agastya Haritaki (Agasthya Rasayanam), sesame oil, Adathodai, Manapagu Bryonia alba, and Rhus toxico dendron are recommended for symptomatic therapy.[58] Arsenicum album 30 and Lianhuaqingwen, a traditional Chinese medicine,[59] have been tested and shown benefit against SARS-CoV-2, while other herbs and foods have shown activity against respiratory infections and lung inflammation.[58] *Allium sativum* (Garlic extract), known to inhibit H1N1 penetration and proliferation in MDCK cells, has also been recommended for COVID-19.[60] A systematic review and meta-analysis of RCTs is published assessing the role of herbal medicine for the treatment of COVID-19. The findings suggest the potential role of herbal medicine; however, high-quality RCTs are needed to validate the hypothesis.[61] Another systematic and meta-analysis has been registered in PROSPERO with an aim to evaluate the efficacy of traditional Chinese medicine in COVID-19.[62] All these studies and recommendations highlight the fact that at this time, it is important to not to overlook the benefit of CAM, instead it is wise to work toward generation of evidence to accept or refute the hypothesis of CAM's beneficial role in COVID-19.

Conclusion

Chemoprophylaxis may potentially be harmful if taken without medical advice and efficacy is till date questionable. An effective vaccine is definitely desirable but time line for developing a vaccine and its use may be stretched. While an effective vaccine and/or a chemoprophylaxis strategy is work in progress, a mission which seems to say, "I'm possible". Some proven measures of preventing spread of infection, such as physical distancing, appropriate masks, and use of handwashing/sanitization, are likely to remain as standard measures for protection.

We summarize a list of RCTs registered with clinical trials registry of India (Table 1).

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