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# Is vaccination the main solution for the COVID-19 pandemic control? Efficacy analysis of pharmacological and non-pharmacological interventions

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## Abstract

***Background:*** *To control the COVID-19 pandemic, governments implemented both pharmacological and non-pharmacological interventions. However, the answers to questions, "How effective are these interventions?" and "Can the pandemic be controlled only by implementation of an intervention?" are very important for decision makers in public health policy.*

***Methods:*** *To evaluate efficacy of the most important pharmacological and non-pharmacological interventions of the COVID-19 pandemic control, a literature search was conducted from 2019 to January 2022 in the Google Scholar and PubMed databases using appropriate keywords.*

***Results:*** *The results of the literature review in efficacy analysis have indicated that many factors and variables influence on the efficacy and effectiveness of the interventions and each intervention alone is insufficient to control of the pandemic and overemphasizing on specific intervention such as vaccination, is misleading and may propagate the disease.*

***Conclusions:*** *Pharmacological and non-pharmacological interventions have no superiority over each other and a logical and feasible combination and implementation of these interventions are required for effective control and successful eradication of the disease according to the pandemic characteristics and countries situation.*

**Keywords:** Covid-19, Vaccination, Efficacy, Pharmacological, Non-pharmacological, Intervention.

## Introduction

Principally, control of a disease is based on combination of actions and programs required for reducing disease incidence, disease prevalence or completely eradicating the disease in the three main preventive stages. These main preventive stages are primary prevention, secondary prevention, and tertiary prevention. For example, primary prevention (e.g. new infections) consists of measures aimed at reducing the incidence of diseases or their risk factors in healthy individuals or a susceptible population, such as immunization. Secondary prevention aims to reduce the prevalence of a disease (a disease or injury that has already occurred). For instance, screening test is a secondary prevention strategy, in order to detect disease in its earliest stages [1-2].

The recent outbreak of the illness COVID-19, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a pandemic with severe social and economic disruption all over the world. The COVID-19 is a highly infectious disease and the highly contagious virus can be spread directly (human-to-human transmission) or indirectly through mucosal membranes (eye, nose, and mouth) via droplets produced when coughing or sneezing, fomites and even via fecal-oral route [3-4]. For these reasons and the rapid spread from China to 213 countries and territories in the globe [4], governments implemented both pharmacological interventions (PIs) such as drug therapy and vaccination and non-pharmacological interventions (NPIs) including travel, personal protective, physical distancing, educational and workplace/public place measures in order to control of the COVID-19 pandemic [5].

The aim of this study is to evaluate the efficacy of the most important PIs and NPIs measures of the COVID-19 pandemic control.

## Literature Search Method

To evaluate efficacy of the most important pharmacological and non-pharmacological interventions of the COVID-19 pandemic control, a literature search was conducted from 2019 to January 2022 in the Google Scholar and PubMed databases using appropriate keywords.

## Results

### Pharmacological Interventions

**Drug therapy:** From the beginning of the COVID-19 pandemic, different medications (antivirals, antimalarial, monoclonal antibodies, corticosteroids, antibiotics and cell-based therapies), alone or in combination with each other, using different dosing schedules have been used under various treatment modalities [6-7]. However, the results of studies are very different and it is difficult to draw firm conclusions about the efficacy of a specific treatment method due to methodological disparities, study limitations and very low evidence certainty [6,8]. For example, in a systematic research study, Cardwell et al. excluded 381 full-text articles of 386, because of wrong study design, population, intervention, setting, outcomes and exposure. They have been concluded that there is no sufficient evidence to use of PIs to control of COVID-19 [9].

At the time of writing, the US Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for molnupiravir (Merck & Co Inc.) and paxlovid™ (combination of nirmatrelvir and ritonavir, Pfizer Inc.) [10,11]. Molnupiravir should not be administered in patients younger than 18 years of age, for pre and post-exposure prevention of COVID-19, in hospitalized patients and its use is limited to situations that the other FDA-authorized treatments for COVID-19 are not accessible [10]. Paxlovid™ is not authorized for pre and post-exposure prevention of COVID-19, for initiation of treatment in patients requiring hospitalization and for use longer than five consecutive days. Paxlovid™ use is associated with severe, life threatening, or fatal events when co-administered with other drugs such as piroxicam, amiodarone, warfarin, phenytoin, colchicine, ergot derivatives, lovastatin, and midazolam [11].

**Vaccines:** Vaccines are our powerful tool to prevent infectious diseases. Despite the challenges in the development, production and distribution of the COVID-19 vaccine, mass vaccination program started in early December 2020. Currently, there are eight COVID-19 vaccines validated for use by the World Health Organization (WHO) given Emergency Use Listing (EUL) [10]. However, the efficacy of these vaccines seems questionable, especially given the emergence of new strains of the virus. For better understanding, this section is presented as question and answer.

**What do the US FDA EUA and the WHO EUL mean?** The WHO EUL is only recommendation of a health product for use based on clinical trial data and acceptable standards of quality, safety and efficacy. National regulatory authority of countries must issue emergency use authorization for any health product and EUL is not subject to the WHO approval [12].

The US FDA EUA is a critical and swift tool against chemical, biological, radiological, and nuclear (CBRN) threats and allows the use of drugs, biological therapeutic products, vaccines or medical devices which are needed to control public health emergencies prior to approval. That means, in an emergency (such as a pandemic), it is impossible to collect all efficacy, safety and quality data required for filing a Biologics License Application (BLA) of a vaccine for full licensure application. Instead, minimum requirements including at least two months of a median follow-up for safety evaluation and at least 3000 vaccinees for assessing the clinical efficacy of vaccines are considered in phase 3 clinical trials for EUA. In setting criteria for EUAs, vaccine manufacturers will follow serious and special adverse events for safety evaluation and from an efficacy perspective. Effectiveness of a vaccine should be supported by conducting a placebo-controlled efficacy trial and showing prevention of symptomatic COVID-19 disease in at least 50% of vaccinees [13-15].

**Does EUA mean that vaccines are proven safe and effective?** Not exactly. However, it suggests that there is a reasonable balance between risks and benefits. In other words, EUAs allow use of unapproved medical products including drugs, vaccines or medical devices to treat, prevent or diagnose life-threatening emergencies, such as COVID-19, when there are no adequate, approved, and available alternatives. For these reasons, EUAs do not come without drawbacks.

Issuing an EUA does not necessarily mean the later FDA approval or licensure. The FDA is a science-based regulatory agency and carefully monitors the efficacy, safety and quality of medical products used with the EUAs, and revokes the EUAs, if proven they have efficacy, safety and quality issues. For example, the FDA revoked the EUA that allowed for chloroquine and hydroxychloroquine to treat hospitalized patients with COVID-19 [16], bamlanivimab for antibody therapy of mild-to-moderate COVID-19 [17] and (Chembio) DPP COVID-19 IgM/IgG System, a COVID-19 antibody test [18].

Initial approval as an EUA and the later revocation or contradictory reports on efficacy or safety of a medical product, can lead to confusion and mistrust in the treatment itself, mistrust of health care systems and erodes the public confidence not only in the current pandemic but also in the event of probable future public health emergencies. For instance, in the case of remdesivir, an academic research [19] and report of the National Institutes of Health (NIH) [20] indicated that the antiviral treatment was beneficial, accelerated recovery of patients with severe COVID-19 and improved mortality rates, while other studies produced conflicting evidence on remdesivir's effectiveness. The studies showed that remdesivir was not associated with statistically significant clinical benefits; reduce the length of hospitalization or death rate [21,22]. The results of a large-scale analysis, which was conducted by the WHO, showed that remdesivir "had no important effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient-important outcomes". Consequently, the WHO recommends against the use of remdesivir in COVID-19 patients [23]. It is necessary to mention that the FDA granted remdesivir EUA request for emergency use and the treatment of COVID-19 [24].

Additional example is the University of Oxford/AstraZeneca (AZ) COVID-19 vaccine (presently VaxzevriaTM). The vaccine was listed for the WHO EUL on February 16, 2021 [12]. The vaccine was extensively distributed worldwide, partly due to the signing of an agreement between COVAX and the vaccine manufacturer, AstraZeneca. Several European countries have suspended the vaccine completely or partially, after several suspected deaths were reported due to blood clotting following vaccination with the vaccine [25].

**Can revocation of medical products by national regulatory authorities affect on public trust?** A detailed and comprehensive study showed that public mistrust and vaccine hesitancy toward the COVID-19 vaccines are rooted in scientific, technical, medical, public health system, and governmental failures rather than public ignorance [26]. An online survey in Australia was also shown that 82.8% of parents who were unsure or unwilling to accept a COVID-19 vaccine, raised issues about efficacy and safety of COVID-19 vaccines [27].

**Do vaccines have the same efficacy on different variants of the SARS-CoV-2?** Scientists classify COVID-19 variants as variants being monitored, variants of concern, variants of interest and variants of high consequence according to the severity of the symptoms, response to treatments, transmissibility, morbidity, mortality and how effectively vaccines will protect against the variant [28-29]. Different vaccine effectiveness were observed against the various COVID-19 variants. For example, Pfizer and Moderna mRNA vaccines as well as Novavax, Janssen, and AstraZeneca vaccines are less effective for South African (B.1.351) variant in comparison with Alpha (B.1.1.7) variant [30,31]. In addition, a new study has found that vaccination alone is not enough to stop the household transmission of the Delta (B.1.617.2) variant [32]. Currently, the same concern has been raised about Omicron (B.1.1.529) variant [33].

**Are side effects of the vaccines fully identified and reported?** As mentioned earlier, vaccine manufacturers consider two months for safety and limited volunteers for efficacy evaluation of the vaccines in clinical trials of EUAs. The US Centers for Disease Control and Prevention (CDC) and the WHO declare that historically, incidence of delayed adverse events following immunization are extremely rare and adverse events generally happen within six weeks after vaccination [12,34]. However, median time from the 2009 H1N1 influenza vaccination to symptom onset of narcolepsy-cataplexy was 11-26 weeks. In addition, median delay between the vaccination campaign and diagnosis of narcolepsy-cataplexy was 45-112 weeks [35,36]. Non-psychiatric medical comorbidities including rapid weight gain and higher BMI (as a known risk factor for metabolic syndrome and diabetes type 2) [37,38] and psychiatric symptoms such as depression, anxiety, and aggressive behavior have been reported several years after the 2009 H1N1 vaccination [39]. Autism spectrum disorders [40], motor, psychomotor and language development deficit [41,42] and a broad spectrum of autoimmune/inflammatory diseases [43] are the other long-term side effects of vaccines.

**Does vaccination provide complete immunity and permanent protection against the SARS-CoV-2?** COVID-19 vaccines reduce only the severity of the disease, the need for hospitalization and death. Reinfection is possible and breakthrough COVID-19 cases happen in people even when they are fully vaccinated (12,44) and the vaccines efficacy against the infection decreases over time [44-46].

**After vaccination, is the implementation of other pandemic control methods (NPIs) eliminated?** Even with vaccination, implementation of NPIs such as wearing face mask, avoiding poorly ventilated places and settings, hand sanitation and maintaining physical distance is required [12,44,47].

**Are vaccinated people still at risk for spreading COVID-19?** The risks of SARS-CoV-2 reinfection and transmission in fully vaccinated people cannot be eliminated and it is still possible for vaccinated people to get COVID-19 and spreading it to anyone else [32]. After a rapid rise in COVID-19 cases (especially Delta variant) even in fully vaccinated people, the CDC and the WHO recommend and emphasize that people regardless of vaccination status (even fully vaccinated), wear masks indoors and implement other prevention strategies [12,48].

**Are the COVID-19 vaccines efficacious?** Principally, a proportional reduction in disease between vaccinees and control group in randomized controlled trials (RCTs) is the base of vaccines efficacy evaluation. RCTs are conducted under idealized conditions in particular population, age group, and geographical setting. In consequence, ethical issues, uncertainty, possible side effects, and validity problems are the challenges of RCTs in mass vaccination [49-51].

Different endpoints are used to define vaccine efficacy. For instance, according to the WHO suggestion, a minimum criterion for COVID-19 vaccine is "clear demonstration of efficacy (on a population basis) ideally with ~50% point estimate" and the US FDA suggested that laboratory-confirmed COVID-19 infection with an endpoint estimate of at least 50% are the appropriate endpoints for the vaccines efficacy assessments. Similarly, the COVID-19 Clinical Working Group of the Coalition for Epidemic Preparedness Innovations has suggested virologically confirmed COVID-19 method as the primary endpoint for assessment of the COVID-19 vaccines' efficacy. Considering asymptomatic, presymptomatic period, the heterogeneity of the signs and symptoms of the COVID-19 infection, variables that affect on the sensitivity of RT-PCR test, as the gold-standard assay for diagnosis of SARS-CoV-2, complicate the achievement of the endpoints. For example, in a medical practical manner, therapeutic procedures are performed in presumed patients with COVID-19 despite repeated negative RT-PCR tests. In addition, there are some considerations in the use of RT-PCR assays as a vaccine efficacy endpoint, including:

- different SARS-CoV-2 genomic targets (including ORF1a or ORF1b, nucleocapsid genes, spike protein genes) with unknown sensitivity and specificity (lack of validation) or with varying reported sensitivity and specificity
- sampling time (in stages of presymptomatic, symptomatic, and recovering from infection)
- absence of differentiation between non-infectious RNA persisting in post infection stage and RNA from live virus
- effect of factors including assay type, timepoint of infection, sample choice, and duration in transit on assay sensitivity
- unclear association between ability to culture of the virus in vitro and detectable RNA by RT-PCR test [52].

There are several other factors, some of which may be difficult to quantify, that challenge efficacy of the COVID-19 vaccines (Table 1). All the mentioned factors affect on assessment of COVID-19 vaccines and consequently, challenging the correct evaluation of the COVID-19 vaccines' efficacy.

**Table 1: Factors challenging correct evaluation of vaccines efficacy in COVID-19 Pandemic.**

| Factors | Examples | Ref |
|---|---|---|
| Vaccine-related | Antigen selection, adjuvants, formulation, delivery mode and waning of immunity over time, technological platforms and optimal dosage | [53,56,57] |
| Host-related | Age, genetic, presence of underlying diseases and infections, individual immunity, susceptibility to the virus, pre-existing immunity due to natural immunity, duration of protection from natural immunity, intensity and risk of exposure to the virus, occupation and protection against reinfection | [53,54,57] |
| Methodology-related | Type of RCTs, diagnostic tools for efficacy evaluation, data collection, maintaining a placebo arm and viral load as a successor for infectiousness | [53-55,57] |
| Geographic-related | The spread of different variants in different geographical regions | [53] |
| Pathogen-related | Unknowns disease, high mutation rate and the emergence of the new evolutionary variants, rapid spread, cross-reactivity with other closely related pathogens, time from symptoms to transmission (latent period) and infectious period | [56,57] |
| Miscellaneous | Intensity and weakness of NPIs implementation by the governments | [54] |

## Non-Pharmacological Interventions

**Mask wearing:** Despite the initial controversy, face mask is now the most important personal protective equipment which is recommended by the WHO, the FDA and the CDC to prevent coronavirus airborne transmission, to protect both the wearer and other people against any large-particle droplets, splashes, or sprays (may contain germs) that the wearer emits by mouth and nose [58,59]. According to the CDC report, several observational and epidemiological studies have been shown that mask wearing is associated with reduced risk of infection, decline in new cases, and reduced the growth deaths rate of COVID-19 [60].

Several factors affecting masks' effectiveness against spread of COVID-19 including:

- Mask parameters: type, level of protection, design, quality of materials, and duration of use
- Individual parameters:
  - education and consequently proper wearing and fitness of mask
  - concentration and size of exhaled breath particles
  - underlying lung disease
  - nose or mouth breathing
  - activities and flow conditions (coughing, sneezing, singing, laughing, talking, and normal or deep breathing)
- Microorganism survival and delivery in air: traditional airborne transmission and/or superspreader, temperature, humidity, resistance to external physical and biological stresses, and ultraviolet (UV) radiation
- Other mitigation measures: maintaining appropriate physical distance and hand sanitation
- Method of efficacy evaluation of masks, for instance, cell culture or reliance on PCR findings [61-67].

Some studies in the CDC report did not distinguish the types of masks (cloth, surgical, or N95) and in some cases, implementation of other intervention strategies such as hand hygiene and physical distancing measures were simultaneously observed with mask wearing. These drawbacks in considering all the above-mentioned factors along with the limitations of the studies debate the reported high effectiveness values of mask wearing (such as 77% and 70%) to reduce transmission of the virus. It must be noted that surgical face masks provide barrier protection to the wearer from splashes (>100 μm) and droplets (5-100 μm) to the area of the wearer's nose, mouth and respiratory tract. They do not provide protection against aerosols (airborne particles <5 μm) which are produced even during a normal breathing and are not classified as respiratory protective equipment [60,63,64]. Evidence from 14 randomized controlled trials has not been confirmed the effectiveness of surgical masks against influenza-like infections [68]. In comparison with surgical masks, N95 respirators provide better protection against respiratory pathogens, especially during aerosol-generating procedures [69]. However, due to the shortage, the CDC recommends N95 respirators for healthcare personnel and does not recommend their use by the public [70].

N95 respirators are not recommended for children, people with difficulty breathing, facial hair, and a disability who cannot wear a mask [59,69]. Individualized fit testing, training, and high price are the challenges of using N95 respirators [71,72]. Incorrect use of face masks may result in self-contamination and virus colonization [73].

**Physical distancing measures:** Although some studies have emphasized the specific physical distancing measures [74,75], but undoubtedly implementation of all types of physical distancing policies including staying at home, isolation and quarantine of patients, closure of public transports, workplaces and educational centers, restrictions on mass gatherings, and lockdowns was associated with a decrease in incidence of COVID-19 [76,77]. However, the effectiveness of physical distancing measures depends on many factors, such as:

- Economic consequences (poverty, living in slums, job insecurity due to lockdown, psychosocial stress because of low income)
- Political aspects (liberal democratic or authoritarian government)
- Aspects of populations and societies
  - cultural
  - behavioral (fear of infection, skepticism, concerns, frustration, boredom)
  - awareness and education
  - people's compliance with pandemic guidelines
  - protection protocols of vulnerable groups such as the homeless, disabled, undocumented migrant workers, drug abusers, and inmates
  - increase in mortality (people in poor physical or mental health are at higher risk of mortality in long term social isolation)
  - family relationships (family violence and child abuse)
- Structure and capacity of healthcare system in control of the pandemic
- Debate consequences of politicians, economists, medical, and public health professionals
- Operating procedures for implementation of the measures
- Debatable role of media [78-81].

As can be seen, implementation of physical distancing measures is very complex and many countries were gradually implemented only a number of the interventions [81]. There is no specific "best measure" for physical distancing measures. From mandatory severe restrictions (Denmark) to voluntary recommendations (Sweden) were seen even in countries with many similarities, especially in political and social systems [82]. On the other hand, minimum person-to-person physical distancing to prevent the spread of COVID-19 (1m and 2m recommended by the WHO and the CDC, respectively), provides minimum distance for prevention of splashes and droplets transmission [83-84]. However, it must be emphasized that COVID-19 could be spread by aerosols [85] and the aerosols can travel 7-8 meters [86,87]. The spread of the virus by air conditioning systems has been reported [88,89].

**Hand hygiene:** Our hands can transfer many pathogens and proper hand hygiene is essential to reduce microbial disease transmission. In terms of COVID-19 prevention, the WHO and the CDC have recommended hand washing with soap and water before putting a face mask and after visiting a public place, sneezing, coughing, blowing nose and taking off a face mask for at least 20 seconds. When soap and water are not available, alcohol based sanitizers (at least 60%) may be used [83,90]. Major contributing factors for the hand hygiene practices have been identified as:

- Education and information on the importance of handwashing (both for people and health care workers)
- Hand hygiene compliance rate
- Handwashing behavior:
  - handwashing after outdoor activity, handling food or cooking, defecation, visiting a sick person, going to any hospitals or clinics for any reason, for respiratory symptoms, sneezing or coughing, and handling pet
  - handwashing before touching the mouth and nose area, eating, handling food or cooking
  - jewelry, artificial nails or nail products wearing
- Sex (females reported higher handwashing frequencies before eating, when arriving home, after using the toilet, before preparing food, after working, after coming in contact with a sick person and after coughing or sneezing than males)
- Education level (individuals with a higher education level practiced handwashing more frequently than those with a lower education level)
- Religion
- Water, soap, and alcohol-based hand sanitizers availability and time factors
- Antiseptic or detergent related parameters:
  - target microorganisms and number of microorganisms
  - innate resistance of microorganisms
  - concentration and potency of antiseptic or detergent physical and chemical factors including temperature, pH, relative humidity, and water hardness
  - any adverse consequences of antiseptic or detergent (for example, odor or skin damage)
  - contact time [91-97].

In addition to the factors mentioned above, other factors must be considered. For example, contact time is a very crucial factor in hand hygiene practice. However, the results of Lio et al. study showed that about one-third of the total population washed their hands for 20 seconds [93]. In addition, hand-hygiene products such as alcohol-based hand sanitizers and antiseptic soap because of skin damage and health risks, should be tested, evaluated and risk-assessed before being used [97]. For instance, the temporary use of technical-grade ethanol which contains more impurities than pharmaceutical ethanol in alcohol-based hand sanitizers is associated with health risks for consumers due to the presence and dermal absorption of toxic contaminants such as methanol (toxic), ethyl acetate (skin defattening), benzene (carcinogenic), and acetaldehyde (carcinogenic and teratogenic) [98,99]. Increased prevalence of contact dermatitis during COVID-19 pandemic

is another example [100,101]. Eventually, hand hygiene must be considered as a useful measure; however, the importance of hand hygiene in prevention of COVID-19 transmission cannot be overemphasized [102].

Considering these factors that affect hygiene behavior is not only important to improve health promotion strategies during the pandemic, but also to improve promotion to sustain hand hygiene behavior after the pandemic as basic prevention measures, which is still crucial in developing countries.

## PIs or NPIs, which one?

Despite methodology challenges such as single studies in specific community, some studies emphasize the effectiveness of NPIs. For instance, decrease in daily case growth rate, death growth rate, reproduction number, ICU admission, and even future reduction in infection and death number have been reported [103,104]. Another study showed that declining NPIs adherence in vaccinated health care workers was associated with further illness and deaths in unvaccinated care facilities residents [105]. On the other hand, other findings suggest NPIs have an essential role in control of COVID-19 transmission until vaccination has been completed. In other words, vaccination has more important role than NPIs [12,106,107].

## Discussion

Since the WHO declared the COVID-19 outbreak a pandemic, governments around the world have been forced to implement both PIs and NPIs to curb the spread of the virus. However, the efficacy of these measures is very variable and depends on several factors, including cultural, political and socio-economical system, age, sex, education level, availability of personal protective equipment, people's compliance with the pandemic guidelines, underlying disease, religion and many other factors that have been omitted for brevity. The multiplicity of influencing factors has caused each measure has, to some extent, control on the COVID-19 pandemic. Despite initial hopes that paxlovid™ and molnupiravir could be game-changers for the pandemic control, however, experts caution that the antivirals may not be safe for everyone and people receiving these new medications will require careful monitoring. The FDA has restricted use of paxlovid™ due to severe or life-threatening interactions with widely used medications and molnupiravir in which other authorized treatments are inaccessible [12,13]. Other concerns are potential mutagenicity and genotoxicity of molnupiravir [108] and impact of paxlovid™ on the growth of the fetus [109].

The rapid development of COVID-19 vaccines is an extraordinary achievement; however, different studies present many factors affect on the evaluation of the vaccines' efficacy, from methodology-related factors to vaccine, host and pathogen-related factors. These factors and their effects challenge and debate vaccination as the main intervention to the pandemic control. Over the past year, rising numbers of COVID-19 outbreaks have indicated that vaccines alone are not sufficient [110] and production of second-generation of vaccines is necessary to terminate the pandemic [111].

To measure COVID-19 vaccine efficacy accurately, selection of accurate trial endpoints, monitoring the effectiveness of COVID-19 vaccines, postlicensure assessment of vaccines (especially the risk of antibody-dependent enhancement even multiple years after vaccination), safety assessment of untested and new vaccine delivery technologies, national and international collaborations, evaluation in certain groups (pregnant women and children) are highly recommended [53,54,57].

NPIs as public health measures have played a critical role in reducing transmission rates and the functioning of society, and the economy. In controlled countries/regions, NPIs can be relaxed. However, in the case of community transmission, NPIs are effective interventions against COVID-19. One effective NPI may be ineffective in another country, even in different population groups within the same country due to multiple influencing factors especially country-specific cultural, behavioral, socio-economical, education of protocols, and individuals education level that influence effectiveness of NPIs. It is clear that each NPI has own capacities and limitations and there is no 'one-size-fits-all' approach for promoting and implementation of NPIs [112]. For these reasons, every country implemented its own combinations of NPIs to prevent COVID-19 at local or national level and the implementation of NPIs should be accommodated according to the pandemic features and capacity for individual countries.

## Conclusion

It is concluded that both PIs and NPIs have their strengths and weaknesses and due to many influencing factors and variables, their efficacy and effectiveness are not complete. These measures have no superiority over each other and overemphasizing on specific measure such as vaccination is misleading and leads to propagation of the disease. Considering control of the pandemic at national or global levels is a very complex process, for effective control and successful eradication of the disease, a logical and feasible combination and implementation of these measures are required according to the pandemic characteristics and countries situation.

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## Conflicts of Interest

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