Combating COVID-19 for human cardiovascular health: From "ISISI" strategies to final victory

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Abstract

The COVID-19 pandemic is still continuing. Current major variants of SARS-CoV-2 (Delta and Omicron) have lead to new uncertainties. Since the infection of SARS-CoV-2 and its major variants has been a high risk factor of cardiovascular health due to major adverse cardiovascular events (MACCE) and outcomes. Thus, the more coverage of vaccination, enough health workers, and related medical resources as well as the "ISISI" barriers from locals or regions to the globe play a critical role in combating COVID-19 and protection of human cardiovascular health.

REVIEW ARTICLE

Combating COVID-19 for human cardiovascular health: From "ISISI" strategies to final victory

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Running title: Combating COVID-19

Abstract

The COVID-19 pandemic is still continuing. Current major variants of SARS-CoV-2 (Delta and Omicron) have lead to new uncertainties. Since the infection of SARS-CoV-2 and its major variants has been a high risk factor of cardiovascular health due to major adverse cardiovascular events (MACCE) and outcomes.

Thus, the more coverage of vaccination, enough health workers, and related medical resources as well as the "ISISI" barriers from locals or regions to the globe play a critical role in combating COVID-19 and protection of human cardiovascular health.

Keywords: cardiovascular, COVID-19, "ISISI", omicron, SARS-CoV-2

Tracing the origin: From unknown to unknown

In both locals or regions and the globe, coronavirus (SARS-COV-2 and its variants) does not stop to spread and the number of COVID-19 cases is still climbing. So far (February 12, 2022), there are more than 402.044 million confirmed COVID-19 cases and over 5.77 million deaths in the globe. Hence, it is a very important and meaningful work since tracing the origin of coronavirus can help us to control the pandemic and ultimately combat COVID-19. But we should follow the principle of "objective, rational and evidence-based". After the global COVID-19 is under control, tracing the origin of SARS-COV-2 and related lessons will help to better control and prevent the outbreak in the future.

Currently, no matter where SARS-CoV-2 and its variants originated, our common goal during the pandemic is to completely combat and control COVID-19. Those endless arguments and doubts are meaningless. "Since bad things have happened, mankind should work together to control the adverse consequences." It can be said that whoever controls the pandemic is the winner. So far, tracing the origin of SARS-CoV-2 is still from unknown to unknown. Moreover, there are its major variants, such as wild-type (D614), Beta, Delta, and Omicron (1, 2). Therefore, we should prefer to believe that "COVID-19 is a global scourge of aliens". This good will is to reunite the countries worldwide, avoid confrontation and division, and combat finally the pandemic together.

Are current vaccines enough?

Currently, the countries worldwide are accelerating to develop novel vaccines and discover new antiviral drugs for control of the COVID-19 pandemic. And the World Health Organization (WHO) expects to end the pandemic by 2022. Therefore, the wide coverage of vaccination in the globe is necessary. However, how to test accurately asymptomatic general population but with high viral load before large-scale vaccination (3), since those are more likely to infect others. Definitely, there are other questions which should be addressed on control and prevention of the COVID-19 pandemic by vaccination.

Is current development of vaccines enough? As we know, there are still the urgent need for novel vaccines against COVID-19 due to rapid variants of the SARS-CoV-2. Second, do vaccines still effectively elicite protective immunity after coronavirus variants? Whether current major variants (Delta and Omicron) will weaken to stimulate immune responses to the S protein of SARS-CoV-2 or not as well as the duration of immunity? Third, there are rising rehabilitation and health workers needs during the pandemic, but rehabilitation and related medical resources are still scarce among many countries.

Thus, on the one hand, we should focus on development of multiple novel vaccines or "universal vaccines" for targeting these variants. However, since there are competing interests inherent in vaccine development and shortcomings in bioethical resources, particularly clinical equipoise conceptualizations, it's not easy to get the best treatment option for the general population. On the other hand, it's indeed time to train more health workers and discover more specific antiviral drugs to combat the pandemic. Fortunately, there have already had Molnupiravir (4), Paxlovid (5, 6), and Chinese combination of BRII-196/BRII-198 (7). In addition, traditional Chinese medicine, small molecules and plant-derived anti-SARS-CoV-2 agents may also have good effects on combating new major variants (Delta and Omicron).

Combating COVID-19 For Human Cardiovascular Health

Generally, it was originally expected that the COVID-19 pandemic would become an "old" after 2020. However, since there are new variants of SARS-CoV-2 in over 100 countries, current status of COVID-19 will change our expectation due to increases in the infectivity and uncertainty. Some locals had to be "lock-down" once again, and more subjects could have "atrial fibrillation" and their cardiac cells may suffer from

unexpected injuries. In fact, due to obvious delayed diagnosis and treatment during the COVID-19 pandemic, there is an increase in the number of deaths among patients with major non-communicable diseases (mNCDs), such as cardiovascular disease (CVD), diabetes, and cancer, due to major adverse cardiocerebrovascular events (MACCE), such as cardiac injury (8) and cardiac arrest (9), and higher mortality rate (10).

Currently, COVID-19 had already been a high risk factor of MACCE and cardiovascular outcomes (11). Moreover, there is a further increase in the prevalence of stress, anxiety, depression among the general population. Hence, it indeed needs benefit–risk evaluations of COVID-19 control measures on short-term and long-term health outcomes. Actually, keeping away from COVID-19 cases and avoiding SARS-CoV-2 infection is to protect individuals' cardiovascular system.

The variants of SARS-CoV-2 in countries worldwide indeed increase local bio-hazard, and there are growing concerns whether current vaccines can provide effective protection since novel spike mutants can yield antibody resistance or variants became resistant to some neutralizing antibodies (12, 13). Traditional vaccines are based on live attenuated or inactivated pathogens, there are many novel vaccines based on DNA, RNA, recombinant protein, recombinant virus, and peptides due to new concepts and technologies in vaccine design.

However, there are still no clear recommendations or a consensus on the developed SARS-CoV-2 vaccines and it is still a considerable risk for individuals who receive a SARS-CoV-2 vaccine (14). Due to the rapid variation of COVID-19, the traditional single dose vaccination has been unable to achieve the expected clinical effect of whole immunity, and the effect of multi-needle vaccination is still uncertain. This further confirms the great significance of positive conduction of the "ISISI" barriers from locals or regions to the globe (Fig. 1) [Isolation; Screening and testing; Individual immunity by a healthy lifestyle, bio-agents, and vaccination; Social and medical supports; International cooperation & information sharing] during the pandemic and post-COVID-19 era.

For example, isolation (social restrictions) is enough effective to contain the pandemic, but without negatively impact even if there is a normal population response to a stressful situation (15). At the same time, active and positive screening of SARS-CoV-2 infection and biomarkers of COVID-19 cases is a determined protective measure. For example, low-spike antibody levels of anti-SARS-CoV-2 predict mortality in critical COVID-19 (16). High lipoprotein(a) is a strong risk factor for ischemic heart disease in COVID-19 cases (17).

Then, can existing and developing vaccines help to end the COVID-19 pandemic in 2022? Will the global pandemic return to its peak due to Delta and Omicron? In fact, there are not yet solid data exist on the infectivity of those who have been vaccinated and how long the vaccine protects against COVID-19. As a preventive and therapeutic strategy for COVID-19, vaccines with high-quality should be safe, immunogenic and stable, and less allergic reactions (18), with a higher neutralizing capacity and a longer duration of immunity (19), a rational price, easy to delivery and rollout with robust equity, and suitable for all ages, and there are pre-existing T cell responses after vaccination in unexposed individuals as COVID-19 convalescent cases (20).

There is the unique pathogenesis of SARS-CoV-2 infection in cardiomyocytes due to those host-virus interactions (21), IL-1β blockade or IL-1β-neutralizing therapies during COVID-19 infection may protect those patients at higher risk of cytokine storm (22). And an innovative, safe, and rapid detection by ^{18}F-FDS PET/CT is available for clinical applications in hospitalized patients with COVID-19 (23). All in all, we expect getting final victory by effective vaccinations as a vital strategy against COVID-19 so as to better protect human cardiovascular health. Fortunately, a recent study showed that three-dose vaccination elicits neutralizing antibodies against the omicron variant of SARS-CoV-2 infection (24).

Future prospects

It is expected that the COVID-19 pandemic will be halted to the maximum extent under the help of vaccination. China has set an example due to the practice of "ISISI" strategies for the COVID-19 pandemic.

So far, there are more than 1.2 billions of Chinese residents who received the whole vaccination, and it's still continuing coverage among non-adults from 3 to 17-year-old. We expect that the pandemic will be effectively halted by not only powerful candidate vaccines but also continuing the "ISISI" barriers which cover antiviral drugs (Molnupiravir, Paxlovid, Chinese combination of BRII-196/BRII-198) (4-7), traditional Chinese medicine, small molecules and plant-derived anti-SARS-CoV-2 agents. It's happy to see a living WHO guideline on drugs to prevent COVID-19 (25). And it's believed that people will combat the COVID-19 pandemic sooner or later under the help of these comprehensive strategies.

After rigorous clinical trial design, current vaccination by receiving developed candidate vaccines is a reliable strategy for against SARS-CoV-2 infection and transmission, and control of COVID-19 in the globe. Both animal models and clinical trials confirmed the protective roles elicited by vaccination of multiple safe and effective vaccines, such as two doses of the mRNA-1273 COVID-19 vaccine (26), StriFK-FH002C (27), the AS03-adjuvanted preS dTM vaccine (28), ChAdOx1 nCoV-19/AZD1222 (29), Two doses of the SARS-CoV-2 BNT162b2 vaccine (30), COVID-19 mRNA vaccines (31), Ad26.COV2.S vaccination (32), AZD1222/ChAdOx1 nCoV-19 vaccination (33). Newly, GRAd-COV2, a candidate vaccine against COVID-19, is safe and immunogenic in younger and older adults (34). However, there are still many challenges since current Omicron variant appear to diminish the protection conferred by pre-existing immunity.

There was historically high excess mortality during the COVID-19 pandemic in some European countries since the beginning of the 20th century (35), but telemedicine service may reduce infection-related mortality (36). Although there are rare adverse events (myocarditis, carditis, thrombosis) in some cases (37-39), vaccination (40) and history of infection (41) have a protection against reinfection and variants (42). And vaccination in organ transplant recipients may increase neutralizing antibody response against SARS-CoV-2 variants (43). In conclusion, on the one hand, we need to rapidly develop novel efficacious vaccines against SARS-CoV-2 and its major variants (Delta and Omicron) since human immunity and early non-neutralizing antibody responses are associated with COVID-19 severity (1, 44); On the other hand, we should rigidly control Omicron variant for restriction of infection and transmission in the globe by the comprehensive "ISISI" strategies.

Currently, megadose vitamin C (45) can be used as a potential treatment, unfractionated heparin (UFH) can directly inhibit binding of spike protein to the human ACE2 protein receptor (46), and protease-activated receptors (PARs) blockers may fight against cytokine release syndrome and COVID-19-associated coagulopathy (47), the options to target complement may halt disease progression and death (48). All in all, a polypharmacology approach or multi-drug treatment (49, 50) may help improve clinical outcomes since there are acute kidney injury (AKI) and fibroproliferative changes in the lung, heart and kidney in COVID-19 cases. Because mass vaccination cannot quickly end the pandemic, it is suggested to adopt an influenza-like vaccination strategy (51). In conclusion, the prevention and control of COVID-19 needs the comprehensive "ISISI" strategies.

Summary

COVID-19 is a major challenge of public health in the globe, which has seriously endangered human health and safety, affected people's daily study, work and life, and halted the world's economic and social development. The pandemic in many countries, regions or locals is still continuing. Current status is still serious due to the Delta and Omicron variants and it's also a high risk factor of cardiovascular health. The "ISISI" barriers based on these comprehensive strategies will help us to combat the SARS-CoV-2 and its variants during the pandemic and post-COVID-19 era, protect cardiovascular health, and get final victory from effective vaccination.

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Data and materials availability

All source data are available upon reasonable request from the corresponding author.

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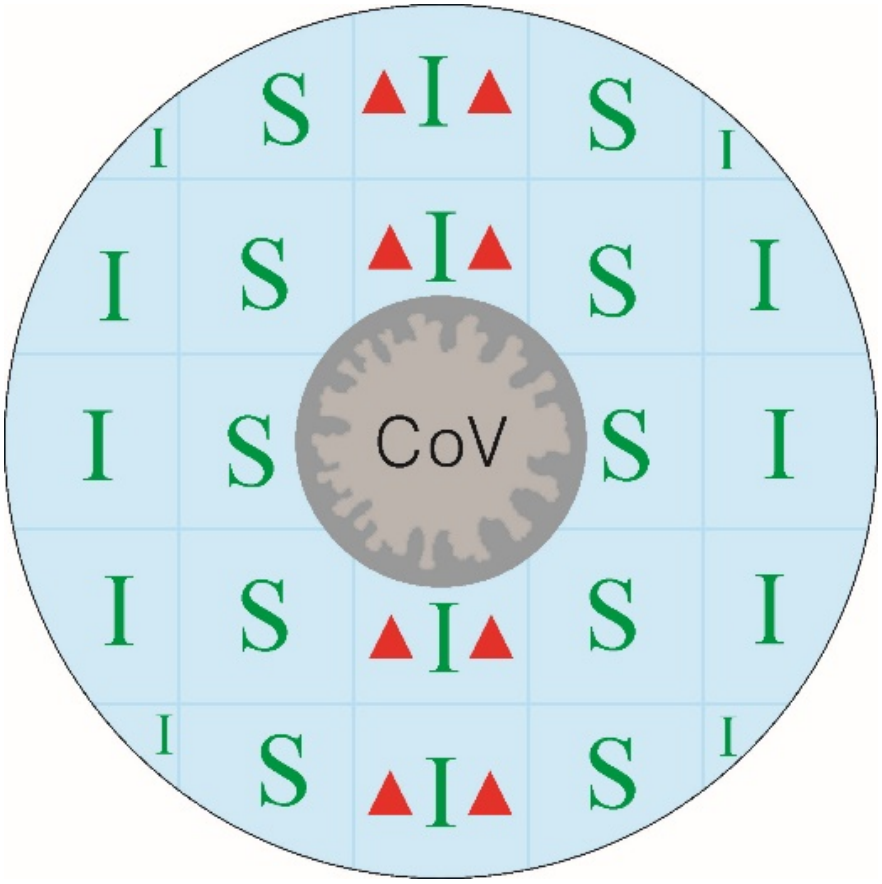

Fig. 1 Combating COVID-19 for Human Cardiovascular Health: From "ISISI" Strategies to Final Victory.

The "ISISI" barriers from locals or regions to the globe just like a great web, which can firmly net coronavirus (SARS-CoV-2 and its variants) and finally eradicate COVID-19. Vaccination as a part of the "ISISI" strategies can help human to combat the COVID-19 pandemic. In fact, keeping away from COVID-19 cases and avoiding SARS-CoV-2 infection is to protect individuals' cardiovascular system. Here, "ISISI" means "Isolation; Screening and testing; Individual immunity by a healthy E(e)SEEDi lifestyle, bio-agents, and vaccination; Social and medical supports; International cooperation & information sharing"; CoV means coronavirus (SARS-CoV-2 and its variants); Red triangle means: vaccination for COVID-19.