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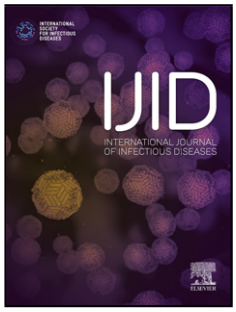


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# Editorial

# Integrated control of COVID-19 in resource poor countries

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**Abstract**

Low and middle income countries (LMICs) face many challenges in controlling COVID-19 in their countries. Health-care resources are limited and so are ICU beds. RT-PCR testing is conducted on a limited scale and treatment options are few. There is no vaccine. Therefore, what low cost solutions remain for the prevention, diagnosis, and treatment of SARS-CoV-2? How should these essential health services be delivered in order to reach the most vulnerable in our societies? In this editorial we discuss several important strategies for controlling COVID-19 including: vaccination, molecular and serological diagnostics, hygiene and WaSH interventions, and low-cost therapeutics. We also discuss the delivery of such services in order to reach the most in need. The proposed integrated control strategy requires immediate action and political will in order to reduce the widening health inequalities caused by the pandemic.

Key words: SARS-CoV-2; Control; Vaccination; Diagnostics; Hygiene; Therapeutics

### *The search for a SARS-CoV-2 vaccine*

There is intense global race to find a COVID-19 vaccine. As of August 29th 2020, 143 vaccine candidates are in preclinical evaluation and 46 candidate vaccines are being tested in human clinical trials (Phase I-III) [1,2]. Nine vaccine candidates have now entered Phase III trials in several countries utilizing thousands of volunteers. The Phase III candidates were developed by Sinovac Life Sciences Co., Ltd, China (NCT04456595), the University of Oxford (ISRCTN89951424); CanSino Biologics, China (NCT04526990), Wuhan Institute of Biological Products (ChiCTR2000034780), Beijing Institute of Biological Products (ChiCTR2000034780),ModernaTX Inc., USA (NCT04470427), Gamaleya Research Institute, Russia (NCT04530396), BioNTech/Fosun Pharma/Pfizer (NCT04368728) and Janssen Pharmaceutical Companies (NCT04505722) [1]. To develop these vaccines, various new and old techniques have been used to produce immune response including Genetic Vaccines where one or more of the coronavirus's genes are used; Viral Vector Vaccines where a virus (unable to replicate) is used to deliver coronavirus genes into cells to make viral proteins; Protein-Based Vaccines using coronavirus spike protein or it's fragment; and Whole-Virus Vaccines using weakened or inactivated viruses [2]. Sinovac Biotech, Co. Ltd Beijing has developed a promising inactivated SARS-CoV-2 Vaccine (Vero Cell) and tested it successfully in Phase I/II trial among 744 healthy Chinese participants aged 18-59 years

(NCT04352608) (Figure 1). The results from Phase I/II trials showed that a two-dose schedule of the vaccine was well-tolerated, safe (without any serious adverse reaction), and immunogenic (produced high titers of antibodies). Sinovac is presently conducting Phase III trials in Brazil, Saudi Arabia, Turkey, Chile, and Indonesia and soon in Bangladesh. According to many vaccinologists, inactivated vaccines may be the best choice against COVID-19 as there is no risk of reversion to a virulent form. Inactivated vaccines have been extremely effective over the past century to induce protection against many deadly viral pathogens such as polio, rabies, HAV and influenza. Another promising vaccine developed by the University of Oxford is a chimpanzee adenoviral vectored coronavirus vaccine which was developed within 100 days after deciphering genetic sequence of the virus. The results published in The *Lancet* showed that a single dose of vaccine was safe and immunogenic in phase I/II trials [3]. Oxford's commercial and manufacturing partner AstraZeneca pharmaceutical already received advance orders for billions of doses worldwide. Combined Phase II/III trials and a separate Phase III study to test the safety and efficacy of the vaccine are being conducted among tens of thousands of participants in the UK, Brazil, and South Africa [4]. These two vaccine candidates have created hope that vaccine will be available for early 2021.

There are still questions of whether these vaccines will be available for LMICs or if vaccine production facilities will be adequate to assure a reliable supply within a suitable timeline frame to meet global demand. More specifically, there must be a transparent global allocation system to prioritize access to the vaccines at low cost for frontline healthcare workers and to people living in poorer countries with a higher risk of severe illness and death. As COVID-19 is highly contagious (R0 2.5), we will need to vaccinate approximately 80% of the population with a vaccine with 80% proven efficacy. To ensure equity of access and international deployment we must support global randomized controlled trials of several leading vaccine candidates through the 'The WHO Solidarity Vaccines Trials' [5]. To provide the vaccines free of cost to resource-poor nations we will need a global fund supported by the World Bank, The Gates Foundation, The Wellcome Trust and G8 nations [6]. Even if successful it is unlikely that vaccination will be a stand-alone strategy to control SARS-CoV-2 [7].

***RT-qPCR diagnosis of COVID-19***

WHO has recommended nucleic acid amplification tests using RT-qPCR for the routine diagnosis of COVID-19 infection [8]. This is the gold standard for diagnosing COVID-19 and practiced all over the world including resource poor countries. However, most LMICs are struggling to test samples and track the true infection rate due to a lack of laboratory facilities, trained manpower and regular supply of the RT-qPCR kits. So, the infection rate these countries are forecasting may actually represent only a tip of the iceberg. For example, at the beginning of COVID-19 pandemic Bangladesh had only one RT-qPCR laboratory at the Institute of Epidemiology and Disease Control Research (IEDCR) designated for diagnosis of COVID-19 infection for the whole country (170 million) but now there are 77 RT-PCR labs (Figure 2) conducting approximately 20,000 daily tests [9]. Lack of trained manpower capable of performing the molecular biology experiments (e.g. viral RNA extraction and qPCR) required to testing COVID-19 and interpreting the results are major limitations in resource poor countries. Recently, several publications have reported the successful use of Loop-mediated isothermal amplification (LAMP)-based protocols to test for COVID-19 in urine, saliva, as well as oropharyngeal and nasopharyngeal swabs both with or without the requirement of viral RNA extraction [10]. So, alternative testing protocols, such as LAMP, that utilize rapid antigen detection with limited resources and available manpower will be extremely useful.

***Serological testing of COVID-19***

Serological tests are comparatively easier to perform, and require less technical expertise and equipment compared to nucleic acid-based detection [11]. Serological tests can complement RT-PCR in the diagnosis of acute infection, sick or hospitalized patients with severe symptoms who have tested negative with RT-PCR, or for determining the antibody status of healthcare professionals (and other workers) who are ready to return to work after being ill with COVID-19. Serological testing could also be used to investigate the attack rate of an ongoing outbreak in the community, detecting the prevalence of asymptomatic carriers and for the selection of donors of convalescent sera for treatment purpose [12]. At the national level, expanding testing capacity through antibody testing will enable large-scale screening at the population level generating crucial intelligence on estimates of disease spread and mortality attributable to COVID-19 and ensure timely implementation of containment measures.

Due to the unprecedented demand for rapid diagnostic testing to enable the efficient treatment and mitigation of COVID-19, the US FDA has allowed expanding access to serology tests, by issuing emergency use authorization for serological tests [13]. One of the lab-based Automated Testing Platforms for serological testing is Elecsys® Anti-SARS-CoV-2 by Roche Diagnostics which is a qualitative total antibody test (IgM & IgG), that detects antibodies against SARS-CoV-2 in patients using the necleocapsid protein. The Elecsys assay has high clinical sensitivity (99.5%; ≥14 days' post PCR confirmation) and overall specificity (99.81%), resulting in highly reliable and accurate results. Moreover, it is a quick test providing results within 18 minutes. Combining such immunoassays with molecular diagnostics is deemed the best approach for Bangladesh and other LMICs and is presently being conducted in 21 states of India [14]. The Directorate General of Drug Administration of Bangladesh has not yet approved any serological tests for the country except for research purposes.

***Low cost therapeutics***

In the absence of a vaccine to tackle COVID-19 many repurposed drugs have been identified in observational series or are being used anecdotally based on in vitro or extrapolated evidence globally. To treat COVID-19 patients, repositioning of old drugs for use as antiviral treatment is an intuitive strategy during the pandemic because the safety profile, side effects, posology, and drug interactions of these drugs are already established. This includes remdesivir, chloroquine, favipiravir, danoprevir, ritonavir, bromhexine hydrochloride, hydrochloroquine, convalescent plasma, and other interventions. In a resource-limited country such as Bangladesh, we strongly feel that if such drugs are scientifically proven to be safe and effective they should be made available to the general population and free for indigent. The icddr, b is present conducting a randomized, double-blind, placebo-controlled trial in three COVID-19 dedicated hospitals in Dhaka city comparing Ivermectin and doxycycline in combination or ivermectin alone for the treatment of adult Bangladeshi patients.

The pharmaceutical industry in Bangladesh continues to produce 98% of the medicines used domestically, and exports high quality drugs to over 150 countries, including Europe and North America. This outstanding growth of the drug industry has occurred following the 1982 drug act of the Government of Bangladesh promoting the local pharmaceuticals. This resulted in local pharmaceuticals being able to produce inexpensive high quality generic drugs that don't require extensive and costly human trials. Bangladesh, as an LMIC, is exempt from patent restrictions till 2032 and is free to copy any drug on the market or in the pipeline, while more developed countries can only copy 'Out of Patent' drugs. Because of this advantage, soon after Abbott Pharmaceutical announced one of its anti-viral drugs (Remdesivir) showed good safety and efficacy against severe COVID-19 in the USA,

Bangladeshi pharma were the first to make generic copies of the drug and export them globally.

***WaSH preventive***

The rapid monitoring of COVID-19 transmission pathways is required for prevention, intervention, and control. Studies have shown that COVID -19 viral RNA can be persistently shed in the feces for a maximum of 33 days after the patient has tested negative for respiratory viral RNA [15]. Although it is yet to be confirmed that fecal-oral transmission is indeed possible [16]. Therefore, safely managing fecal wastes from infected, recovering and recovered patients poses a significant challenge in developing countries and in urban slums. Despite several uncertainties, new horizons are opening up as shown by recent reviews on testing for SARS-CoV-2 in wastewater for early detection and monitoring of outbreaks. Thus far researchers have found traces of the SARS-CoV-2 in the sewage in the Netherlands, Australia, China, India, the United States and Sweden. Evidence on hand hygiene and influenza potentially provides a useful comparison for COVID-19. A systematic review by Saunders-Hastings et al. (2017) shows frequent handwashing to have a large and significant protective effect against pandemic influenza [17] (Figure 3). Aiello et al. (2008) found that handwashing reduces the rate of respiratory infections by removing respiratory pathogens from the hands, and thus preventing them from entering the body or passing on to other people [18]. Further evidence suggests that washing hands with soap after defecation and before eating can cut the respiratory infection rate by up to 25% [19]. Ensuring convenient and accessible handwashing techniques are needed on entering or leaving the household and in public places especially after coughing or sneezing.

***Delivery of essential health services***

A potential outbreak response program for COVID-19 prevention could be deployed at three levels comprising: a mass strategy, a district/ward strategy and a household strategy. A ‘mass strategy’ could be deployed within a city or town where residents will be informed of the ‘COVID prevention program’ in their respective district or ward via: SMS text phone messages; local health centers; EPI centers; pharmacies; and community notice boards. Health education would focus on the risk factors for COVID-19 and better cough hygiene practices. Mass media, on COVID-19 could showcase *Protect your family from COVID-19* video to illustrate effective WaSH practices to lower risk. As part of a ‘district/ward strategy’ an Early Warning Surveillance System may be deployed using: rapid diagnostic testing (e.g., Roche antibody test for suspected COVID cases) at health facilities and local hospitals; periodic testing of sewage systems for the presence of SARS-CoV-2 in municipality sewage water; Android-based phone reporting of real-time test results; GIS risk mapping of patients’ addresses. A family emergency WASH kit could be utilized as a ‘household strategy’ for families with a newly diagnosed family member. The kit for COVID-19 could comprise: a prevention poster for the family on how to minimize the risk of acquiring and transmitting COVID-19; ‘soapy water’ package (soap and 3 dispensers) enough for a family of five for 30 days; daily household disinfectant with bleach (3-6% Sodium Hypochlorite); and wearing of masks within the house.

***Conclusions***

Vaccination alone will not halt the COVID-19 pandemic. Low cost evidence-based integrated control strategies will be required. We must ensure access to reliable diagnostics in order to determine the true burden of disease in the community. To support the existing health system, data on the safety and effectiveness of locally available, affordable, and cost-effective therapeutic drugs needs to be generated in order to treat COVID-19 patient. A combination of effective vaccination, treatment and WaSH will ensure enhanced protection

against COVID-19. Collaboration at the international, national, regional and local level is parmount if we are to halt the spread of infection and end the pandemic.

**Conflict of Interest, funding and ethical approval**

We declare no conflict of interest. No funding was required or ethical approval sought.

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Figure 1. Sinovac'sSARS-CoV 2 (Vero Cell) inactivated vaccine. One of China's leading vaccine candidates.

Figure 2. icddr, b virology laboratory were approximately 500 *RT-qPCR* COVID-19 are performed daily for the government by 10 staff members.


Figure 3. A public foot operated hand washing station used to halt transmission.