Review Article

Tackling COVID-19 in Nepal: Opportunities and Challenges

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ABSTRACT

The COVID-19 pandemic has become a global challenge that has driven nations to take some extreme measures in an attempt to prevent outbreaks and save lives. The scientific communities are trying their best to understand the activities of SARS CoV-2 virus to target effective strategies against it. The whole world is trying its best to contain the infection, Nepal is no exception. Nepal underestimated the likelihood of the COVID 19 outbreak during early January however with the increasing case strong measures have been initiated. Nepal reported 2,099 confirmed cases with 266 recoveries and 8 deaths by June 2, 2020. The focus on social distancing and since the middle of March countrywide lockdown has been taken as a strategy to control the rate of infection but the challenge lies in its continuation. There is also a challenge in extension of testing and other public health intervention.

Timely action, testing, tracing, tracking, treating, and togetherness have been seen as the most effective strategies to date. Due to the increasing cases of infection and death, it has triggered disruption to social and mental wellbeing of the global citizens. The confusion and uncertainty rise fueling misinformation, stigma and discrimination which are negatively impacting the prevention strategies adopted by different nations. There is a need for proper communication strategies and community engagement alongside the togetherness of all concerned entities fighting against this wicked virus globally. In light of this global need, this paper aims to provide some insights into the strategies and challenges revolving around COVID-19 prevention and control

Keywords: COVID-19, SARS-CoV-2, novel coronavirus 2019, strategies, challenges

Access this article Online		Article Info.
Quick Response Code	Website:	**How to cite this article in Vancouver Style?**
Scan Me for Full Text	www.jkahs.org.np	Marahatta S, Paudel S. Tackling COVID-19 in Nepal: Opportunities and Challenges. Journal of Karnali Academy of Health Sciences 2020;3(Covid-19 Special Issue):1-12.
	DOI: https://doi.org/10.3126/jkahs.v3i0.29231	Received: 6 May., 2020 Accepted: 2 June 2020, Published Online: 3 June 2020 Conflict of Interest: None Source of Support: None

INTRODUCTION

COVID-19 emerged as an unknown outbreak of pneumonia in Wuhan on December 2, 2019.[1,2] During the first week of January 2020, the genome sequence of the virus was isolated and shared with World Health Organization (WHO)to be identified as novel coronavirus.[3] The WHO declared the COVID-19 outbreak as a pandemic when the confirmed cases reached to 118,319 with 4,292 deaths worldwide on March 11, 2020.[4,5] By June 1, 2020, COVID-19 accounts for 6,057,853 confirmed cases and 371,166 death worldwide.[5]

In the context of Nepal, the country saw its first COVID-19 case on January 25, 2020 in a 32 years old Nepalese male student who returned from the Wuhan City of China but later recovered and tested negative on reverse transcription polymerase chain reaction (RT-PCR) assessed in January 31.[6] The second case was detected only after more than a month on March 23, 2020 in a 19-years-old Female student returning from France. Nepal saw its first case of local transmission on April 4, 2020 when 34-years-old women from Kailali district tested positive for SARS-CoV-2 and she didn't have any prior history of travel. This marked Nepal to be at the second stage of infection.[7-9] There have been 2,099 confirmed cases of COVID-19 of which 266 had recovered and 8 deaths have been recorded until June 2, 2020.[7] In the initial phase, Nepal failed to capture the significance of this global problem as not much was done to prevent it.[6,8] But with the increase in number of cases Nepal is increasing its effort to combat with COVID-19 through different measures which initiated form international travel restrictions, banning of public gathering, boarder closure and finally a long country-wide lockdown.[10] Nepal is trying its best to increase the number of isolation and quarantine facilities, essential personal protective equipment along with rapid diagnostic tests and COVID-19 confirmative test through RT-PCR.[7]

METHODOLOGY

The related literature for this review paper was assessed from PubMed and Google Scholar using the combination of keywords: "COVID-19" OR "SARS- CoV-2" AND "Challenges". The manual search for literature were also performed form the reference list of retrieved articles. We further visited the WHO and government's official webpages for the updated information.

Diagnostic practice in Nepal

In context of Nepal, recently the serological test based on antibodies detection is used to assess the suspected case at community level. The problem with current practice is that those who are tested positive in this Rapid Diagnostic Test (RDT) are only subjected for RT-PCR confirmation while those who are found to be tested negative are sent home without further confirmation.[7] This is a treacherous public health act which puts the whole country at risk of outbreak. It is well established that there are no perfect test kits.[11-14]

There is always a possibility that the test result might be false negative (failing to detect infection among infected) or false positive (showing infection among non-infected).[15-17] There is no threat if some false positive cases are referred for confirmation test and kept under isolation but if we fail to cover false-negative cases then the outcomes can be catastrophic. If the suspected cases are not properly examined and are allowed to return to their community due to false-negative test results, the person is more likely to transmit the infection. If a single person of any particular community is found to have positive RDT result, the whole community should be

assessed using standard diagnostic test which is rRT-PCR. [18, 19] The Indian Council of Medical Research (ICMR) has built up a strategy for using antibody-based RDT in which to rule out the risk of missing false-negative cases, the strategy document proposes that the suspected case with negative RTD results should also be assessed with RT-PCR test if necessary and if RT-PCR is not performed initially there should be another antibody test after ten days while keeping the suspected individual in-home quarantine.[20]

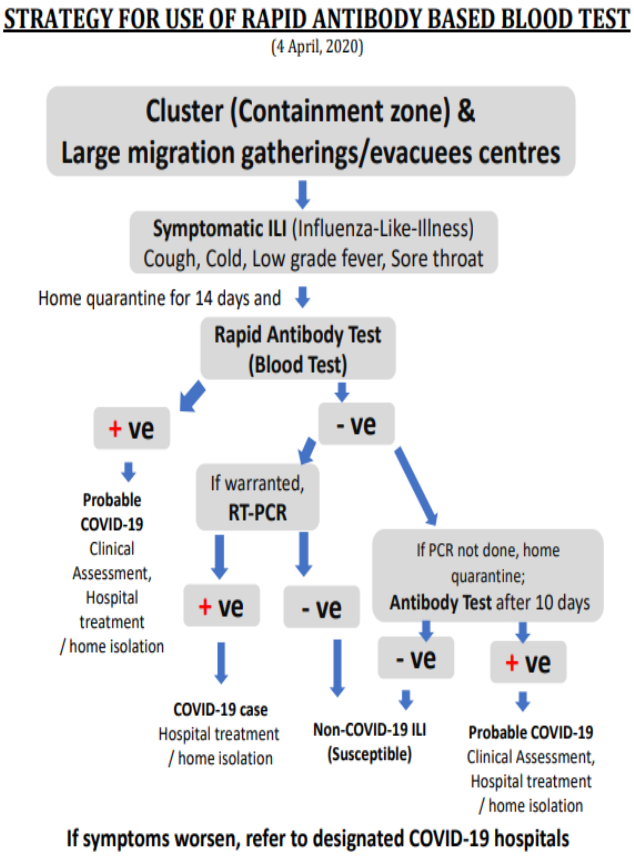

Figure 1: Strategy for Use of Rapid Antibody-Based Blood Test by ICMR[20]

Diagnostic tests and their utility

The rRT-PCR affords the feast features to anticipate or rule out the likelihood of the SARS-CoV-2 infection.[18, 19] But it is not able to rule out the false-negative absolutely.[14, 21]Technologically, it's hard to run this test in low care setting meanwhile it also demands sophisticated technology, and hands-on skills to deal right from the sample collection, sample processing and conduct the testing adhering to strict Standard Operating Procedure (SOP).[14, 22]Though, WHO has provided guidance for Laboratory testing among suspected human cases for COVID-19on 2 March 2020,[23] how well are the procedure followed remains questionable.

Selection of the primers specific to the viral genetic integrity in specific geographic and population settings is yet another challenge.[22] Neither country has been able to introduce perfectness but is trying to establish the test in a better way to make the best possible prediction. Test, Test and Test have been applauded as the best strategy to address COVID 19. [9, 24] Our fundamental challenge here is how to adopt the best quality test to materialize our strategy. Which primer can best predict the presence or absence of SAR-COV-2 virus via rRT-PCR is one of the key challenges that the molecular biologists are facing.[25] A study by Zhao J et.al[14] has illustrated the sensitivity of different test in detections SARS-CoV-2 at different time duration (Table 1)

Table 1: Sensitivity of different COVID-19 test at different days after onset of disease as per Zhao J et.al[14]

SARS-CoV-2 tests	Days after onset of disease symptoms			
	1-7 days	8-14 days	15-39	Total
RNA by RT-PCR	66.7% (95% CI: 55.7-76.4)	54.0%(95% CI: 44.8-63.0)	45.5 % (95% CI: 32.0-59.5)	67.1%(95% CI: 59.4 - 74.1)
Total Antibody (Ab)	38.3% (95% CI: 28.5-48.9)	89.6% (95%CI: 83.2-94.2)	100.0%(95%CI: 96.0-100.0)	93.1%(95% CI: 88.2-96.4)
IgM	28.7% (95% CI: 19.9-39.0)	73.3%(95% CI: 65.0-80.6)	94.3% (95% CI: 87.2, 98.1	82.7%(95% CI: 76.2-88)
IgG	19.1% (95% CI: 11.8-28.6)	54.1%(95% CI: 45.3-62.7)	79.8% (95% CI: 69.9-87.6)	64.7%(95% CI: 57.1-71.8)
RNA+Ab	78.7% (95% CI: 69.1-86.5)	97.0%(95% CI: 92.6-99.2)	100.0%(95% CI: 96.0-100.0)	99.4% (95% CI: 96.8-100.0)

Test results			Clinical Significance
RT-qPCR	IgM	IgG	
+	–	–	Patient may be in the window period of infection.
+	+	–	Patient may be in the early stage of infection.
+	+	+	Patients is in the active phase of infection.
+	–	+	Patient may be in the late or recurrent stage of infection.
–	+	–	Patient may be in the early stage of infection. RT-qPCR result may be false-negative.
–	–	+	Patient may have had a past infection, and has recovered.
–	+	+	Patient may be in the recovery stage of an infection, or the RT-qPCR result may be false-negative.

Figure 2: Clinical Significance of different SARS-CoV-2 test results[22]

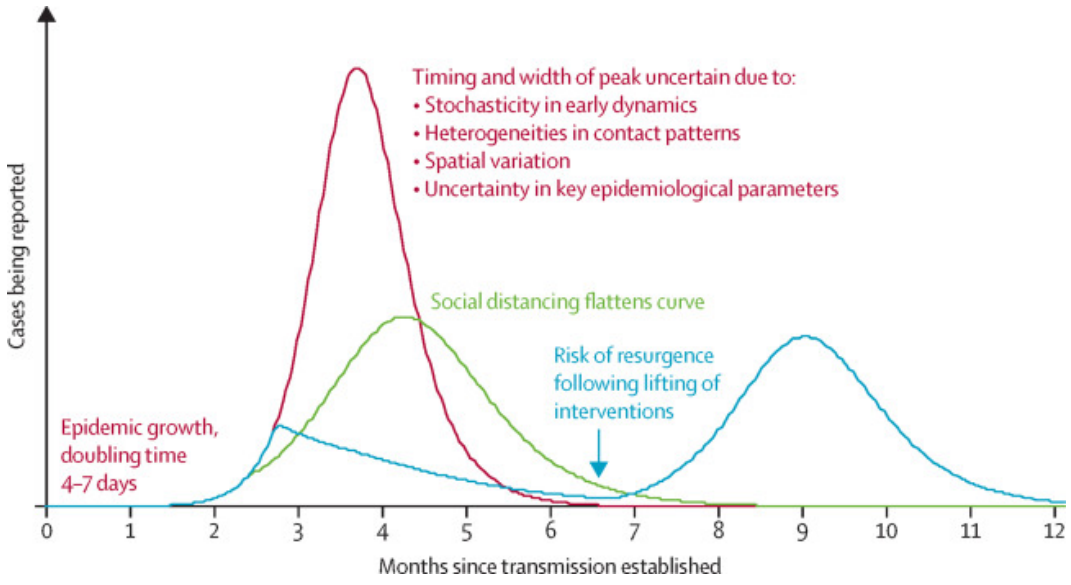

Figure 3: Illustrative simulations of a transmission model of COVID-19 as per Anderson et.al[26]

Scientific communities are also divided on test issues. We have not been able to make the people understand it in people's language. The interpretations of the test should be done in terms of clinical decision making at individual care setting and defining the infection at population settings taking account of the immunological basis. Since the virus provokes complex immune features this should be cautiously taken into account while designing and interpreting the tests.

Lessons from countries that used diagnostics in effective ways

It is apparent that while many countries struggle with their increasing cases and loss of lives some countries have contained the virus outbreak and flattened the curve before it was too late. The effective strategies adopted by these countries can be summarized as six T's strategies of timely action, testing, tracing, tracking, treating, and togetherness. It has been observed that the social distancing measures reduce the value of the effective reproduction number "R" of SARS-CoV-2, resulting in reduction of transmission. But there is always a risk of resurgence of infection when such interventions are lifted to manage the economic burden and impact.[26]

6T (Timely Action, Testing, Tracing, Treating, Tracking, And Togetherness)

Timely actions

If you look at some of the countries who were able to control the COVID-19 outbreak even at the early time of its spread, we can look at the facts provided by Taiwan, Hong Kong, and Singapore. They took proactive measures implanting travel restrictions on passengers coming from the mainland[27] even when the WHO at that time recommended travel bans were not necessary.[28]In context of Nepal, it was only after middle of March, the government suspended visa-on-arrival services for all countries and few days later restricted the passengers from Europe, United Kingdom, West Asia and the Middle East to enter Nepal via airways.[29]Following this, on 23 March, Nepal closed its land border with India and China.[10]By 18 April 2020, there were 30 confirmed cases in Nepal of which 29 cases were imported from other countries while only one was suspected to have local transmission.[30]

Testing

Test, Test and Test have been applauded as the best strategy to address COVID 19.[24] Learning form the SARS epidemic of 2003, South Korea took another proactive measure of testing hundreds of thousands of people for infection and tracking the potential carriers in the early phase of infection which has been acknowledged as the major contributing factors that help South Korea to prevent major outbreaks.[31] Similarly, learning from South Korea, Germany has increased its testing facilities with 123 laboratories across the nation carrying out 116,655 PCR tests per day while the United Kingdom is hoping to increase its capacity to perform 100,000 tests per day by the end of April.[32]

Rapid Diagnostic Tests

The currently used rapid diagnostic kits are of two types: one based on detection of SARS-CoV-2 viral protein in respiratory samples such as in sputum and throat swabs and second is the detection of human antibodies generated in response to the SARS-CoV-2 infection in blood or serum.[17]

Tracing the presence of human antibodies against SARS-CoV-2 in blood samples of people suspected of COVID-19 infection are the most common types of rapid diagnostic tests in use. [13, 33, 34] However, studies suggest

that the antibodies are produced only in the second week after the onset of symptoms in majority of cases.[14, 15, 33, 35, 36]Studies performed among RT-PCR test positive COVID-19 patients have observed that the antibody response can be weak, late or absent among the patients.[14, 15] The strength of antibodies produced depends on several factors such as age, severity of infection, use of certain medications and presence or absence of comorbidities which suppress immune systems.[14, 15, 37] Due to this reason, it can be expected that through this method, the diagnosis of COVID-19 infection is only possible in the recovery phase when the patient's immune system starts to fight against the infection and by this period the infection could have already spread among population.[17]Hence, while using these types of serological test the duration of infection should be kept into account as it highly influences the presence or absence of antibodies as illustrated in figure 4.[22]

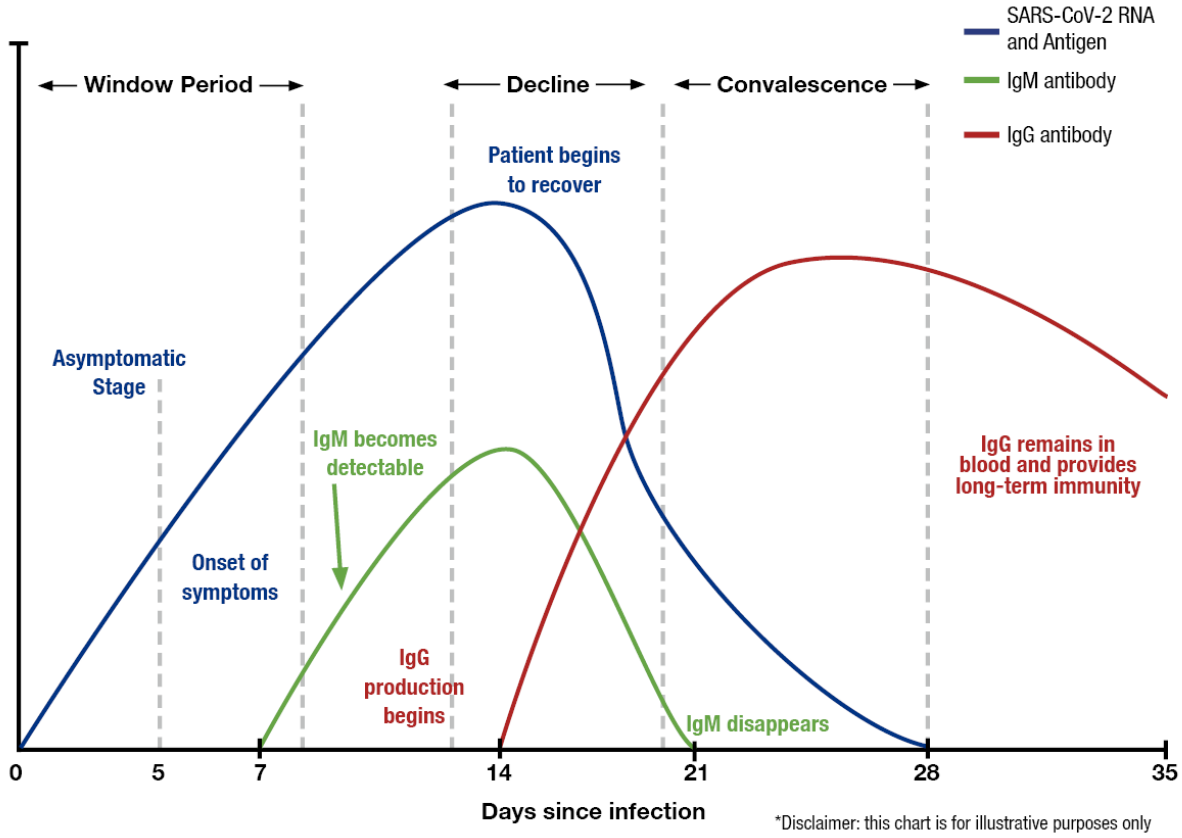

Figure 4: Presence of different antibodies at different days after the infection[22]

The antibody detection tests targeting COVID-19 may also cross-react with other pathogens, including other human coronaviruses giving false-positive results while the tests have issues with sensitivity so could give false-negative results. [15-17]In addition to this it should also be noted that these serological tests just measure the level of antibodies and there is no evidence suggesting serological tests can reveal if the individual is immune or protected from reinfection.[17]

Another rapid diagnostic test available is the detection of the presence of viral proteins or antigens in respiratory samples. For this test to function, the antigen should be present in sufficient concentrations so it could bind with the specific antibodies fixed to a paper strip. There are several factors which influence

credibility of these tests such as duration of onset of illness, concentration of viral antigen in specimen, the precise formulation of regent in test kits and the quality of specimen collection and processing. [17] Due to these reasons and limited information available regarding the test WHO does not currently recommend using this antigen-based RDT for patient care, however, there is high stress for its use in research to understand its performance and potential diagnostic utility.[17]

There are many limitations with these tests and which affords the challenge to-rule out the false positive from the true positive cases. However, they can contribute to some extent to public health intervention. In these contexts, we are currently using the antibody-based rapid screening test to suspect those who had recent infection.

Tracing And Tracking

In consort with the proper testing, the focus should also be provided on constant surveillance and monitoring of the communities who are at high risk of infection. This is of most importance as their mobility, sanitary behaviors and community engagement highly influence the dynamic of transmission of SARS-CoV-2 virus. Another effective measure adopted by South Korea is a robust contact tracing system. It has helped for timely identification of the networks of possible suspected cases and areas. South Korea has developed an emergency alert system which informs all the citizens about the locations and places visited by the infected person with a timestamp in the district. This enables people to know if they have come in contact with the infected person or have visited the same place at that time duration. This sharing of information has helped to motivate citizens for self-testing in case of suspicion and also to take preventive measures such as disinfecting the places.[38]However, these measures come in cost of disrupting privacy which has created some unseen consequences but at these hard times, it can be seen as a trade-off between privacy of a person and a collective effort to save lives. Furthermore, Korea Centers for Disease Control and Prevention (KCDC) has divided the contact tracing into four stages: i) Investigation (basic information about areas visited by the patient is identified via interview); ii) exposure risk assessment (more objective information such as medical records, cellular GPS data, credit card transactions, CCTV footages may be collected); iii) contact classification (based on the collected information); iv) contact management (based on their classification people are subject to self-quarantine (home quarantine) along with health education and symptom monitoring).[39]

Treatment

At present, there are no effective vaccines or any anti-viral treatment that are available against COVID-19. The WHO has initiated a global clinical trial as “Solidarity trial” in an attempt to discover the effective medications for SARS-CoV-2 by comparing new and currently in use anti-viral drugs. [40, 41] Though multiple drugs are under clinical trials, it should be considered that it might do more harm to the patient than benefiting them.[8, 9, 42] In absence of effective medicine or treatment mechanism against COVID-19, the treatment is symptomatic for the management of the symptoms and prevention of the complications.[9] The patient with severe infection can be helped with Oxygen therapy to prevent complications. Similar, mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock. [9, 43] Learning from past respiratory infections such as SARS-COV, treatment measures such of use convalescent plasma therapy to boost the

immune system has been purposed.[44] Similarly, intravenous high-dose vitamin C treatment has also been recommended for the treatment of lung injury caused by hyper-activation of immune effector cells.[9, 45] Thru the learning from previous epidemic resulted by different human coronavirus (HCoVs), the WHO has released a document summarizing guidelines and scientific evidence for the management and treatment of complications resulted from SARS-CoV-2 infection.[46]

Togetherness

With all the confusion and crisis going around due to COVID-19 outbreak it is certain to provoke social stigma and discriminatory behaviors against people of certain ethnic backgrounds as well as anyone perceived to have been in contact with the virus.[47]Presence of stigma can contribute to the spread of infection more as it can undermine social cohesion and prompt possible social isolation of groups making it difficult to control the outbreaks. Stigma can drive people to hide their illness in fear of discrimination, which can come as a barrier for seeking health care immediately and limit adoption of healthy behavior making the situation worse.[48]So the whole society-needs restructuring and remodeling to best cater the demands created by the nasty virus. How the world will cope and move forward in this extraordinary situation determines our existence and sustainability. It is a critical issue to think about the communication strategies to be adopted to support and enable communities to take effective action to combat the disease as well as avoid fueling fear and stigma.[48]

If we look at the global scenario, currently most of the countries are practicing certain measures of social-distancing either in name of complete lock-down, physical distancing or home quarantine. Disruption in mobility, disturbed socialization alongside confusion, rising fear, uncertainty and economic constraints has been brought frustration and panic among the global population. This has been seen in different forms of anti-lockdown protest, rallies and actions violating governments measures against COVID-19.[49] In response to control such civil unrest and prevent the risk of outbreaks there is a need to create an environment in which the disease and its impact can be discussed and addressed openly, honestly and effectively.[48]

Social Distancing and Mental Health

The globe is facing extraordinary situations as the virus is challenging our mode of living. As a social being social integration and togetherness have been considered as our values which have been compromised by different community containment measures. Either if it is complete lockdown or any measures of social-distancing or physical distancing, the virus has not just threatened individual's lives but also has challenged our social fabrics. Distancing one another physically is resisting the community model we have been adopting. It is well understood that these pandemic crises could result in massive mental health impacts, so acknowledging these facts the WHO has advised that the public fears and anxiety should not be ignored and it should be addressed in individual, community and government levels.[50] But in lack of proper governance and struggles to control infection and save lives the psychological impacts lead by COVID-19 pandemic have been overshadowed in present context.

We have been compelled to move from physical to virtual mode and architect our livelihood differently. In this chaos, the children are more likely to experience fear and anxiety while no one could escape from fear of illness, death, or losing someone.[50] Schools and universities are compelled to redesign their

model. It has been foreseen, closing the schools for long could amplify the mental health impact in children's as they might lose the sense of structure and stimulation that is provided by school environment, as well as they couldn't get the opportunity to be with their friends and get the social support which is essential for good mental well-being.[50] Similar effect could be seen in the young and elderly population.

Alternative to Lockdown

Many countries are looking for an alternative to lockdown or home quarantine where the economic and social activities could be executed safely. In case of South Korea, it never imposed any curfew or lock-down but was still able to flatten the curve by taking timely actions, increasing its testing facilities and constantly monitoring and tracking suspected individuals in early phase of an outbreak. [39] Similar scenario can be observed in Taiwan where the government and citizens took early actions such as screening of arrivals, comprehensive testing and contact tracing before emergence of any major outbreaks.[51] But for many countries, this approach might not be suitable now due to large number of infections and lack of testing facilities and health workforce.

In Sweden, different parties are proposing for scaling up the system of short-term layoffs to tackle the economic burden caused bythe SARS-CoV-2 outbreak. The proposal enables the employees to reduce their working hours for certain duration where the central government will cover a clear majority of the cost-reducing economic burden to employers and employees.[52]

Another alternative that has been purposed by some politicians is Herd Immunity.

Herd Immunity

It is evident that herd immunity can protect the population from the infection and its consequences. The issue is how to develop herd immunity. The development of herd immunity depends on the rate of transmissions of infection (R_0) and it is estimated that R_0 of SARS-CoV-2 ranges between 2 to 3.[53-55] Simply the herd immunity can estimated as Herd immunity $=R_0-1/R_0$ $=2-1/2$ $=1/2$ i.e. at least 50% of the people need to be infected to gain herd immunity. Inline with this analysis, a study that used effective reproductive number (R_t) at 3 found the critical level of population immunity $P_{crit,}$ (acquired via vaccination or naturally-after recovery from COVID-19) required for herd immunity against COVID-19 is 0.67. This means at least two-thirds of the population have to be immune to acquire herd immunity.[56] The issue is if we try this gamble as per British Prime Minister advocacy for herd immunity, to create a herd immunity we must allow 50 percent of the population to be infected. In doing so it will lead to additional burden to hospitals with 15% more hospital admission for ICU and ventilators mostly for the vulnerable population while losing an estimated 5% of the population. Moreover, it is very much expensive at the cost of human lives.

Based on the global estimation it has been suggested that the COVID-19 infection fatality rate is around 0.3-1 percent.[57] If 70 percent (reproductive rate R0=3) of an entire population gets sick, that means that between 0.35-0.7 percent of everyone in a country could die, which is a catastrophic outcome. The sad fact is that herd immunity just isn't a solution to our pandemic woes. Yes, it may be an option when we have a vaccine developed. Until we have a vaccine, anyone talking about herd immunity as a preventative strategy for COVID-19 is simply wrong.

Fortunately, there are other ways of preventing infections from spreading, which all boil down to avoiding people who are sick. So stay home, stay safe, and practice physical distancing as much as possible. Lockdown strategy focusing on extreme physical distancing is the blanket approach that helps to buy time and decrease the transmission in the community. [8, 9, 26] Meanwhile it synergies the testing strategy and support to differentiate the infected from health individuals reducing the transmission. Ultimately after a certain time followed by lockdown, it will offer ground for the newly infected people to transmit the infection so-called the second wave of the disease.[26,58] Hence if we can develop vaccine by the time we can comfortably protect the population-what the global community is expecting. Another possible intervention if proven to be feasible would be the administration of prophylactic therapy. It is difficult to say if effective prophylaxis can be approved for use in human population.

CONCLUSION

The recent COVID-19 outbreak has challenged the social, economic and political integrity of the world. Though the scientific community is doing their best to understand the virus and seek the best way to mitigate its effect, the infection continues to rise while claiming significant toll of human lives. In context of Nepal, though the country underestimated the infection in its initial phase, it has been trying its best to prevent further infection as the rate of infection increased. Different nations are dealing with their COVID-19 infection differently. The most effective strategies that have been seen till date can be summarized as six T strategies of **timely action, testing, tracing, tracking, treating, and togetherness.** It has been noted that COVID-19 is not just linked to respiratory illness anymore, the raising infection, deaths, confusion and uncertainty has marked its impact on social and mental wellbeing. The rise of social stigma and discrimination among COVID-19 patients has been seen to have negative impact on its preventive strategies. The infection cannot be control or contained only by the scientific communities, healthcare workforce and/or any political strategies. There is a need for community engagement alongside the togetherness of all concerned entities fighting against this wicked virus globally.

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