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The 2019 novel coronavirus disease (COVID-19) pandemic: A review of the current evidence

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A novel coronavirus (nCoV) spillover event, with its epicenter in Wuhan, People's Republic of China, has emerged as a public health emergency of international concern. This began as an outbreak in December 2019, and till February 28, 2020, there have been 83,704 confirmed cases of novel coronavirus disease 2019 (COVID-19) globally, with 2,859 deaths, resulting in an overall case fatality rate of 3.41 per cent (95% confidence interval 3.29-3.54%). By this time (February 28, 2020) 58 countries or territories and one international conveyance (Diamond Princess Cruise Ship) were affected. As a part of the global response to manage and contain the pandemic, major emphasis was placed on generating research intelligence to guide evidence-based responses to contain the virus, which was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), owing to its genetic similarities with the SARS virus. This review summarizes the emerging evidence which can help guide the public health response, particularly in India. Key areas have been identified in which research needs to be conducted to generate critical intelligence for advising prevention and control efforts. The emergence of SARS-CoV-2 has once again exposed the weaknesses of global health systems preparedness, ability to respond to an infectious threat, the rapidity of transmission of infections across international borders and the ineffectiveness of knee-jerk policy responses to emerging/re-emerging infectious disease threats. The review concludes with the key learning points from the ongoing efforts to prevent and contain COVID-19 and identifies the need to invest in health systems, community-led response mechanisms and the need for preparedness and global health security.

Key words COVID-19 - epidemic - MERS-CoV - novel coronavirus - pandemic - quarantine - severe acute respiratory syndrome coronavirus 2 - transmission

Introduction

Coronaviruses (CoVs) represent a major group of viruses mostly affecting human beings through zoonotic transmission. In the past two decades, this is the third instance of the emergence of a novel coronavirus, after severe acute respiratory syndrome (SARS) in 2003 and

Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012[1,2]. The repeated emergence and global scale of transmission, significant number of deaths, infection and mortality of care providers and healthcare workers (HCWs), and higher risk of death in vulnerable or susceptible groups, have been the major causes of concern. Integrated early warning and response systems are an effective way to raise a timely alarm about these emerging and re-emerging pathogens, but few tools are available to enable pre-emptive prediction of such diseases. The Global Virome Project has been initiated with the objective of creating a global atlas of pathogenic viruses, with the specific objective of identifying spill-over events[3,4]. The project has not been without its critics, and is not yet close to providing evidence which can be translated into preparedness action[5]. This underscores the importance of preparedness of the health system to deal with dangerous pathogens and better control of endemic infections.

The process of naming the novel coronavirus (2019-nCoV) which emerged in Wuhan, China, in December 2019, has created some controversies[6]. In this review, the WHO convention of referring to the disease condition as novel coronavirus disease (COVID-19) has been followed[7]. The virus will be referred to as SARS-related CoV-2, or SARS-CoV-2[8].

COVID-19 has been labelled as a public health emergency of international concern (PHEIC)[9], and the epidemic curves are still on the rise[10]. Here, we summarize the clinical and public health aspects of COVID-19 and SARS-CoV-2, and the lessons gleaned from the global responses so far. As more data continue to emerge, the epidemiology of the disease will come into sharper focus.

Agent: Severe acute respiratory syndrome-coronavirus 2

The SARS-CoV-2 is a beta-coronavirus belonging to the family of *Coronaviridae*. Essentially a zoonotic disease, the first human coronavirus outbreak was recorded in 1965 - HCoV-229E, followed by two outbreaks of similar capacity - SARS-CoV and MERS-CoV in 2003 and 2012, respectively[2,11-13].

Meta-genomic sequencing of RNA samples isolated from the bronchoalveolar lavage (BAL) fluid of patients suffering from severe acute respiratory illness (SARI) in the city of Wuhan identified a novel RNA virus as the causative pathogen. Till now, 11 complete genome sequences of SARS-CoV-2 isolates are available. Six of the whole genome-sequenced SARS-CoV-2[14,15] were isolated from different parts of China and five were isolated from Japan[16]. Genome sequences of different isolates are highly similar and showed more than 99 per cent sequence identity. The genome of SARS-CoV-2 harbours 10 coding sequences (CDS), which encode polyprotein, surface glycoprotein, membrane glycoprotein and nucleocapsid phosphoprotein (Fig. 1).

The orf1ab polyprotein, encoded by the genome of SARS-CoV-2 virus isolated from the Japanese patients, has 24 nucleotide deletion. Genome deletion in the Japanese SARS-CoV-2 virus was also observed at the UTR locus and extreme 3'end of the genome. Phylogenetic analysis using complete genome sequence of SARS-CoV-2 revealed that its genome sequences are very similar (~90%) to the SARS-like CoVs. Analysis of receptor binding domains suggests that SARS-CoV-2 possibly uses angiotensin-converting enzyme-2 (ACE-2) as a cell receptor to infect the host[17].

Phylogenetic analysis suggests that although bats may act as the original reservoir for SARS-CoV-2, there is a possibility of yet another unidentified intermediate host, which was likely being sold at the seafood market in Wuhan before the outbreak[18]. When the first cases emerged in December 2019, bats were likely in hibernation, and if there was an intermediate host, it might have played a role in continuing local transmission of the virus. Hence, despite there being about 89 per cent similarity with the genomic sequence

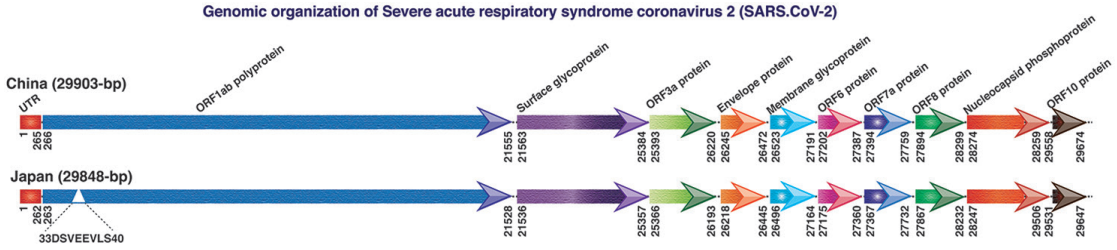

Fig. 1. Genomic organization of severe acute respiratory syndrome-coronavirus 2. ORF, open reading frame. *Source*: Refs 14, 16.

of bat-SL-CoVZC45 and bat-SL-CoVZXC21, there still remain doubts regarding its direct ancestors. It has been hypothesized that game animals, the consumption of which is culturally acceptable in China, may also represent a bridging host which instigated the spread of the virus from bats to human beings[19].

The ICMR (Indian Council of Medical Research)-National Institute of Virology (ICMR-NIV) has carried out extensive data collection from bats, which may provide critical insights for the ongoing spillover event. However, given the current state of the evidence, it remains difficult to say whether this virus will become entrenched, with endemic, seasonal or annual epidemics (like pandemic H1N1 influenza)[20,21], or it would extinguish like SARS. The knowledge base around developing robust signals which can predict or detect the emergence of viruses of this group, or their mutant forms, is still developing. The gaps in the current evidence leave us no choice but to prepare for combatting epidemic spillovers in the years ahead.

Speculations have been rife about the virus being artificially created, however, evidence accumulated by mining the genomic data of the emergent virus has failed to substantiate such claims of a human-modified origin[22,23]. The ambiguity regarding the transmission pathways and intermediate host(s) has further fueled conspiracy theories[24].

Epidemiology of COVID-19

Clusters of COVID-19, first reported from the Wuhan Metropolitan in People's Republic of China, in December 2019, have rapidly assumed a global form[25-28]. The data reported in the current review are based on the real-time updates available through the WHO Situation Reports and the Johns Hopkins University Center for Systems Science and Engineering (JHU CSSE) data visualization site[29] till February 28, 2020. All confidence intervals (CIs) reported here have been computed as the exact central CI of a proportion[30].

As of February 28, 2020, there have been 83,704 confirmed cases of COVID-19 globally, with 2,859 deaths[31]. Most cases (78,824 of 83,704; 0.9416 - 95% CI 0.94 to 0.9433) and deaths (2,790 of 2,859; 0.9758 95% CI 0.9696 to 0.9809) have been reported from mainland China. Of the 36,654 recovered cases reported, 36,268 (0.9895 95%CI 0.9884 to 0.9905) hailed from Mainland China. Outside of Mainland China, most cases were registered in South Korea (2,337 cases), on board the Diamond Princess (705) and Italy (655). The highest number of deaths outside China were reported from Iran (26 deaths), Italy (17 deaths) and South Korea (13 deaths)[31].

COVID-19 remains a highly infectious disease, with reproductive number (R_0) estimates ranging from 1.4 to 3.5. The early WHO estimate of R_0 was 1.4 to 2.5[10]. Preliminary studies, conducted at the beginning of the outbreak, reported higher estimates of R_0, in the range of 2.24-3.58[32]. Two recent estimates place it in the range of 2.0-3.1 and at 3.11 (95% CI 2.39-4.13)[33,34]. All the estimates of transmissibility indicate that self-sustaining human-to-human transmission is the only plausible explanation for the magnitude of the on-going outbreak[35]. The case fatality rate (CFR) of COVID-19 has been seen to be higher in China (2.1%) than outside (0.5%)[29]. Mortality in Wuhan was even higher at 4.9% while it was 3.1 per cent in the Hubei province. A significant proportion of deaths in China (26%) occurred in elderly people, aged over 60 yr. However, at this juncture, when the epidemic is still evolving, temptations to make policy decisions based on mortality data should be reined in[36].

On February 12, 2020, there was a spike in cases, with 14,840 cases reported overnight[29] (Fig. 2). This rapid escalation of numbers was attributed to the fact that in the WHO situation report-24[10], in addition to the laboratory-confirmed cases, clinically diagnosed cases, which accounted for 13,332 (90% of the cases reported overnight), were also added. Previously reported as probable or suspected cases, the introduction of the clinically confirmed case has been reflected in the numbers reported since February 12, 2020.

The high mortality observed in China, at the beginning of the outbreak, was only part of the whole story. The differences could be accounted by missed cases in the initial days, and the effectiveness of critical care protocols and aggressive management techniques utilized outside China[36]. In any case, as epidemiologic experience from outbreak research shows, as long as the epidemic is ongoing, CFR is likely to change, especially as case detection becomes more accurate, and less severe cases are also accounted for[37].

The mean incubation period was 5.2 days (95% CI 4.1-7.0 days) in a study covering 425 cases, and the median incubation period was 3.0 days (range 0-24 days) in another study based on 1,324 cases[25,38]. It might be possible that the single case, with an outlying incubation period of 24 days, was actually a second exposure, rather than a single

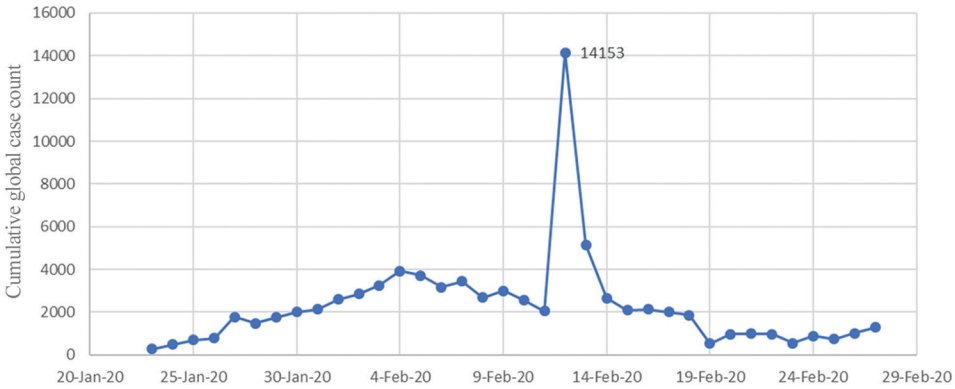

Fig. 2. Cumulative global case counts (February 29, 2020). *Source*: Ref. 29.

infection incubation period. This assertion, made at a WHO Press Conference (link of video: *https://youtu.be/a0Nu5MURFe4?t=2166*), has led WHO to reinforce the current recommendations regarding isolation and quarantine[38].

The incubation period for COVID-19 remains comparable to other recent epidemic viral diseases - SARS (2-7 days)[39] and MERS-CoV (2-14 days)[40], but it is slightly longer than swine flu (1-4 days) and seasonal influenza (1-4 days)[41]. A study looking at 88 cases of importation or travel-related spread estimated the mean incubation period to be 6.4 days (2.1-11.1 days)[42]. The estimates generally show a lot of variance based on sample size and epidemiologic profile of patients, and as more data become available, more accurate estimates are likely to emerge. As of February 28, 2020, COVID-19 has been reported from 58 countries and territories around the world, and one international conveyance, the Diamond Princess Cruise Ship[43].

The first four cases to be identified were linked to the Huanan (Southern China) Seafood Wholesale Market and were picked up by local healthcare facilities running the surveillance programme for 'pneumonia of unknown aetiology'[25,44]. The transmission chain analysis undertaken by WHO indicates that except for 16 cases for whom no clearly established epidemiological link could be identified, all other cases were associated with the ongoing transmission in China[10]. However, given the paucity of the evidence around this group of zoonotic viruses, it remains difficult to predict if the disease will eventually have a seasonal pattern. The four cases needed to set off the epidemic in China may not be representative, especially if the initial cases have been missed. The critical force of infection needed to establish a propagated epidemic is also unknown at this point, although it may be possible to model the effects based on assumptions. This also has direct bearing on the transmissibility of the disease, the specific estimate of which is yet to converge. In addition to the uncertainties around the agent and host factors associated with SARS-CoV-2, there are significant unknown factors about the environmental stability of the virus, and how effective fomites are in its transmission, especially in tropical countries. Bats have been implicated as reservoirs[45], and given their wide flight range in Asia, specific host control is difficult and unrealistic.

Case definitions

Case definitions being used currently are based on the WHO's interim guidance documents[46].

SARI - An acute respiratory infection with a history of fever or measured temperature >38°C, and cough, onset within 10 days and requiring hospitalization.

Surveillance case definitions for SARS-CoV-2 - A person with SARI with no other aetiologies with one of the following: (*i*) History of travel to Wuhan, Hubei Province, China, in the last 14 days; and (*ii*) Patient is a HCW who has been caring for patients with SARI of unknown aetiology.

Patient with acute respiratory illness and at least one of the following: (*i*) Close contact with a confirmed or probable case of SARS-CoV-2 in the 14 days before illness onset; and (*ii*) Worked or attended a health care facility in the 14 days before onset of symptoms where patients with hospital-associated SARS-CoV-2 infections were reported.

A sensitive and specific definition for community-based surveillance remains elusive. The indicators for referral and their outcome impact are yet to be ascertained systematically. Questions around

the need to quarantine children, minimum period of quarantine and its mental and socio-economic costs, relative to the current outbreak, remain poorly explored.

Clinical manifestations

The most common symptoms at illness onset are fever (99%), fatigue (70%), dry cough (60%), myalgia (44%) and dyspnoea[26,27,46]. Less common symptoms are headache, dizziness, diarrhoea, nausea and vomiting[47]. Symptoms such as pharyngeal pain, dyspnoea, dizziness, abdominal pain and anorexia are more likely to be present in patients with severe illnesses[27]. In addition, patients who are elderly, have underlying co-morbidities including hypertension, diabetes, cardiovascular disease and cerebrovascular disease are more likely to have adverse outcomes.

The most common laboratory abnormalities among patients hospitalized with COVID-19 are marked lymphopenia, prolonged prothrombin time, elevated lactate dehydrogenase and elevated D-dimer. These laboratory abnormalities are similar to the ones seen in SARS-CoV and MERS-CoV infections. Bilateral patchy shadows and ground-glass opacities are seen on chest imaging. The most common complications of COVID-19 are acute respiratory distress syndrome, arrhythmias, acute cardiac injury, shock and acute kidney injury[47-49]. The in-hospital transmission of the virus is very high with rates as high as 40 per cent. Of the hospitalized patients, the mortality rate is around 4-5 per cent[47-49]. There is adequate descriptive evidence in the published literature to develop a complete clinical picture of the disease. However, there is a need for planned constructions for providing multidisciplinary care in an integrated, single-service area. Further, designing and building these isolation wards, using humane and helpful esthetics, is also an essential step in empowering health systems to mount an adequate response to the surge in cases.

Diagnosis

Patients who satisfy clinical case definition and are epidemiologically linked to a history of travel from the city of Wuhan in the last 14 days, or have come in contact with a reverse transcription (RT)-PCR confirmed case or with a patient who is under investigation for SARS-COV-2 within the same period, are considered to be suffering from COVID-19[50]. As the asymptomatic transmission of the virus has been established[51,52], persons with epidemiological risk exposure should practice strict adherence to standard precautions and control of contact-based transmission.

Preferred clinical samples for establishing the laboratory confirmation of a suspected case include nasopharyngeal and oropharyngeal swabs collected using Dacron swabs, expectorated sputum, BAL fluid, endotracheal aspirate and tissue. The clinical sample is to be collected in a sterile container with normal saline which covers the sample; serum samples are collected in pairs in red cap vials (plain vials) with clot activators during both the acute phase and the convalescent phase of the illness[53]. For the transportation of samples to the laboratory, the swabs should be placed in a commercially available viral transport medium. The guidelines recommend triple packaging of the sample[54].

Appropriately filling the laboratory request form is vital once a clinical sample is collected from a suspected patient. Information regarding the patient's demographic details, date, time and anatomical site of the sample collection, tests required and the clinical history, symptoms, and risk factors need to be mentioned to mitigate risks of transmission if the sample turns out to be positive. The sample package must be labelled with UN3373 for Category B Biological Substances[55]. The receiving facility must be informed beforehand about the case and the transport of the sample.

The WHO recommends that the culture of the virus must be done in a BSL-3 laboratory and the RT-PCR be done in a BSL-2 laboratory[53,56]. While handling specimens of SARS-COV-2, one must ensure that neither the sample nor the HCW is contaminated to minimize any risks and to ensure accuracy of diagnosis. Isolation of SARS-COV-2 can be done in cells lines and the diagnosis has to be confirmed by RT-PCR. Charité Berlin, from Germany, was the first to develop the assay and standardize the protocol for real time RT-PCR[57]. The test detects the presence of three genes- *E, RdRp* and *N.* This is done in a step -wise process, with the three genes tested in sequence only if the one before is positive.

In laboratory-confirmed case of COVID-19, two samples collected from anatomically distinct sites or two samples collected from the same site during two different days of illness, are positive in two different assays or on repeat PCR[58]. The seroconversion of the disease is seen by detection of antibodies in convalescent phase serum, after a negative result in acute phase serum sample or a four-fold rise in antibody titres between the acute and convalescent phases. Seroconversion can be confirmed by ELISA or indirect fluorescent antibody test (IFA)[59].

Prevention of transmission

SARS-CoV-2 spreads *via* respiratory droplets and physical contact. It is essential to practice precautionary measures to prevent transmission. Standard precautions consist of hand hygiene, use of personal protective equipment (PPE) and respiratory and cough etiquettes. Hand hygiene should be done with alcohol-based hand rubs (ABHRs) containing 60-80 per cent ethanol. Hand washing following the correct steps with soap and water should suffice. Cloth towels should be avoided for drying hands and disposable tissue papers should be preferred. PPE consists of the medical masks or particulate respirators, face shields or goggles, gowns, gloves and shoe covers[60,61]. For droplet and contact-based transmission, medical masks or procedure masks with head straps should suffice. This should be worn before entering the patient area and should be taken off only after leaving the same. It is mandatory for persons in the community settings who are symptomatic, the patients who are in home care setups and suspected cases of COVID-19 with mild respiratory symptoms and healthcare workers (due to their elevated risk of exposure) need to wear medical masks at all times followed by hand hygiene and correct disposal[61]. Particulate respirators (NIOSH-certified N95, EU standard FFP2 or equivalent) should be used by HCWs involved in aerosol-generating procedures (AGPs). Face shields/goggles are to be used by all HCWs while performing AGPs. Long-sleeved, sterile, waterproof gowns, made of non-absorbable materials are to be worn. When gowns are not available, waterproof aprons should be used. Powder-free, latex gloves should be worn while handling infected patient's material. This should not be considered as a replacement of hand hygiene. Shoe covers should also be used in healthcare settings to prevent contamination of clothes. Respiratory and cough etiquettes should be adhered to: covering the nose and mouth while sneezing and coughing, using disposable tissue paper instead of cotton cloth, and if nothing else is available, using the flexed elbow, followed by appropriate hand hygiene.

Symptomatic patients in the community settings should be discouraged from congregating in public or crowded areas. Information, education and communication (IEC) messages should encourage self-deferral and self-containment for patients who are symptomatic. For home care, patients should be placed in a well-ventilated room. In healthcare settings, the patient should be placed in a negative pressure room.

Quarantine

According to WHO, "The International Health Regulations (IHR) are an international legal instrument that is binding on 194 countries across the globe, including all the Member States of WHO. Their aim is to help the international community prevent and respond to acute public health risks that have the potential to cross borders and threaten people worldwide"[62]. The IHR defines "the rights and obligations of countries to report public health events and establish a number of procedures that WHO must follow in its work to uphold global public health security"[62]. In line with the principles outlined in IHR, the Ministry of Health and Family Welfare, Government of India, has issued travel advisories from time to time, considering the surge in cases of COVID-19 in China. The travel advisory states, "Indian travellers are hereby advised to refrain from travelling to China. Existing visas (including eVisa already issued) are no longer valid for any foreign national travelling from China. People travelling to China henceforth will be quarantined on return"[63].

The medium- and long term impact of such travel bans remain to be seen, but modelling studies suggest that in the short-term, these are unlikely to have meaningful impact on global transmission of SARS-CoV-2, unless sustained 90 per cent travel restrictions are implemented in combination with more than 50 per cent reduction in local transmission[64]. Such bans may only provide a symbolic shield unless the ongoing outbreak is staunched. Ethical concerns of imposing such travel bans have also been questioned[65].

Diamond Princess, a cruise ship docked off Yokohama in Japan, was quarantined for two weeks after a tourist who disembarked at Hong Kong tested positive for SARS-CoV-2[66,67]. The cruise ship had over 3,700 passengers and crew, of whom 705 were tested positive for SARS-CoV-2, making it the second largest site of outbreak outside China at one point[68].

On January 23, 2020, the Government of the People's Republic of China imposed a lockdown on Wuhan to quarantine and prevent the spread of the disease[69]. This was a drastic public health measure[65,70]. While the benefits of such a move remain to be seen, the long-lasting negative impacts of such a measure should not be underplayed[71]. Such drastic measures can lead to social, psychological and economic stressors on the whole population, leading to long-lasting adverse health outcomes[72]. Instead of coercive top-down quarantine approaches, which are driven by the authorities,

community and civil-society led self-quarantine and self-monitoring could emerge as more sustainable and implementable strategies in a protracted pandemic like COVID-19[73].

Therapy

Like SARS, SARS-CoV-2 also uses the ACE2 receptor for entry into the cell[74]. This potentially opens up the possibility of using the same therapeutic strategies that were effective in blocking SARS. Currently, there are no definitive, proven treatments, although multiple pharmacological options are being explored. A spate of clinical trials has been initiated in the wake of the outbreak. Some of the trials which have initiated recruitment of patients are looking at the effectiveness of using washed microbiota transplantation[75], remdesivir[76,77], ritonavir-lopinavir combination[78], vitamin C infusion[79], darunavir and cobicistat[80], hydroxychloroquine for pneumonia[81], umifenovir[82] and traditional Chinese medicines[83], to name a few options. The Chinese guidelines of using α-interferon combined with the repurposed lopinavir/ritonavir combination (*Kaletra*) have also been used widely for the treatment of hospitalized patients[84]. Improvement in the first US patient of COVID-19 after treatment with remdesivir[85], and subsequent experience of clinical response in animal models has generated interest in the agent[86].

Treatment of COVID-19 is mostly supportive based on the organ systems affected. The setting of patient management, *i.e.,* intensive care unit or high dependency unit versus general wards, should be decided early on in the course of the disease, considering the high mortality rate among hospitalized patients and the facilities available for containment of infection. Published evidence from preliminary therapeutic experiences indicated that patients requiring hospitalization were managed with broad spectrum antibacterial antibiotics and glucocorticoids[26]. The treatment course may warrant management of respiratory failure with non-invasive ventilation, mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Additional intensive care therapies such as vasopressors and renal replacement therapy may be required while managing SARS-COV-2 infections.

Vaccine

The WHO R&D blueprint and its Working Group conveyed an informal consultation on prioritization of vaccine candidates against SARS-CoV-2 in Geneva on January 30, 2020[87,88] and identified at least five leading candidate vaccines for SARS-CoV-2[89].

As on February 13, 2020, the WHO expert group did not release a prioritization list, nor did the US Clinical Trials registry show any registered clinical trials on vaccines against SARS-COV-2. Among the different candidates in the pipeline, nucleic acids and viral vectored vaccine are being tried. INO-4800 is one of the leading candidates developed by Inovio Pharmaceuticals and Beijing Advaccine Biotechnology based on a DNA plasmid vaccine Electroporation device. Inovio aims to begin phase I clinical trial in the US simultaneously with Beijing Advaccine in China[90]. Clover Biopharmaceuticals is developing a recombinant subunit vaccine based on the trimeric S protein (S-Trimer)[91]. All the vaccine studies are currently in the preclinical phase.

WHO at the core of global response

WHO and the Global Research Collaboration for Infectious Disease Preparedness hosted a two-day meeting at WHO Headquarters in Geneva on February 11-12, 2020, which brought together major research funders and scientists from across the world "to assess the current level of knowledge about the new COVID-19 disease, identify gaps, and work together to accelerate and fund priority research needed to help stop this outbreak and prepare for any future outbreaks"[92]. A Global Surveillance for human infection for COVID-19 has been established by WHO, and globally, 16 laboratories have been identified for confirmatory referral testing. In South-East Asia Region, two laboratories in Thailand - NIH Nonthaburi and Armed Forces Research Institute of Medical Science Bangkok, and one in India - ICMR-NIV, have been identified for referral testing[93].

The WHO has developed interim guidance documents for laboratory diagnosis[53,94], home care for patients with suspected novel CoV[95], advice on the use of masks during home care and in healthcare settings in the context of COVID-19 outbreak[61], clinical management, infection prevention and control in healthcare settings[96], risk communication and community engagement, and global surveillance for human infection with COVID-19[97]. WHO has also developed an online course to provide general introduction to emerging respiratory viruses, including COVID-19, meant for people at large as well as healthcare workers[98]. For quickly setting up emergency isolation and quarantine facilities, WHO has also prepared a disease commodity package that includes an essential list of biomedical equipment,

medicines and supplies necessary to care for patients with COVID-19[99].

The 2003 SARS outbreak was hypothesized to have originated from a mutated coronavirus from small carnivorous animals sold in a live animal market in Guangdong, China[100], the likely source(s) potentially including masked palm civets, raccoon dogs and Chinese ferret badgers[101-103]. Similarly, the 2012 MERS-CoV outbreak was found to have originated from dromedary camels[1,104]. In anticipation that COVID-19 cases might be linked to the exposure to a live wild animal market, the Chinese Government has banned wild animal business on January 21, 2020[19]. These spillover events further highlight the importance of adopting the One Health framework in approaching the pre-emption and prevention of novel and emerging dangerous pathogens[105,106].

HCWs are always exposed to an elevated risk of exposure to infectious diseases and may contribute to the morbidity and mortality, as seen in previous outbreaks of Nipah and Ebola Virus Disease[107-111]. Transmission of infection from asymptomatic patients has been a major concern as exemplified in the incident where a patient undergoing surgery infected 14 HCWs before the onset of fever[112]. An early case series identified that hospital-associated transmission infected 40 healthcare workers, and 17 hospitalized patients, who represented 29 and 12 per cent of all cases in the series, respectively[26]. In addition to the infection threat posed by SARS-CoV-2, the mental health issues of dealing with a lethal infectious disease have also been substantial, with generalized anxiety disorders, depression, poor sleep emerging as major issues[113,114].

In the aftermath of the SARS-CoV-2 outbreak, many countries, including India, initiated the travel bans and visa suspensions, with subsequent reports of incidents of stigma and discrimination against Asians, or Asian-appearing people. This phenomenon has been observed globally[115]. In response, WHO, in collaboration with the International Federation of Red Cross and Red Crescent Societies and United Nations Children's Fund, has developed a guide for preventing and addressing social stigma[116]. In addition, in the statement released by the second meeting of the IHR (2005) Emergency Committee for the Novel Coronavirus outbreak, WHO has cautioned Member States against engendering any policies which promote stigma and discrimination: "Countries are cautioned against actions that promote stigma or discrimination, in line with the principles of Article 3 of the IHR"[9].

Summary

There have been several lessons to glean from the global response to the SARS-COV-2 threat. Most responses have been reactive, with little preparedness investment in health systems and through community engagement and empowerment[117]. However, the emphasis on data sharing, the rapid development and distribution of interim guidance documents by WHO and open-access pre-print sharing of rapidly emerging evidence reflect a paradigmatic shift in providing a data-driven global-epidemic response[118]. This unprecedented effort at providing information to global practitioners has led to a more concerted response, helping to mount international, multi-country, mitigatory actions[119]. However, there have been elements of imposed travel restrictions and red-lining of affected areas, the long-term impacts of which, on sectors such as economy, agriculture and mental health remain to be seen. In this run to devise technological and medical solutions to yet another PHEIC, we have not focussed on opportunities to strengthen health systems and community resilience, through people-centric approaches.

The original source of the outbreak, the intermediate host, an effective treatment regimen, tools for early diagnosis in asymptomatic patients and tools to predict emergence of novel pathogens all remain elusive. Clinical trials have begun to identify vaccines and effective and safe treatment regimens, but efforts to identify drugs that can be repurposed and used, off-label, remain limited. Further, epidemiologic determinants and reservoirs which are likely responsible for the recent explosive case counts in Italy and Iran are yet to be identified.

The response mounted to the COVID-19 threat has largely been reactive. The lack of a reliable Early Warning, Alert and Response System, inability to mount transparent containment measures, lack of community engagement for self-deferral and isolation, and overdependence on quarantining measures have exposed the fissures in the ability of health systems across the world. It has clearly demonstrated the weak preparedness against emerging and re-emerging dangerous pathogens across the world. Despite the enforcement of the IHR (2005), strengthening international capacity to respond to PHEICs remains a hurdle. Further, initiation of militarized control efforts, discriminatory travel restrictions and poor coordination

and planning, has shown the limited ability to handle an outbreak with pandemic potential across the world.

The infectious disease threats of our times are far from over, and if these are to be contained with lower magnitudes of loss to human life and economy, we need to invest in building up people-centric health systems, which pre-empt and prevent, rather than work in reactive, feedback loops driven by the burden of human misery[120,121].

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