



## Editorial

### The enigmatic COVID-19 pandemic

The world is now completing eight months of the unexpected onslaught by a novel coronavirus - SARS-CoV-2 leading to COVID-19 pandemic. A <140 nm sized virus has overwhelmed even the most resource-rich, powerful and technologically advanced nations. Despite global efforts to contain it, the pandemic continues to persist, accelerate and cause humongous mortality, morbidity and unimaginable economic loss. Over 23 million cases in 216 countries/territories and 806,410 deaths have been reported to the World Health Organization (WHO)<sup>1</sup> as on August 24, 2020.

With an estimated loss of US\$ 375 billion to the American economy alone every month<sup>2</sup>, this virus has virtually paralyzed the global economic activities. The 'new normal' way of life is being silently accepted. It now appears that pandemics shall always be imminent. These cannot be prevented but perhaps could be responded better only with strategic preparedness and effective implementation of accurate, evidence-based, practical and validated affordable interventions.

Implementation of efficient public health actions is possible on the foundations of sound scientific knowledge of the characteristics of SARS-CoV-2. Despite extensive research on all aspects of COVID-19 pandemic, the world is still struggling with the origin of the virus, public health implications of the mutations in the viral genome, availability of a diagnostic test with better sensitivity and specificity, understanding the immune response to the virus, its pathobiology and clinical spectrum, and availability of safe and efficacious specific antiviral drugs and a vaccine. These unknowns have made it an enigmatic pandemic till now.

Origin of the virus continues to be a mystery. SARS-CoV-2 is believed to have originated from an animal reservoir. Experimental infections have shown several species of animals that were permissive, while a

few were resistant<sup>3</sup>. However, their role in the ongoing pandemic is not clear. There is a distinct possibility of bats being the natural reservoir and possibly pangolins serving as the intermediate host<sup>4</sup>. Genetically, pangolin-CoV is 91.02 per cent identical to SARS-CoV-2. High similarity between the whole genome sequence of SARS-CoV-2 and the BatCoV, RaTG13 strain, (90.55%) has been observed<sup>4</sup>. Convincing evidence demonstrating animal-to-human transmission or sustained animal-to-animal transmission of SARS-CoV-2 is yet awaited.

SARS-CoV-2 virus shows evolutionary divergence similar to other RNA viruses<sup>5</sup>. Mutations are a natural unstoppable phenomenon in this virus leading to emergence of several clades with geographical propensity. The role of quasispecies resulting from these mutations remains unclear and needs further elucidation. The claim that D614G mutation in the spike protein of SARS-CoV-2 can increase its infectivity needs further exploration<sup>6</sup>.

The Indian SARS-CoV-2 viruses could be classified under all the globally known circulating clades *i.e.* G, O, V, S and L with potential origin mainly from Oceania, Europe, Middle East and South Asia regions<sup>7</sup>. Several studies are required to fully unravel the genetic diversity and understand implications for epidemiological studies, control strategies and development of diagnostics and immunoprophylactic agents.

The rapid spread of COVID-19 in communities across the globe, and resurgence (second waves) suggest the possible role of asymptomatic persons in its transmission. If strong supportive evidence becomes available, it may advocate continued use of masks and the use of other public health measures<sup>8</sup>. During early phase of COVID-19 pandemic, it was presumed to be a non-relapsing disease. New studies suggest possibility of repeated virologically confirmed

infections<sup>9</sup>. Confirmation of reactivation or reinfection and their epidemiological importance are awaited. Serosurveillance is generally a sensitive tool to determine the extent of infection and immunity in the general population. Only a few field-based studies have generated serosurveillance data but with inconclusive inferences. A recent seroprevalence study showed that most of the population of Geneva, Switzerland, remained uninfected during this wave of the pandemic, despite the high prevalence of COVID-19 in the region<sup>10</sup>. Such studies raise red flags on continuous susceptibility of the population to COVID-19 and inability of the virus to produce widespread immunity. It may contribute to a 'second wave' of cases. The role of reduced use of non-pharmaceutical interventions in facilitating a second wave as community engagement wanes, requires further investigation<sup>11</sup>.

SARS-CoV-2 has caused huge mortality among the elderly. In Europe, 90 per cent of the deaths occurred in Italy, Spain and France, 95 per cent of these occurred in elderly above 60 yr, most of whom had at least one underlying comorbidity<sup>12</sup>. Undoubtedly, almost one-third of the population of these three countries is over 65 yr of age, and their mortality is not comparable to similar populations in developing countries namely India. Unusual affliction and mortality caused by this virus in different age groups and in different countries making elderly and those with comorbidities highly vulnerable are still being investigated to facilitate development of age-specific validated prevention, prophylactic and therapeutic protocols.

As the pandemic is progressing, several extrapulmonary presentations of COVID-19 are becoming obvious. These include thrombosis, myocardial and renal damage, injury to gastrointestinal system, liver and central nervous system<sup>13</sup>. Studies are needed to ascertain the extent of spectrum of clinical manifestations to assist in development of specific protocols for clinical diagnosis and case management. Children were believed to be least affected by SARS-CoV-2. The absence of typical respiratory features in young children is being observed frequently<sup>14</sup>. Complications in the form of a multisystem inflammatory syndrome are being increasingly noted. In these children, the virus could not be isolated from the respiratory tract. Clinical features pertained to cardiovascular and gastrointestinal systems have been reported. The role of oral route in virus transmission in children is becoming a possibility and needs investigations. This is a new dimension of disease

epidemiology with uncertain impact on the progression of the pandemic<sup>14</sup>.

Four technologies are currently being utilized for laboratory support to COVID-19<sup>15</sup>. These are real-time reverse transcription-polymerase chain reaction (RT-qPCR) and loop-mediated isothermal amplification for the detection of viral RNA, and lateral flow assays and ELISA for both antigen and antibody detection. The gold standard continues to be RT-qPCR. This test is valuable at the early stages of infection, when the individual may not be symptomatic. However, it has limitations of low stability, false negativity and long processing time<sup>16</sup>. Additional research is needed to determine the impact of false-negative RT-qPCR results; since false negativity facilitates continuous transmission of the virus in the community. Availability of an ideal gold standard diagnostic test with sensitivity and specificity exceeding 95 per cent remains elusive. Among the alternative diagnostic methods artificial intelligence (AI) algorithms integrated with observations on chest computerized tomography (CT) findings and clinical symptoms have the potential to rapidly diagnose COVID-19<sup>17</sup>. This calls for further studies, international validation and improved access to CT infrastructure and AI skills in COVID care centres.

No new drug has been found to have specific efficacy in treating cases with COVID-19. Several drugs are being repurposed. Remdesivir, favipiravir, lopinavir/ritonavir either alone or in combination with ribavirin, hydroxychloroquine plus azithromycin, dexamethasone, teicoplanin, ivermectin, interferon and monoclonal and polyclonal antibodies have been approved by the regulatory authorities in different countries for prophylactic or emergency therapeutic use<sup>18</sup>. As per an earlier systematic review, convalescent plasma therapy in COVID-19 seems to be safe, clinically effective, and reduces mortality<sup>19</sup>. In India, even a plasma bank has been established<sup>20</sup>. Nevertheless, making convalescent plasma accessible to all patients is a huge challenge.

All viral infections attract comprehensive immune response comprising humoral and cellular components. Although several studies have suggested activation of these responses along with excessive inflammatory response (cytokine storm) which culminate in pathological tissue damages in COVID-19, yet there is a limited understanding of immune response and the pathways that trigger it<sup>21</sup>. Clinical trials demonstrate immunogenicity and protection for a limited period. The Ad5 vectored

COVID-19 vaccine showed humoral responses against SARS-CoV-2 that peaked at day 28 post-vaccination in healthy adults, and rapid specific T-cell responses were also noted from day 14 post-vaccination<sup>22</sup>. The definition of the protective immune mechanism and duration of persistence of protective immunity remain elusive till date. The uncertainty of long-term immune response has potential implications for the efficacy of vaccines. The real impact of vaccines on this pandemic will become evident only once it has been widely in use for a few months in different populations. As of now, vaccine is being considered as the ultimate intervention to contain the pandemic<sup>23</sup>. The global race to make it available to the world has been accelerated. Currently, there are about 165 different candidate vaccines for COVID-19 being developed around the world and several of these are in different phases of clinical trials<sup>24</sup>. The main types of vaccines include: replicating and non-replicating viral vector-based vaccines, whole virus-based (inactivated or attenuated), nucleic acid-based (DNA and RNA), recombinant protein, peptide-based vaccines and virus-like particles. To date, only one adenoviral vector-based vaccine has been approved by the Russian regulatory authorities<sup>25</sup>. The global community awaits data from phase 3 clinical trial to assure itself of its safety and efficacy.

Three vaccine candidates (inactivated, DNA based recombinant and ChAdOx1 nCoV-19 vaccine consisting of the replication-deficient simian adenovirus vector ChAdOx) are currently in early phases of human trials in India<sup>26</sup>. Commercial production of COVID-19 vaccine and possible imports are likely to commence by the end of 2020. Global procurement and distribution of vaccine to ensure its universal access has been planned by the WHO, Global Alliance for Vaccines and Immunizations (GAVI) and Coalition for Epidemic Preparedness Innovations<sup>27</sup>. India has developed a blueprint for efficient deployment of the vaccine, supported by IT-based vaccine tracker. Immunizing the entire population, prioritizing high risk segments, assuring quality in logistics and undertaking post-vaccination surveillance for adverse effects and impact on disease burden shall be huge challenges for any health system. Among the non-specific approaches, BCG vaccine is being incriminated to regulate cytokines secretions for early protection against SARS-CoV-2. Further studies are needed to understand the role of the BCG vaccine<sup>28</sup>.

With a few exceptions, a lockdown was imposed in almost all the countries to promote social distancing and

preparing health system capacity to respond to pandemic. In the absence of specific antiviral drugs or vaccines, non-pharmaceutical interventions undertaken by the communities assumed critical importance in curtailing viral transmission. Community engagement, especially of poor and illiterate is always difficult to ensure<sup>29</sup>.

The COVID-19 pandemic has attracted the entire focus and efforts of the health system. Usual health services to communities have become restricted because health facilities are overwhelmed with COVID-19 patients. People are also apprehensive about visiting health institutions for fear of contracting COVID-19. Important components of health services that have suffered most include health needs of children, women, elderly with non-communicable diseases and management of other therapies (e.g. cancers, tuberculosis and HIV) and health emergencies<sup>30</sup>. The pandemic has pushed back progress made under the Millennium Development Goals and is hampering achievement of ambitious UN Sustainable Development Goals. It is still not clear as to how the global community will make up for the pandemic-induced setback to its critical operations of major disease elimination programmes such as for tuberculosis<sup>30</sup>.

Science has so far answered fewer questions on this pandemic than numerous ones that have emerged. Unknowns exceed known. Combating the pandemic shall require complete understanding of the virus, its pathogenesis, epidemiological and clinical dimensions, and availability of safe and efficacious therapeutic and prophylactic tools especially for vulnerable and high risk populations. Answers to these research questions may get us closer to having reliable and affordable pharmaceutical and non-pharmaceutical interventions to address global challenges posed by this powerful, versatile and enigmatic virus, thereby hopefully restoring normalcy in the world.

**Conflicts of Interest:** None.

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