COVID 19: A Review outbreak and the critical role of pathology during corona virus disease 2019 (COVID-19) and other viral outbreaks

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ABSTRACT:
Coronavirus disease 2019, abbreviated to COVID-19 and sustained by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the latest biological hazard to assume the relevance of insidious world- wide threat. One obvious question that is now engaging the minds of many scientists and healthcare professionals is whether and eventually how laboratory medicine could efficiently contribute to counteract this and other (future) viral outbreaks. Despite there being evidence that laboratory tests are vital throughout many clinical pathways, there are at least three major areas where *in vitro* diagnostics can also provide essential contributions to diagnostic reasoning and managed care of patients with suspected or confirmed SARS-CoV-2 infection. These include etiological diagnosis, patient monitoring, as well as epidemiologic surveillance. Nonetheless, some structural and practical aspects may generate substantial hurdles in providing timely and efficient response to this infectious emergency, which basically include inadequate (insufficient) environment and shortage of technical and human resources for facing enhanced volume of tests on many infected patients, some of whom are with severe disease. Some proactive and reactive strategies may hence be identified to confront this serious healthcare challenge, which entail major investments on conventional laboratory resources, reinforcement of regional networks of clinical laboratories, installation of mobile laboratories, as well as being proactive in establishing laboratory emergency plans.

Keywords: coronavirus; COVID-19; laboratory medicine; laboratory tests.

INTRODUCTION:
The impact of the virus is more among advanced aged ones and people with comorbidities, whereas it shows less impact among adults. Luckily until this point, infants and child are really infected without any deaths but the future knowledge of this virus is obscure. Most of the infected individuals are asymptomatic initially but it might be advanced to pneumonia, acute respiratory distress syndrome (ARDS) and multi organ dysfunction and its mortality rate is evaluated to go from 2 to 3%. Diagnosis involves exclusive molecular tests That were used to examine the respiratory secretions and usual or poor WBC count with more C-reactive protein (CRP) were observed in common laboratory findings. asymptomatic individuals or with mild infection shows abnormal CT chest scan. Basically steady and supportive treatment is required and the job of antivirals is yet to be set up. Strict infection control measures at hospitals and home separation of suspicious individuals with infection was done for the prevention of virus transmission because this COVID transmits more quicker than its two progenitors SARS-CoV and MERS-CoV but has less

mortality. The worldwide impact of this novel pandemic is yet unsure. [1]
Coronavirus disease 2019, abbreviated to COVID-19, is the latest biological hazard to assume the relevance of insidious worldwide threat. The responsible pathogen is a virus belonging to the Coronavirus family, finally defined as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) for high sequence identity (i.e. up to 80%) with the homologous virus which caused the SARS outbreak in 2003 (i.e. SARS-CoV) [1]. At the time of writing this article, SARS-CoV-2 has already infected over 115,000 people in more than 115 different countries, causing nearly 4000 related deaths [2]. Structural analysis shows that SARS-CoV-2 probably derives from a bat SARS-like coronavirus, which has been then transmitted to humans after emergence of mutations in the spike glycoprotein (protein S) and nucleocapsid N protein [3]. The mutation that occurred in the former protein is especially important, whereby viral spike glycoprotein mediates the entrance of the virus into the cell through cell receptor binding and membrane

fusion. On the other hand, the N protein regulates the process of viral replication, thus influencing transcription and assembly. altogether, mutations in these two proteins would then explain the unique characteristics of SARS-CoV-2 compared to the original SARS-CoV,

i.e. enhanced infectious potency in humans, combined with relatively mitigated pathogenicity. In support of the former aspect, the effective reproductive number (R; i.e. the average number of secondary cases per infectious case) has been estimated at 2.6 (credibility interval, 2.1–5.1) for SARS-CoV-2 compared to 1.1 for SARS-CoV, whilst the doubling time of the epidemic has also been calculated as

days (comprised between 1.0 and 7.7 days) compared to approximately 16 days for SARS-CoV [4]. As concerns the mortality, the World Health Organization (WHO) provides daily estimates, which are obviously in progress due to the ongoing epidemics, the last of which attests that the death rate of COVID-19 is 3.9% in China (3123/80,904) and □2.4% abroad (686/28,673; e.g. 5.0% in Italy, 366/7375), compared to □9.6% (774/8098) for SARS and 34.4% for Middle East respiratory syndrome (MERS; 866/2519). Between 8 and 15% (depending on the geographical setting and individual characteristics) of all SARS-CoV-2 positive cases can be classified as severe or necessitating intensive care unit (ICU) admission. Although the mortality rate of COVID-19 seems

hence for now lower than that of SARS or MERS, the number of patients needing urgent critical care is remarkably larger than that of the two previous viral outbreaks, and may foster the collapse of local health care.

This is not the first case, nor it will probably be the last that a viral outbreak has become a public health concern, though COVID-19 displays distinctive features compared to previous coronavirus epidemics such as SARS and MERS, in that the pathogenicity of SARS-CoV-2 seems for now lower and the incubation, longer (usually up to 2 weeks), so the risk of contagion is magnified and the number of cases (and deaths) grows exponentially [5, 6]. This is not really surprising if we look at the future mortality projection of the WHO between the years 2016 and 2060 [7], whereby the number of deaths for lower respiratory infections is expected to increase by over 50% during the next 40 years (i.e. from 2.96 to 4.62 million deaths per year). This notable increase in mortality for pneumonia and other lower respiratory infections predictably encompasses also those caused by coronaviruses, as interstitial pneumonia evolving toward acute respiratory distress syndrome (ARDS) in 10–15% of cases – is the most frequent and severe complication of SARS-CoV-2, which can then be followed by the onset of viral sepsis, disseminated intravascular coagulation (DIC) and multiorgan failure (MOF) [8, 9].

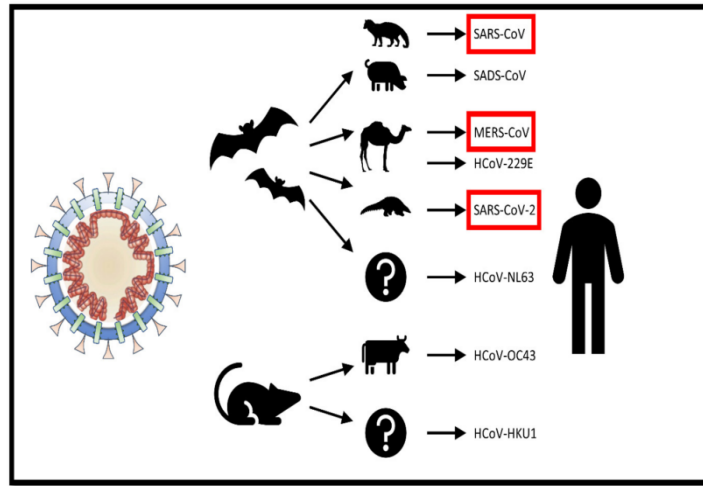**Figure 1: It was presumed that covid 19 spreads from consumption of bat's meat.**

Figure 2: Further, it was hypothesized that the transmission was from bats to animals and animals to humans.

Figure 3: It was thought that Pengulia was sold in Wuhan sea food market of china , which could be the source for covid 19.

Figure 4: According to Chinese researchers, Pengulia was used as a traditional Chinese medicine for nose bleeds, headache, heart diseases and cancer etc. So DON'T BLAME THEM FOR AS A SOURCE OF INFECTION.

Transmission Cycle of SARS CoV 2

Bat Coronavirus
(Miniopterus bat coronavirus HKU8)

Direct contact

Intermediate host
Manis pentadactyla

Direct contact

Human to human
transmission

Droplet spread/
Direct contact

Incidental host
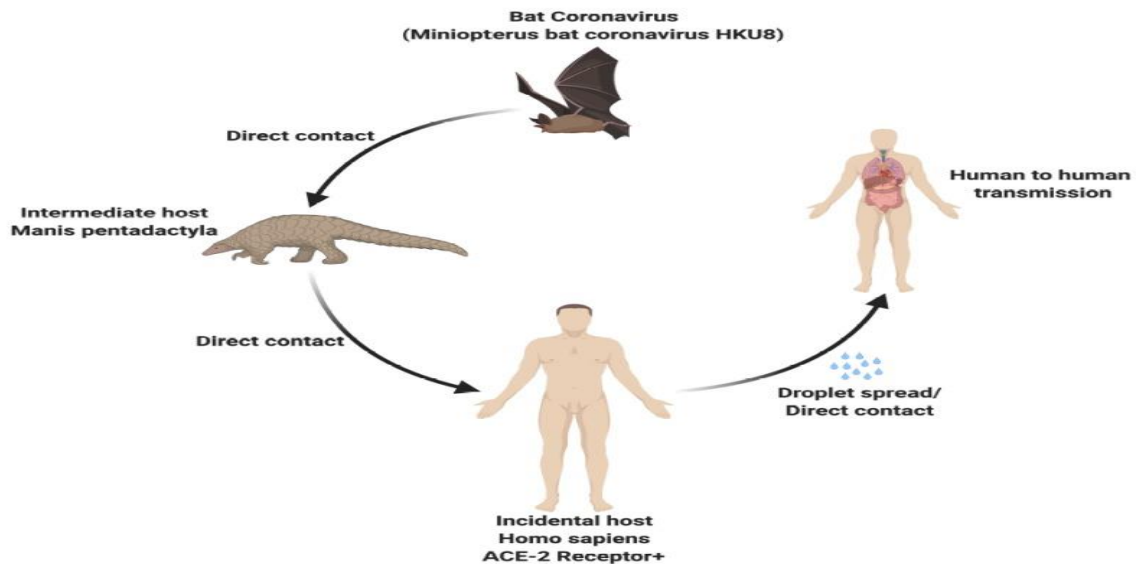**Homo sapiens**
ACE-2 Receptor+

Figure 5: Later on it was confirmed that out of various species of bat , the Miniopterus HKU8 is the intermediate host to pengulia and consumption of this could be the direct source of infection . That's why social distancing is important to avoid transmission.

TRANSMISSION:

Maintaining close contact and droplets of infected persons are the major route of transmission in case of SARS- CoV where as minute chances of transmission can also occur through sweat, stool, urine, and respiratory secretions. Upon entering the virus in the human body its primary targets are enterocytes and pneumocytes, where thereby establishes a cycle of infection and replication. CoV has other target sites which includes epithelial renal tubules, tubular epithelial cells of kidney, immune cells, and cerebral neuronal cells. [10,11]
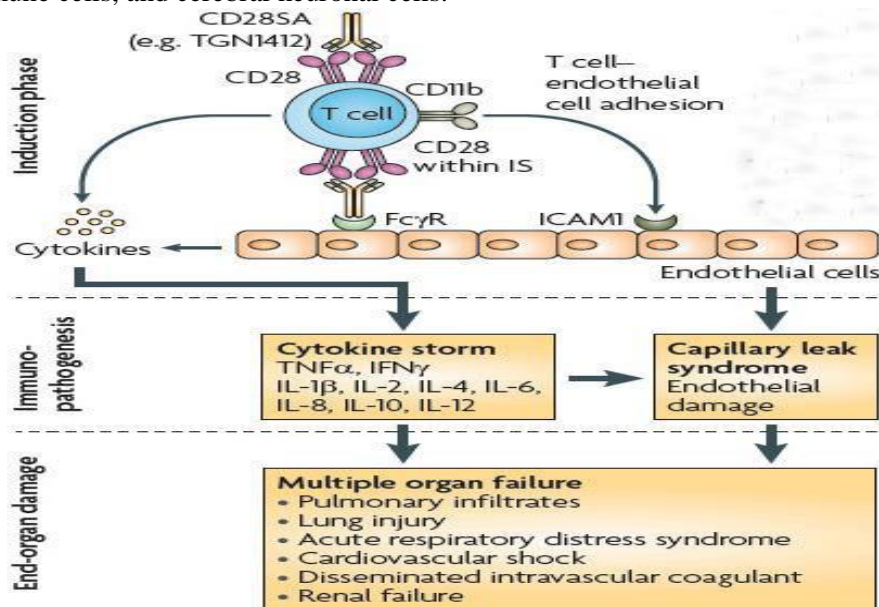

Figure 6: The protagonist of this storm is (IL-6). IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. Although the main role played by IL-6 is proinflammatory, it can also have anti-inflammatory effects. It is also implicated into the pathogenesis of the cytokine release syndrome (CRS) that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction.
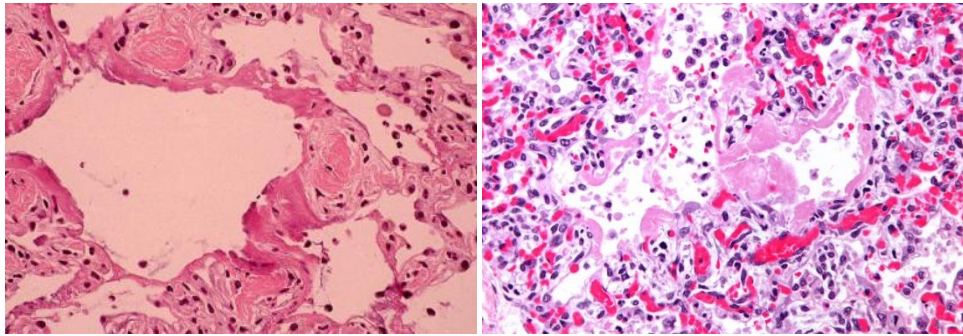
Figure 7 & 8 : Tian et al- reported histopathological data obtained on the lungs of two patients who underwent lung lobectomies for adenocarcinoma. Apart from the tumors, lungs of both 'accidental' cases showed edema and proteinaceous exudates as large protein globules, vascular congestion, inflammatory clusters of fibrinoid material and multinucleated giant cells and hyperplasia of pneumocytes.

Etiological Diagnosis:

The etiological diagnosis of SARS-CoV-2 is the first and most obvious setting where laboratory diagnostics plays an essential role. Both the WHO and the US Centers for Disease Control and Prevention (CDC), along with other national and international scientific organizations, have timely released detailed information for in house development of reverse transcription polymerase chain reaction (RT-PCR) tests, which have hence been straight for wardly implemented by many reference laboratories worldwide [12], and are now undergoing clearance by many regulatory agencies. A crucial aspect that shall be underscored here is the need for developing rapid and effective communication among distant laboratories and research centers. The enormous diffusion of this virus, with positive cases identified in over 115 worldwide

countries and in almost every continent, highlights the vital need for developing diagnostic workflows even in the lack of physical sources of viral genomic nucleic acid, whereby the chance that outbreaks will spread to distant countries and become pandemic diseases is increasingly more likely, as recently demonstrated by COVID-19. Notably, the willingness of Chinese scientists to rapidly share genomic information has enabled to develop RT-PCR assays even before SARS-CoV-2 started to circulate in many countries, thus providing a timely and effective diagnostic response to a probable health crisis [13]. Nevertheless, as the ample volume of tests needed to face a large outbreak such as that sustained by SARS-CoV-2 overcomes the through put capacities of single facilities, whilst shipment of samples toward reference laboratories is an important cause of diagnostic delays, the

availability of commercial diagnostic kits in peripheral centers shall be part of the strategy for early and accurate identification of the largest possible number of infected patients. Despite the obvious emergency to promptly develop efficient diagnostic tools, a thorough analytical and clinical validation of commercial RT-PCR tests before their introduction into the market and usage in clinical laboratories remains indispensable. Otherwise, the risk of generating false-negative (or positive) test results may undermine the huge efforts made by healthcare authorities for containing the outbreak. This risk is tangible, as clearly highlighted by a recent publication showing that some patients with clinically evident SARS-CoV-2 disease had initial negative RT-PCR test results, which then turned to be positive at a later stage [14]. Availability of licensed diagnostic kits and uniformity of testing protocols across different nations are other important aspects for providing a clear and reliable epidemiologic picture. Despite the communication channels with China remaining opened all around the world for weeks after the initial outbreak in Wuhan, public governments and national health authorities have set rather heterogeneous testing protocols, occasionally too ample, and often too narrow.

Patient monitoring

The second essential contribution that laboratory medicine could provide in the diagnostics of 2019-nCoV infection encompasses staging, prognostication and therapeutic monitoring of COVID-19. Not only RT-PCR tests will be vital for verifying the course of the infection, as well as the possible presence and extent of viremia, but many other laboratory tests may help assessing disease severity and predicting the risk of evolution toward ARDS, DIC and/ or MOF. A systematic literature review, which has recently been published [14], has

highlighted the most important abnormalities observed in patients with COVID-19, mostly encompassing lymphopenia, increased values of C reactive protein (CRP), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR) and D-dimer, along with diminished concentration of serum albumin. Even more importantly, a number of hematological parameters were also found to predict progression toward severe or critical forms of COVID-19, including leukocytosis, neutrophilia and lymphopenia. In addition, an innovative parameter called MDW (monocyte volume distribution width – DxH 900 hematology analyzer, Beckman Coulter, Brea, CA, USA) was found to be significantly increased in all COVID-19 patients, especially those with worst clinical conditions (personal data, not shown). For prognostication purposes, also increased values of LDH, aspartate amino transferase (AST), alanine amino transferase (ALT), total bilirubin, creatinine, cardiac troponins, D-dimer, prothrombin time (PT), procalcitonin and CRP, together with decreased values of serum albumin, have been found of value. The importance of hemostasis tests has then been emphasized in another study [15], including 94 patients with COVID-19, and showing that PT and D-dimer are significant predictors of disease severity. This finding not only supports the pivotal role of hemostasis testing in severe and/or systemic infectious diseases [16], but also confirms that consumption (disseminated)

coagulopathy may be one of the most severe complications of patients with COVID-19. These figures have also been confirmed in a subsequent study, which pooled data of 1099 patients with laboratory confirmed SARS-CoV-2 infection from 552 hospitals in 30 Chinese territories [17], demonstrating that COVID-19 patients have lymphopenia (83.2%), thrombocytopenia (36.2%), increased values of CRP (60.7%), LDH (41.0%),AST (22.2%), ALT (21.3%) and D-dimer (43.2%). In keeping with previous findings, the most predictive parameters of severe COVID-19 disease were lymphopenia (96.1% vs. 80.4%; odds ratio [OR], 5.96; 95% confidence interval [CI], 2.58–13.75), thrombocytopenia (57.7% vs. 31.6%; OR, 2.96; 95% CI, 2.07–4.22), leukocytosis (11.4% vs. 4.8%; OR, 2.54; 95% CI, 1.43–4.52), increased values of CRP (81.5% vs. 56.4%; OR, 3.40; 95% CI, 2.15–5.40), procalcitonin (13.7% vs. 3.7%; OR, 4.14; 95% CI, 2.06–8.33), LDH (58.1% vs. 37.2%; OR, 2.13; 95% CI, 1.45–3.14), AST (39.4% vs. 18.2%; OR, 2.92; 95% CI, 1.97–4.34), ALT (28.1% vs. 19.8%; OR, 1.59; 95% CI, 1.04–2.43) and D-dimer (59.6% vs. 43.2%; OR, 1.94; 95% CI, 1.27–2.97), whilst the median hemoglobin value was also found to be lower in patients with severe COVID-19 (128 vs. 135 g/L; p 0.01). Each of these prognostic parameters retain a specific clinical and biological significance, which, altogether, can contribute to reflect the evolution toward more unfavorable clinical pictures.

Lymphopenia	**Decreased immunological response to the virus**
Leukocytosis	**Bacterial (super) infection**
Neutrophilia	**Bacterial (super) infection**
Increased value of MDW	**Severe viral infection/viremia/viral sepsis**
Thrombocytopenia	**Consumption (disseminated) coagulopathy**
Increased value of CRP	**Severe viral infection/viremia/viral sepsis**
Increased value of procalcitonin	**Bacterial (super)infection**
Increased value of LDH	**Pulmonary injury and/or widespread organ damage**
Increased value of amino transferases	**Liver injury and/or widespread organ damage**
Increased value of bilirubin	**Liver injury**
Increased value of creatinine	**Kidney injury**
Increased value of cardiac troponins	**Cardiac injury**
Decreased value of albumin	**Impairment of liver function**
Prolongation of prothrombin time coagulopathy	**Activation of blood coagulation and/or disseminated**
Increased value of D-dimer coagulopathy	**Activation of blood coagulation and/or disseminated**

Figure 9 : : Potential clinical and biological significance of abnormal laboratory values in patients with coronavirus disease 2019 (COVID-19).
CRP, creactive protein; LDH, lactate dehydrogenase; MDW, monocyte volume distribution width

<u>Surveillance</u>:
A third, though not less, essential support given by diagnostic testing to counteracting viral outbreaks is the identification of anti-SARS-CoV-2 antibodies, both immunoglobulin G (IgG) and M (IgM). Although serology testing cannot be

typically advocated as a reliable surrogate of RT-PCR for diagnosing acute viral infections, it maintains an essential role for both investigational and surveillance purposes [18]. Notably, a combined IgM-IgG rapid immunoassay has also been recently developed, which is apparently

characterized by better diagnostic accuracy (i.e. up to 89% sensitivity and up to 91% specificity) than either IgM or IgG test alone [19]. Widespread application of this and other rapid serological tests may hence enable to gain valuable epidemiological data in the fight against this viral epidemic.

Organizational issues:

The impact on laboratory organization is another essential aspect that needs to be clearly acknowledged when facing large outbreaks like that sustained by SARS-Cov-2. With several thousands of infected patients, with part of them needing diagnostic testing and/or hospitalization, the daily activity of clinical laboratories for both routine and urgency testing may be rapidly saturated or even overwhelmed and disrupted, whereby the role of medical laboratory services is expected to be mainly reactive rather than proactive. Clinical laboratories, even the most recently constructed, have been designed and organized to sustain a limited (i.e. "customized") volume of tests [20], so recruiting human and technical resources for facing unexpected health crises would not be so easy at the down of the third millennium. Laboratory automation, availability of high-throughput instrumentation [21], along with lower number of employees and reduced healthcare funding (especially for public facilities) have all contributed to considerably reduce the flexibility to develop emergent responses [22]. The availability and extended use of point-of-care testing (POCT) devices shall be regarded as an additional useful tool during outbreaks and other biological hazards, especially those sustained by viral infections [23, 24]. The lesson learnt from the recent outbreak in China is indeed paradigmatic, whereby the currently available healthcare resources were totally insufficient to manage the impressive number of patients seeking care in Wuhan. The situation has forced public authorities to rapidly build an entirely new 645,000-square-foot hospital, with approximately 1000 beds, ICUs, isolation wards and even a clinical laboratory inside. This is indeed a valuable strategy, but not all worldwide countries would be able to react in such a rapid and efficient manner, i.e. building new facilities in less than 2 weeks. Therefore, additional strategies shall be envisaged. The first and perhaps most important lesson that policymakers and hospital administrators shall learn from COVID-19 is that continuing to cut down human and economic resources will then generate huge organizational issues when the entire system of care, including laboratory diagnostics, will be challenged by an enormously amplified volume of tests to manage emergent situations [25]. A second important aspect is deciding how this and other emergencies could be efficiently managed. Existing laboratories may be asked to enhance their usual throughput and contextually reduce their turnaround time, but this may not be sustainable always and anywhere. Urgent personnel recruitment for managing an enhanced volume of serological or molecular tests will be needed, and shall be arranged as soon as possible considering that hands-on training is necessary for those who lack direct experience or skills in virological assays. Healthcare staff may also be temporarily moved from one laboratory to another (e.g. from a biochemistry to a virology laboratory), and this may have an impact on the efficiency of the former facility to maintain the usual throughout and turnaround time for routine and urgent nonvirological tests. Therefore, establishment of an efficient network of regional clinical laboratories, involving those which are not directly challenged by the outbreak and where samples can be conveyed, is a feasible solution, provided that a straightforward regulation for specimen transportation and biosafety is set and monitored .This, in turn, highlights an unavoidable need to place major efforts for allowing better and wider harmonization of laboratory results and information, encompassing both analytical and extra-analytical issues [26–28].

Conclusions

The managed care of patients with SARS-CoV-2 infection entails early identification, rapid isolation, timely establishment of infection prevention and control (IPC) measures, together with symptomatic care for patients with mild disease and supportive treatment for those with severe COVID-19. Several lines of evidence attest that previous viral outbreaks may have been characterized by retarded identification and delayed healthcare response [29], and COVID-19 shall not be considered an exception to this rule [30]. Awareness and preparedness to face highly contagious viral outbreaks, such as that sustained by SARS-CoV-2, become imperative for preventing the health system from being strained and laboratory services from collapsing. Irrespective of its inherent definition [10], it is now virtually incontestable that laboratory medicine will increasingly provide an essential contribution to the diagnostic reasoning, managed care and therapeutic monitoring of the vast majority of human diseases [31], thus including infectious diseases [32, 37] and COVID-19, which has now been defined as global health emergency by the WHO. The virus can easily spread from one person to another person it is strictly prohibited to visit populated areas.

Message:

The future prospective of covid 19 infection control depends on the immunity of individuals i.e . Herd immunity and prevention by using masks. It also known that Vaccines are not available in market and still trials phases are going on The only possible way to escape the virus is to avoid contact with infected person and maintaining strictly social distance. It is individual responsibility to take care a prevention which is better than cure.

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