Living with Coronavirus (COVID-19): a brief report

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Abstract. – The world will never be the same after the current COVID-19 pandemic. We may have to live with the coronavirus for a long time. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has resulted in a major burden on the global health system and economy. This report describes the current COVID-19 landscape and its socioeconomic implications. Despite the concerns for second waves of infection, gradual lifting of lockdown restrictions has occurred worldwide to relieve economic pressures and likely contributes towards possibly surging of outbreak although region wise variation exists due to several other biological factors, such as testing capacity and basic healthcare facilities among susceptible population within that region. Different prediction models have been put forth to forecast the spread of the current outbreak. However, it is challenging to perceive the precise changes happening in the real world as every time dynamics differ same as other epidemics cannot possibly be exactly superimposed to COVID-19. Currently, to decrypt the conundrum for effective antiviral drug against SARS-CoV-2 is in full swing. Due to high rate of mortality and it expeditiously spread is it decisive to understand the biological properties, clinical characteristics, epidemiology, evolution, pathogenesis for vaccine development and pathogenicity studies against the viral curb. Instant diagnostic and adequate therapeutics serve as a major intervention for the management of pandemic containment. Our study aims to analyze the impact of current measures and to suggest appropriate administrative strategic planning rather than to make somewhat authentic prediction in relation to the current scenario. Our predictive analysis study should be helpful against prevention, cure and control of the current outbreak of COVID-19 till the availability of cure or vaccine.

Key Words:
COVID-19, Coronavirus, Pandemic, SARS-CoV-2, Lockdown, Testing, Infection, Therapeutics, Diagnosis.

Introduction

As potentially lethal pathogens to humans, viruses have caused several pandemics throughout history. On December 19, 2019, a novel virus called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged, which causes the Coronavirus disease 2019 (COVID-19). The infectious disease started in patients who presented with severe pneumonia of unknown origin in Wuhan City, Hubei Province of China, the seventh largest city in China with 11 million residents. The spread of COVID-19 has progressed rapidly, and the World Health Organization (WHO) declared it a pandemic on March 11, 2020 due to the appearance of 118,000 cases over 110 countries[1-3]. On January 10, 2020, genome sequencing classified the virus as part of the Betacoronavirus genus, confirming that the outbreak was due to a novel coronavirus. The primary source of transmission of this outbreak outside of Wuhan was due to infected air travelers, and Thailand reported the first case outside

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of China on January 13, 2020. Within China, new cases were reported outside Wuhan from Guangdong and Beijing on January 19[3,4].

COVID-19 Global Effects

So far COVID-19 has spread over 213 countries and worldwide, the number of cases of coronavirus have reached more than 38 million, with more than one million deaths; the number of recovery cases has reached over 25 million till October, 2020. Global distribution of COVID-19 has been depicted in Figure 1. According to WHO statistics, at the time of this manuscript's preparation, the countries with the highest incidence of COVID-19 is the United States (US) (the first case was reported on Jan 23, 2020)[5,6] followed by Brazil (Feb 27, 2020), Russia (Feb 1, 2020), United Kingdom (Feb 1, 2020), Spain (Feb 1, 2020), India (Jan 30, 2020), Italy (Jan 31, 2020), France (Jan 24, 2020), Germany (Jan 28, 2020), Turkey (March 12, 2020), and Iran (Feb 19, 2020)[7].

SARS-COV-2 in Depth

SARS-CoV-2 is similar to Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) virus in terms of its pathogenicity[8,9]. However, a genetic recombination event in the RBD region at the S protein of SARS-CoV-2 conferred higher infectivity compared to SARS-CoV[10]. Coronavirus belongs to the *Coronaviridae* family in the *Nidovirales* order. The name "corona" originates from its crown-like glycoprotein spikes on the outer surface (envelope) of the virus. The size of coronavirus ranges from 65 to 125 nm in diameter. The subgroups of coronaviruses family are alpha (α), beta (β), gamma (γ) and delta (δ) coronavirus[10]. The RNA genome of SARS-CoV2 is single-stranded consist of 29,891 nucleotides, which encode 9,860 amino acids. The exact origin is still not fully understood, but 89% genomic similarity with bat SARS suggests that SARS-CoV-2 may have evolved from a strain present in that animal. Mutations may have caused the spread of SARS-CoV 2 into humans[11].

The *Orthocoronavirinae* subfamily of *Coronaviridae* (order *Nidovirales*) is further classified into four CoVs genera: Alphacoronavirus (alpha-CoV), *Betacoronavirus* (beta-CoV), *Deltacoronavirus* (delta-CoV), and *Gammacoronavirus* (gamma-CoV). Five sub-genera exist within the beta CoV genus. Genomic analyses reveal that bats and rodents are likely the main source of alpha CoVs and betaCoVs. On the other hand, deltaCoVs and gammaCoVs likely originate from avian species[12]. Coronaviruses are positive, single-stranded RNA viruses, and to date, seven

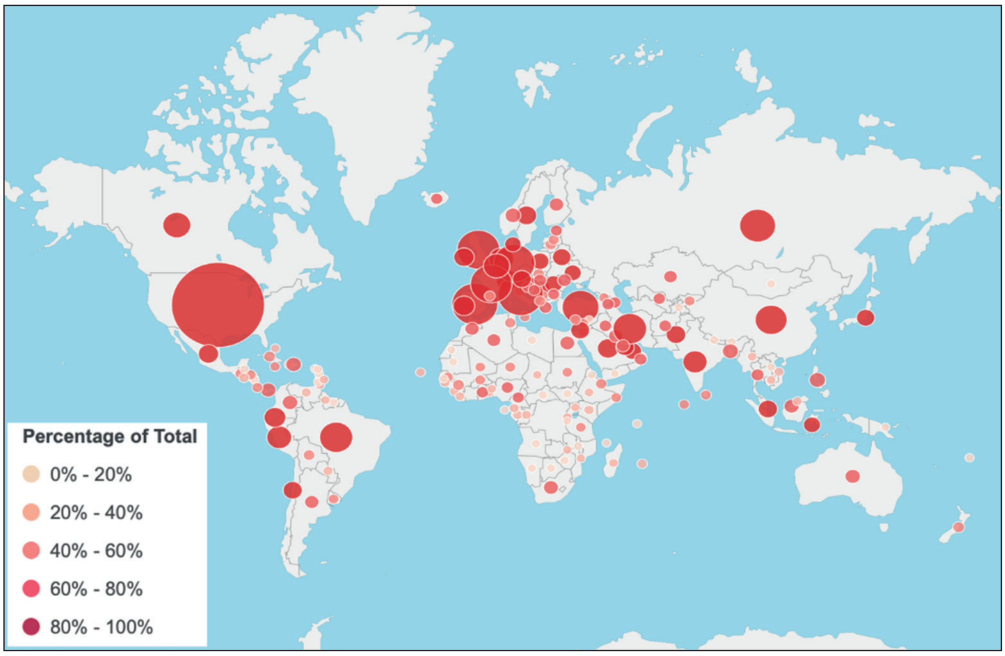

Figure 1. Virus Enveloped the Whole World. The global distribution and relative prevalence of COVID-19 are illustrated as the percentage of total confirmed cases. As the numbers for COVID-19 cases are changing rapidly, this chart only provides an approximation of the current scenario on June 7, 2020 from the John Hopkins Corona Resource Centre. Cases predominate in the United States and Europe.

human coronaviruses (HCoVs) have been identified. SARS-CoV-2 falls within the *Betacoronavirus* genera[2,13]. Other reported human CoVs are SARS-CoV and MERS-CoV.

Clinical Manifestation

Members of the seven previously reported HCoVs are capable of causing enteric, respiratory, neurological, and hepatic diseases. It has been projected that healthy carriers of any CoV comprise approximately 2% of the global population, while respiratory infections are found in 5% to 10% of the population. Four mostly present with cold symptoms; however, SARS-CoV, SARS-CoV-2, and Middle East respiratory syndrome coronavirus (MERS-CoV) are more commonly linked to fatal illness[12,14-19]. The outbreak of COVID-19 began in Wuhan City, where several pneumonia patients were reported and found to be associated with the Huanan seafood and animal wholesale market[20,21]. The human to human transmission is considered as a major route of viral transmission[22,23]. The presence of SARS-CoV-2 in the stool of COVID-19 patients and in the sewage water of Chinese hospitals where SARS patients have been treated also suggest the possibility of oral-fecal transmission[24-27].

The common symptoms associated with COVID-19 patients feel rigor, sore throat, high fever, shortness of breath, headache, nausea, vomiting, dry cough and diarrhea[28,29]. In elderly and immunity patients, severe lower respiratory tract infections have been reported. SARS-CoV-2 can be overlooked or misdiagnosed due to an incubation period of 2-14 days and similarity of presenting symptoms with the common cold. These challenges result, in part, in increased transmission and outbreak among people[15-17]. Only 2-10% of COVID-19 patients had gastrointestinal symptoms mainly vomiting, diarrhea, and abdominal pain. The study conducted on 99 confirmed SARS-CoV-2 patients of Wuhan Jinyintan Hospital, Wuhan, China, had symptoms of fever, shortness of breath, cough, muscle ache, fatigue, headache, sore throat, chest pain, diarrhea, nausea and vomiting[30,31]. SARS-CoV-2 also infects hematological, digestive and the urinary system thus virus can be observed in urine, stool and blood samples.

Viral Transmission Model

The route of entry of SARS-CoV-2 is related to the binding of viral "spike" protein to a human cell surface receptor known as angiotensin-converting enzyme 2 (ACE2) while another cell surface human protein TMPRSS2 assists in activation of the coronavirus spike protein and facilitate viral cell entry[32,33]. The major targets of SARS-CoV are specific type of cells present in lungs, nasal passage and intestines that expressed ACE2 and TMPRSS2. Type II pneumocytes cells in lungs, absorptive enterocytes in intestines and goblet secretory cells in nasal passages serve as the main route of viral transmission in human body[34,35]. The levels of ACE2 are high in the lungs, therefore, it is considered to play an important role in the progression of lung disorders in relation to COVID-19.

The average incubation period of SARS-CoV-2 infection is 5.1 days, while 97% of infected patients develop symptoms within 11.5 days[30,36]. Based on these reports, it is suggested that out of 10,000 cases 101 cases will show the sign of infection after 14 days of isolation[37,38]. Thus, incubation period is the major key for control of SARS-CoV-2 infection. Following contact with a confirmed or suspected SARS-CoV-2 case, 14 days observation are recommended[14,39].

Diagnosis of SARS-COV-2

Serological techniques are widely used for diagnosis of SARS-CoV-2 infections through estimation of different levels of blood cells[33,37,38]. The variation in the levels of blood cells in SARS-CoV-2 infected patients are the major indicator of the type and severity of the disease[14,37]. According to the study conducted on 99 confirmed patients of SARS-CoV-2 infection, the levels of lymphocytes, platelets and albumin was decreased in contrast with increased levels of neutrophil, ALT, AST, D-dimer, bilirubin, creatinine, and LDH[30,40,41].

Another method of detection of unique viral sequences by using amplification technique of nucleic acids is reverse Real Time-PCR (rRT-PCR)[42,43]. The protocol of Reverse Real Time-PCR (rRT-PCR) for detection of SARS-CoV-2 infection is based on alignment and similarity of known bat linked coronavirus genome sequence and SAR-CoV in addition with five other sequences obtained from SARS-CoV-2[25,44]. Current diagnostic methods by RT-PCR are based on targeting the three viral genes: E gene (encode for the envelope protein), RNA-dependent RNA polymerase gene (RdRp) and the nucleocapsid (N) gene[45,46]. With the higher sensitivity and specificity, recently other assays[28,45,47] have been developed targeting the separate region of the RdRp/Hel gene of SARS-CoV.

Potential Therapeutic Approaches Against COVID-19

Till now, scientists are still working to find the effective treatment or vaccine to combat against the SARS-CoV-2 (COVID-19) as infection rate and mortality increases on daily basis. There is an essential need of developing an effective strategy and currently available antiviral drugs are useful in clinical manifestation improvement[48]. Currently, used antiviral drugs are selected as they have been previously found to be an effective treatment against various viral infections for instance SARS, Ebolavirus (EBOV), human immunodeficiency virus (HIV), influenza virus (InfV) and MERS. These drugs usually act as a nucleoside analogues, may be in the form of guanosine or adenine and could target the RNA-dependent RNA polymerase (RDRP)[49]. Potential antiviral drugs, such as remdesivir, corticosteroids, tocilizumab chloroquine, hydroxychloroquine, interferon, ribavirin, tocilizumab, and sarilumab have been used as a potential agent for the treatment[50]. Remdesivir (RDV), a nucleotide analogue inhibitor of RDRP (RNA-dependent RNA polymerase), is known to exert its broad-spectrum antiviral activity through inhibition of viral replication by premature termination of RNA transcription. It has been considered as one of the most effective treatment against COVID-19 infection by reducing the recovery time and lowering the mortality rate[51]. However, unfortunately later in the COVID-19 patients with acute respiratory failure and pneumonia, remdesivir was not found to be associated statistically significant with clinical improvements. Remdesivir shows broad antiviral spectrum against HIV, hepatitis B virus, MERS-CoV and SARS-CoV, both *in vivo* and *in vitro*[52]. In order to clarify the effectiveness of the drug, there is a need of puzzle to solve related to mode of viral replication, immunological pathways and pathogenesis[53]. Favipiravir (FPV), a guanine analogue known to target RdRP (RNA-dependent RNA polymerase) of many RNA viruses, is also considered as a potential treatment against COVID-19, it was initially approved for influenza viral infections. Although its *in vitro* efficacy on SARS-CoV-2 is still under investigation, its effectiveness on RCTs COVID-19 recruiting patients is now under evaluation in combination with interferon-α[54]. Chloroquine and hydroxychloroquine have been mainly used in autoimmune diseases (e. g., lupus and rheumatoid arthritis) and as an antimalarial agent. There is a wide discrepancy from the existing studies shedding the significance of need RCTs in order to access its efficacy as a potential agent against treatment of COVID-19 infection[55]. Passive immunotherapy is the procedure to extract neutralizing antibodies from newly recovered patients (high titer of antibodies in sera present in newly recovered patients) and to injected it into infected patient results for deactivating the virus. However, mechanism behind the neutralization action of these antibodies is still unknown. This mechanism is not only effective against SARS-CoV2 infection but also found to be a potential treatment from SARS and MERS viral infections. Corticosteroids has great potential because immunosuppressive activity required to alter the progression of the pneumonia, and in addition it has anti-inflammatory effect. However, due to their negative effects on anti-viral immune responses the use of corticosteroids against the treatment of COVID-19 is controversial. Another potential option is Bacillus Calmette-Guérin (BCG; weakened strain of Mycobacterium bovis) vaccination which could be effective against COVID-19 infection but this method of treatment does not recommend by WHO and clinical trials are still ongoing to confirm its role as a potential agent against SARS-CoV-2 infection[56].

Governmental Strategies to Tackle the Current Outbreak

Testing Capacity

So far, the key factor of inconsistency and limited availability of COVID-19 testing data is due to dependence on publicly available resources. Region wise variation exist in a way they report confirmed positive cases. So far none of the country testing capacity is more than 17% of its total population. Countries should only report the number of viral tests performed when reporting the testing numbers of infection as antibody or serology test does not count active viral infections therefore do not provide the real picture of number of active cases of COVID-19 infection. The limited testing capacity usually represents a smaller number of cases compared to the actual cases within that region.

Other factors that affect the testing rate or data is availability of testing supplies, testing time or technology used, possibility of false negative results due to inappropriate testing timing during the course of infection. Among the developing countries, Pakistan with over 220 million population the testing size remains as low as around 14,000 per day[57]. As shown in Figure 2, Brazil is at top with 62% of total cases so far confirmed from the test. China is among the lowest rate in terms of percent of positive cases confirmed so far from the test this could be because the rate of spread of infection in China is so fast. Considering the US with highest number of cases so far has only 9 percent of cases confirmed from the available tests. Data available so far, in South Asia the highest number of single day 20,167 coronavirus test reported on 3rd June 2020 conducted is in Pakistan.

Lockdown Restrictions

Lockdowns, curfew, air ban, isolation wards, closure of educational institutions, private and governmental sector offices, social distance measures, ban on social gathering, border closure, closure of public places, shops, ban on religious commemoration & congregational prayer are all kinds of possible governmental measures enforced partially or completely worldwide to stop the spread of infection. Around 3 billion people in India were under pandemic lockdowns, the biggest lockdowns among all. In various countries of Europe around 300 million people were facing pandemic lockdown. Stringency and enforcement of pandemic lockdown varies within and among nations[58]. However, there are some Asian countries which enforced strict non pharmaceutical measures, such as wearing face mask, gloves and follows social distancing rules instead

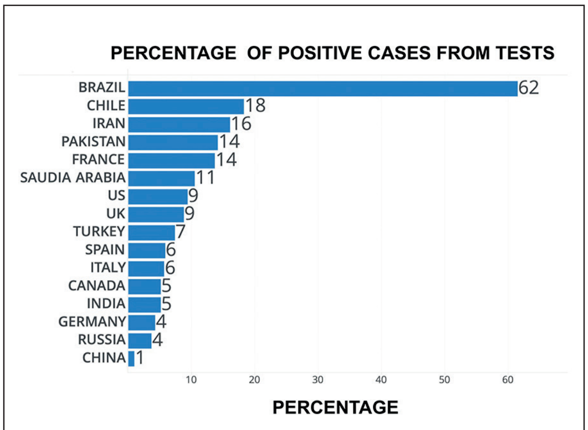

Figure 2. Worldwide Testing Scenario in COVID-19 progression. The percentage of confirmed cases from the total number of tests is illustrated in the graph for most infected countries. Based on data of 7th June 2020.

of strict lockdowns, including South Korea, Japan, and Indonesia[59-61]. As reported, after lifting the lockdowns restrictions sudden record in number of cases has been observed in some countries[57,62]. Timeline for lockdown implementation varies worldwide depending upon rate of spread of the infection, testing capacity, public response in following of SOPs and the incidence of the first reported case as control measures taken by government of respective region[63].

Since the worldwide incidence of COVID-19 outbreak, the number of cases has sharply increased however country wise variation persists due to several social and biological factors. As illustrated in Figure 3, implementation of lockdown reduces the expansion of infections with different extend. The pre and post lockdowns effects can clearly be seen in the graphs, in incidence of number of cases. In the majority of the countries flattening of the curve has been observed after the implementation of lockdown. In China, the epicenter of the initial disease outbreak, after the enforcement of lockdown by 23rd Jan 2020, flattening of curve has been observed after almost a month from lockdown. According to prediction model Figure 3, the effects of post lockdown in rate of incidence of COVID-19 infection has been more evident in Brazil, India, Chile and Pakistan compared to other countries; however, the impact has been observed among all countries.

Lockdowns are not a permanent or long-term solution of the current outbreak, instead the lockdowns should be imposed in regular intervals with appropriate SOPs till the availability of vaccination or proper medication. Print, electronic and social media need to play a positive role to increase public awareness of preventive measures.

Possible deviation from the expected prediction is possible as represented in grey shaded region as confidence interval varies among countries. In countries such as US, Spain, Italy and Turkey at initial time of outbreak before lockdown death rate are similar to recovery rate, however, gradual increase in recovery rate has been observed compared to rate of death as a result of lockdown restrictions as depicted in prediction model Figure 4. Before lockdown, in Brazil and France the death rate is comparatively higher from recovery rate but during the lockdown the recovery rate gradually increased.

In countries, such as Russia, India, Germany, Iran, Chile, Saudi Arabia, Pakistan, Canada and China, a higher rate of recovery is observed as compared to the death rate as post lockdown

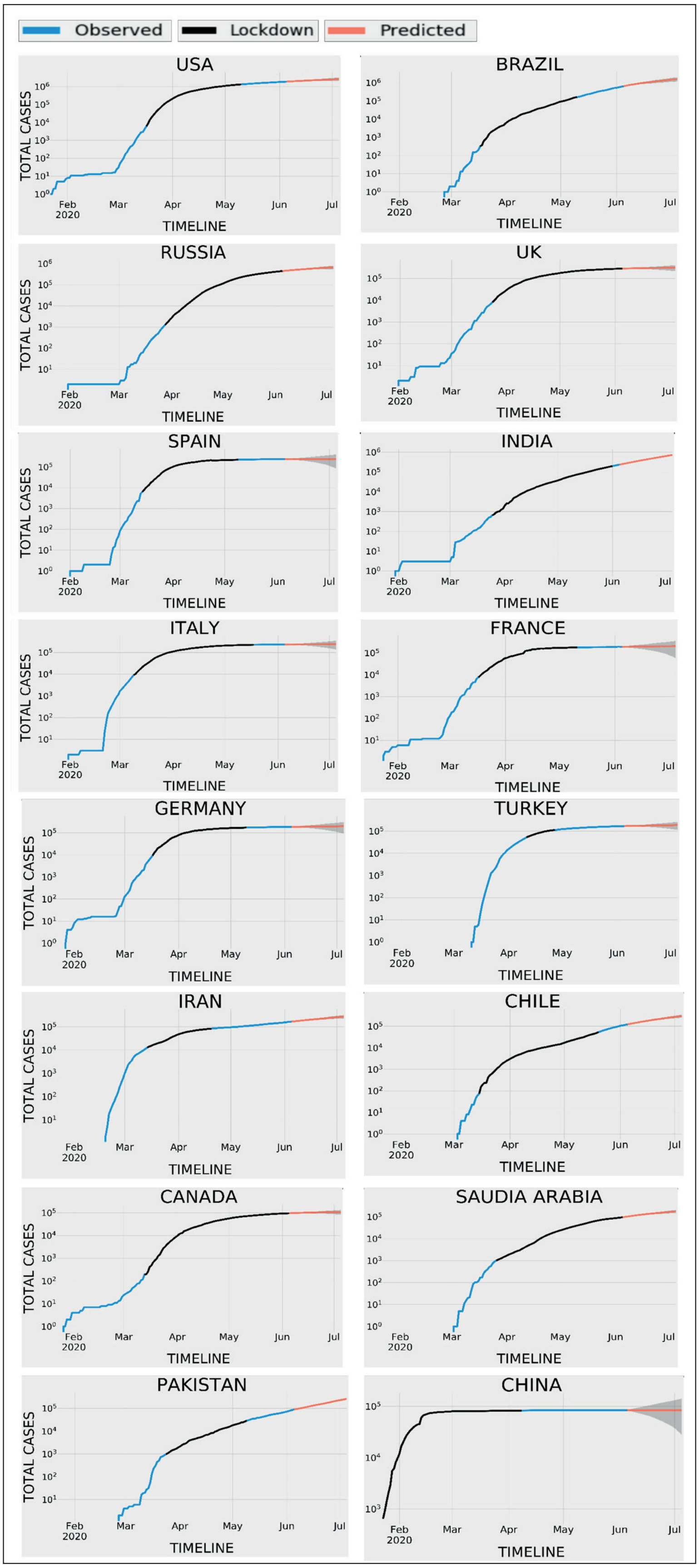

Figure 3. Worldwide impact of lockdown on COVID-19 outbreak with predicted scenario. Prediction model for worldwide distribution of coronavirus outbreak is depicted in graph from the first reported date for the most infected countries arranged accordingly in descending order of total number of cases. The country-wise trend from the date of first reported infection for total number of cases in respect to lockdown enforcement varies. Relying on magnitude of COVID-19 the length of lockdown indicated in black line varies among different countries. After lockdown, the total number of cases as shown in blue line has been under control. The trend of COVID-19 progression has been predicted till July 2020. The data are provided by World Health Organization (WHO) Coronavirus Disease (COVID-19) and Global COVID-19 lockdown tracker database till 7th June 2020.

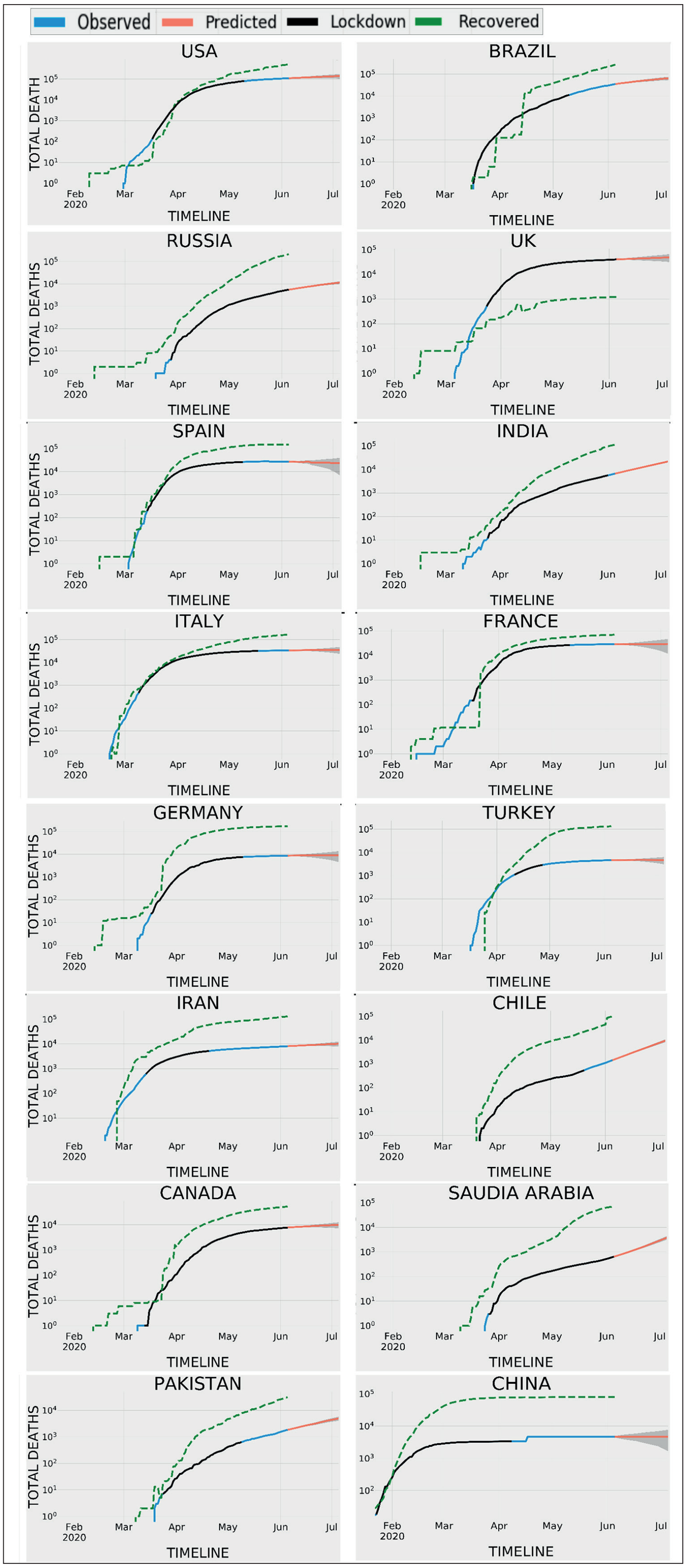

Figure 4. Worldwide impact of lockdown on death and recovery rate associated with COVID-19 outbreak with predicted scenario. Prediction model for worldwide distribution of death and recovery rate due to coronavirus outbreak is depicted in the graph from the first reported date for the most infected countries arranged accordingly in descending order of total number of cases. The country-wise trend for total number of deaths and recovery cases in respect to lockdown enforcement varies. Relying on magnitude of COVID-19 the length of lockdown indicated in black line varies among different countries. After lockdown, total number of observed deaths as shown in blue line has been under control. Compared to UK, in other countries the rate of recovery improved after the lockdown. Prediction based on spread of COVID-19 is represented in the orange line made till July 2020.

effect. Despite of the lockdown in UK, the number of deaths bypasses the number of recovered cases. As per prediction model, death rate could increase as a result of lifting of lockdown restrictions due to hike in number of cases, therefore, gradual or partial lifting of lockdown restrictions from the least infected region will reflect a better strategy along with the following of the proper guideline provided by the government.

Worldwide efficient testing strategies along with the strict implementation of non-pharmaceutical interventions could be the best and effective strategy against the spread of virus. The major constraint to control the infection as virus and symptoms both are invisible, therefore, a sensible approach is the best solution against the spread of infection. The other biggest challenge faced by the government is to tract and distinguish the people who are asymptomatic and shows positive as never develop any type symptoms for COVID-19 from pre-symptomatic carriers those who also test positive followed by gradual appearance of the symptoms.

According to the recent studies done across six countries in US, China, South Korea, Italy, France, and Iran the impact of enforced restrictions (event cancellations, travel bans, school closings, suspended religious services and stay home orders has been accessed). In the US it is estimated that if there would be no lockdown, there will be about 60 million people infected compared to 1.9 million reported so far as a result of restrictions. The prominent effect has been observed in China and reduces the number of infections in 285 million people while currently reported cases reached to 84,000 cases so far. More or less significant impact has been seen which saved around 54 million infections in Iran, around 49 million in Italy, 45 million in France and 38 million in South Korea. A study[64] done in Imperial College London stated that the lockdown restrictions prevent 3.1 million deaths among 11 European countries during the lockdown timeline from March till May 4. Therefore, sensible exit lockdown strategy needs to be enforced to effectively control the spread of the infection.

Conclusions

Pandemics have always been a threat due to their deadliest effects on human lives. Our living habits may permanently be changed, travelling is changing, use of hand sanitizer or gloves may be a part of our life, more jobs online as people learnt to work from home, social gathering may never be a norm in the further years. In some countries, cases are declining while in South Asia and Africa, Central and South America, they are still booming. Countries where cases are decreasing can possibly face the sudden surge of cases: concern of second peak. The only effective control of the existing pandemic is to minimize the transmission among carriers especially in susceptible population followed by expansion of testing capacity, isolation of confirmed cases and quarantine. In general, lockdown is not a long-term solution but enforcing it in regular intervals with strict SOPs followed by nation wise policies may help. People have to live with coronavirus for a long time, let us accept this reality and learn to live with it. Herd immunity may be an option, but it can raise a second wave. Let’s trust and respect the health workers and scientist, working for humanity. However, there is an immediate need of extensive collaborative research to sum up the current research analysis for better allocation and engagement of resources for research and development related to COVID-19.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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