Journal of Medicine and Biology

Review Article | Vol 2 Iss 2

Global Risk, Diagnosis and Treatment of Coronavirus Disease (COVID-19): The Pandemic

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Abstract

Apart of global community is currently suffering severely from the pandemic coronavirus disease (COVID-19) which is fastly spreading around the world, crossing all the barriers of nations, religions, ethnicities and races. The disease is believed to be originated from Wuhan city of China, exhibits symptoms which includes fever, cough, fatigue, headache, diarrhea, hemoptysis, and dyspnea. Many nations of the world have applied preventive measures such as using masks, following hygiene practices, maintaining social distance and avoiding public contacts to combat COVID-19 and few countries have also declared the state of emergency. The scientific and medical fraternities are busy researching on new drug which can cure COVID-19. Chloroquine and Hydroxychloroquine could be effective tools against SARSCoV-1 and 2. The present review is focused on understanding the present methodologies of detection, tracing and quarantine of COVID-19 patients. In addition, the global risk, diagnosis and treatment of this pandemic disease are also discussed in detail in this review.

Keywords: ***Coronavirus; COVID-19; Hydroxychloroquine; Pandemic; Quarantine***

Received Date: April 21, 2020; **Accepted Date:** May 02, 2020; **Published Date:** May 09, 2020

Introduction

In December 2019, there was a worldwide outbreak of a new type of coronavirus named novel coronavirus (COVID-19), originated from Wuhan, Hubei province, China and spread throughout the world within a short period of time. It is also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The SARS-CoV belong to a lineage B of genus

Citation: Temesgen A Gelaw, Global Risk, Diagnosis and Treatment of Coronavirus Disease (COVID-19): The Pandemic. J Med Biol 2(2): 54-64.

Betacoronavirus of the *Coronaviridae* family including genes coding for 16 non-structural proteins (nsp, in ORF1ab domain), the structural proteins like spike protein (S), envelope (E), membrane (M), nucleocapsid (N) and other several genes [1].

On 11th March 2020, the World Health Organization (WHO) declared this outbreak as pandemic [2]. The leaders from all around the globe declared COVID-19 as the war against the humanity. It causes severe respiratory tract infection in humans. Many nations have already declared the state of emergency in order to combat COVID-19. At present; countries including America, Spain and Italy have witnessed record number of casualties.

COVID-19, not only upended our life, but also affected animals across the globe from coughing tiger in New York to emboldened goats on the street of Wales and dogs of Hong Kong. This could be a case of human to animal and vice versal transmission [3]. Thus, pet animals will also act as agents for COVID-19 transmission and need care and protection.

Current evidence indicates that SARS-CoV-2 spread to humans via transmission from wild animals illegally sold in the Huanan sea food whole sale market [4]. Phylogenetically, the *Coronaviridae* family SARS-CoV-2 is approximately 79% and50% distinct from SARS-CoV and MERS-CoV respectively [5]. Markedly, SARS-CoV-2 shares a 96.3% genetic similarity with RaTG13 (bat corona virus obtained in Yunnan in 2013) though bats are not the immediate source of SARS-CoV-2 [6]. This review is an attempt to explore and evaluate the risk posed by COVID-19 against global population. The authors have also tried to throw some light on latest statistics of this pandemic with its diagnosis and treatment.

COVID-19 Global Risk

As of April 9, 2020, the outbreak of COVID-19 generated 1,536,094 confirmed cases, 89,877 deaths and 340,176 recoveries worldwide. In addition, the total number of active cases is 1,106,041 as shown in Table 1. In China during the outbreak of the SARS-CoV-2 pandemic, 42,000 doctors and nurses from all over the country supported Wuhan [7]. But these days, the pandemic colonizes the world and the crisis overweighs in Italy, Spain, USA, France, UK and Iran [8] where the cumulative death record reached 47,636.

S. No.	Types of Cases	Number of Cases
1	Infected population	15,36,094
2	Number of deaths	89,877
3	Number of recoveries	3,40,176
4	Number of active cases	11,06,041
5	Number of active cases (Mild condition- 96%)	10,57,546
6	Number of active cases (Critical condition- 4%)	48,495

Table 1: The details of worldwide infected cases of COVID-19.

Countries like China, Israel, Cuba, and Egypt have sent their medical team to Italy where the pandemic deny the life of many thousands. Moreover, many soldiers of the war (restless doctors and devoted medical professionals) lost their life by SARS-CoV-2 while treating the patients.

The world is facing a critical global health emergency [9]. COVID-19 outbreak has brought the world to stand still with unparalleled and unforeseen impact in personal lives, economy, society and livelihood. There are growing risks of a global

recession with a massive loss of jobs. Based on the latest developments (quarantine measures, travel bans, border closures in most of Europe, which represents 50% of international tourism, and in many countries including America, Africa and the Middle East). The evolutions in Asia and the Pacific and the patterns of previous crises (2003 SARS and 2009 global economic crisis), UNWTO (World Trade Organization) estimates international tourist arrivals could decline by 20% to 30% in 2020. This would translate into a loss of 300 billion USD to 450 billion USD in international tourism receipts (exports) almost one third of the 1.5 trillion USD generated globally (Figure 1) in the worst case scenario [10].

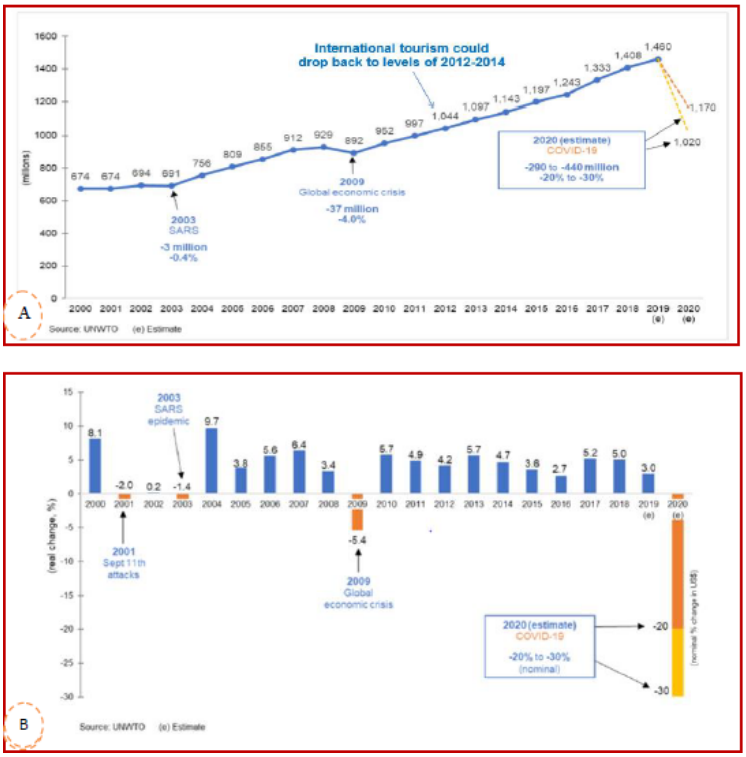

Figure 1: 2020 forecast - international tourist arrivals, world (millions); international tourism receipts world real change (%). Due to COVID-19 outbreak, the tourism sector will show drastically decline and will face unexpected losses (Chart was reproduced from UNWTO World Trade Organization, Impact assessment of the COVID-19 outbreak on international tourism Updated 24 March, 2020. Copyright 2020 UNWTO [10].

The European Commission established Coronavirus Response Investment Initiative (CRII) and proposed to direct EUR 37 billion under the cohesion policy to the COVID-19 outbreak with ultimate objective to provide; support to the healthcare system (financing of health equipment and medicines, testing kits and treatment facilities, e-health, disease prevention, the provision of protective equipment's and medical devices, to ensure access to health care for vulnerable groups), liquidity to corporates in order to tackle short-term financial shocks and temporarily support national short time working schemes [11].

The crisis is being aggravating all over the world and obligatory measures on allocation for quarantine, travel bans, border closures, school and university closures, industry labour reductions and at most limited and authorized movement sanctions including closure of religious institutions are now being taken by countries. Moreover, especially in developing countries there is market inflation by some immoral merchants. Thus, the COVID-19 pandemic is now critically retarding the world economy and some countries are observed to take market stabilization budgetary allocations (for instance USA allocated 2 trillion USD).

If the disease distribution will increase by this speed, as the WHO estimated and announced, there will be critical death increment reports in developing countries especially in Africa.

The education sector implemented country-wide school and university closures (Figure 2). More than 1.52 billion children and youth are currently out of school. In addition, just about 60.2 million teachers are no longer in the classrooms [12]. Countries are experiencing E-learning, Plasma (TV) and radio learning approaches. Institutions have adopted work from home concept worldwide and started taking online classes to the students of all categories starting from schools to universities.

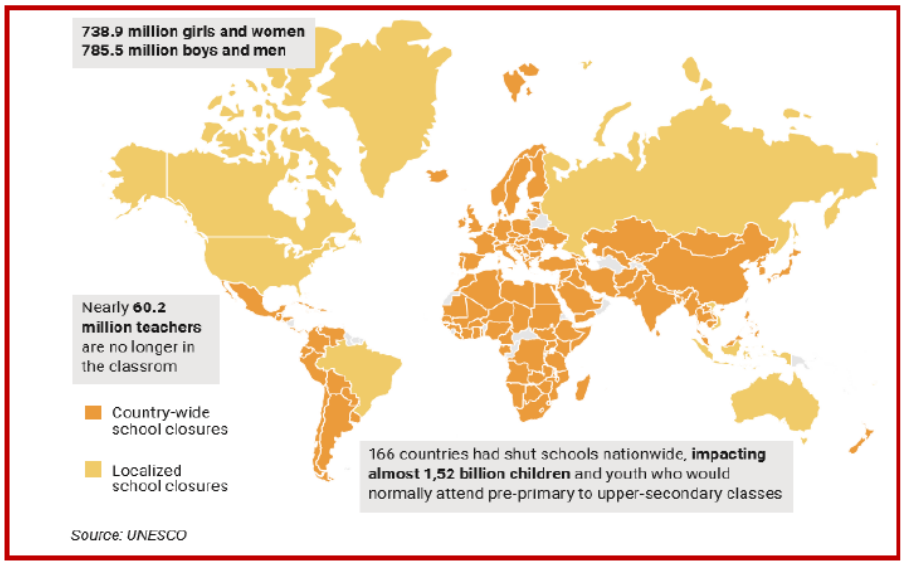

Figure 2: Countries affected by school closures [11] (as on 26 March 2020) (87% of the world enrolled school and university student population are out of school 12). (Map reproduced from UN, European Commission. Communication from the commission to the European parliament, the European council, the council, the European central bank, the European investment bank and the Euro group. Coordinated economic response to the COVID-19 Outbreak, Brussels, 112 finals, 2020). Copyright 2020 UN, European Commission.

Overall, the financial sectors will face losses drastically that will be reasonably unable to rehabilitate within a short period of time. According to UNECA (United Nations Economic Forum for Africa) economic impact assessment report, Africa will face 1.4% age point (3.2% to 1.8%) decline expected from effects of COVID-19 as on March 2020 (29 Billion USD) and due to of global supply chain disruption, demand side shocks, slowdown in investment due to job losses, inflationary pressures due to supply side shortages (Food and Pharma) and unanticipated increases in health spending of up to USD 10.6 billion, the continent revenue losses could lead to unsustainable debt. Henceforth, African governments could review and revise their budgets to reprioritize spending towards mitigating expected negative impacts from COVID-19 on their economies [13].

Additionally, people around the world are getting in psychological crisis due to stress as a consequence to complete lockdown situations across the globe. The people of the globe are experiencing, for the first time, complete rigid life style locking in their homes for a long period of time. Of course, administrations in the respective countries are struggling hard day and night to keep their people at home by providing all the required items on daily basis. The security and police departments are using their force beyond their capacities to maintain law and order on the right path. Since, stress will trickle down immunity, people have to get relaxed and follow the physician lesson as well as stay home to save life.

Diagnosis of COVID-19

Rapid and accurate detection is crucial to control COVID-19 outbreak in the community and health centres [14] throughout the globe. The currently available diagnostic tests for SARS-CoV-2 includes reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP) [15].

According to China National Health Commission, laboratory examinations including nasopharyngeal and oropharyngeal swab tests, are now become a standard assessment for SARS-CoV-2infection diagnosis. For earlier identification, two one-step quantitative RT-PCR (qRT-PCR) assays were developed to detect two different regions of the SARS-CoV-2 genome (ORF1b and N) [16]. Additionally, three novel RT-PCR assays targeting the RNA-dependent RNA polymerase (RdRp)/helicase (Hel), spike (S), and nucleocapsid (N) genes of SARS-CoV-2 were developed [17].

Treatment of Covid-19

Generally, there are no treatment options for suddenly occurring viral diseases [18,19]. There is no current Food and Drug Administration (FDA) approved evidence of any specific anti-COVID-19 treatment for patients. But literatures reviewed some antivarals and drugs will have a treatment role to SARS-CoV-2. An appropriate therapeutic strategy is to repurpose existing drugs [20].

Antiviral agents

Several antiviral agents have been reported being used to treat several virus infections. Lopinavir inhibits the protease activity of coronavirus in-vitro and in animal studies. Based on the experience accumulated from the SARS and MERS outbreaks, Lopinavir is an effective treatment, indicating that it will be a potential treatment option for COVID-19 [21,22]. The guanosine analogue, ribavirin is used to treat several virus infections and pronounceable results were obtained in a MERS-CoV rhesus macaque model [23]. Moreover, SARS-CoV-2 RNA-dependent RNA polymerase model is targeted by ribavirin after sequence analysis, modelling, and molecular docking [24] which increase its promising potential as an antiviral against SARS-CoV-2 [25].

During the outbreak of Ebola virus, the antiviral agent remdesivir was designed [26] and it showed broad-spectrum antagonistic activity against several RNA viruses [27]. IFNb showed superior antiviral activity to Lopinavir and Ritonavir in-vitro [8,28]. This is supported in a mouse model of SARS-CoV pathogenesis, where both prophylactic and therapeutic remdesivir showed improved pulmonary function and reduced lung viral loads and severe lung pathology [29]. In a case report, lopinavir/ritonavir (Kale-tra®) and arbidol showed significant improvements in COVID-19 patients [30] where the efficacy and safety needs further clinical trials. Moreover, trials of antiviral agents in COVID-19 patients with have been conducted.

Chloroquine and Hydroxychloroquine

Chloroquine is a widely used anti-malarial and autoimmune disease drug which has been reported to be a potential broad-spectrum antiviral drug [21,31-34]. India produces 70% of the world's supply of Hydroxychloroquine. India recently agreed to supply this drug to many countries including America after the demand for supply. India exported 6.62 billion USD worth of Hydroxychloroquine and related formulations.

Chloroquine blocks virus infection through endosomal pH increment and with glycosylation interference of SARS-CoV cellular receptors [34, 35] and thereby it has proven potentiality to block viral infection [36]. Furthermore, chloroquine can be taken as a broad antiviral agent because it has quinone reductase-2 inhibition role. Quinone reductase-2 is involved in sialic acid biosynthesis (required for ligand recognition). It is noted that both human coronavirus HCoV-O43 and orthomyxo viruses uses sialic acid moieties as a receptor [36,37].

The in-vitro anti-SARS-CoV-1 effect of chloroquine was reported in previous experimental studies [38]. It primarily attributed to a deficit in the glycosylation receptors, so that it cannot bind to the angiotensin-converting enzyme-2 expressed in lung, heart, kidney and intestine [39]. The anti-viral and inflammatory actions of chloroquine lead to several trials in response to the COVID-19 pandemic [40]. Since SARS-CoV-2 utilizes the similar surface receptor angiotensin-converting enzyme-2 [37]. It is believed that chloroquine can also interfere with angiotensin-converting enzyme-2 receptor glycosylation thus prevents SARS-CoV-2 attachment to the target cells [9,25,36-38,41] (figure 3).

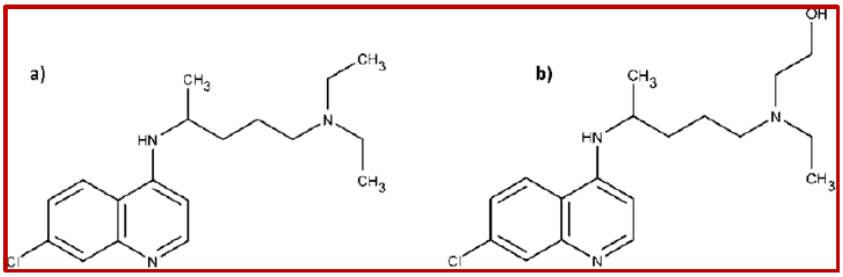

Figure 3: Molecular structures of a) Chloroquine and b) Hydroxychloroquine.

Chinese researchers studied the effect of chloroquine in-vitro (using Vero E6 cell line infected withCOVID-19) and found it to be highly effective in reducing viral replication. It was found easily achievable with standard dosing due to its favourable penetration in the target site such as lung [38]. The first human trial ever conducted with chloroquine involving more than 100 patients of COVID-19 revealed, the patients were found chloroquine superior to the control group with reduced symptom duration, pneumonia exacerbation and radiological improvement as well as upholding virus-negative sero-conversion with the absence of severe side effects [21,34,40]. Chloroquine was evaluated in SARS CoV-2 infection and showed very good in vitro efficacy [36]. Therefore, is included in the recommendations for the prevention and treatment of COVID-19 pneumonia [40]. Moreover, The National Health Commission of the People's Republic of China officially announced and recommended the inclusion of chloroquine in the next version of the guidelines for the prevention, diagnosis, and treatment of pneumonia caused by COVID-19 [34].

In the previous SARS outbreak, hydroxychloroquine was reported to have anti-SARS-CoV activity in vitro [42]. Using physiologically-based pharmacokinetic models, hydroxychloroquine was found to be more potent than chloroquine in SARS-CoV-2-infected Vero cells [41]. Cytokines IL-6 and IL-10 have been reported to be increased in response to SARS-CoV-2 infection [43,44].

Both chloroquine and hydroxychloroquine are exactly matching in structure (Figure 3) and mechanism of action except an additional hydroxy moiety in one terminal in hydroxychloroquine. Thus, both act as a weak base to change the pH of acidic intracellular organelles, which aids membrane fusion. It is believed that both chloroquine and hydroxychloroquine could be effective tools against SARSCoV-1 and 2 [9,25,34,37,41].

Clinical trial studies were launched by Chinese hospitals and the Oxford University to evaluate the efficacy of hydroxychloroquine and chloroquine against COVID-19 infection [45] and if the clinical data confirms positive results, these drugs may be used in SARS-CoV-2 prophylaxis and curative treatment [37]. Moreover, studies showed hydroxychloroquine plus azithromycin was found synergistically effective in clearing viral nasopharyngeal carriage (measured by polymerase chain reaction) in only three-to six days in COVID-19 subjects [21,46,47]. It is noted that azithromycin shown synergetic antiviral effect against Zika and Ebola viruses in-vitro [47].

Corticosteroids

The clinical outcomes of coronavirus and similar outbreaks do not support the use of corticosteroids. There is no unique reason to expect that patients with COVID-19 infection will benefit from corticosteroids, and such a treatment may be harmful [25,48]. Since corticosteroids suppress lung inflammation [43], corticosteroids could be prescribed at the right time for the right patients.

Antibodies

Like SARS-CoV, the receptor-binding domain in the S protein of SARS-CoV-2 binds to human ACE2 receptor to gain access into host cells [49]. During infection, the S protein elicits an immune response [50,51]. More than 90% of these antibodies are directed against S protein. This implies the S protein can be the target for SARS-CoV-2 antibody development [20].

Vaccine and therapeutic antibody development against COVID-19 has important implications. It is known that there is relatively high identity of the receptor-binding domains in SARS-CoV and SARS-CoV-2. The spike protein in COVID-19 is the major inducer of neutralizing antibodies. Providentially, the SARS-CoV-specific human monoclonal antibody CR3022 binds potently with the COVID-19 receptor-binding domains [52]. Until the development of COVID- 19-specific antibodies, for prevention and treatment of COVID-19 infections, CR3022 may be a potential therapeutic candidate, alone or in combination with other neutralizing antibodies [26].

Vaccines

The structure of SARS-CoV-2 S protein enables the rapid development and evaluation of medical countermeasures [53]. It provides the basis for further studies for vaccination optimization strategies of the emerging infection. Even if vaccine development is a long process, and no vaccines are available at the time of a pandemic outbreak [54], there will be a promising vaccine developed for COVID-19. This will be possibly achieved because majority of the vaccines being developed for coronaviruses target the spike glycoprotein or S protein [55].

There is also considerable global investment and effort towards development of a vaccine. On February 24, 2020, Moderna Company in collaboration with US (NIAID) announced experimental mRNA COVID-19 vaccine (mRNA-1273), which is ready for human testing [56]. It was outstandingly fast track cycle to develop an initial vaccine. The clinical trial of safety and immunogenicity of mRNA-1273 is under investigation (https://ClinicalTrials.gov Identifier: NCT04283461). Moreover, a new oral SARS-CoV-2 vaccine which uses food-grade safe Saccharomyces cerevisiae as a carrier and targets the S protein has been successfully developed at Tianjin University [21,57]. Moreover, it was noted that Israel scientists are in the ongoing research and in other ways the African Country Ethiopia with the collaborative effort of traditional medical practitioners and scientists reported hopeful clinical trial study was successfully conducted (the country Ministry of health,

www.https://moh.gov.et and National television News). It is hopefully expected that the results of all the ongoing trials will give more insight on prophylaxis and help in better prevention of the widely spreading disease.

Universal Safety Precautions/Preventive Approaches

Maintenance of hand hygiene by sanitizing and washing is the first line of defense against COVID-19. The public fear has significantly contributed towards maintaining the personal hygiene of the individuals. The people around the world practice good hygienic measures in hospitals, schools, offices, laboratories and other public places [58]. But there are also some who give little attention for it. It was noted that hand washing with soap and other sanitizers, maintaining social distance, covering nose and mouth while coughing and sneezing, face masking, avoiding contact of fingers with mouth, nose and eyes are the most important safety precautions recommended by WHO. Many people across the world are currently facing shortage of hand sanitizers and face masks [59], which show that the public is remarkably using the precautions. In contrary, some countries reported that measures were taken on those who illegally deposited the safety materials in their store or shops [60]. Furthermore, in many countries, efforts are in place to demonstrate proper hand washing and mask usage techniques, as well as awareness creation through various communication media and channels. On top of that various governmental and private institutions as well as charity clubs and youth associations are providing remarkable supports for those in need of food, shelter and house. Since scientists recommend not eating uncooked meat [58], refraining from using sea foods and uncooked meat and meat products can be also taken as one preventive approach of COVID-19.

Conclusion

The WHO declared pandemic COVID-19 is aggressively spreading throughout the world and depriving the life of many thousands. It is noted that there are no treatment options for suddenly occurring viral diseases and no FDA approved drug or vaccine is available to treat and prevent COVID-19. Researchers throughout the world are in search of treatment strategies and most agreed that lopinavir/ritonavir (Kale-tra®), chloroquine, hydroxychloroquine and hydroxychloroquine plus azithromycin will have synergetic antiviral effect against COVID-19. Due to the limited availability of diagnostic tests in developing countries and immunity of victims, the seviority and mortality rate will synergistically rise. And by this speed, the pandemic will kill extra people and it needs coordinated global investment and effort towards development of a vaccine. Current trials will lead to the development of SAR-COV-2 vaccine and to make this attempt real, the world shall stand together with cooperative hand.

Recommendations

To cease the spread of COVID-19, the society around the world shall stay home with continued hand washing thereby keeping social distance and other precautions recommended by WHO [61]. Also, it is better to avoid pet and wild animal contact. Moreover, unless prescribed by the physician, it is not recommended to use the mentioned drugs and antiviral agents.

Conflict of Interest

The authors declare no competing interests regarding the publication of this paper.

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