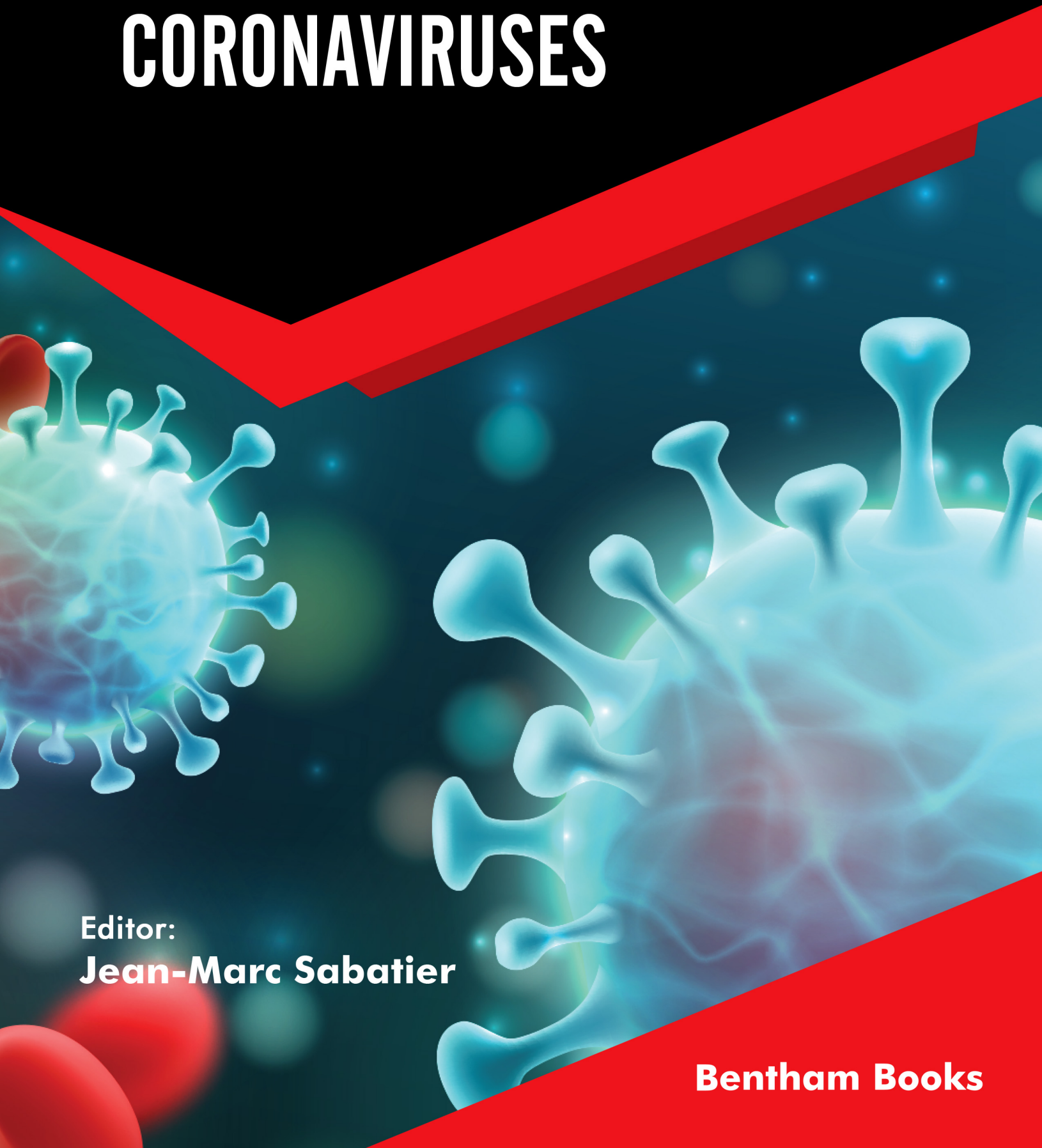
CORONAVIRUSES



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PREFACE

In this difficult period of the SARS-CoV-2 (and its variants) infection responsible for Covid-19 diseases, the importance of scientific works and reviews dealing with these viruses has never been more essential and vital. This book brings together essential data regarding prevention (vaccination), detection, and various approaches (chemotherapeutic drugs and antibodies) to the potential treatment of coronavirus infections. It consists of six chapters concerning, (1) the effect of candidate drugs chloroquine and hydroxychloroquine on QT interval in infected patients with Covid-19 diseases (chapter 1 by Aleem *et al*.), (2) the impact of the Covid-19 pandemic for the South Asian Association for Regional Cooperation (SAARC), comprising the Bangladesh, Bhutan, Maldives, Nepal, Pakistan, Sri Lanka, India, and Afghanistan (Chapter 2 by Kanwar *et al*.), (3) the humoral immune response in humans based on anti-SARS-CoV-2 antibodies to treat Covid-19 diseases (chapter 3 by Çalık1 *et al*.), (4) the antiviral potential of herbal-based immunomodulators (chapter 4 by Kumari *et al*.), (5) the various methods and strategies for diagnosing SARS-CoV-2 (and its variants) infection in hosts/humans (Chapter 5 by Narvekar *et al*.), and (6) the resistance to the spread of SARS-CoV-2 and related Covid-19 diseases within a population based on the pre-existing immunity of a high proportion of individuals as a result infection or previous vaccination (chapter 6 by Tiwari & Sahu). Such a book comprising a compilation of key data on SARS-CoV-2 and Covid-19 should certainly be a tool of crucial importance for researchers around the world working on these research themes, as well as for clinicians confronted to a growing number of patients with Covid-19 (data from 20th April 2021: 141 million cases of SARS-CoV-2 infection worldwide, with over 3 million deaths).

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CHAPTER 1

Effect of Chloroquine and Hydroxychloroquine on the QT Interval in Patients with COVID-19: A Systematic Review

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Abstract: Coronavirus disease 2019 (COVID-19) has been a major global health crisis since the influenza pandemic of 1918. Based on data from *in vitro* studies, traditional antimalarial agents, chloroquine and hydroxychloroquine, have been proposed as potential treatment options for patients with COVID-19. Both these medications have also been noted to prolong the QT interval, which increases the risk of drug-induced *torsade de pointes (TdP)* or sudden cardiac death (SCD) when used in non-COVID-19 patients. We reviewed the published clinical studies evaluating the QT interval in COVID-19 patients treated with chloroquine/hydroxychloroquine with or without azithromycin. A literature search using Google Scholar, and PubMed was done for studies published from December 2019 to September 2020. Studies with no specific description of the QT interval were excluded from this review. We identified twelve studies that qualified our criteria, which included 2595 patients. This review addresses the pathophysiology of QT prolongation and the incidence of the magnitude of QT prolongation associated with these medications when used in the treatment of patients admitted with COVID-19. Although most incidences of QT prolongation occurred two or more days after the initiation of these medications, early events of QT prolongation on the first day of therapy have also been reported. Notably, the combination of chloroquine/hydroxychloroquine with azithromycin was associated with a higher incidence of QT prolongation. Although QT prolongation is evident in all the described studies, none of these studies were designed to address the risk of QT prolongation associated with these medications in the outpatient setting or when used as prophylaxis against COVID-19. With the currently available literature, caution with close monitoring of the QT interval is advised when using these antimalarial agents in patients hospitalized with COVID-19 infection.

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Keywords: Chloroquine, Coronavirus disease 2019, Covid-19, Drug-induced torsade de pointes (*tdp*), Hydroxychloroquine, Hydroxychloroquine and azithromycin, Qt prolongation, QTc prolongation, SARS-CoV-2, Sudden cardiac death.

INTRODUCTION

COVID-19 caused by a beta coronavirus is included in the same subgenus as the severe acute respiratory syndrome (SARS-CoV) virus. Since the cases of an acute respiratory illness caused by the COVID-19 were initially reported in China in December 2019, the viral infection has spread worldwide, with about four million confirmed cases and more than three hundred thousand death [1]. There has been an urgency to mitigate this illness with experimental therapies and drug repurposing. Currently, there are over 25 potential drugs that are being investigated, with ten in active clinical trials [2]. Traditional antimalarial agents, chloroquine and hydroxychloroquine, have been suggested as potential treatment options for patients with COVID-19 infection based on their *in vitro* activity against the virus [3]. During the early course of the pandemic, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA), allowing the use of chloroquine and hydroxychloroquine in adult hospitalized patients with COVID-19 outside of a clinical trial . The issuance of the EUA has enabled the conduct of randomized controlled trials(RCTs) to test for the efficacy and safety of these medications [4]. In this systematic review, we aimed to discuss the latest available data regarding the specific complication of QT prolongation associated with the use of chloroquine and hydroxychloroquine in patients with COVID-19 infection.

Pharmacodynamics and Pharmacokinetics of Chloroquine and Hydroxychloroquine

Chloroquine is a 9-aminoquinoline that was first synthesized in 1934 from its parent compound quinine, which was derived from the bark of the tropical cinchona tree [5]. Hydroxychloroquine (HCQ) belongs to the same molecular family as chloroquine and differs from its counterpart by the presence of a hydroxyl group [5, 6]. Historically, chloroquine and hydroxychloroquine have been used as antimalarial agents for decades. With the noted immunomodulatory properties of these medications, they have been used widely for the treatment of chronic systemic inflammatory diseases like rheumatoid arthritis and systemic lupus erythematosus [5]. The pharmacokinetics of hydroxychloroquine is similar to that of chloroquine; however, hydroxychloroquine is reported to be less toxic than chloroquine [5]. Both chloroquine and hydroxychloroquine have excellent

oral absorption, bioavailability, low blood clearance and, very long half-lives (40 days and 50 days) and are eliminated by hepatic as well as renal excretion [7 - 9].

The antiviral properties of chloroquine have been explored as early as 1987 [10]. *In-vitro* studies have demonstrated the effectiveness of these medications on different RNA viruses, including human immunodeficiency virus (HIV) [6, 11]. However, *in vitro* success of these drugs has not been replicated in clinical trials [6, 12]. *In vitro* studies have shown hydroxychloroquine to inhibit SARS-CoV-2 replication with a 50% maximal effective concentration (EC50) [13]. They are also known to block virus infection by increasing the endosomal pH and interfering with glycosylation of cellular receptors of SARS-CoV [12]. Chloroquine and hydroxychloroquine demonstrate their anti-inflammatory properties by blocking the secretion of pro-inflammatory cytokines such as IFN-gamma, TNF-α, IL-6, and IL-1 [5]. This anti-inflammatory action of chloroquine and hydroxychloroquine has been hypothesized to be beneficial in countering the inappropriate immune activation by SARS-CoV-2, leading to ARDS [14].

Effect of Chloroquine and Hydroxychloroquine Against SARS-CoV-2

In vitro Studies

Based on previous preclinical data demonstrating hydroxychloroquine having anti-SARS-CoV activity in the last SARS outbreak [15], Yao *et al.* studied the activity of chloroquine and hydroxychloroquine *in vitro* against SARS-CoV-2. Hydroxychloroquine was noted to be more effective than chloroquine *in vitro* against SARS-CoV-2 infection [3]. Liu *et al*. also described the positive effect of chloroquine and hydroxychloroquine on SARS-CoV-2 *in vitro* and concluded hydroxychloroquine to be superior to chloroquine in inhibiting SARS-CoV-2 *in vitro*. Chloroquine was associated with a significant reduction in quantitative real-time ET-PCR viral load in Vero E6 cells infected with SARS-CoV [13]. Chloroquine was also noted to inhibit the entry and post-entry stages of the SARS-CoV virus at fluid concentrations, which could be achieved at doses usually used in patients with rheumatoid arthritis [9, 16].

In vivo Studies

Data from several initial nonrandomized control studies showed significant improvement in clinical symptoms and early viral conversion rates with the use of hydroxychloroquine and chloroquine in patients with COVID-19 [17 - 20]. These studies, however, did not address the cardiac adverse effects of these medications, precisely their effect on QT interval by these medications. Data from further observational studies examining the clinical efficacy of these drugs could not replicate the positive results demonstrated by the initial trials [21 - 23]. A double-

CHAPTER 2

COVID-19: Impact of Pandemic on SAARC Nations

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Abstract: The recent outbreak of Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), from Wuhan, China, has turned out to be a global pandemic after sustained human to human transmission. While developed nations like the USA, Spain, Italy, Germany, and so forth have not been able to handle the episode, the situation at the moment is devastating in the South Asian Association for Regional Cooperation Countries, popularly known as SAARC countries. The present report is an attempt to understand the measurable correlation of the coronavirus cases, casualties, and mortality rates in the SAARC nations. It also analyses the drugs being tested in these countries to battle against the deadly virus. Moreover, the response of SAARC nations against COVID-19 and the effect of lockdown on daily life, economy, environment, and education have been discussed. Finally, to mitigate the COVID-19 pandemic, a strategy has been chalked down based on the knowledge obtained from the rest of the world.

Keywords: COVID-19, Coronavirus, COVID pandemic, Economy, Environment, Mortality rate, Mitigation, Pandemic 2020, SARS-CoV-2, SAARC nations.

INTRODUCTION

An outbreak of a Severe Acute Respiratory Syndrome CoronaVirus disease 2019 (COVID-19) from Wuhan, China, has been declared a global pandemic by the World Health Organization (WHO) on 11th March 2020. SARS-CoV-2 is a beta Coronavirus like MERS-CoV and SARS-CoV. A group of researchers believes that coronavirus may have spread from animals (bats) to humans *via* pangolin and later spread through human - to - human contact, which afterward led to an

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international community spread. The structure of SARS-CoV-2 has been shown in Fig. (**1**) [1]. The whole world has come under the effect of this Chinese originated virus, where a total count of positive cases has gone to 50,250,314, and deaths have risen to 1,255,906 (by 6th November 2020). (Source: Worldometer)

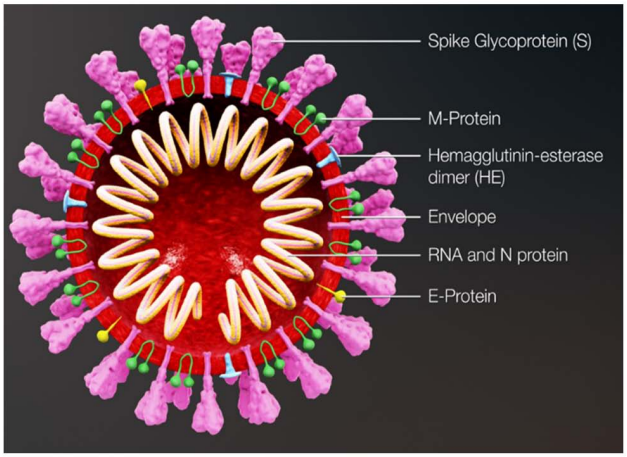

Fig. (1). Structure of SARS-CoV-2 https://www.scientificanimations.com/coronavirus-symptoms-a-d-prevention-explained-through-medical-animation/.

China is a growing economic player that has always tried to play a strategic role in neighboring countries. Despite being only an observer in the South Asian Association for Regional Cooperation (SAARC), its role has been the most discussed one and has always been seeking an expansion. With an outbreak of this deadly virus, China has greatly impacted the SAARC nations. Although this SARS-CoV-2 virus has drastically affected the whole world, it is important to visualize the impact of this deadly virus on economically struck developing nations grouping referred to as SAARC. Since the impact of this virus on the European nations has been constantly documented, no such report has been written on SAARC nations. Moreover, SAARC countries make up 21% of the total world population, so the fate of the world post-COVID-19 will be largely dependent on COVID-19 impact on SAARC nations.

The SAARC is the regional intergovernmental organization and geopolitical union of states in South Asia. It is a cluster of 8 countries, namely, Afghanistan, Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka. It was established on 8th December 1985 in Dhaka. Its dialogue is often conducted in the form of SAARC meetings to promote economic and regional integration. In this pandemic time, to chart out a common strategy to combat the COVID-19 in the region, India initiated a SAARC video conference on 15th March 2020. India offered the establishment of a rapid response team of doctors and specialists,

online training capsules, sharing of software, common research platform, evacuation of citizens, *etc*., as relief measures during the video conference. As a way forward, the COVID-19 Emergency fund was proposed on voluntary contributions from all the countries. To collate COVID-19 data, a website 'http://www.covid19-sdmc.org/' has been created by the SAARC Disaster Management Centre. Furthermore, India has developed an electronic platform called the 'SAARC COVID-19 Information Exchange Platform (COINEX)' accessible to all the SAARC countries.

STATISTICAL ANALYSIS

As of 6th November 2020, the SAARC member states have reported a total number of 9,417,660 positive cases, and out of that, 8,674,024 have been recovered, whereas 140,584 faced death (Source: Worldometer). The highest number of cases has been reported in India (8,411,724), followed by Pakistan (340,251), Bangladesh (213,254), Nepal (182,923), Afghanistan (41,935), the Maldives (11,893), Sri Lanka (12,970), and the lowest in Bhutan (358). Amongst the SAARC member states, India has the highest population, which can justify the maximum number of cases in the country. Fig. (**2**) shows the mortality rate, total tests, cases per million profiles, and recovery percentage for all the 8 SAARC countries.

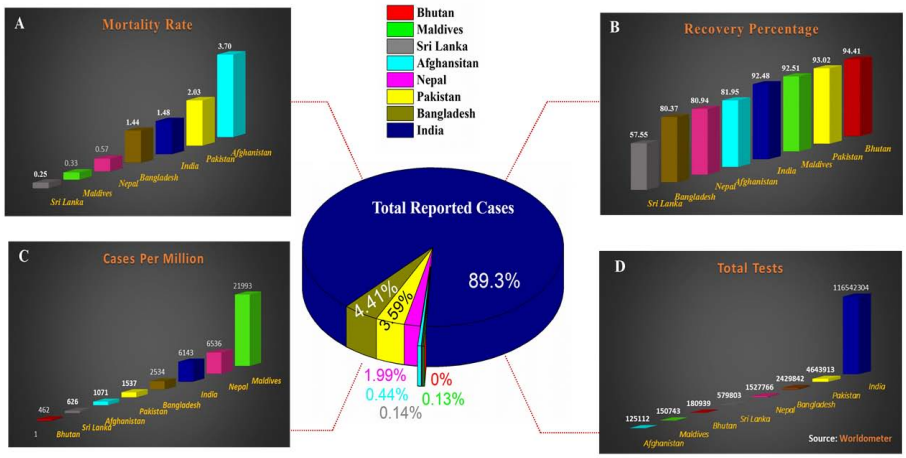

Fig. (2). Data compilation from the total reported cases- **A)** Mortality rate **B)** Total tests **C)** Cases per million profiles, and **D)** Recovery percentage (Source: Worldometer) for all the 8 SAARC countries till 6th November, 2020.

The number of deaths has been found to be continuously increasing in near geometric progression with the rise in the number of cases for each country except

CHAPTER 3

Neutralizing Antibody-Based Therapies against COVID-19

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Abstract: The novel coronavirus infection (COVID-19) that emerged from Wuhan, China in December 2019 caused a global health crisis. With confirmed cases worldwide exceeding 40 million and continuing to grow, many research groups have been working to develop therapeutics and vaccines against COVID-19. In fact, some vaccine candidates are currently being tested in the clinical phase. The primary target of most of the studies is the spike glycoprotein of the SARS-CoV-2 virus, which binds to ACE2 receptors and allowing the virus entry to the host cells for the initiation of infection. Drugs such as Hydroxychloroquine and Favipiravir only aim to minimize symptoms but cause severe side effects in patients. On the other hand, neutralizing antibodies represents an important strategy for the treatment of COVID-19. Therapeutic neutralizing antibodies against SARS-CoV-2 spike protein can induce antibodies to block virus binding and fusion, thus inhibiting viral infection. Clinical studies show that antibodies obtained from plasma of recovered patients can improve prognosis and increase the survival rate. However, obtaining a high amount of plasma-based antibodies is a major problem in practice, therefore there is an urgent need to develop and produce reliable, high-yield, and specific antibodies against COVID-19. Instead of convalescent plasma therapy, monoclonal antibodies, and other antibody-based therapies such as IgY antibodies, camelid antibodies/nanobodies offer a promising alternative. In this chapter, a perspective on antibody-based approaches currently developed against SARS-CoV-2 by given some fundamental knowledge about these neutralizing antibodies and their potential for the treatment of COVID-19 is presented.

Keywords: Camelid antibodies, Convalescent plasma therapy, IgY antibodies, Monoclonal antibody, Neutralizing antibodies, SARS-CoV-2.

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INTRODUCTION

The new coronavirus, SARS-CoV-2, which emerged in Wuhan, China's Hubei province, in late December 2019, spread to many countries in a short time and became an international pandemic affecting the whole world. According to the World Health Organization, the pandemic affected over 40 million people in the world and caused the death of more than 1 million people.

COVID-19 can cause different clinical manifestations ranging from asymptomatic disease to fatal disease [1]. The disease may initially show little or no symptoms. Typical symptoms of COVID-19 are fever, sore throat, cough, fatigue, shortness of breath, weakness, and muscular pain, however, new symptoms are reported every day such as loss of the sense of smell because the clinical outcomes of the disease have been clarified yet [2]. The disease is usually transmitted through respiratory droplets, hands, or surfaces contaminated by the virus and the incubation period of the disease is generally between 3-14 days [3].

Experimental and clinical studies of antiviral drugs (such as remdesivir, chloroquine, hydroxychloroquine, ritonavir), convalescent plasma transfusion, and vaccine formulations against COVID-19 disease have been ongoing. The safety of some antiviral drugs such as favipiravir and remdesivir used in the treatment of the disease is not certain and clinical studies are still ongoing [4]. Another treatment option is plasma transfusion from the recovered patient, but the difficulty in obtaining plasma during recovery and limited resources (donor) make clinical application difficult [5]. Drug and vaccine studies against COVID-19 disease are a key strategy both to prevent widespread viral infection and to reduce morbidity and mortality [2].

Currently, more than 230 vaccine candidates are in pre-clinical and clinical development to prevent SARS-CoV-2 infection [6]. On December 11, 2020, the first vaccine for Covid19 disease, the Pfizer-BioNTech COVID-19 (BNT162b2) mRNA vaccine (Pfizer, Inc; Philadelphia, Pennsylvania) had been approved by the Food and Drug Administration (FDA) with Emergency Use Authorization (EUA) [7]. Moderna COVID-19 (mRNA-1273) vaccine (ModernaTX, Inc; Cambridge, Massachusetts) is the second mRNA vaccine approved by the Food and Drug Administration (FDA) with Emergency Use Authorization (EUA) on December 18, 2020 [8]. Also, an adenoviral vector vaccine, ChAdOx1 nCoV-19 (AZD1222), developed by a group from the University of Oxford is currently being evaluated in phase II/III efficacy trials [9]. In today's drug and vaccine studies, new molecular biotechnological methods are more preferred in order to obtain products that are therapeutically more effective with fewer side effects [10]. Since the ‘90s, with the development of recombinant gene technology and

molecular immunology, antibodies created against various diseases *in vitro* or *in vivo* have been humanized by gene engineering. The binding kinetics of antibodies have been increased and the ability to work in coordination with the immune system in a physiological environment has been gained. Because of these developments, antibody-based therapeutic applications gain important potential in clinic studies [11]. Antibody therapy, one of the fast and effective treatment in contrast to the traditional vaccine approaches, against SARS-CoV-2 offers a promising strategy in the control of the pandemic in terms of prophylactic and therapeutic purposes.

Coronaviruses consist of 4 main protein domains structurally; the surface spike (S) glycoprotein, the membrane (M) protein, the small envelope (E) glycoprotein, and the nucleocapsid (N) protein [12]. The spike (S) glycoprotein on the surface of the SARS-CoV-2 has an important role in the viral entrance [13]. In recent studies, it has been proven that the S protein of the SARS-CoV-2 virus is more likely to bind to the ACE2 receptor than other coronavirus types which cause the new coronavirus to spread faster among humans [14]. The S1 subunit of the S protein binds to angiotensin-converting enzyme 2 (ACE2) receptors, which are commonly found in respiratory system cells. The S2 subunit of the S protein mediates the fusion of the viral membrane to the host cell membrane [1]. Thus, blocking the S protein, which has an important role in the entry of the virus into the cell, with neutralizing antibodies is one of the main strategies of antibody therapies [15]. S1 subunit, particularly the S1-RBD, S1-N-terminal domain (NTD), and S2 domain has been the main target of neutralizing antibodies due to their high functionality in infection of the virus [16].

In this chapter, a perspective on neutralizing antibody approaches based on monoclonal antibodies, convalescent plasma antibodies, IgY antibodies, and camelid antibodies and their potential for the treatment of COVID-19 are presented.

Convalescent Plasma Therapy

Immune or convalescent plasma means plasma collected from recovered individuals with high titers antibodies. Convalescent plasma contains antibodies and proteins against the pathogen. Convalescent plasma therapy (CPT) is the administration of blood plasma taken from people recovered to individuals suffering from the same disease [17, 18]. The concept of CPT was created in the 1880s against diphtheria and tetanus toxins by using antibodies obtained in the blood of actively infected animals [19, 20]. After that CPT has been used for over a century. In the early 1900s, the use of CPT for infectious diseases such as poliomyelitis, small measles, and mumps was studied [21 - 23].

CHAPTER 4

Antiviral Potential of Immunomodulators Based Medicinal Plants against Novel Coronavirus-19: Against the Pandemic

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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the coronavirus family and is responsible for coronavirus disease 2019 (Covid-19 is a new animal origin communicate or infectious disease). The first case of Covid19 was reported in Wuhan, China, in December 2019, and due to its rapid increase and high incidence rate, it has become a pandemic health problem worldwide. It mainly attacks the host's immune system and impairs the regulation system, playing a significant role in its pathogenesis, causing covid-19 disease. Still, we are waiting for such molecules that can act as immunomodulators and enhance the body's immune system against the disease. This literature-based chapter was prepared by searching numerous relevant SCI and SCOPUS articles on the SARS-CoV-2 and COVID-19, herbal formulation and its active molecules from different databases like- Google Scholar, PubMed, and ResearchGate. Here, we were trying to highlight or repurpose several Immunomodulators (Alkaloids, Glycosides, Flavonoids, Sapogenins, and Curcumin) of plant origin. Plant-derived Immunomodulators are capable of stimulating/suppressing the components of the host immune system and both innate and adaptive immune responses. However, in this present review, we will discuss some phytoactive chemicals, which act as immunomodulators, and their immunomodulation mechanism in the host. Hopefully, this work shall encourage the researcher community to undertake further work on plant-based antiviral therapy with potential immunomodulatory activity, which might be responsible for modulating the host immune system to cure Covid-19. Besides, we discuss the further prospect of this study.

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Keywords: Alkaloids, COVID-19, Curcumin, Flavonoids, Glycosides, Immunomodulators, Medicinal plants, SARS-CoV-2, Sapogenins.

INTRODUCTION

In the current scenario, pandemic diseases (is known as Communicable diseases/ infectious diseases) are a major-public-health concern at the global level and are the reason for high morbidity, mortality, and transience that require extensive medical services. Due to the high rate of mutation on the viral surface, it is challenging to develop antiviral drugs or medicines that can fight against the virus or suppress its toxin effect *via* targeting viral elements. Generally, the transmission of any viral disease is spread worldwide due to travel and instant urbanization, making it a serious hazard to public health and safety [1].

Although communicable diseases (Malaria, tuberculosis, leprosy, influenza, smallpox) have played a devastating role in the past centuries, the novel coronavirus has contributed to a terrible outbreak in the 21st century, crossing several continental boundaries of the planet. However, it is closely associated with Severe Acute Respiratory Syndrome(SARS-CoV) and Middle East Respiratory Syndrome(MERS-CoV) within the human population. Symptoms including fever (high temperature), dry cough, and dyspnea are very similar to viral respiratory symptoms like flu, and its clinical features are quite similar to pneumonia [2].

Currently, it is clear that novel Covid-19 is the 3rd most dangerous animal origin pandemic disease and in 2019 first case of Covid19 was reported in Wuhan (China) with similar pneumonia symptoms (mild to moderate respiratory issues). Now, approximately 215 countries have been affected [3], and the spread has caused a high mortality rate (ranging from 100 to 100000 death so far) worldwide; however, World Health Organisation (WHO) had been declared in March 2020 that Covid19 was pandemic [4]. Continuously, cases were increasing and reached more than 23,584,259 with a high death rate (812,517), and now, SARS-CoV-2 is officially known as ICTV (International Committee on Taxonomy of Viruses), and that causes the most significant transform, globally [3, 4].

Still, covid-19 is rapidly increasing because there is no available specific treatment or drug. Therefore, we need to develop the best way to treat/manage/ prevent this infectious disease. Due to the adverse effect of chemical drugs, we still need the natural resource of Immunomodulators that can replace them in therapeutic regimens.

This study has provided better solutions in the prevention and treatment of Covid19, and some proven immunomodulators can be employed as a preventive antiviral medicine to oppose the symptoms of COVID-19. This present chapter

here tries to repurpose the ancient plants' based Immunomodulators and provides a new approach for fighting the viral disease / microbial infections and their diffusion.

MATERIAL AND METHODS

Science Direct & Scopus, PubMed, Springer Link, ResearchGate, Wiley Online Library, and Google Scholar databases and Elsevier were searched, restricting the search to research articles published in English and peer-reviewed or preprint journals available. The search language rules were built with a professional librarian's guidance and included the following search terms: SARS-CoV-2, COVID-19, Medicinal plants, Immune system, Immunomodulators, Alkaloids, Glycosides, Flavonoids, Sapogenins, Curcumin and antiviral herbal formulation other- Charak Samhita, Sushrut Samhita, athar-vaveda.

The authors of this current review included recent reports, ancient literature, herbal formulation reports, and review articles. The present chapter search was conducted from May to December 2020, and obtained cited literature from various index journals was screened (from 1997 to 2020).

A GENERAL OVERVIEW ON THE NOVEL CORONA VIRUS-2019 AND ITS STRUCTURE

Genomic material of the novel coronavirus-2019 is- positive-sense single-stranded RNA virus (PSSSRNA); member of Orthocoronavirinae (includes four genera, namely alpha (α), beta (β) delta (δ) and gamma (λ) coronavirus subfamily, and the family Coronaviridae [5, 6] and mainly type α & β- CoVs infect mammals [7]. Recently, our planet found that human-affected virus family members of coronavirus -SARS-CoV-2, which have seven human-susceptible strains, mainly cause mild infections and cause severe respiratory tract infections [8].

The researcher has found a very close relationship between SARS-CoV-2 and other betaCoVs through their genomic sequencing studies. It resembles Sarbecovirus; however, 79% homology with SARS-CoV and also utilizes the same pathway as ACE2 (Angiotensin-converting enzyme 2, present on the cell of lungs, arteries, heart, *etc.*, serves as the entry point into cells for viruses) receptors to infect its hosts (human) with MERS-CoVs [8 - 10].

Some studies have defined some crucial differences between SARS-CoV-2 and other betaCoVs, making more infectious SARS-CoV; they have high transmission efficiency from human to human within a short time. SARS-CoV-2 has a primary reproduction number from other epidemic theories, denoted by R0 means transmission potential of a Cov-19-disease, *i.e.*,4.7 to 6.6 and highly infectious.

CHAPTER 5

Diagnostic Measures for COVID-19: Current Status and Advances

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Abstract: The outbreak of COVID-19 in China and its gradual spread over the entire globe, irrespective of age, sex or origin, has posed a major threat to the health of the entire human population. Investigations subsequent to the virus outbreak revealed that the unknown etiology was a novel coronavirus, later referred to as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The treatment and survival of patients have been largely dependent on an accurate diagnosis of this infection, both in symptomatic and asymptomatic individuals. Thus, highly sensitive and specific laboratory diagnostic methods are imperative for the accurate diagnosis of this condition. This manuscript focuses on various molecular and diagnostic imaging tools for reliable diagnosis of COVID-19 and the correlation of their outcomes with those from previous coronavirus epidemics. The molecular diagnostic tools include real-time reverse transcription polymerase chain reaction (rRT-PCR), ELISA based detection of early humoral response and DNA sequencing. The manuscript will also focus on national and international policies of testing, additional developments, issues and challenges faced in the diagnosis of COVID-19. The chapter will, therefore, highlight the current regime followed, developments and the probable lacunae that, if overcome, could improve the diagnostic schema of this disease.

Keywords: COVID-19, CRISPR, CT scan, Diagnosis, ELISA, FELUDA, Oximetry, RT-LAMP, RT-PCR, SARS-CoV-2, SHERLOCK.

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Jean-Marc Sabatier (Ed.)

INTRODUCTION

The sudden upsurge of coronavirus disease-19 (COVID-19), which originated in Wuhan, China, has engulfed several countries across the globe. It is a global health concern that causes severe respiratory tract infection in humans, as declared by the World Health Organization (WHO). As of August 2020, there were 25 million cases of COVID-19 in several countries across the world, of which 16.4 million cases had recovered, while 0.85 million patients had succumbed to the disease-associated fatalities. The illegal sale of wild animals in the Huanan Seafood Wholesale Market and human consumption of these animal species has been speculated for causing the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which eventually resulted in the devastating outbreak of COVID-19. Subsequent investigations revealed that a considerable section of the population diagnosed with COVID-19 was not directly linked to this source, indicating person-to-person transmission [1].

SARS-CoV-2 belongs to the family of viruses called Coronaviridae, which possess a single-strand, positive sense RNA genome of approximately 26-32 kilobases. The viral hosts of this family include birds and mammals. Novel coronaviruses have been identified in the recent past, such as the coronavirus of bat origin that led to fatal acute diarrhea syndrome in pigs in 2018 [2]. Coronaviruses, which are pathogenic to humans, usually result in mild clinical symptoms. However, there have been exceptions, such as the severe acute respiratory syndrome coronavirus (SARS-CoV), which originated in Guangdong, southern China, in November 2002. It resulted in 8000 human infections and 774 deaths in 37 countries during 2002-03. The other exception was the Middle East respiratory syndrome coronavirus (MERS-CoV), which was first detected in Saudi Arabia in 2012. It resulted in 2494 laboratory-confirmed infections and 858 deaths as reported in September 2012. Phylogenetic analysis revealed that SARS-CoV-2 shares a sequence identity of approximately 79% with SARS-CoV and approximately 50% with MERS-CoV [3, 4]. Interestingly, SARS-CoV-2 shares a very high sequence identity of approximately 96.3% with the bat coronavirus RaTG13, which was observed in bats from Yunnan in 2013. However, it has been reported that bats are not the immediate source of SARS-CoV-2 [5].

COVID-19 affects different people in different ways. Most infected people are known to develop mild to moderate illness and recover without hospitalization. The most common symptoms of COVID-19 include fever, fatigue, dry cough or dyspnea. The less common symptoms include aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell. After being declared as a pandemic, governments across the world have implemented lockdowns and strict control measures to curb the spread of this disease. Maintaining physical

distancing and wearing masks in public are two widely accepted measures that have been observed to control the spread of COVID-19. Despite several preventive measures, cases continue to increase due to the highly contagious nature of this disease and several other factors that are country-specific. The treatment regime for COVID-19 is not specific, and positive cases have been treated using existing anti-viral medicines with an aim to repurpose them. Citizens across the globe are eagerly waiting for a reliable vaccine candidate to be available in the market to obtain relief from the catastrophe caused by this pandemic [1, 6].

Considering the current status of the treatment and vaccination regime for COVID-19, it is very important to follow the sequential strategy of case identification, contact tracing, isolation and testing using a very specific and sensitive laboratory diagnostic technique, as also followed during previous epidemics of SARS-CoV and MERS [7]. In India, several cities have followed the well-known COVID-19 management strategy of 3Ts – testing, tracing and treatment. Considering the population of India, it is difficult to test every individual. However, it cannot be an excuse to justify the insufficient testing in majorly affected cities such as Mumbai, India. Even in the absence of rapid testing kits, oximeter readings were monitored to measure oxygen saturation in densely populated areas such as Dharavi, Mumbai, while massive door-to-door thermal screenings were done in Bengaluru, India. Apart from these strategies, institutional quarantine, stringent containment, use of data analytics for future predictions, regular updates on smartphones through mobile applications such as *Aarogya Setu* and online training and protocols for healthcare workers have been part of the COVID-19 management strategy in India.

It is not practical to use viral cultures for establishing an acute diagnosis of SARS-CoV-2 as it takes a minimum of three days to cause cytopathic effects in cell cultures and also requires biosafety level-3 facilities, which are not available at many healthcare institutions. Considering these drawbacks, reverse transcription-polymerase chain reaction (RT-PCR) has been employed for an accurate laboratory diagnosis of COVID-19 worldwide. The complete genome of SARS-CoV-2 was available early in the epidemic, which facilitated the development of specific primers and standardized laboratory protocols for COVID-19. Several serum antibody-antigen detection-based diagnostic tests are also being developed for quick diagnosis of COVID-19 [8 - 10]. This chapter discusses various diagnostic methods available for COVID-19, including PCR and ELISA based molecular assays. The issues and challenges in the accurate diagnosis of COVID-19 have also been discussed, along with the advancements in this area. The patent summary of COVID-19 diagnostics has also been covered. The chapter will, thus, discuss the complete scenario of COVID-19 diagnosis.

CHAPTER 6

Herd Immunity: An Indirect Protection Against COVID-19

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Abstract: COVID-19 is an infectious as well as contagious disease caused by severe acute respiratory syndrome (SARS) - Cov2 virus. As of date there is no specific treatment for coronavirus infection. Only symptomatic treatment is given to corona positive patients. Herd immunity is a natural phenomenon providing indirect protection against infectious diseases that are contagious. The principle behind herd immunity is that if enough immune persons are present in a community, then that will interrupt the transmission of an infectious agent and provide indirect protection for susceptible or unimmunized individuals. There are two ways to achieve herd immunity, either by mass vaccination or by allowing the disease to make its round through the population. Since vaccine development is a time taking process, herd immunity can be achieved by unleashing the virus in a controlled way. Sweden is the world leader of herd immunity in the fight against the corona virus. However, there are limitations to using herd immunity worldwide to stop the spread of this novel corona virus.

Keywords: COVID-19, Herd immunity, Vaccination.

INTRODUCTION

Immunity is the defense mechanism of our body against any pathogen or invading agent. The study of immunity is called immunology. There are 3 lines of defense. The first line is the physical barrier which includes the surface barriers like intact skin, mucous membrane, tear, saliva, urine and other body fluids [1, 2]. The second line of response is the non-specific response against any pathogen. The third line of defense is the specific immune response to a variety of pathogens in a specific manner. This specific immune response is adapted or acquired when the first two lines are inadequate [3, 4].

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Immunity can be innate or acquired. Innate immunity is due to an individual's constitutional make up. It is a non-immunological response. Negroes are resistant to yellow fever than whites because of innate immunity [5, 6]. When the innate immunity is inadequate, acquired immunity develops. Acquired immunity can either be active or passive. Both active and passive immunity can either be naturally acquired or artificially stimulated [7, 8]. Types of immunity are shown in Fig. (**1**).

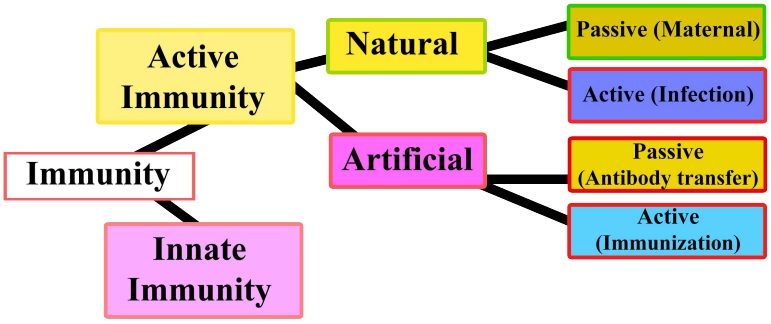

Fig (1). Types of immunity.

Antigen is the foreign substance when introduced into the body that can produce disease. Our body in response to antigen produces antibodies. The antibodies can eliminate antigens to make us free from diseases [9, 10]. In the first exposure to antigen, the body recognizes the antigen and subsequently produces antibodies specific to the antigen. The production of antibodies is a time taking process. So, there is every chance of disease in the first exposure itself if enough load of the pathogen is introduced into the body. During the second exposure, the antibodies are already there, so they can eliminate the antigen [11, 12].

Following a clinical infection, a person naturally acquires immunity as antibodies are developed against the pathogen. So, the person never suffers from the disease for the second time if he suffers from the disease like polio, diphtheria *etc* [13]. During a sub-clinical infection (the person is exposed to the pathogen without any symptoms), the pathogen load is not enough to produce the disease but can protect the person during second exposure because of presence of antibodies [14]. Immunity developed after clinical or sub-clinical infection is called active immunity as the immune system is in action mode after the exposure of antigen to produce antibody. Naturally the fetus obtains the antibodies from its mother which can protect the fetus up to 6 months after birth. This is called passive immunity [15].

Both active and passive immunities can also be acquired or stimulated artificially. The live attenuated (toxoid) or killed (suspensions of microorganisms) form of the pathogen (antigen) can be administered to induce the production of antibodies [16]. These preparations are called as vaccines. Passive immunity can be produced artificially by directly injecting antibodies produced in an animal like horse, sheep, ox, rabbit, *etc* [17]. The antigen or venom is injected into the healthy animal to induce production of antibodies in the animal. When a satisfactory degree of immunity is produced, a large volume of blood is withdrawn from the animal and serum is separated [18]. This serum now contains the antibody (immunoglobulin) or the anti-venom or anti-toxin and accordingly the preparations are known as sera or anti-sera [19]. In emergency cases of infections with novel infectious agents, since the antibody preparations are not developed, the convalescent plasma containing antibodies from individuals who have recovered from that novel infection can be administered [20 - 22].

The antigen containing preparations (vaccines) can stimulate active immunity. The immunity develops slowly but has a lasting effect. They are used for long term prophylaxis. The antibody containing preparations (sera and anti-sera) can stimulate passive immunity. The immunity provided is immediate but temporary. They are used for therapeutic purpose and short-term prophylaxis [23, 24]. Vaccination of children has protected them from many diseases which were once the major cause of morbidity and mortality [25, 26]. The World Health Organization (WHO) and the governments of different countries are encouraging and facilitating mass immunisation through planned vaccination programmes [27].

When a large percentage of individuals in a population or community are immunized against an infection either through mass immunization or post infection, then they provide protection to those persons who are not immune. In this condition, we say the population has developed herd immunity [28, 29]. COVID-19 is a pandemic caused by severe acute respiratory syndrome (SARS) - Cov2 virus. Since there is neither specific treatment nor vaccines for corona virus infection, herd immunity can be achieved through infections only by allowing the infection to run through the population in a controlled way.

HERD IMMUNITY

Herd immunity is also known as herd effect or community immunity or population immunity or social immunity. In herd immunity, all individuals in the population are not immune. A certain percentage of the population is only immune. Immune persons act as a barrier for the non-immune persons and protect them against the infection. When herd immunity is achieved, the population will

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