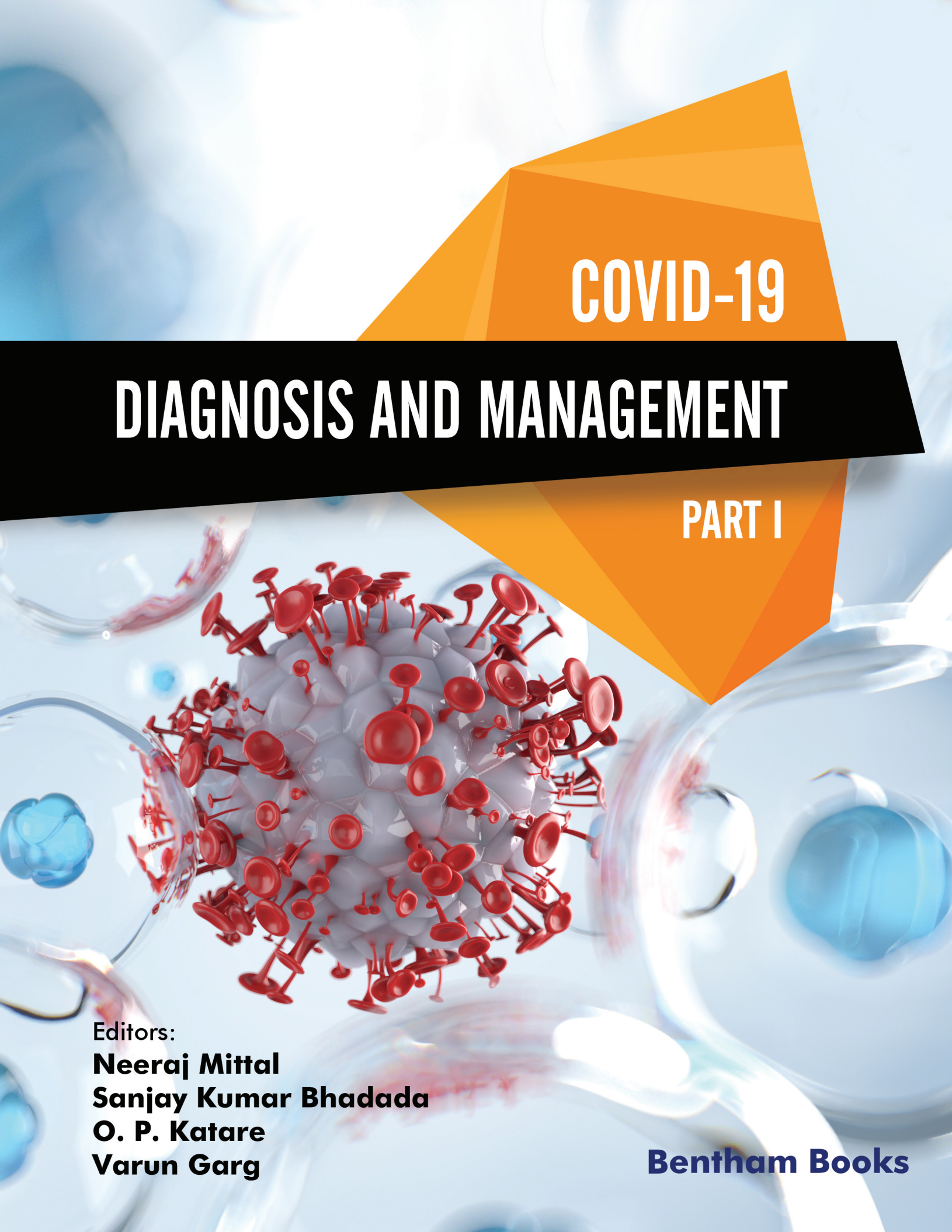
COVID-19

DIAGNOSIS AND MANAGEMENT

PART I



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COVID-19: Diagnosis and Management-Part I

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ISBN (Online): 978-1-68108-808-2

ISBN (Print): 978-1-68108-809-9

ISBN (Paperback): 978-1-68108-810-5

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FOREWORD

It is my proud privilege to introduce the book "COVID-19: Diagnosis and Management", which is authored by a group from PGIMER, Chandigarh. The timing of this monograph is very apt as it has been about 9 months since the start of the COVID-19 pandemic, and it is now that we are starting to unravel the various mechanisms of disease pathogenesis and treatment modalities for this viral infection which has infected 29 million people, out of which about 1 million have died till date globally.

It has been the need of the hour to come up with a treatment for this pandemic disease. Moreover, it is of utmost importance that all the information related to COVID -19 should be compiled in one place, a goal which this book will fulfill.

Though the tests for diagnosis of the infection have been developed in the start of the pandemic, there are still some issues in diagnosis, including the sensitivity of the best test available, *i.e*., Real-Time Polymerase Chain Reaction.

The book is very well organized and has been divided into two parts; each part is comprised of 6 chapters and covers all the aspects of COVID-19 from the history to the treatment of the disease. Based on the best scientific studies available, the editors and authors have used their vast professional experience to discuss the all clinical aspects of COVID-19, including clinical presentation to diagnosis in the first part and treatment of COVID-19 in the second part, and I am very sure that this compendium will become the benchmark to refer to for any information required on COVID-19.

Whenever we write books, we must have in our minds, as clearly as possible, the affirmation of Carlyle Guerra de Macedo, who was the Director of Pan American Health Organization, relative to the responsibility of what is being published: "It must be remembered that behind each table, every report or material examined, there are lives, there are people, there is suffering, waiting for our efforts and human solidarity." Both the parts of the book are very well organized, and the readers will get a mine of information available to date on COVID-19 in one place, and it would be helpful to both the clinicians and the lab professionals for day-to-day guidance in various matters. The monograph is comprehensive but is written in a lucid manner that is easy to grasp, and even complex topics are made simple for understanding.

I am also sure that as the knowledge of the virus evolves further, the authors will certainly keep updating the work from time to time, further adding to the importance of the book. I would like to congratulate the editors/authors for this tremendous effort, and I am very sure that this book will surely be of use to readers around the world and help them in the diagnosis and management of patients with COVID-19 and will also go a long way in the efforts to help fight the pandemic, which is being faced by the humanity now.

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PREFACE

The coronavirus disease 2019 (COVID-19) outbreak has spread throughout the globe and has been declared as a pandemic by the World Health Organization (WHO) on 11th March 2020. To date, *i.e.*, 1st September 2020, there are more than 25, 327, 098 confirmed cases of COVID-19 worldwide, and around 848, 255 deaths have been reported. Clinicians and scientists across the globe need all the information on this pandemic disease on one platform. This book, "COVID-19: Diagnosis and Management", is a concise and visual reference for this viral disease. This book has been divided into two parts I and II.

Part I will provide a comprehensive knowledge which will cover all the aspects related to COVID-19, such as: 1) History of coronaviruses, 2) epidemiology of COVID-19 3) clinical presentation of this viral disease, 4) how to diagnose it, whereas part II of the book covers the prevention and treatment methodology of this communicable disease.

Key Features:

1. Chapter wise description and segregation of all the areas from pathophysiology to diagnosis and management of COVID-19 in two different parts of the book.
2. Six chapters in the first part that begin with the history of the coronaviruses and their introduction.
3. Multiple tables and figures which summarize and highlight important points.
4. Covering all the aspects of COVID-19, making this a perfect textbook for virologists and medical students.
5. A summary of the current standards for the evaluation and diagnosis of COVID-19.
6. A detailed list of references, abbreviations, and symbols.

This book is an essential reference for practicing and training virologists, pulmonologists, medical students, scientists working in various research labs, pharmaceutical and biotechnology industries on COVID-19.

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CHAPTER 1

History of Pandemics

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Abstract: Pandemic is the term coined for the widespread of a disease or infection on a very large scale and across borders. COVID-19, an outcome of the spread of coronavirus, reportedly started from China and spread to almost all the countries of the world. Though it is not for the first time that there was an outbreak of a disease at such a high magnitude but the duration for which it has continued to grapple the world with its virulence and contagious nature, it has become important to take a peek into the history of other pandemics of the world too. Before COVID -19, about 20 major outbreaks of infectious diseases took place and claimed millions of lives in a sweep. The awareness of government bodies, WHO, and non-government organizations grew better with every pandemic. Understanding the role of basic hygiene, self-immunity, social distancing, living in coherence with other living and non-living components of the planet are some positive outcomes of these pandemics. These pandemics also necessitated the need for discovering new drugs and vaccines.

This chapter describes the major pandemics in the history of mankind, the origin and types of coronaviruses, the association of different types of coronaviruses with the ranges and severity of infections, and the origin of COVID-19.

Keywords: AIDS, Black Death, Contagious, Corona, COVID-19, Ebola, Epidemic, Flu, H1N1, Host, Outbreaks, Pandemic, Plague, SARS, Swine flu, Vaccine, Virulence, WHO, Yellow fever.

INTRODUCTION

The terms pandemic, epidemic, outbreak are primarily categorized based on the number of cases of a condition often used to describe infections. These terms have described the comparison of the expected number of cases in a particular time and how far-off cases have spread in the geographical area. Some conditions, such as cancer, hypertension, violence, beneficial behaviors, or even positive behaviors, can also be defined in the same way (Morens *et al*., 2009).

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The term ‘pandemic’, has its origin derived from the Greek words *pan* (meaning “all”) and *demos* (meaning “the people”). Pandemic refers to a spread of contagious illness that spreads across the countries or world, usually affecting a larger area than an ‘epidemic’. It is important to note that a disease that is affecting a large number of people or widespread cannot be said to be a pandemic till it is contagious (Fig. **1**). For example, cancer kills many people, but it is not a contagious disease, so not included as a pandemic (WHO, 2011).

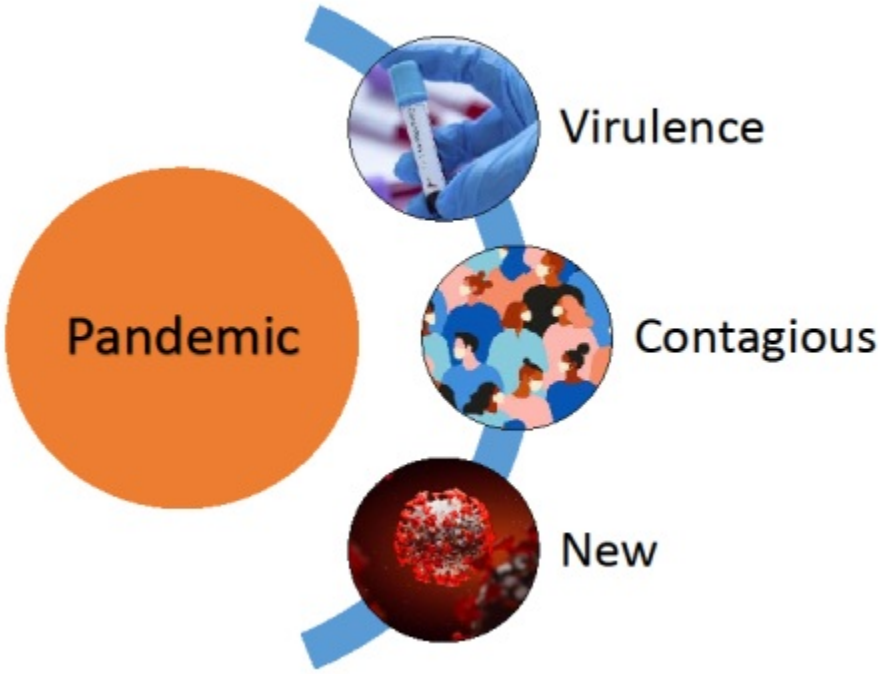

Fig. (1). The essentials of a pandemic.

The word “epidemic” is derived from the two Greek words *epi* meaning “upon or above”, and *demos* “the people”. An *epidemic* is an outbreak of disease that rapidly spread to a large population in a short period of time. For example, severe acute respiratory syndrome (SARS) took the lives of approx. 800 people worldwide during the epidemic of 2003 (Morens *et al*, 2009). An *outbreak* is an increase beyond expectation in the number of cases of a disease or condition occurring among a specified population in a limited geographic location and period of time (Gregg, 2002). The multi-state outbreak of *Salmonella Muenchen* in 1981 is an example of the outbreak.

Evidence suggested that the human population has suffered from many pandemics throughout history, be it the earlier form of smallpox or Spanish flu or the recent

incidence of Ebola or Covid. In world history, we can see a number of significant pandemics like cholera, dengue, plague, smallpox, AIDS, tuberculosis, influenza, West Nile disease, and severe acute respiratory syndrome (Rewar *et al*., 2015; Qiu *et al*., 2016). In 1999, WHO issued a printed paper on pandemic readiness overview, which was further revised in 2005 and 2009 while planning for an influenza pandemic. In this guidance, WHO defined different phases of pandemic and required appropriate actions for each phase. The revision includes the explanation of a pandemic and declaration of its leading phases (WHO, 2011). There have been many pandemics declared at different times as enlisted in Table **1**.

THE ATHENIAN PLAGUE

The plague has been responsible for three pandemics in history, including the 6th, 14th, and 19th centuries. The Athenian plague occurred during 430–26 B.C. It originated from Ethiopia, after that, it was distributed in Egypt and Greece. It is a well-known infectious disease primarily affecting rodents. *Yersinia pestis* bacteria is a causative agent of Athenian plaque that is related to the Enterobacteriaceae family. It is transferred in humans from rodents through skin-piercing by infected fleas. Transmission of bacteria in an uninfected person is possible by droplet contact, direct or indirect contact with infected material (Huremovic *et al*., 2017). Initial observed symptoms of the plague were headache, conjunctivitis, rashes on the whole body, and fever. After that patients showed severe symptoms like cough up blood, severe stomach cramps along with vomiting, and attacks of "ineffectual retching". Generally, on the seventh or eighth-day infected persons die (Thucydides, 2017). Approximately 75000 to 100000 people died due to the plague of Athens (Litteman *et al*., 2009).

Table 1. Chronology of pandemics.

Serial No.	Name of Pandemic Event	Year	Origin
1	Plague of Athens	430 B.C.	Ethiopia
2	Antonine Plague	165-190 A.D.	Italian peninsula
3	Justinian Plague	541-750 A.D.	Egypt
4	Japanese Smallpox	735-737 A.D.	Japan
5	Black Death	1347-1351	China
6	Aztecs Disease	1519-1520	Aztecs, America
7	London Plague	1665-1666	London
8	The Great Plague	1738	Central and Eastern Europe
9	Cholera 6 Outbreak	1817-1923	India

CHAPTER 2

Introduction to COVID-19

Hitesh Malhotra[1,*], **Anjoo Kamboj**[1] and **Peeyush Kaushik**[1]

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Abstract: In the mid 20th century, virologists identified a new category of the virus, which has a fringe of projections on its surface that appears like a crown and named coronavirus. Coronavirus belongs to the family of pleomorphic spherical viruses recognized by bulbous surface projection and ssRNA. As the virus belongs to the family of RNA-virus, the chances of mutation are very high, which further increases its pathogenicity. The coronavirus mainly attacks the respiratory tract and ultimately leads to respiratory failure. Recent outbreaks of coronaviruses are severe acute respiratory syndrome and the Middle East respiratory syndrome, which cause a great threat to human health with a high mortality rate. Later on, in late 2019, a new form of coronavirus appears in Wuhan, China where numbers of people are recognized with pneumonia-like symptoms. The condition was entitled with COVID-19 by WHO on Feb 2020, which was declared to be pandemic by the same agency in Mar 2020. The COVID-19 is considered to be originated from bats, which then transmit to humans due to the consumption of contaminated animal raw. The virus is highly contagious and spread at a very high rate, which produces global health risks. Further various existing treatment is used for treating the infection but still the precise and accurate treatment yet to be investigated.

Keywords: ACE-II, Air droplets, Breathlessness, China, Chronology, Coronavirus, COVID-19, Genome, Helicase, Membrane protein, MERS, Pneumocytes, Pneumonia, Replicase, Respiratory distress syndrome, SARS, Structural proteins, Virus, World, Transmission.

INTRODUCTION

The coronavirus belongs to a family of viruses that mainly affects the respiratory tract infection with prime symptoms, such as hyperthermia, pneumonia, breathlessness, and acute or chronic pulmonary infections. The coronavirus mainly affects animals, but recent investigations in the late 20th century reported some human cases. In 1930, the first coronavirus case was reported in chickens recognized by pneumonia-like symptoms and termed as avian infectious bronchitis virus. Further, in late 1960, the first human coronavirus case was

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reported (Pyrc *et al*., 2007). In 1968, electron microscopy of the virus was done and termed as **"Coronavirus"** due to its crown-like appearance, clearly depicted in Fig. **1**(**A** & **B**). Later on, in 1975, the International Committee on the Taxonomy of Viruses introduced a family Coronaviridae. In 2005, the family Coronaviridae was further split into two subfamilies, the Coronaviruses, and the Toroviruses (Tyrrel *et al*., 1968).

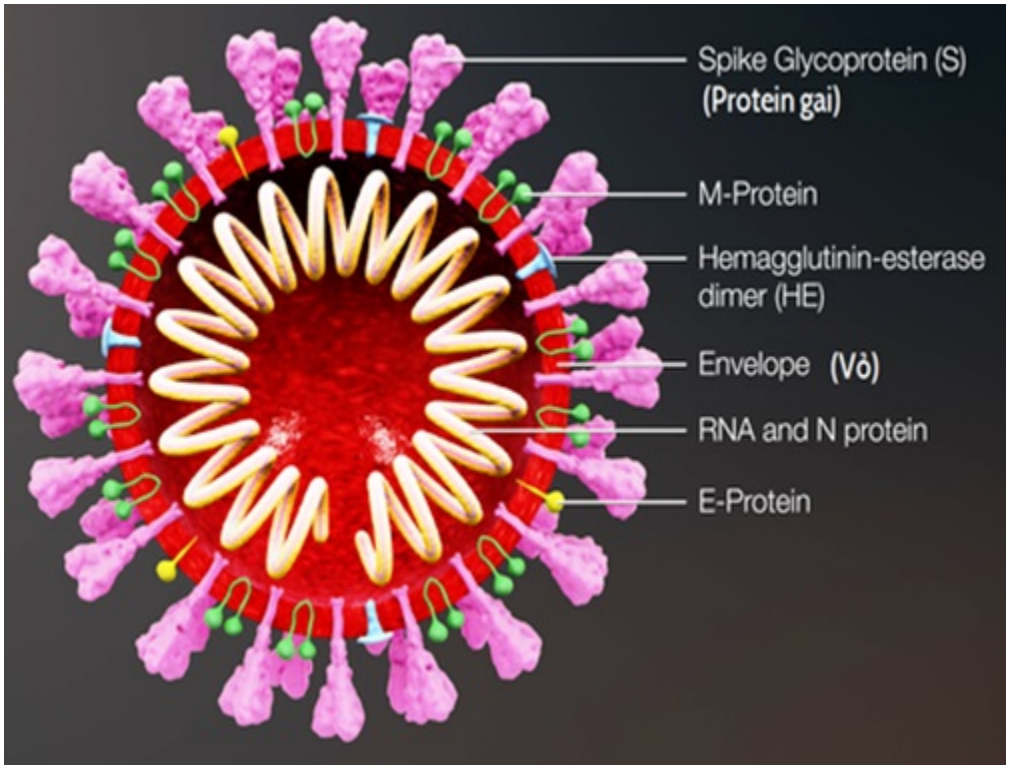

Fig. (1). Structure of Coronoavirus **(A)** Electron Microscopy and **(B)** Model of CoV.

Based on serological reactions, the coronavirus is divided into three groups or genera *i.e*. Group-I, Group-II, and Group-III (McIntosh *et al*., 1974). Group-I includes viruses that cause infection in animals only, like the Porcine epidemic diarrhea virus and feline infectious peritonitis virus. It also includes the viruses that produce respiratory infections in humans, such as Human Coronavirus 229E (HCoV-229E) and KHU1. The Group-II viruses are Porcine hemagglutinating encephalomyelitis virus, bovine coronavirus, and equine coronavirus, which shows pathogenicity in animals, while HCoV-OC43 and HCoV-NL63 produce pneumonia-like conditions in humans. Group-II viruses that cause infections in rodents are murine hepatitis virus (MHV) and Rat sialodacryoadenitis CoV, which produce enteritis, hepatitis, and encephalitis in addition to respiratory infections.

Lastly, infectious bronchitis virus (IBV), Turkey coronavirus, and pheasant coronavirus are classified under Group-III viruses.Table **1** summarizes the types of CoV (Cavanagh *et al*., 2020). All the CoV possess some common characteristics, which are as follows:

1. The shape of coronavirus is spherical with an average size of 80-220 nm.
2. The virus is covered with an envelope having club-shaped peplomers.
3. It all contains a tubular nucleocapsid structure with helical symmetry.
4. All are composed of single-stranded RNA with a genomic size of 27-32 kb.
5. The coronavirus contains numerous structural proteins, but some are present in all, such as nucleoprotein, peplomer glycoprotein, a transmembrane glycoprotein, and hemagglutinin esterase.
6. While some non-structural proteins are also present in CoV, such as RNA dependent RNA polymerase.
7. The newly-formed viruses *i.e*. virions are generally assembled in the endoplasmic reticulum and Golgi cisternae.
8. The mutation is very common in CoV and due to this reason, a diverse host range was exhibited (Enjuanes *et al*., 2000).

Table 1. Different types of coronavirus.

Group	Virus	Host	System Affected
I	229E	Human	Respiratory Infection
	TGEV	Pig	Respiratory & Enteric Infection
	PRCoV	Pig	Respiratory Infection
	Canine coronavirus	-	Enteric infection
	FeCoV	-	Enteric infection
	FIPV	Cat	Respiratory, enteric & neurologic infection
	NL-63	Human	Respiratory Infection
II	OC43	Human	Respiratory & enteric infection
	MHV	Mouse	Intestinal & neurological infection
	Sialodacryoadenitis CoV	Rat	Neurological infection
	Hemaagglutinating encephalomyocarditis virus	Pig	Respiratory, enteric & neurological infection
	BCoV	Cow	Enteric infection
	HKU1	Human	Respiratory infection
	SARS-CoV	Human	Life-threatening respiratory infection
III	IBV	Chicken	Respiratory infection, Hepatitis
	Turkey CoV	Turkey	Respiratory & Enteric infection

CHAPTER 3

COVID-19: Epidemiology

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Abstract: In the history, the year 2019 will be remembered as the year that has witnessed the beginning of a pandemic, primarily affecting the respiratory tract and then, spreading from human to human. A total of 25.18 million reported cases and 0.84 million deaths, as of 30th August 2020, and still counting, were caused by a novel coronavirus named COVID-19 that originated in Wuhan, China. By the beginning of the year 2020, this virus spread to several countries like Singapore, South Korea, Japan, Italy, Spain, Germany, the United Kingdom, and the United States of America. Between January 2020 and March 2020, the disease took a paradigm shift and started to affect the majority of European countries like Italy, Spain, France, Germany and UK. In the majority of the patients with a competent immune system, this disease goes unnoticed or without symptoms, thus making them highly susceptible to spread this disease to whoever comes in their contact. Aged patients (>60 years) or patients with chronic health issues like heart diseases, cancer, diabetes, and weak immunity are at greater risk of developing the symptoms. In severe conditions, patients need hospitalization and respiratory support (respirators/ventilators), thus causing an overload on the health system of the world. This initiated the movement of "flattening the curve" by social distancing and isolation to decrease the burden on the health system and to decrease the spread of the disease.

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Keywords: China, Confirmed Cases, *Cordon sanitaire*, Coronavirus, COVID-19, Curfews, Epidemiology, Geographical distribution, Global Epidemiology, Hotspots, Lockdown, National Responses, Non-essential, Outbreak, Pandemic, Person-to-person Transmission, Quarantines, SARS-CoV-2, WHO Region, Wuhan.

INTRODUCTION

The year 2019 has witnessed the beginning of a pandemic majorly affecting the respiratory tract; however, effects on the other body organs have also been reported (Singh *et al*., 2020a). The pandemic has affected 25,182,329 people across the globe, with a total death toll of 846,936 registered up to 30th August 2020. The total recovered cases from the COVID-19 pandemic are 17,515,059 and the active cases till 30th August 2020 are 6,820,334. Half of the total affected population of the world resides in the USA, Brazil, and India. This disease spreads from human to human *via* air-borne droplets. This pandemic is not the first pandemic world has ever seen; however, it is one of the biggest of our times and the most vulnerable after World War II. The severity of this can be estimated from the fact that it is as destructive as the influenza pandemic in 1918, which emerged after World War I and caused deaths of tens of millions of people due to lack of antibiotics. Similarly, Acquired Immune Deficiency Syndrome caused by a retrovirus was equally lethal before it was controlled by using antiretroviral drugs (DiMaio *et al.*, 2020).

Broadly, pandemics are the epidemics that spread worldwide and thus are not confined to any particular geographical region. This current world epidemic originated in Wuhan, China is caused by a novel coronavirus and has been named coronavirus disease 2019 or COVID-19. Due to its similarity with SARS (Severe Acute Respiratory Syndrome), ICTV (International Committee on Taxonomy of Viruses) coined it as SARS-CoV-2 virus. COVID-19 was officially proclaimed as PHEIC Public Health Emergency of International Concern by WHO on 30th January 2020 with various countries starting to impose travel restrictions, issuing traveling warnings, and also exercising travel bans (Malviya *et al.,* 2020; Tang *et al.*, 2020). However, the lag between identification of the first case of COVID-19 infection to realizing its person to person transmission and to declare it as a world pandemic led it to spread to various countries and as of now at least 208 countries are infected with this infection (Hamid *et al.*, 2020).

Fortunately, due to previous exposure and understanding of coronavirus infections, such as SARS (Severe Acute Respiratory Syndrome) and Middle Eastern Respiratory Syndrome (MERS), this causative agent of SARS-CoV2 was quickly identified and its genome was rapidly sequenced to help researchers around the globe to develop potential drugs and/or vaccines. Fig. (**1**) shows various events and developments happened so far related to SARS-CoV-2.

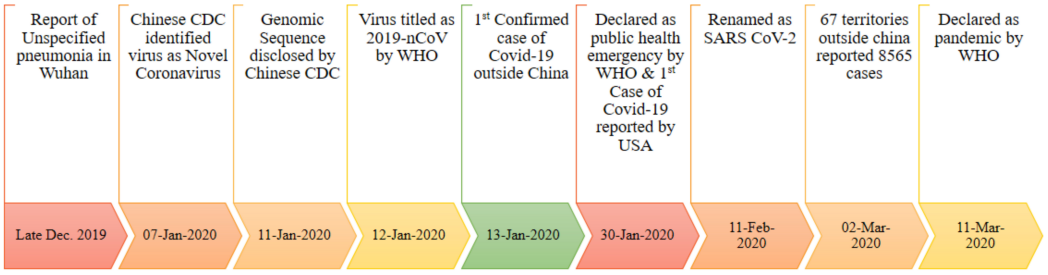

Fig. (1). Timeline of various developments in SARS-CoV-2 (Gennaro *et al.*, 2020; Park, 2020; Sun *et al.*, 2020; Srivastava *et al.*, 2020; Hamid *et al.*, 2020; Tang *et al.*, 2020).

In this chapter, we shall discuss the epidemiology of the COVID-19 pandemic. Basically, epidemiology is the study of various determinant factors of health and disease-related conditions or events in a sample population or globally, and the purpose of this study is to control the various factors related to disease and to control the spread of the disease. Therefore, from studying the epidemiology of COVID-19, one can conclude the frequency and pattern of this disease. In this chapter, the data has been collected and reported up to 12th June 2020. We shall discuss various determinants and factors like geographical distribution of the disease, patterns in the global spread of the pandemic, *etc.* Further, we shall discuss the comparison of the number of cases of COVID-19 in different WHO regions along with the effect of lockdown on the spread of the pandemic. Besides, the condition of the COVID-19 pandemic in India along with some published reports by clinicians/researchers will be discussed in the latter part of the chapter.

GEOGRAPHICAL DISTRIBUTION

On 13th January 2020, the first confirmed case of COVID-19 outside China was reported in Thailand. It made the situation clear that this virus is no longer confined to China or the provenances nearby Wuhan. Soon after, reports of confirmed cases started to emerge from different countries in Asia. In January 2020, this virus spread to many Asian countries like Thailand, South Korea, and Japan and also cases of patients affected by COVID-19 started to appear in the western part of the world, including Italy, Spain, Germany, the UK, and the USA. In early February, WHO realized that the occurrence of COVID-19 is very high and ranges between 2.24 to 3.38. From the end of January 2020 to March 2020, it took a paradigm shift and disease started to affect the majority of European

CHAPTER 4

Pathophysiology

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Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causal pathogen of the novel coronavirus disease 2019. This novel Covid-19 has created a serious public health crisis throughout the world. The primary symptoms of coronavirus infection are common cold and influenza-like illness and with time it causes pneumonia. Although various studies are going on throughout the world, its actual pathophysiology is not very well clear to date. The Coronavirus is a positively charged single-stranded RNA virus. This virus gets easily transmitted from human to human. Numerous investigations have been found that the virus enters into the human body *via* its spike (S) proteins. The S-protein binds to ACE2 receptors and silently comes in contact with alveoli *via* blood. This entry hypersensitizes various receptors, epithelial cells, macrophages, T-cells, dendritic cells and thus implants pro-inflammatory cytokines and chemokines, resulting in stressful conditions. Studies found that Hemagglutinin-Esterase protein, Spike protein, Nucleocapsid protein, small envelope protein, internal proteins, group-specific proteins take part in viral pathogenesis, whereas, replication proteins (eIF4A, Cyclophilin, 3CLpro, RdRp) participates in Coronaviruses (CoVs) replication and translation phases, influencing both pathogenesis and pathophysiological conditions. In this chapter, we elaborate on viral pathogenesis, the various functions of proteins, structural, enzymatic, and accessory that are linked with the pathological conditions and will also highlight the correlation causing physiological alteration associated with this infection.

Keywords: ACE2 receptors, Covid-19, Hemagglutinin-Esterase protein, Life cycle, Membrane protein, Nsp1 protein, Nsp3 protein, Nsp8 primase, Nsp12 polymerase, Nsp13 helicase, Nsp14 protein, Nsp15 protein, Nsp16 protein, Nucleocapsid protein, Orf3b, Orf6, Orf7a, Pathogenesis, Pathophysiology, Spike proteins, Thrombosis, Transmission.

INTRODUCTION

Coronavirus (CoV) is a member of the Coronavirinae subfamily, which comprises a single positive-stranded RNA virus. The various endogenous proteins present in

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it are integral membrane (M), spike (S), nucleocapsid (N), envelope (E), and other accessory proteins, which not only facilitate its entry into the cells but also helps in replication (Fig. **1**) (Garoff *et al*., 1998). There are 3 different categories of CoVs- category 1, which includes human coronavirus 229e and transmissible gastric enteritis virus; category 2 includes human CoV-OC43, murine hepatitis virus, and bovine CoVs; class 3 comprehends avian infectious bronchitis virus (Fehr and Perlman, 2015). On 31st Dec 2019, China alerted WHO of a huge number of pneumonia-like cases in Wuhan city. After continuous investigations, Chinese scientists and WHO claimed the presence of a new strand of CoVs causing this pneumonia-like problem. CoV symptoms include- dry cough, shortness of breath, and respiratory distress. This virus has spread to almost every part of the world and costs about 469,587 lives worldwide till 23rd June 2020. From various investigations, WHO had declared that these CoVs are spreading through contacts by infected persons or patients. The S-protein of CoVs binds with ACE2 receptors and silently comes in contact with alveoli *via* blood. Initially, at the time of infection, the CoVs contaminates the epithelial cells, macrophages, T-cells, dendritic cells and execute pro-inflammatory cytokines and chemokines takes place, initiating stressful condition. In this chapter, we are discussing the viral pathology associated with proteins, enzymes, and accessory along with their roles in pathogenesis.

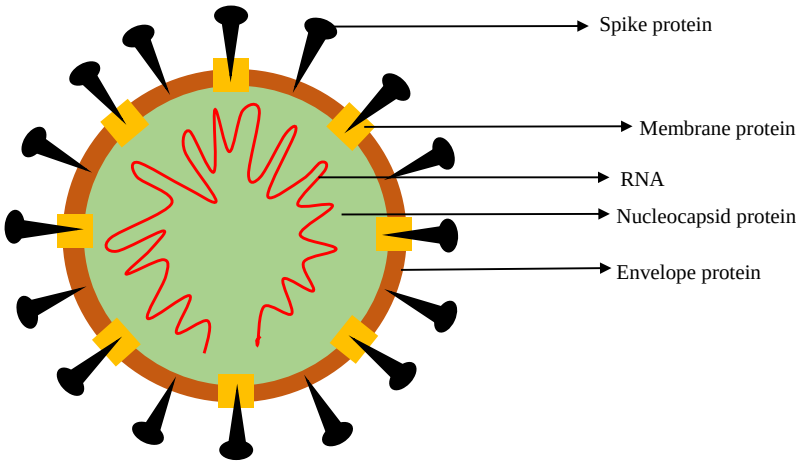

Fig. (1). Structure of CoV.

TRANSMISSION OF COV

Available reports have found that the CoVs are conveyed from animals to humans through close contact with animals like pigs, camels, and bats, are more susceptible to CoV infection, creating a reservoir (Mackay and Arden, 2015). At the early stage of CoV infection, the primary symptoms are not well expressed but as it gets matured and replication occurs CoVs slowly start to show their

symptoms. The incubation time of CoV infection is 2 to 14 days. It has been found that Covid-19 gets transmitted from an individual to another *via* cough, sneezing, hands shaking and thus found to get settled themselves at the respiratory tract (Gunalan, 2011) (Fig. **2**).

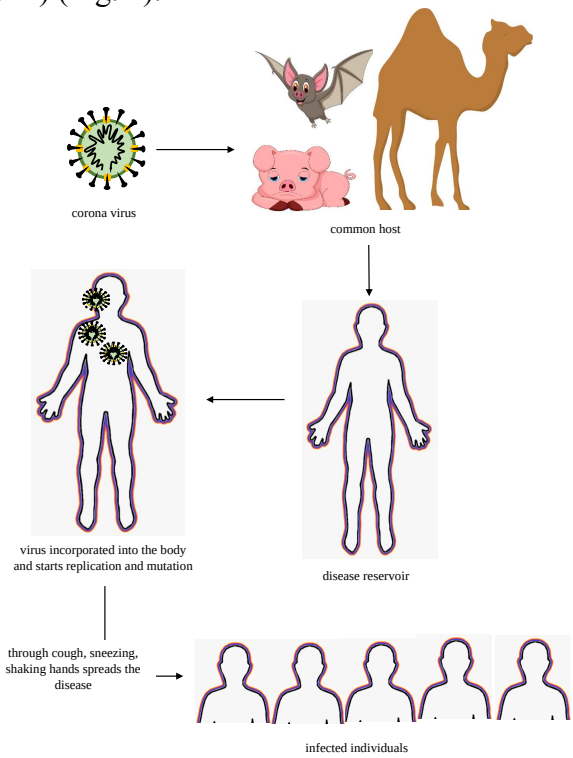

Fig. (2). Schematic representation of transmission of CoV.

Virus Life Cycle

The CoV life cycle has been summarized in this portion by discussing the various functions of viral proteins. It has been found that CoV with the help of the S-proteins gets attached with specific cellular receptors and thus initiates a conformational structural alteration of spike proteins, resulting in the liberation of the nucleocapsid into cells. After entering inside the cells, the 5' end of RNA, orf1a, and 1b gets translated to form pp1a and pp1ab. The orf1a represents the papain-like protease (PLpro) and a 3C-like protease (3CLpro), which acts to progress the pp1a and pp1ab to mature replicase protein (Lee *et al*., 1991; Ziebuhr *et al*., 2001). The orf1a X domain encodes the ADP-ribose1”-phosphatase activity (Ziebuhr, 2005; Snijder *et al*., 2003), while the orf1b encodes a helicase and an RNA-dependent RNA polymerase (RdRp) which is processed by pp1ab (Gorbalenya, 2001). This orf1b also encodes various other enzymatic activities-

CHAPTER 5

Clinical Presentation and Comorbidities

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Abstract: Presently, the whole world is going through a historic yet a troublesome situation following COVID-19 outbreak. The clinicians have observed a wide variety of respiratory and non-respiratory clinical manifestations in COVID-19 patients. Accumulating reports revealed that the clinical features of COVID-19 may include asymptomatic/mild symptoms, neurological, cardiovascular complications, severe pneumonia and mortality. The most common features noticed are fever, dry cough, sore throat, shortness of breath, sputum production, fatigue, and myalgia. Recently, US health protection agency has also reported repeated shaking along with chills, loss of taste and smell in new case studies as additional symptoms. In addition to this, COVID-19 patients may show clinical signs like persistent pressure and pain in the chest, blue lips or face, confusion and GIT disturbances (diarrhea, nausea, vomiting and abdominal discomfort). The current ongoing pandemic has remarkably affected almost every age group of humans, starting from infants less than 3 months, adults, elder and older patients. Furthermore, the clinical presentations in these groups of COVID-19 infected patients were found to show considerable inter-individual variations. The findings also suggested that the comorbid conditions (heart injury, hyperglycemia, hypertension, neurodegenerative diseases) in elder/older patients further complicate the health of COVID-19 patients.

In the present book chapter, the clinical presentation of COVID-19 in pediatric, adults and geriatric group of population will be emphasized along with the higher susceptibility of COVID-19 in comorbid patients.

Keywords: ACE-2, Adolescents, Anosmia, Asymptomatic, Atypical symptoms, Comorbid, Comorbidity, Consolidations, Cutaneous, Dyspnea, Fatigue, Fever, Gastrointestinal, Ground glass opacities, Immunity, Incubation period, Neonates, Neurological, Pneumonia, Respiratory distress, Respiratory symptoms, SARS-CoV-2, Septic shock, Spikes, Vaccination.

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INTRODUCTION

At the beginning of the COVID-19 outbreak, the clinicians have encountered a substantial diversity in the clinical presentations, such as different incubation periods among different age groups, noticeable variations in the onset of symptoms and degree of severity (moderate, serious and critical). Besides the most common respiratory symptoms, an array of complications has been found to be associated with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection. Moreover, asymptomatic (transmit virus but never have symptoms) and presymptomatic (transmit virus and symptoms appear later) transmissions have also raised concerns. The present chapter elaborates the typical and atypical clinical features discerned in original clinical cases of COVID-19 patients. Besides, the factors (age, Angiotensin-Converting Enzyme 2 (ACE2), gender, blood group, previous immunization, comorbidity) responsible for the high inter-individual variations of clinical outcomes have also been discussed in detail.

CLINICAL PRESENTATIONS OF COVID-19 INFECTION

In COVID-19 patients, it is found that after exposure, the virus takes an incubation period of 2-14 days. According to the findings of clinical cases, the COVID-19 infection starts showing its mild symptoms after a median incubation time period of approximately 5.1 days (McIntosh, 2020). However, Lauer and his coworker estimated that 97.5% of COVID-19 infected patients presented severe symptoms by 11.5 days (Lauer *et al.,* 2020). The diverse respiratory and non-respiratory symptoms observed to date are compiled in Table **1**.

Table 1. Respiratory and non-respiratory symptoms of COVID-19.

Respiratory Symptoms (Hassan *et al.,* 2020; Cascella *et al.,* 2020; Wang *et al.,* 2020)			
Mild Cases • Infection resides only in upper respiratory tract. • Fever, nasal congestion, dry cough, headache, sore throat and malaise.	**Moderate Cases** • Respiratory manifestations include cough, shortness of breath, and tachypnea.	**Severe Cases** • Patients are reported to have severe pneumonia. • Acute Respiratory Distress Syndrome (ARDS), PaO_2/FiO_2< 300, SpO_2 ≤93%, tachypnea, severe dyspnea. • Fever can be absent or moderate.	**Acute Respiratory Distress Syndrome** • It indicates worsening/failure of the respiratory system. • ARDS can be of different types on the basis of values of PaO_2/FiO_2. Severe (≤ 100 mmHg). Moderate (100-200 mmHg). Mild (200-300 mmHg).

(Table 1) cont.....

• Dyspnea is absent. • Radiographic manifestations are not present. • Most of the cases have been found to be mild. • Mild cases may deteriorate into severe cases if precautions will not be acquired.	• Severe symptoms are absent.	• In critical cases, cardiac injury, RNAaemia, respiratory failure or multiple organ dysfunction have also been found. • Comorbidities such as hypertension, diabetes, cancer, cardiovascular problems further increase the fatality rate in severe cases of COVID infection.	Its different values indicate different degrees of hypoxia. • Deterioration of ARDS can also be correlated with altered AST (aspartate transaminase) and ALT (alanine transaminase) levels. • Ground Glass Opacity (GGO) (86%), bilateral (76%), peripheral (33%) distribution, consolidation (29%), crazy paving (19%) are the prominent features found in computed tomography (CT) scan.
Non-Respiratory Symptoms (unusual Manifestations)			
Neurological	Altered mental state, musculoskeletal disturbance, acute necrotising encephalopathy ischaemic stroke, headache, dizziness, Guillain-Barre syndrome.		
Ocular	• In China, 32% of infected patients showed ocular manifestations, for example, chemosis and conjunctival hyperaemia. • Tears and conjunctival seepage have shown the presence of COVID-19. • In severe COVID-19 cases, pseudomembranous and hemorrhagic conjunctivitis was also found. • Development of ptechiae, tarsal pseudomembranous, mucous filaments in 63-year-old COVID-19 positive male. • External ocular infections could occur lately due to the spread of infection and physicians should take care if ocular complications exist for >2 weeks in COVID-19 patients (Navel, Chiambaretta and Dutheil, 2020).		
Taste and Smell	• Olfactory dysfunction (Anosmia) is typically found to be present only in the most severe cases. • Bilateral obstruction in olfactory clefts due to inflammation; however no abnormalities were found in olfactory bulbs and tracts (Giacomelli *et al.,* 2020; Temmel *et al.,* 2004; Eliezer *et al.,* 2020). • Anosmia may persist with or without dysgeusia and manifest itself either in the early stage of progression or in patients with mild symptoms (Xydakis *et al.,* 2020; Carrillo-Larco *et al.,* 2020).		
Cardiovascular	Heart failure, cardiac arrhythmias, pacemaker conduction defects, infections such as myocarditis and myopericarditis, chest pain (Yang *et al.,* 2020; Bonow *et al.,* 2020; Inciardi *et al.,* 2020; Driggin *et al.,* 2020; Wang *et al.,* 2020; Zhou *et al.,* 2020).		
Hematological Symptoms	Hypercoagulable state in COVID-19 patients increased the threat of thrombotic occlusion		
	Mediastinal lymphadenopathy was also found in patients with a severe form of COVID-19 (Valette *et al.,* 2020)		

CHAPTER 6

Diagnosis

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Abstract: Diagnosis of COVID-19 is supremely valuable in unraveling the complex dynamics involved in SARS-CoV-2 infection and in vaccine development. With an extremely high transmission rate, and initial symptoms similar to other human respiratory viruses, there has been a tremendous urge to develop and supply accurate and rapid procedures for testing the presence of SARS-CoV-2 in a plethora of patient specimens. Scientific and healthcare communities globally have been racing to develop critically needed test kits and ensure ample supply worldwide. Containing the spread of COVID-19 poses multiple challenges, including being able to correctly identify asymptomatic viral carriers that result in the silent spread of the virus, and diagnosing the infection at early stages. Current strategies employ molecular and serological testing techniques in lower and upper respiratory tract samples. The first type detects the presence of viral genetic material and can diagnose an active COVID-19 infection, whereas serological immunoassays detect viral antibodies, which can help identify individuals who have developed an adaptive immune response to the virus, as part of an active or prior infection. The newly authorized antigen tests are designed for the rapid detection of viral antigenic proteins. More elaborative diagnostic testing based on viral genomic sequencing can determine the rate and degree of mutational variability associated with SARS-CoV-2 and identifying newly emerging viral strains for more effective vaccine development. The chapter also highlights the role of rapid, easy-to use point-of-care diagnostic tests in alleviating the challenge posed by the strain on the healthcare system and mitigating the cost of care for both individuals and the government.

Keywords: Antibody, Antigen, Biomarker, Biosensor, Chest CT, COVID-19, CRISPR, Cytokine, Detection, Diagnosis, ELISA, Hematological analysis, Immunoassay, Isothermal amplification, Microarray, POC tests, RT-PCR, SARS-CoV-2, Serology, Viral RNA.

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COVID-19: A PANDEMIC DISEASE

With the current stage of the pandemic and the associated challenges presenting major hurdles, it is evident that highly sensitized and precise diagnostic measures for COVID-19 are paramount for rationalizing infection control initiatives, as well as for case identification and contact tracing (Chan *et al.*, 2020). There is an urgent necessity for rapid yet accurate SARS-CoV-2 diagnostic methods, with emphasis on what type of tests are available in the region, under what in circumstances these tests can be used, and who should be tested (Patel *et al.*, 2020).

Similar to other infectious diseases, effective COVID-19 diagnosis relies on various parameters such as patient history, respective epidemiological conditions, clinical symptoms, and, radiological and hematological analysis. However, standard guidelines state two categories of COVID-19 tests; viral RNA tests (molecular tests) to detect the presence of SARS-CoV-2 in an active infection state, and serological tests to identify whether the subject (patient) has been exposed earlier/previously to the virus and the presence of virus-specific antibodies in the serum (Li *et al.*, 2020b). Some techniques are onerous and technically taxing, hence, there is an urgent need for rapid, cost-effective, and selectively diagnostic point-of-care (POC) tests for COVID-19 capable of providing quick yet accurate, results within a duration of possibly a few minutes (Moitra *et al.*, 2020). These POC tests allow medical diagnostic testing at the time and place of patient care while offering extra benefits of speed of diagnosis and ease of use. The current POC tests available in the market utilize the aforementioned diagnosis strategies of nucleic acid detection and analysis of antigen and/or antibodies in various sample specimens (mostly nasopharyngeal swabs). POC tests are pictured to supplement laboratory testing and enable testing to be available for remote communities and populations that lack readily accessible laboratory settings. In such secluded, crisis-struck locations, small and portable mobile POC platforms are optimal for deployment, although they are lower throughput and run one sample at a time in a specified time-frame of 5-30 minutes. They can be of great value to test moderately symptomatic patients outside clinical settings (Yang *et al.*, 2020). Higher throughput, facility-based POC platforms are also available for use in hospitals and medical centers for diagnosing top-priority specimens, such as that of frontline healthcare workers and critically-ill patients. Although POC tests are a handy component of the rapid diagnostic strategy to battle the ongoing outbreak, they are strictly recommended to be used only in conjunction with PCR-based detection. Laboratory testing undoubtedly remains the foremost testing mechanism because of the presence of complex technology specifically designed to perform a sizeable number of tests at a time. Thus, parallel use of these serology-based detection techniques alongside

molecular techniques is the way forward for mitigating the global, as well as regional load of the disease (CDC-Fact-Sheet, 2019).

COVID-19: EARLY DETECTION BASED ON SYMPTOMS

Clinical Analysis

Clinical presentation of COVID-19 is vague as symptoms coincide with other seasonal respiratory infections simultaneously circulating in the respective territorial population. It is observed that infected patients present with symptoms ranging in severity. Fever (37.5° C and above) must be carefully interpreted as even in severe cases; it can be present in moderation or even absent. Upper respiratory tract viral infection, noted as the leading symptom, was reported in more than 80% infected patients which also include mild fever, dry cough, soreness of the throat with probable nasal congestion, headache, fatigue, or malaise. Patients with moderate infection present symptoms like shortness of breath or tachypnea in children in addition to mild symptoms. On the other hand, highly infected patients are diagnosed with severe pneumonia, having fever associated with severe dyspnea, respiratory distress, cyanosis in children, tachypnea, and hypoxia (Cascella *et al.*, 2020). Particularly, a chest computed tomography (CT) is the expert's recommendation for the severely infected individuals and works as an auxiliary tool alongside other standard diagnostic methods. The current pandemic status depicts that it has no age-limits as it affects the newly-born and the aged people; however, those who have crossed the age of 50 are at a relatively higher risk. Additionally, patients with a history of other comorbidities such as cardiovascular disease, diabetes, lung disease, and other types of immune suppression are also at the risk of getting an infection due to their compromised immune system. Despite measurements of the severity and other symptomatic conditions, the identification marks for the COVID-19 cases, epidemiological circumstances of the respective locations and other parameters may vary from place to place, other factors which affect the diagnosis and identification of the patients (Harapan *et al.*, 2020).

According to WHO, screening for the routine causes of respiratory illness, which delineates the season of the respective location, is the rudimentary step as and when the patient first appears with the symptoms. If a sample yields a negative result, it should be sent to a referral laboratory for SARS-CoV-2 detection. Real-time RT-PCR assay is the preferred molecular test for detecting SARS-CoV-2 infection in a clinical specimen, while serology-based techniques are used as adjunct tools. Specimen for testing must be collected from both the upper respiratory tract (*i.e.*, nasopharyngeal (NP) and oropharyngeal (OP) swabs) as well as the lower respiratory tract (*i.e.*, expectorated sputum, endotracheal

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Varun Garg

Dr. Varun Garg completed his PhD in Pharmaceutics from the School of Pharmaceutical Sciences, Lovely Professional University. He has published 27 papers in international journals and authored 2 book chapters. He has presented 12 papers at national and international conferences. He has developed himself with a unique profile involving an interplay of research, technical, and medical skills. He has experience of 7 years in medical affairs and has worked with Biocon and Zydus Cadila. Apart from his academic activities, he is actively involved in presenting his research work at different national and international scientific forums.