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The Novel Coronavirus SARS-CoV-2: Epidemiolgy, Virology and Pathogenesis

Held on 30/06/2020, in front of the jury composed of:

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Dedication

To my Parents whom i love,
the Father i respect and the Mother i adore.

To my Sisters whom i value, even when its not always mutual.

To my Grandmother and aunt TouTou whom i cherish.

To the Class of Fundamental Microbiology 2020, for believing in me by being their delegate.

To Frizzy & Chula for the best company through college years.

To my peaceful Soul that i appreciate and my scientifique Spirit that i applause.

To ME...!

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I would firstly like to thank GOD for all of his strength, glory and protection in this pandemic.

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For all of my teachers of biology and specifically microbiology at the University of Tlemcen, for enlightening my way towards loving and appreciating science, thank you.

"Raising Awareness versus Raising Alarm, the public can't be better informed if the information isn't better"

-T.K. Naliaka.

ملخص

ملخص

تميزت نهاية عام 2019 بانتشار مرض غامض بدأ في ووهان ، الصين ، والذي انتشر وأمرض ملايين الأشخاص في جميع أنحاء العالم إلى حد إعلان منظمة الصحة العالمية أنه جائحة. سلالة جديدة من الفيروسات التاجية سميت SARS-CoV-2 من قبل ICTV ، تختبر قدرات عالمنا الحديث وأنظمة الرعاية الصحية الخانقة ، وفي الوقت نفسه تجمع جميع أبحاث العلماء والسلطات الحكومية لمكافحة مرضها الصحي المليء بالتحديات ، المسمى COVID-19.

كان الهدف من هذا العمل ، بما يتماشى مع وضعنا الحالي ، هو تقديم لمحة عامة عن بيولوجيا هذا الفيروس الجديد ومرضه التدريجي ، مع الأحداث التسلسلية للجائحة المستمرة ، أثناء وجودنا في قلبها ، بعيدًا عن الخوف و الذعر ، وكذلك إظهار عواملها وبعض الإجراءات العالمية ضدها ، على أمل إبطاء الانتشار الفيروسي ، الذي أثر على كل من الجوانب الاجتماعية والاقتصادية والسياسية ، مما أدى إلى إلغاء أحداث متعددة ، وإلزام الاحتواء الصارم والمبادئ التوجيهية للحجر الصحي في مختلف البلدان ، بما في ذلك الجزائر.

سمح لنا هذا العمل بشرح والمساعدة في فهم الأدلة العلمية لقابلية الانتقال العالية والتغير السريع ، والأصل المحتمل لحيوان آكل النمل البنغولي وكذلك العملية المعدية من خلال مستقبلات ACE2 لهذا الفيروس التاجي. في نفس الوقت تم تصنيف التدخلات المرضية الرئيسية في المضيف البشري ، مما يؤدي إلى استجابة مناعية ذات وجهين يمكن أن تكون واقية أو ضارة. لم يتم العثور على لقاح حتى الآن وتم تطبيق مجموعة متنوعة من الموافقات العلاجية بدلاً من ذلك ، في مسألة لتهدئة الالتهاب الرئوي الفيروسي القاتل.

العالم بأسره يشاهد بلا حول ولا قوة ، حيث ينتشر SARS-CoV-2، مع حالات مصابة/ متوفاة يومية عالية، حيث لا يزال المرض يمر عبر مسارات متعددة الطرق. إن طبيعة COVID-19 تكشف عن نفسها مع انتشار الجائحة ، ولكن متى وكيف وهل حقاً ستنتهي؟! سؤال مهم جدا ...!

الكلمات المفتاحية:، SARS-CoV-2، COVID-19 ، فيروس ، ACE2، الجائحة ، الالتهاب الرئوي ،الصين ، منظمة الصحة العالمية.

Abstract

The end of 2019 was marked by the outbreak of a mysterious illness that started in Wuhan, China, spread and sickened millions of people around the globe to the extent of being declared as a pandemic by the WHO. A novel coronavirus strain named SARS-CoV-2 by the ICTV, testing the capabilities of our modern world and suffocating health care systems, meanwhile gathering all of scientist's researches and governmental powers to fight off its health challenging disease, named as COVID-19.

The objective of this work, consistently with our current situation, was to present, an overview of the biology of this novel virus and its progressive disease, with chronological events of the ongoing pandemic, while being in the heart of it, far from fear and panic, as well as showing its factors and some of the global procedures against it, in hopes of slowing the viral spread, that is affecting both of the social, economic and political aspects, resulting in the cancelation of multiple events, and obligating strict containment and quarantine guidelines in different countries, including Algeria.

This work allowed us to explain and help comprehend with scientific evidence the high transmissibility and the rapid mutability, the possible origin of a pangolin as well as the infectious process through the ACE2 receptors of this coronavirus. Classifying at the same time the major pathological involvements in the human host, triggering a two-faced immunity response that could be both protective or harmful. No vaccine is yet found and a variety of therapeutic approches has have been applied instead, in a matter to calm the fatal viral pneumonia.

The entire world is helplessly watching as SARS-CoV-2, spreads, with a daily alarming high affected/deceased cases, where the disease is still going through versatile pathways. The nature of COVID-19 is revealing itself as the pandemic unfolds, but when, how and will it really ever be over?! a question by far important…!

Key-words: SARS-CoV-2, COVID-19, ACE2, Virus, Pandemic, Pneumonia, China, WHO.

Résumé

La fin de 2019 a été marquée par le déclenchement d'une mystérieuse maladie à Wuhan en Chine, qui s'est propagée et rendu malade des millions de personnes dans le monde au point d'être déclarée une pandémie par l'OMS. Une nouvelle souche de coronavirus nommée SARS-CoV-2 par l'ICTV, testant les capacités de notre monde moderne et étouffant les systèmes de soins de santé, tout en rassemblant toutes les recherches des scientifiques et les pouvoirs publics pour lutter contre sa maladie représentant un défi pour la santé, nommée COVID-19.

L'objectif de ce travail, en cohérence avec la situation actuelle, était de présenter, un aperçu sur la biologie de ce nouveau virus et de sa maladie évolutive, avec les événements chronologiques de la pandémie en cours, tout en étant au cœur de celle ci , loin de la peur et de la panique, présentant aussi ses facteurs et certaines des procédures mondiales à son encontre, dans l'espoir de ralentir la propagation virale, affectant à la fois les aspects sociaux, économiques et politiques, entraînant l'annulation de multiples événements, et l'imposition de strictes directives de confinement et de quarantaine dans différents pays, dont l'Algérie.

Ce travail nous a permis d'expliquer et de faire comprendre avec des preuves scientifiques la haute transmissibilité et la mutabilité rapide, l'origine possible d'un pangolin, aussi bien que le processus infectieux à travers les récepteurs ACE2 de ce coronavirus. Classant en même temps ses principales implications pathologiques chez l'hôte humain, déclenchant une réponse immunitaire à deux faces qui pourrait être soit protectrice et/ou nuisible. Aucun vaccin n'a encore été trouvé et une variété d'approches thérapeutiques ont été appliquées, afin de calmer la pneumonie virale mortelle.

Le monde entier regarde impuissant, la propagation du SARS-CoV-2, avec un nombre alarmant de nouveau cas/décès, où la maladie suit toujours des voies polyvalentes. La nature de COVID-19 se révèle à mesure que la pandémie se déroule, mais quand, comment et sera-t-elle vraiment terminée?! une question de loin importante…!

Mots-clés: SRAS-CoV-2, COVID-19, ACE2, Virus, Pandémie, Pneumonie, Chine, OMS.

TABLE OF CONTENTS

List of Abbreviations

3CLpro: 3-chymotrypsin-like protease.

AA: Amino Acids.

AAK1: protein kinase 1.

ACE2: Angiotensin Converting Enzyme 2.

AITD: Autoimmune Thyroid Disease.

AKI: Acute kidney injury.

ALB: Albumin.

ALK- phos: Alkaline phosphatase.

ALT: Alanine Transaminase.

AMS: Altered Mental Status.

APC: Antigen-Presenting Cell.

ARDS: Acute respiratory distress syndrome.

AST: Aspartate Transaminase.

ATI: Acute Tubular Injury.

BoNT: Botulinum Toxin.

CDC: Centers for Disease Control and Prevention.

CFR: Case Fatality Rate.

CLD: Collectrin-Like Domain.

CNS: Central Nervous System.

COVID-19: Coronavirus disease 2019.

CP: Convalescent Plasma.

CPK: Creatine phosphokinase.

CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats.

CRP: C-Reactive protein.

CSF: Cerebrospinal Fluid.

CSS: Cytokine storm syndrome.

CTL: Cytotoxic T-Cell.

CT: Computed Tomography

CoVs: Coronaviruses.

DAD: Diffuse Alveolar Damage.

DAMPs: Damage-Associated Molecular Patterns.

DM: Diabetes Mellitus.

E: Envelope Protein.

EC: Extracellular Domain

EBV: Epstein-Barr Virus.

ELISA: Enzyme-Linked Immunosorbent Assay.

EM: Electron Microscopy.

EMMPRIN: Extracellular Matrix Metalloproteinase Inducer.

ENS: Enteric Nervous System.

ER: Endoplasmic Reticulum.

FCS: Furin Cleavage Site.

FDA: Food and Drug Administration.

G-CSF: Granulocyte Colony-Stimulating Factor.

GBS: Guillain-Barré syndrome.

GGO: Ground Glass Opacities.

GIS: Geographic Information Systems.

HCoV: Human Coronavirus.

HLH: Hemophagocytic Lymphohistiocytosis.

Hb: Haemoglobin.

HSPA5: Heat Shock Protein A5.

ICTV: International Virus Classification Commission.

IFN: Interferon.

IFR: Infection Fatality Rate.

IL: Interleukin.

IL-6R: Interleukin-6 Receptor.

IP- 10: Interferon Gamma-Induced Protein 10.

IgG: Immunoglobulin G.

IgM: Immunoglobulin M.

IHC: Immunohistochemistry.

JAK: Janus kinase.

JAK-STAT: Janus kinase-signal transducer and activator of transcription.

KD: Kawasaki disease.

LDH: Lactate Dehydrogenase.

LIF: Leukaemia Inhibitory Factor.

M: Membrane Protein.

MCP-1: Monocyte Chemotactic Protein 1.

MCP-3: Monocyte Chemotactic Protein 3.

MERS: Middle East Respiratory Syndrome.

MHC-class 1: Major Histocompatibility Complex-class 1.

MHC-class 2: Major Histocompatibility Complex-class 2.

MIP-1A: Macrophage Inflammatory Proteins-1Alpha.

MIS-C: Multisystem Inflammatory Syndrome in Children.

mRNA: Messenger RNA.

MSCs: Mesenchymal Stem Cells.

N: Nucleocapsid Protein.

NAbs: Neutralizing antibodies.

NATCM: National Administration of Traditional Chinese Medicine.

NF-kB: Nuclear Factor kappa-light-chain-enhancer of activated B cells.

NHI: National Health Insurance.

NK: Natural Killer.

NLR: Neutrophil-to-Lymphocyte Ratio.

NTD: N-terminal domain.

Nsps: Non-Structural Proteins.

O2: Oxygen.

OE: Olfactory Epithelium.

PACMAN: Prophylactic Antiviral CRISPR in huMAN cells.

PAMPs: Pathogen-Associated Molecular Patterns.

PD: Peptides Domain.

PLpro: Papain-Like Protease.

PRRs: Pattern Recognition Receptors.

QFPDT: Qing Fei Pai Du Tang.

QR: Quick Response.

RA: Rheumatoid Arthritis.

RBC: Red Blood Cells.

RBD: Receptor Binding Domain.

RBM: Receptor Binding Motif.

RdRp: RNA-polymerase-RNA-dependant.

RNA: Ribonucleic Acid.

RT-qPCR: Real-Time quantitative Reverse-Transcription Polymerase Chain Reaction.

S: Spike protein.

SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus-2.

SARS-CoV: Severe Acute Respiratory Syndrome-Coronavirus.

SARS: Severe Acute Respiratory Syndrome.

SHERLOCK: Specific High Sensitivity Enzymatic Reporter UnLOCKing.

siRNA: Small interfering RNA.

SNPs: Single Nucleotide Polymorphisms.

TBIL: Total Bilirubin.

TCID: Tissue-Culture Infectious Dose.

TCM: Traditional Chinese Medicine

TLR: Toll-Like-Receptor.

TMPRSS2: Transmembrane Serine Protease 2.

TMPRSS: Transmembrane Serine Protease.

TNF: Tumoral Necrosis Factor.

Th: T helper.

UAV: Unmanned Aerial Vehicles.

UK: United Kingdom.

USA: United States of America.

UTR: Untranslated Regions.

VTM: Viral Transport Medium.

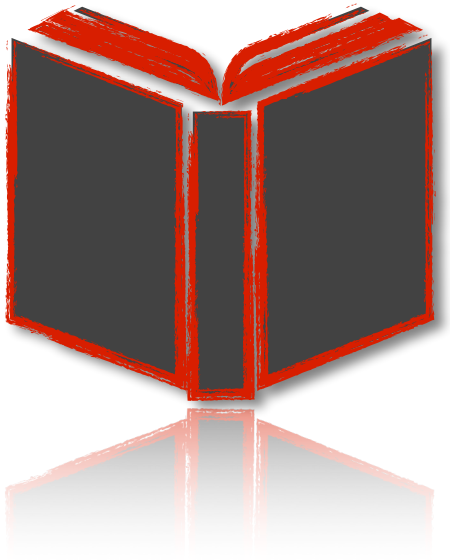
VVV: Viral-Vectored Vaccine.

WBC: White Blood Cells.

WHO: World Health Organization.

List of Figures

List of Tables



INTRODUCTION

INTRODUCTION

In the new decade of the 21st century, surfaced the first public health emergency of global concern **(Banerjee *et al.,* 2020).** A mysterious illness started from Wuhan, China, has sickened millions of people throughout the world**.** A newly emerged strain that is currently testing the capabilities of our modern world for dealing with unfamiliar pathogens **(De Soto *et al.,* 2020).** Meanwhile**,** the infection spread globally within a short time due to extensive international travels to celebrate the Chinese Lunar New Year **(Jogalekar *et al.,* 2020).**

The causative agent was a novel coronavirus (nCoV/ β-coronavirus) scientifically named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the similarity of its structure to severe acute respiratory syndrome related coronaviruses **[(Akram & Mannan, 2020) ; (Alanagreh *et al.,* 2020) ; (Lam *et al.,* 2020) ; (Romano *et al.,* 2020) ; (Tang *et al.,* 2020)],** previously known by the provisional name of 2019 novel coronavirus (2019-nCoV), which causes the COronaVIrus Disease COVID-19, a highly contagious and progressive infectious disease **[(Bhowmik *et al.,* 2020) ; (Cheng *et al.,* 2020) ; (De Soto *et al.,* 2020) ; (van Doremalen *et al.,* 2020) ; (Gorbalenya *et al.,* 2020) ; (Gu *et al.,* 2020) ; (Haque & Akram, 2020) ; (Jogalekar *et al.,* 2020) ; (Lu *et al.,* 2020) ; (Li *et al.,* 2020) ; (Oberemok *et al.,* 2020) ; (Sungnak *et al.,* 2020) ; (Talluri, 2020) ; (Valencia, 2020) ; (Wang *et al.,* 2020) ; (Wu, 2020) ; (Xu *et al.,* 2020) ; (Yeo *et al.,* 2020) ; (Zheng *et al.,* 2020) ; (Zhou *et al.,* 2020)].**

The world is currently reeling in an alarming outbreak of this novel coronavirus **(Kumar *et al.,* 2020),** that continues to spread across the globe with a reported case fatality rate of ~3–4% worldwide, that varies geographically, and final mortality estimates vary weekly as many cases are currently ongoing **[(Cheng *et al.,* 2020) ; (Guarner, 2020) ; (Lan *et al.,* 2020) ; (Valencia, 2020)].** The dramatic change of events through this pandemic has prompted an exponential increase of scientific interest in coronaviruses globally **(Mani *et al.,* 2020).**

This work, which is topical given its correlation to what is happening at the moment in our lives, would present a perception and an insight of scientific proofs of all that surrounds and involves the novel coronavirus and its disease in relation to the human kind and the normalcy of its life, that would no longer be kind of normal, in regards of the high transmissibility, the fast mutability and the severity of its disease, with the unfortunate absence of a 100% effective treatment nor a possible vaccine that can stop the spread.

Through the first chapter of this thesis, we are going to start with the chronological events of the viral pandemic by the numbers, its factors and worldwide procedures against it, showing how some countries managed the outbreak in ways others couldn't, including Algeria's status.

By the second chapter, we would briefly classify the family of Coronaviruses and their history in epidemics, then we will be introducing the novel virus with its virology, origin and how it spreads via the diverse routes of infection, after that, we are going to mention effective test methods for the viral infection, in addition to some direct forms of prevention.

With the last chapter, we will have ended our work, by classifying the major pathological roles of this novel virus and how host immunity reacts to it, showing that it might involve both scenarios of being protective and harmful, we will also be listing some of the highly opted for, preventive and therapeutic approaches used at the time being for recovery.

CHAPTER ONE:

EPIDEMIOLOGY

Chapter One: Epidemiology

Today, earth faces many complex problems, such as emerging infections, that a single discipline, institution or country cannot respond to alone **(El Zowalaty & Järhult, 2020).** The entire world is anxiously watching as SARS-CoV-2 virus, spreads from country to country **(Morawska & Cao, 2020).** Unemployment rates are growing and economy is continuously shrinking in many affected countries to a point where, the International Monetary Fund declared this pandemic the worst crisis since the depression at the beginning of the 20th century **(Vince, 2020).** The current Coronavirus pandemic represents also the most dramatic healthcare crisis linked to acute and highly infectious diseases in the 21st century **(Chaari & Golubnitschaja, 2020).**

I. Generality

The world is becoming divided into a group of countries within reach of eradicating the COVID-19, and another group of countries in which is leading inexorably toward universal presence of the disease with possibly herd immunity **(McGeoch & McGeoch, 2020),**

Global efforts to contain the virus were mixed and infection/death rates are not the same between countries, age groups, or even races **(Atzrodt *et al.,* 2020).** There have been multiple global epicenters like United States of America (USA), United kingdom (UK), Italy, Spain, France, Germany, Turkey, Iran and Russia **[(Chatterjee *et al.,* 2020) ; (Lau *et al.,* 2020)].** But, the main epicenter of the disease was Guangdong, China, from where it spread internationally **(Arshad Ali *et al.,* 2020),** on account of aggressive containment strategies, the acceleration of new cases in China has slowed whereas that outside of China has increased **(Rabi *et al.,* 2020).** The pandemic wave, appeared first in Asia followed by Europe deeply touching Italy, Spain, and France, then spread to America, Australia and lastly Africa, mainly via returning travelers from China **[(Chaari & Golubnitschaja, 2020) ; (Hamidouche, 2020)].** By June 20, close to nine million (8.908.555) cases and almost half million deaths (466.266) were registered **(figure 1) (Worldometre, 2020).**

Amid the outbreak, a continuous rise in mortality rates has been observed **(Lau *et al.*, 2020).** According to epidemiologists, the fatality rate of COVID-19 could change as SARS-CoV-2 can mutate **(Chatterjee *et al.*, 2020),** moreover, quality, quantity and capacity of healthcare systems substantially contribute to the successful management of hospitalized patients and can reduce mortality rates **(Lau *et al.*, 2020).** The worldwide mortality rate of 6.9%, was reported by the WHO as of May 8, 2020, with death rates ranging from ~1% in Chile and Palestine to 14% in Italy **(Atzrodt *et al.*, 2020).**

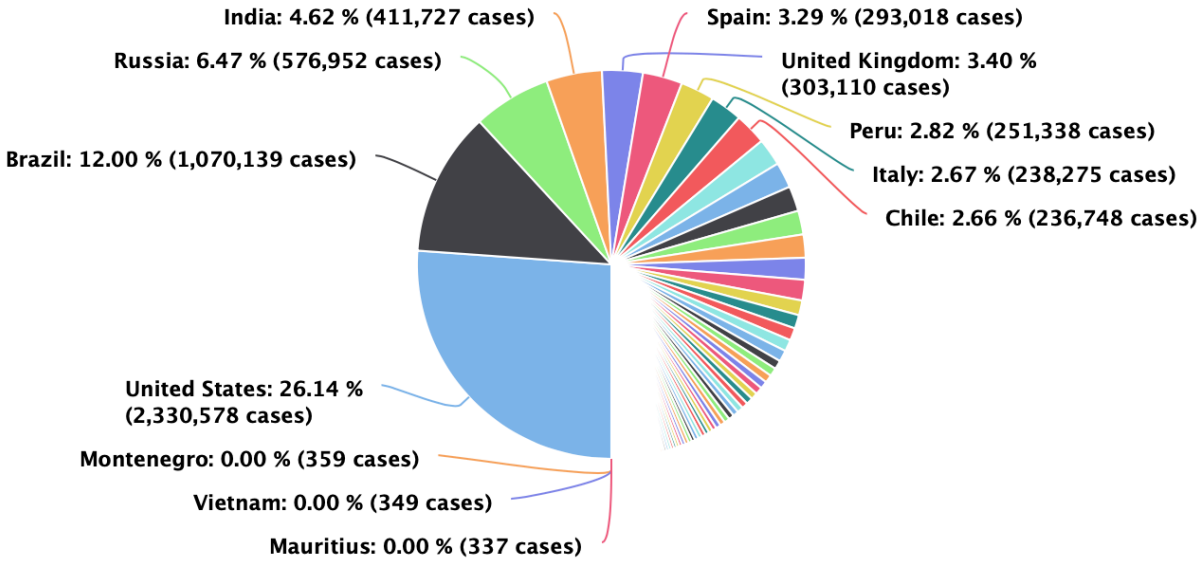


Figure 1: Distribution of COVID-19 cases (As of June 20) (Worldometre, 2020).

II. Timeline of the pandemic

Ahead of January 1st, 2020, 55% of the infected cases were linked to the Huanan Seafood Wholesale Market, and the first case of SARS-CoV-2 infection confirmed outside of China was on January 13th in Thailand, and then on 16th of the month, the first infected case was confirmed in Japan, but these cases were always linked to the Huanan Seafood Wholesale Market **(Helmy *et al.*, 2020).**

As of midst of February 2020, China bears the large burden of morbidity and mortality, whereas the incidence in other Asian countries, Europe and North America remained low so far **(Velavan & Meyer, 2020).** Through rapid and frequent international air travel, the novel virus infections have spread to over 36 countries around the world confirming approximately 80000 infectious patients and above 2500 deaths **[(El Zowalaty &**

Järhult, 2020) ; (Lin *et al.,* 2020)]. On February 27th, Saudi Arabia suspended the year round Umrah pilgrimage, even with the low transmission of the virus, in contrast with Iran, which did not intervene in the religious pilgrimage in Qom and has seen large regional outbreaks **(Ebrahim *et al.,* 2020).**

As of March 2nd, the number of daily new cases outside of China was nine times higher than those within China **(Rabi *et al.,* 2020),** and the WHO warned that COVID-19 is a "public enemy number 1" and potentially more powerful than terrorism, declaring Europe to be the new center of the pandemic on March the 13th, due to the massive increase of confirmed cases **[(Helmy *et al.,* 2020) ; (Yi *et al.,* 2020)].** After one day of their statement, over 140.000 cases were reported worldwide with more than 5400 deaths, surpassing the combined number of cases and deaths of the two previously emerging coronaviruses, SARS-CoV and MERS-CoV **(Rockx *et al.,* 2020).**

Afterwards, the area with the highest number of confirmed cases was Italy, whereas of 16 March, marked 24.747 reported cases, and 13.938 cases in Iran have been also confirmed, with a totality of 169.930 confirmed cases, about half of which were within mainland China **(Rabi *et al.,* 2020).** The analysis of data with a simple model revealed that the recovery rate is the same for Italy and China, while infection and death rate appear to be different, with a mortality rate of 4% to 8% in Italy and lower in china with 1% to 3% **(Fanelli & Piazza, 2020).** Although the containment measures implemented in China have reduced new cases by more than 90%, this reduction was not the case in other countries **(Atzrodt *et al.,* 2020).**

At the beginning of April, Italy has been hit very hard with 110.574 cases and 13.155 documented deaths related to COVID-19 infection, this could be explained by the fact that the country has the most elderly population in Europe and the second most elderly population in the world after Japan, with a high proportion of patients with history of smoking and high rates of chronic obstructive pulmonary disease and ischemic heart disease, not to mention, that the Italian life is famous for its socialization and frequent congregations and clustering **(Boccia *et al.,* 2020),** strikingly, as of 13th of April, the world enlisted 1.773.084 confirmed cases, 111.652 deaths, and 467.074 recoveries **(Helmy *et al.,* 2020).**

After the rapid spread of SARS-CoV-2 infectious disease worldwide, between February and April 2020, a total of 5.267.419 confirmed cases and 341.155 deaths were

marked on May 25th, in the last weeks a decrease in new infections was observed in European countries, and the confirmed cases are not as severe as before **(Petrosillo, 2020),** with the virus strongly hitting Europe, afterwards came the United States of America, which is recording a daily growth of 25.000 new cases, making it the most hit country with 30% of all world cases and still rising **(Vince, 2020).** By June 1st, 2020 more than 6 million individuals and more than 370 thousands case fatalities were documented worldwide **(Saeed *et al.*, 2020).**

III. Procedures and Factors of the pandemic

III.1. Community mitigation measures

Many countries obligated containment measures such as isolation, quarantine, lockdown with police patrolling the streets, social distancing, also closures of public schools/ universities, prohibition of any social gatherings and contact phone tracking, plus the travel bans and quarantine procedures for incoming travelers, in an effort to contain the spread of COVID-19 and decrease the public health burden **[(Cohen & Kupferschmidt, 2020) ; (Dai & Locasale, 2020) ; (Ebrahim *et al.*, 2020) ; (Lau *et al.*, 2020) ; (Morawska & Cao, 2020) ; (Rabi *et al.*, 2020) ; (Saeed *et al.*, 2020) ; (Vince, 2020)],** even on having strict guidelines on funerals, given the role of bodily fluids in viral transmission and crowding during the event **(Ebrahim *et al.*, 2020).**

It is important to understand that, the concept of social distancing is not to eradicate the COVID-19, but more of, to slow down its transmission, flattening the curve of afflicted population, hence declining the pressure on the health care systems and economy, in this manner, reduce the fatality rate **(Chatterjee *et al.*, 2020).** Other mass gatherings like the 2020 Olympic Games and Hajj pilgrimage will definitely need a lot of reconsidering **(Ebrahim *et al.*, 2020).**

Imposing controls has had a significant impact on the pandemic **(Li *et al.*, 2020)**, where four parameters were important to assess the magnitude of the risk posed by the SARS-CoV-2, the transmission rate, the incubation period, the case fatality rate (CFR), and the occurring of asymptomatic transmission **(Rabi *et al.*, 2020).**

III.2. Factors of the viral spread

Older age, male gender, obesity and existing immune deficiencies were the main risk influencing factors **[(Prabhakar *et al.,* 2020) ; (Qin *et al.,* 2020) ; (Sahu *et al.,* 2020) ; (Yi *et al.,* 2020)].** There's a wide range of other factors that may play a significant role in total case numbers like, the use of safety measures in public transportation, population density, age structure of the country, demographics and back-ground disease in the population, adding to that, the quality of the health systems or insufficient medical coverage, and how media presents the urgency of this immediate health threat, also, the local temperature and humidity factors, cultural and religious practices **[(Atzrodt *et al.,* 2020) ; (Boccia *et al.,* 2020) ; (Lau *et al.,* 2020)].**

However, statistical correlation study has proven that COVID−19 does not depend on external weather factors **(Chatterjee *et al.,* 2020),** likewise **Baker *et al.,* (2020),** recent results, imply that both tropical and temperate locations are up for severe outbreaks of the disease and that summertime temperatures will not effectively limit the spread of the infection, but this doesn't mean that climate is not important in the longer term. For the moment, there is no evidence that higher temperatures may modify virulence or pathogenicity of SARS-CoV-2 **(Petrosillo, 2020).**

Dense communities are at particular risk and the most vulnerable region, certainly is Africa, due to insufficient diagnostic capacities **(Velavan & Meyer, 2020).** The impact of a similar epidemic as currently seen in Europe, would be devastating in Africa, since it has some of the poorest countries in the world with a poorly resourced health systems**. Martinez-Alvarez *et al.,* (2020),** believe that the epidemic has started later in Africa than for other regions globally because of the limited international air traffic, and besides in having young populations, rather than the climate conditions.

III.3. Control strategies

COVID-19 case numbers depend on testing efforts, and mortality rates depend on the local definition of COVID-19 related deaths **(Lau *et al.,* 2020).** The key to success has been a large, well-organized testing program, combined with extensive efforts to isolate the infected and trace their contacts. For example the USA has had a slow start, having problems with its test kits, beginning with only 74 tests per million inhabitants, compared with 5200 tests per

million in South Korea which didn't order lockdown and had good outcomes. Only after propagation, USA began to roll out testing on a mass scale after that it was a little late **(Cohen & Kupferschmidt, 2020).**

Elsewhere, in Europe, Germany was a front-runner, it statistics number of deaths from the virus, were remarkably low in comparison with other countries, especially its neighbors, this relatively low fatality rate can be attributed partly to the nation's early and high level of testing among a wide sample of the population, including milder cases in younger people, with more than 100,000 tests processed per week **[(Cohen & Kupferschmidt, 2020) ; (Stafford, 2020)].**

Modern geographic information systems (GIS) technologies, communication through map-based Dashboards, also supported the critical decision-making, sharing and understanding the spread of the SARS-CoV-2 in the communities **(Kamel Boulos & Geraghty, 2020).**

The SARS outbreak was a wakeup call for Taiwan which made it implicate a quick strategy in adopting specific approaches for case identification, containment, and resource allocation to protect the public health, using new technologies, including Quick Response (QR) code scanning, tracing with the National Health Insurance (NHI) smart card and online reporting of travel history and health symptoms to classify travelers including border control, maximizing response system efficiency, activating early proactive measures, promoting transparency and public education, enforcing social cohesion, and fostering a public sense of urgency, in addition to an active role in resource allocation for setting the price of masks and using government funds and military personnel to increase mask production **[(Chiu *et al.,* 2020) ; (Wang *et al.,* 2020)].** Taiwan also, had the foresight to create a large stockpile of face masks that other countries might now consider it as part of future epidemic plans **(Feng *et al.,* 2020).**

China, has rolled out perhaps the most ambitious, agile, and aggressive disease containment effort in history, in addition to building two COVID-19-dedicated hospitals in Wuhan in about 1 week, and launching an unprecedented effort to trace contacts of confirmed cases via widely used mobile phone apps, where they helped enforce the restrictions and allowing the government to keep on track of people's movements **(Kupferschmidt &**

Cohen, 2020). New technologies were also used, like the unmanned aerial vehicles (UAV) that were transporting crucial medical supplies and patient lab samples and drones that held broad disinfectant operations **(Kamel Boulos & Geraghty, 2020).**

The engagement in mass testing might have contributed to the quick control of the outbreak in countries like Germany and South Korea, whereas the reluctance to provide mass testing of those exhibiting symptoms of infection done in the UK and United States has, arguably, prolonged the outbreak **(Atzrodt *et al.,* 2020).**

Chatterjee *et al.,* (2020), hypothesize that social isolation or social distancing might restrict the spreading of SARS-CoV-2 as it may slow down the spread factor**,** and it is not known whether a new pandemic wave may emerge when lockdown measures are removed **(Boccia *et al.,* 2020).** It is essential for governments to consider this before the return to normal life **(Atzrodt *et al.,* 2020).**

IV. Epidemiological status of COVID-19 in Algeria

In Africa, the first confirmed case was reported in Egypt on the 14th of February 2020, and by the end of April, there were over 37.000 registered cases, due to a wide range of factors, such as the number of imported infections, the low capacity to conduct tests for COVID-19 as well as poor surveillance efforts**.** Many countries in Africa are on high alert for incoming cases from Europe and USA, taking measures such as quarantine of arrivals or shutting down travel from affected countries **(Sun *et al.,* 2020),** indicating, that travel is the most important contributor to disease **(Ebrahim *et al.,* 2020).**

Algeria was considered as one of the three African countries with the highest importation risk of COVID-19, with Egypt and South Africa **(Lounis, 2020).** The first case of COVID-19 in Algeria was reported on February 25th, 2020, when an Italian national tested positive in Ouargla, a few days later, on March 1st, two cases were reported in Blida region in the North of Algeria, following their contacts with two Algerian nationals who came from France and were COVID-19+. After that, a cluster of cases was formed making the province of Blida the epicenter of the epidemic in Algeria. Since then the spread of the virus in Algeria has gone through different endemic phases, with number of national cases diagnosed begun to increase **(figure 2) [(Ababsa & Aouissi, 2020) ; (Hamidouche, 2020) ; (Kada *et al.,***

2020) ; (Rouabah *et al.*, 2020)]. As of June 20th 11.631 cases, 837 deaths and 8324 recoveries were registered **(Worldometer, 2020).**

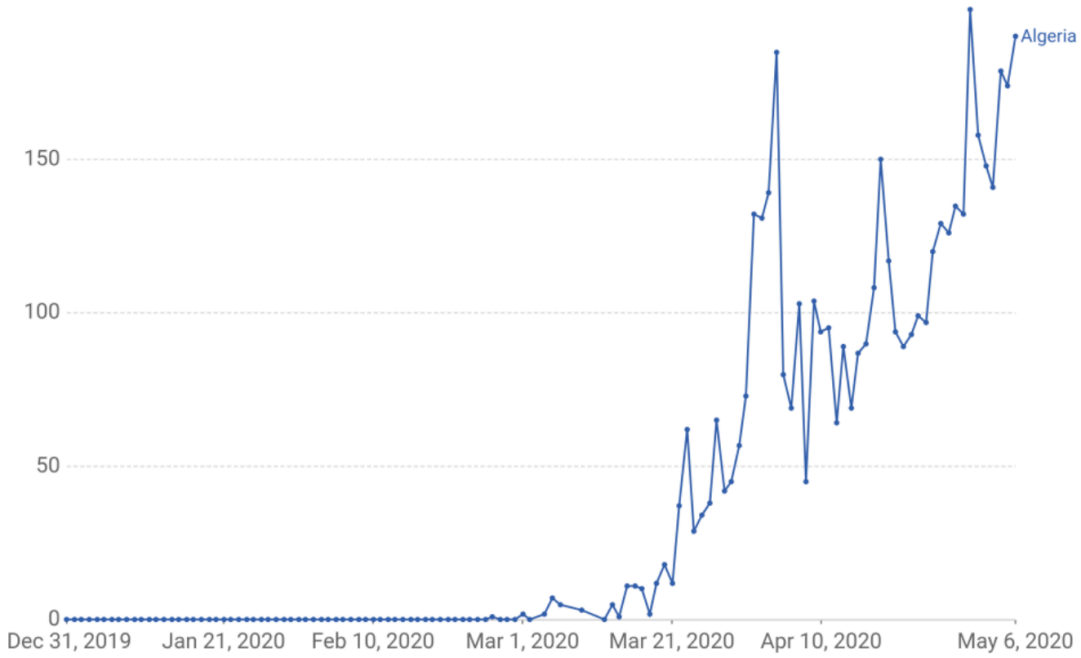


Figure 2: Daily confirmed COVID-19 cases in Algeria (Lounis, 2020).

The laboratory analysis was one of the weakest links of Algeria in dealing with COVID-19 pandemic, low number of daily tests and the relatively long test-to-result time increased the probability of an asymptotic infectious individual spreading the virus before being quarantined **[(Lounis, 2020) ; (Rouabah *et al.*, 2020)].**

The containment and quarantine established on March 24 in the country**,** were undoubtedly the most effective solution to contain the virus progression. It started by prohibiting sports gatherings, followed by schools, then worship places, also public transport and travel restriction like stoping planes and boats from and to Algeria **[(Ababsa & Aouissi, 2020) ; (Lounis, 2020)].** Their establishment of when only 264 cases were identified, resulted in the improvement of the situation **(Kada *et al.*, 2020).**

In Algeria, the overall CFR, first estimated at 15.78 % on 13 April, begin to decrease 7 days after generalization of therapeutic protocol, to reach 7,09 % on May 26 **(figure 3)**, confirming the effectiveness of the measures taken and the merits of using hydroxychloroquin/azithromycin protocol that was put in place on March 23rd, for complicated cases, it was extended to all the cases confirmed on April 06th. **Rouabah *et al.*,**

(2020), estimated by their own Mathematical Compartmental Model, that hopefully, the number of new infections in Algeria will vanish by mid-September, if not the case of a second wave, which would result from the heavy unconsciousness of the Algerian people and the State's poor mismanagement**.**

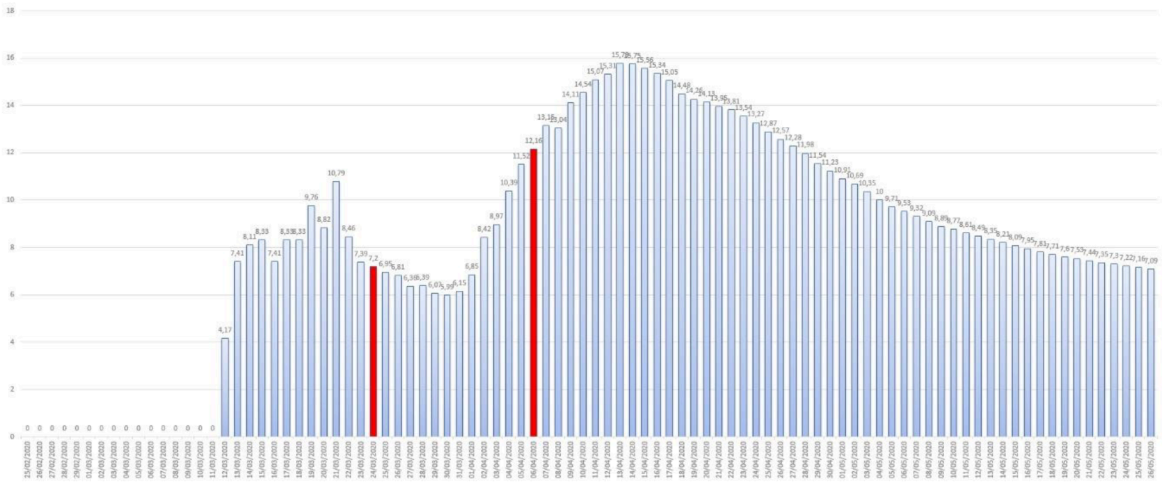
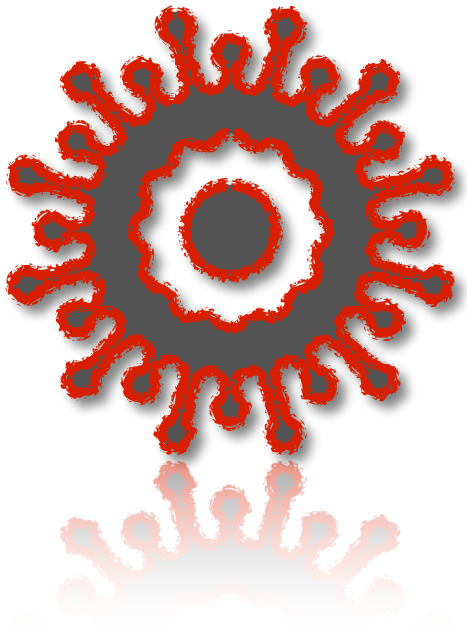


Figure 3: Case-Fatality Rate of COVID-19 in Algeria (Kada *et al.*, 2020).

with first red marking: introduction of hydroxychloroquin/azithromycin protocol and second red marking: generalization to all positive cases**.**



CHAPTER TWO:

SEVERE ACUTE RESPIRATORY SYNDROME-CORONAVIRUS-2 (SARS-COV-2)

Chapter Two: Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2)

About 70% of the emerging pathogens infecting humans originate from animals, and Coronaviruses (CoVs) make the forefronts of these pathogens **(Ou *et al.,* 2020).** Among the viral-mediated pandemics that have been rapidly spreading worldwide in the last twenty years, CoVs dependent outbreaks seem to be the most severe implicated in lung pathology **(Tsiambas *et al.,* 2020).** Therefore, the increasing frequency of the emergence of zoonotics that have crossed species barrier to infect humans, resulting in respiratory illnesses including a pneumonia that is fatal **(Stawiski *et al.,* 2020),** are of grave concern because of their high mortality rate **(Prates *et al.,* 2020).** Moreover, new coronaviruses appear to emerge periodically in humans, mainly due to the high prevalence and wide distribution of coronaviruses, the large genetic diversity and frequent recombination of their genomes, and the increase of human-animal interface activities too **(Wu *et al.,* 2020).**

I. History of coronavirus epidemics

Coronaviruses have caused two large-scale epidemics in the past **(Zhou *et al.,* 2020),** and gained much attention as the causative agents for the outbreaks of human respiratory syndromes such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) which arose from zoonotic transfer from animals to humans **[(Chen, 2020) ; (Gildenhuys, 2020) ; (Mani *et al.,* 2020) ; (Ou *et al.,* 2020)].**

Severe Acute Respiratory Syndrome (SARS-CoV) outbreak occurred in Between November 2002 and July 2003 and had a 9.6% fatality rate, leading to 8098 infections and 774 deaths with the majority of cases in mainland China and Hong Kong, it transmitted from animals in open-air markets **[(Akram & Mannan, 2020) ; (Guarner, 2020) ; (Letko *et al.,* 2020) ; (Lu *et al.,* 2020) ; (Mani *et al.,* 2020) ; (Taherizadeh *et al.,* 2020) ; (Yeo *et al.,* 2020)].**

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) which was first detected in Saudi Arabia in 2012, nine years later after SARS outbreak, it spread to the Middle East, with a 35% fatality rate of cases **(Akram & Mannan, 2020),** it caused 2465 confirmed cases worldwide, 896 fatalities and the virus is still circulating by lower severity

[(Guarner, 2020) ; (Lu *et al.,* 2020) ; (Mani *et al.,* 2020) ; (Taherizadeh *et al.,* 2020) ; (Yeo *et al.,* 2020)].

Both SARS-CoV and MERS-CoV are zoonotic viruses, bat/civet and dromedary camels are their hosts, respectively **[(Akram & Mannan, 2020) ; (Oberemok *et al.,* 2020)].** Nevertheless, it is likely that SARS-CoV-2 may also have had an intermediate animal host before it was transmitted to humans similarly to SARS and MERS **(Jogalekar *et al.,* 2020).**

The end of 2019 was marked by the emergence of a novel coronavirus, severe acute respiratory syndrome coronavirus 2, which caused an outbreak of viral pneumonia, firstly documented in Wuhan, China that started from a local seafood market in Huanan, where a probable zoonotic source has been speculated to originate **[(Hoffmann *et al.,* 2020) ; (Lai *et al.,* 2020) ; (Lam *et al.,* 2020) ; (Ou *et al.,* 2020) ; (Sungnak *et al.,* 2020) ; (To *et al.,* 2020) ; (Valencia, 2020) ; (Walls *et al.,* 2020) ; (Wang *et al.,* 2020) ; (Wu *et al.,* 2020) ; (Yan *et al.,* 2020) ; (Yeo *et al.,* 2020) ; (Zhang *et al.,* 2020) ; (Zhang *et al.,* 2020) ; (Zhou *et al.,* 2020)].**

The outbreak caused by COVID-19 virus, was identified in Wuhan City, in the Hubei province of southern mainland China on the 31st December 2019 and was reported to the World Health Organization (WHO), then on January 7th, the Chinese Center for Disease Control and Prevention (CDC) isolated and confirmed this pathogen as a novel type of coronavirus through a throat swab of a sick patient **[(Alméciga-Díaz *et al.,* 2020) ; (Bhowmik *et al.,* 2020) ; (van Doremalen *et al.,* 2020) ; (Li *et al.,* 2020) ; (Mani *et al.,* 2020) ; (Morawska & Cao, 2020) ; (Sahu *et al.,* 2020) ; (Tang *et al.,* 2020) ; (Xia *et al.,* 2020) ; (Xiao *et al.,* 2020) ; (Xu *et al.,* 2020) ; (Zhang *et al.,* 2020)].**

The 2019 novel coronavirus was named "2019-nCoV" by the WHO on the 12th of January **(Akram & Mannan, 2020).** Later on the thirtieth of the same month, WHO declared that the virus is a «public-health emergency of international concern» **[(Valencia, 2020) ; (Walls *et al.,* 2020) ; (Wu *et al.,* 2020)].** After that, the International Virus Classification Commission (ICTV) classified 2019-nCoV as Severe Acute Respiratory Syndrome Coronavirus 2 on February 11th and around the same time, WHO named the virus disease as COVID-19 (**figure 4) [(Akram & Mannan, 2020) ; (Anastasopoulou & Mouzaki, 2020) ; (Guarner, 2020) ; (Lai *et al.,* 2020) ; (Wang *et al.,* 2020) ; (Xia *et al.,* 2020)].**

The SARS-CoV-2 is the third novel coronavirus to cause a large-scale epidemic in the twenty-first century **[(Alanagreh *et al.*, 2020) ; (Banerjee *et al.*, 2020) ; (Coutard *et al.*, 2020) ; (Gu *et al.*, 2020) ; (Guarner, 2020) ; (Gurwitz, 2020) ; (Kandeel *et al.*, 2020) ; (Oberemok *et al.*, 2020) ; (Stawiski *et al.*, 2020) ; (Xu *et al.*, 2020)].** Although, previous MERS and SARS had higher mortality rate, the specificity of this novel virus is that it spreads much more rapidly **(To *et al.*, 2020).** It has spread globally to the extent that WHO declared it as a pandemic on March 11th **[(Bhowmik *et al.*, 2020) ; (Dagur & Dhakar, 2020) ; (De Soto *et al.*, 2020) ; (Ma & Holt, 2020) ; (Romano *et al.*, 2020) ; (Sahu *et al.*, 2020) ; (Valencia, 2020) ; (Zhang *et al.*, 2020) ; (Zhao *et al.*, 2020)].**

The viral pandemic progressed worldwide with a significant resultant morbidity and mortality **[(Cheng *et al.*, 2020) ; (Shang *et al.*, 2020)],** and is still rapidly spreading across the world and the numbers of affected and those deceased are increasing at an alarming rate **(Prabhakar *et al.*, 2020),** while having devastating societal and economic impacts **[(Prates *et al.*, 2020) ; (Shang *et al.*, 2020)].**

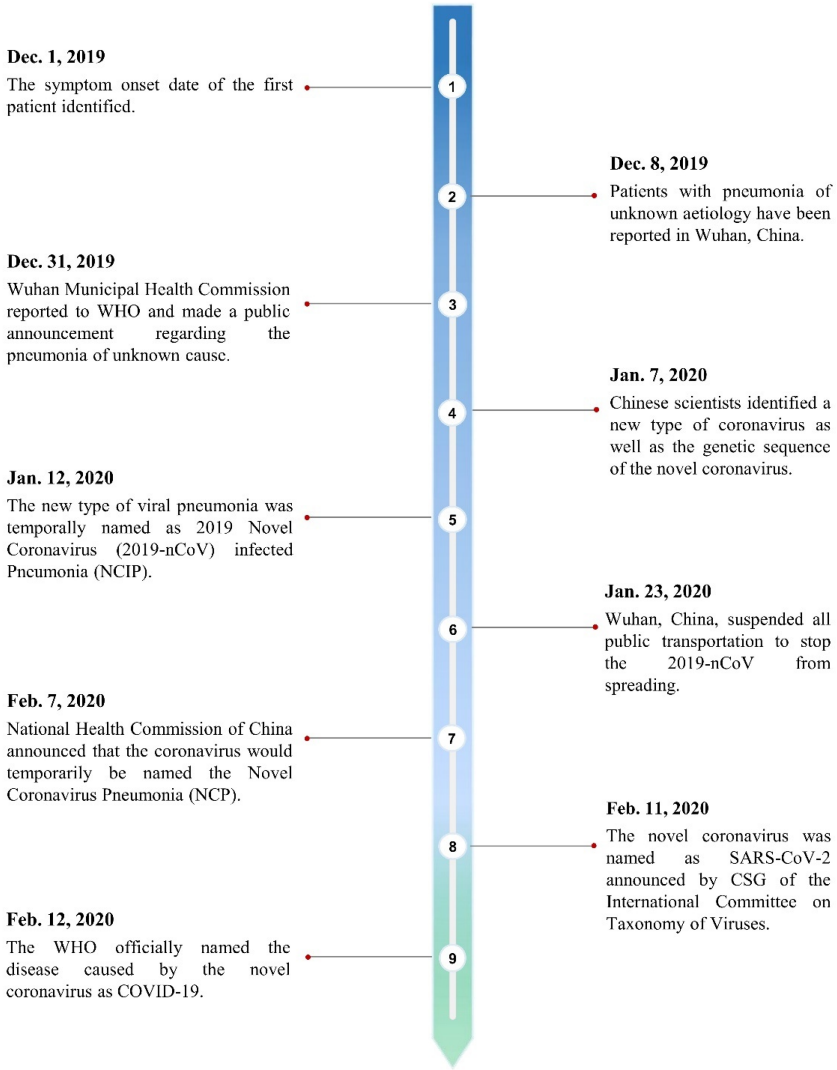


Figure 4: The timeline development of SARS-CoV-2 (Yan *et al.*, 2020).

II. Coronaviruses

Coronaviruses (CoVs) are a large group of viruses common among many animals, including humans and are widely distributed in nature **(Alanagreh *et al.*, 2020).** They are spherical with spikes on the surface **[(Anastasopoulou & Mouzaki, 2020) ; (Taherizadeh *et al.*, 2020) ; (Wu *et al.*, 2020)],** large peplomers that make it look like a crown-shaped outer coat seen on the electron-microscopy **(figure 5)**, hence the name corona, meaning "crown" or "halo", resembling the "solar corona" appearance **[(Alanagreh *et al.*, 2020) ; (Cheng *et al.*, 2020) ; (De Soto *et al.*, 2020) ; (Dhar Chowdhury & Oommen, 2020) ; (Valencia, 2020)],** thus, representing the structural protein "S-protein" of Coronaviruses **(Coutard *et al.*, 2020).**

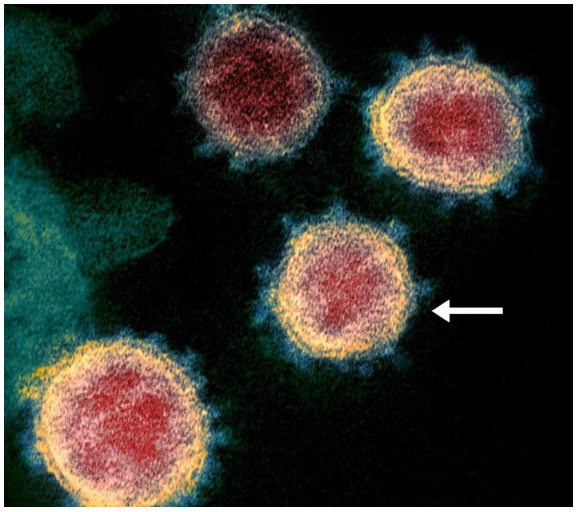


Figure 5: Electron microscopy (EM) image of SARS-CoV-2 virions with the arrow pointing at a single virion (Valencia, 2020).

CoVs have a total of 39 species under the broad realm of *Riboviria* within the order *Nidovirales* belonging to the family of *Coronaviridae and* suborder *Cornidovirineae* (**figure 6) [(Gorbalenya *et al.*, 2020) ; (Lu *et al.*, 2020) ; (Mani *et al.*, 2020) ; (Taherizadeh *et al.*, 2020) ; (Valencia, 2020)].** They're enveloped**,** non-segmented**,** single-stranded positive-sense RNA viruses with the largest known RNA genome (26-32kb) **[(Alanagreh *et al.*, 2020) ; (Anastasopoulou & Mouzaki, 2020) ; (Coutard *et al.*, 2020) ; (Dagur & Dhakar, 2020) ; (De Soto *et al.*, 2020) ; (Guarner, 2020) ; (Hillen *et al.*, 2020) ; (Kandeel *et al.*, 2020) ; (Mani *et al.*, 2020) ; (Pillaiyar *et al.*, 2020) ; (Valencia, 2020) ; (Wang *et al.*, 2020) ; (Wu *et al.*, 2020) ; (Yeo *et al.*, 2020)].** The *Coronavirnae* subfamily has four genera that includes *Alphacoronavirus* , *Betacoronavirus*, *Gammacoro*navirus and *Deltacoronavirus***,** While α- and β-CoVs infect mammals especially bats, the γ- and δ-CoVs generally infect birds **[(Akram & Mannan, 2020) ; (Anastasopoulou & Mouzaki, 2020) ; (Mani *et al.*, 2020) ; (Ou *et al.*, 2020) ; (Stawiski *et al.*, 2020) ; (Taherizadeh *et al.*, 2020) ; (Tsiambas *et al.*, 2020) ; (Wu *et al.*, 2020)].**

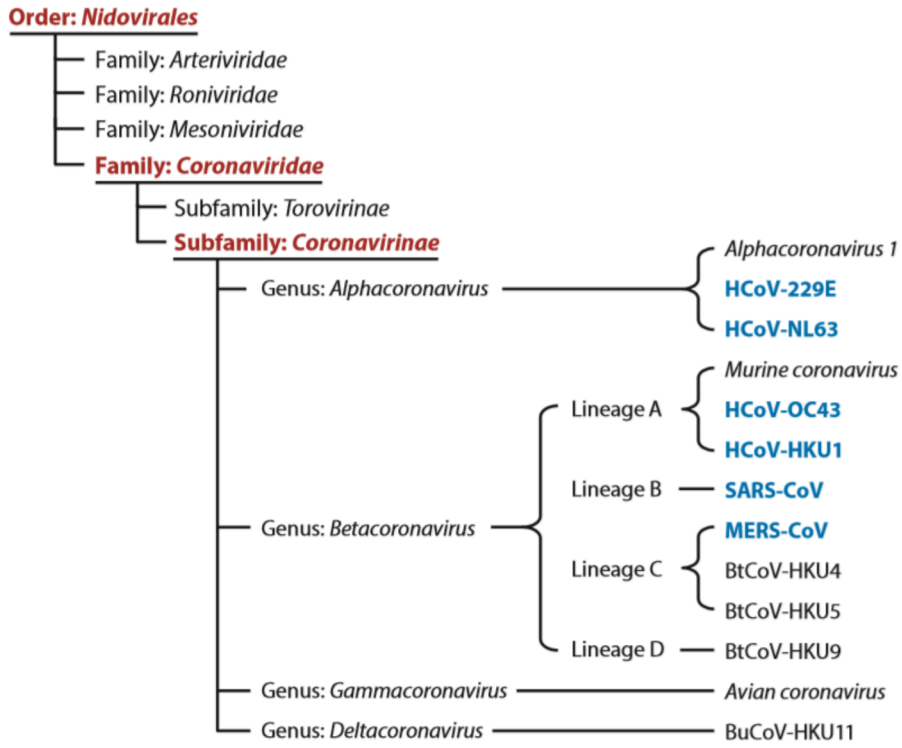


Figure 6: Classification scheme of HCoV and other coronaviruses (Yan *et al.*, 2020).

Animal coronaviruses are zoonotic in nature, and they are capable of generating mutant viruses which can pass thought other hosts such as humans **(Taherizadeh *et al.*, 2020).** They have been identified in several avian hosts, as well as in various mammals, including camels, bats, masked palm civets, mice, dogs, and cats **[(Akram & Mannan, 2020) ; (Dagur & Dhakar, 2020) ; (Lu *et al.*, 2020)],** however, these viruses are naturally hosted and evolutionarily shaped by bats, their natural reservoir**,** in which they have in a mistering way, crossed species barrier to infect humans resulting in respiratory illnesses including a fatal pneumonia **[(Stawiski *et al.*, 2020) ; (Tang *et al.*, 2020) ; (Wu *et al.*, 2020)].** CoVs frequently undergo recombination, gaining large swaths of genetic material at once **(Letko *et al.*, 2020).** Moreover, they have error-prone RNA-dependent-RNA-polymerases (RdRp) and mutational events that frequently occur, resulting in quasi-species diversity that is closely associated with adaptive evolution and the capacity to cause disease **(Chen, 2020).**

Although the history of CoVs began in the 1940's, The first human coronavirus was isolated from the respiratory secretions of a man suffering a common cold by Tyrell and Bynoein in the 1960's **[(Cheng *et al.*, 2020) ; (Pillaiyar *et al.*, 2020) ; (Taherizadeh *et al.*, 2020) ; (Valencia, 2020)].** Since the mid-1960's, six pathogenic species have been identified as human coronaviruses (HCoVs) that specifically infect humans and cause disease (**table 1)**

[(De Soto *et al.,* 2020) ; (Pillaiyar *et al.,* 2020) ; (Valencia, 2020) ; (Wu *et al.,* 2020)]. These include the αCoVs: HCoV- NL63 (Human CoV-NL63) and HCoV-229E, the βCoVs: HCoV-OC43 (Human CoV-OC43), HKU1 (Human CoV U1), with low pathogenicity causing mild flu-like symptoms, conversely to SARS-CoV and MERS-CoV, which are highly pathogenic **[(De Soto *et al.,* 2020) ; (Mani *et al.,* 2020) ; (Stawiski *et al.,* 2020) ; (Taherizadeh *et al.,* 2020) ; (Valencia, 2020) ; (Walls *et al.,* 2020) ; (Wu *et al.,* 2020) ; (Xu *et al.,* 2020)],** posing a serious threat to humans and a range of mammalian hosts, causing respiratory, enteric, gastrointestinal, renal, hepatic and neurologic diseases **[(Ou *et al.,* 2020) ; (Pillaiyar *et al.,* 2020) ; (Prabhakar *et al.,* 2020) ; (Stawiski *et al.,* 2020)].**

Table 1: Classification, discovery, and natural host of the coronaviruses (Pillaiyar *et al.,* 2020).

HCoV genera	Coronaviruses	Discovery	Cellular receptor	Natural Host(s)
α-Coronaviruses	HCoV-229E HCoV-NL63	1966 2004	CD13 ACE2	Bats Palm Civets, Bats
β-Coronaviruses	HCoV-OC43 HCoV-HKU1 SARS-CoV MERS-CoV	1967 2005 2003 2012	9-O-Acetylated sialic acid ACE2 DPP4	Cattle Mice Palm Civets,Bats, Camels

III. Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2)

III.1. Generality

SARS-CoV-2 is the seventh pathogenic member of the human coronaviruses **[(Andersen *et al.,* 2020) ; (Banerjee *et al.,* 2020) ; (Taherizadeh *et al.,* 2020) ; (Wu *et al.,* 2020) ; (Xu *et al.,* 2020)],** a new zoonotic virus **(Prabhakar *et al.,* 2020),** that has crossed the species barrier to infect humans **[(Bhowmik *et al.,* 2020) ; (Chen, 2020)],** which is evolving rapidly where aged mutations are persisting or diluted away and new mutations are arising **(Yang *et al.,* 2020),** causing a severe respiratory syndrome in humans **(Yan *et al.,* 2020).**

The virus is highly contagious, spreading quickly around the world, affecting all individuals specially the elderly, those with diverse genetic and immunological backgrounds, notably whom with multiple underlying disorders and varied demographics like sex and

environmental conditions **[(Bhowmik *et al.,* 2020) ; (De Soto *et al.,* 2020) ; (Li *et al.,* 2020)].**

The severity of the disease is most often an important indirect factor in a virus ability to spread **(Chen, 2020).** Complications are mainly associated with virus load, virulence, route of infection, age and immune status of the host **(De Soto *et al.,* 2020).**

III.2. Origin of the virus

Even though the exact origin of the virus remains unclear, the question still circulates. Has the new virus responsible for the actual pandemic, came from animals or from a laboratory**? (Oberemok *et al.,* 2020).**

Phylogenetically, SARS-CoV-2 has shown the close association with a couple of bat coronaviruses, bat-SL-CoVZC45, and bat-SL-CoVZXC21 with 88% similarity, then 79% with SARS-CoV, 50% for MERS-CoV and the highest was RaTG3 with 96% **[(Bhowmik *et al.,* 2020) ; (Jiang *et al.,* 2020) ; (Jogalekar *et al.,* 2020) ; (Lai *et al.,* 2020) ; (Romano *et al.,* 2020) ; (Yan *et al.,* 2020)],** adding to those, the Pangolin-CoV with a 91.02% similarity (**figure 7**) (**Oberemok *et al.,* 2020).**

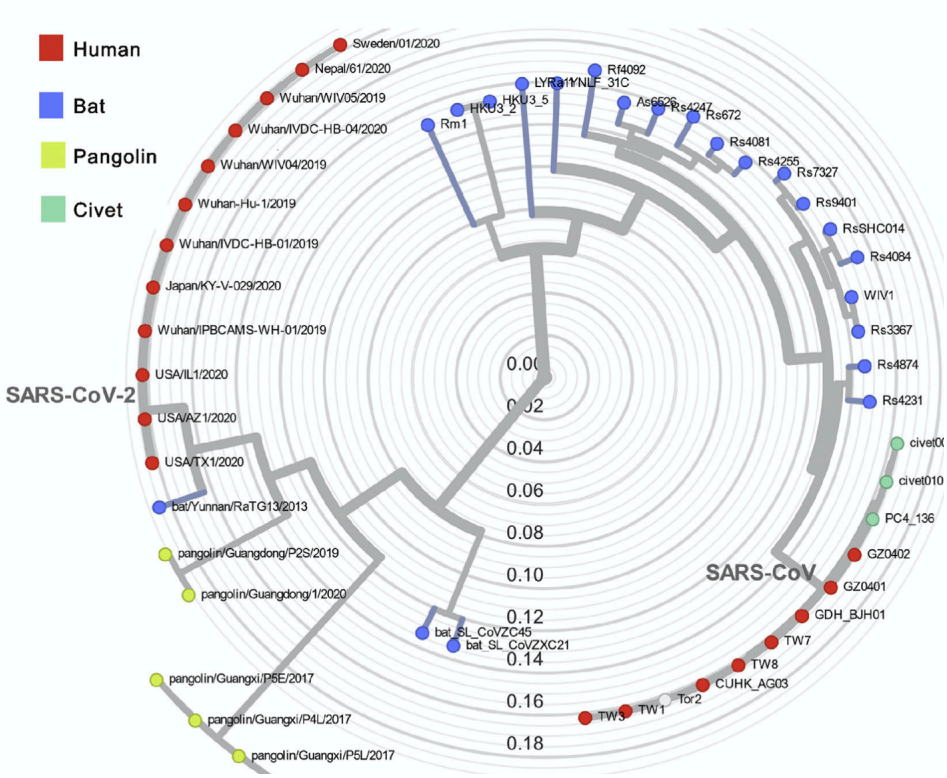


Figure 7: The phylogenetic tree of SARS-like coronaviruses complete genome sequences and genome of SARS-CoV, MERS-CoV and SARS-CoV-2 (Li *et al.,* 2020).

Genetic and structure analyses indicate that SARS-CoV-2 is a novel coronavirus, that originated due to natural selection either in an animal host before zoonotic transfer and/or natural selection in humans following zoonotic transfer **[(Anastasopoulou & Mouzaki, 2020) ; (Andersen *et al.,* 2020)].**

Many of the early cases were linked to Huanan seafood Wholesale market in Wuhan city, Hubei province, where the virus is thought to have originated **[(Akram & Mannan, 2020) ; (Chen, 2020) ; (Lu *et al.,* 2020)].** Until now, no other mammals other than bats documented to be infected by a SARS-CoV-2 except Pangolins (**figure 8) [(Akram & Mannan, 2020) ; (Lam *et al.,* 2020) ; (Zhang *et al.,* 2020)].** Accordingly to several studies, pangolins may have provided a partial spike gene to SARS-CoV-2, due to the compatibility in critical functional sites of the novel virus and the virus isolated from a pangolin **(Tang *et al.,* 2020),** in addition to the high sequence similarity of 97.4% amino-acid in the receptor-binding domain (RBD) to Guangdong pangolin coronaviruses, hypothesizing a selectively-mediated convergent evolution rather than recombination **(Lam *et al.,* 2020).** This also suggests, that the pangolin species may be long-term reservoir hosts for these viruses, which is surprising as pangolins are solitary animals with relatively small population sizes **[(Akram & Mannan, 2020) ; (Zhang *et al.,* 2020)].**

Oberemok *et al.,* (2020) suggest, based on genomic alignments that the COVID-19 virus may be the result of recombination of genetic material from two different viruses, one similar to the Chinese horseshoe bat virus and the other closer to the pangolin virus (two divergent viruses could have infected the same organism simultaneously).

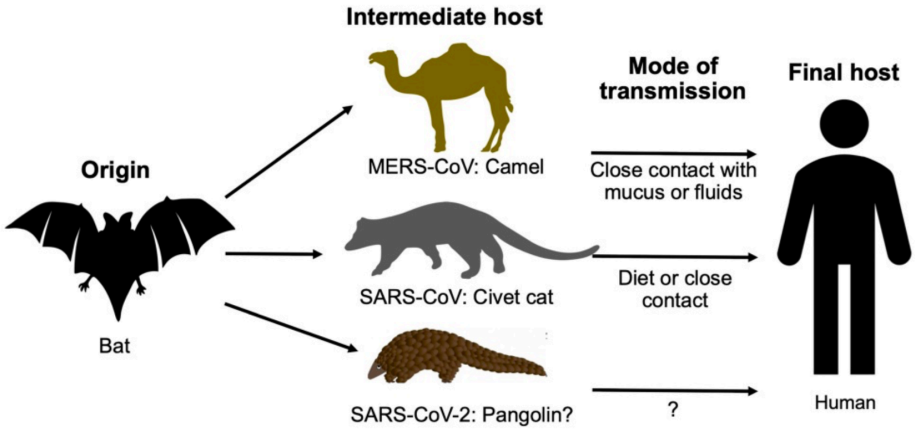


Figure 8: The intermediate hosts of SARS-CoV-2, SARS-CoV, & MERS-CoV (Yi *et al.,* 2020).

Given, the high-affinity binding of the virus spike protein to human ACE2, and finding of SARS-CoV like coronaviruses from pangolins with nearly identical RBDs, provides a much stronger and more parsimonious explanation of how SARS-CoV-2 acquired these via recombination or mutations, argues against any culture-based scenarios or being the product of purposeful manipulation**.** Likewise, genetic data irrefutably show, that SARS-CoV-2 is not derived from any previously used virus backbone **(Andersen *et al.*, 2020).**

III.3. Classification

SARS-CoV-2 is a member of the B-lineage of the *Betacoronavirus* genus, clustered into the *Sarbecovirus* subgenus, belonging to the family of *Coronaviridae and* the sub-family of *Coronavirinae* (**figure 9) [(Chen, 2020) ; (De Soto *et al.*, 2020) ; (Jiang *et al.*, 2020) ; (Lai *et al.*, 2020) ; (Lan *et al.*, 2020) ; (Oberemok *et al.*, 2020) ; (Romano *et al.*, 2020) ; (Talluri, 2020) ; (Walls *et al.*, 2020) ; (Wang *et al.*, 2020) ; (Xu *et al.*, 2020)].**

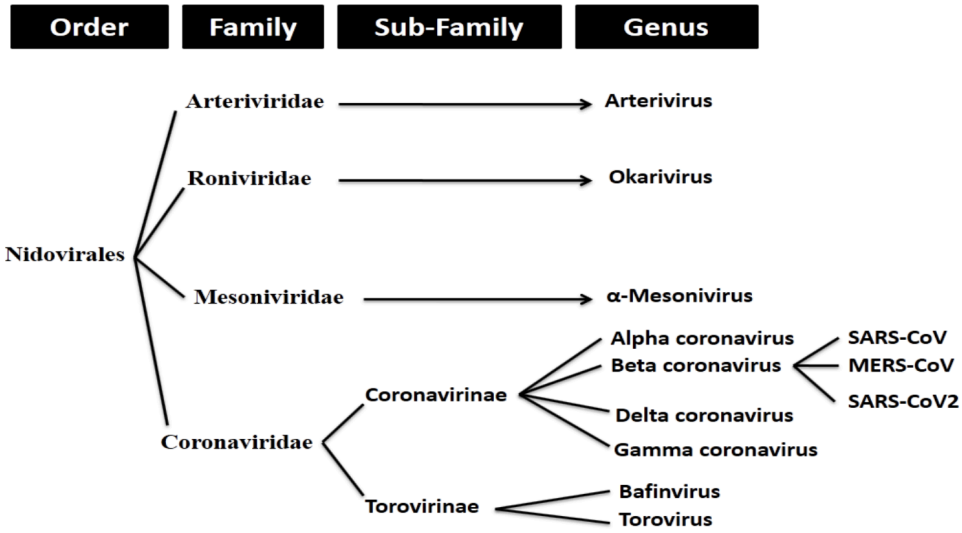


Figure 9: Classification of coronaviruses (Rehman *et al.*, 2020).

III.4. Structure

The virion is spherical, approximately 120 nm in diameter with a helical nucleocapsid enveloped by a host-derived lipid bilayer, that possesses crown-like distinctive spikes, about 9 to 12 nm on their surface with an RNA genome packaged into it (**figure 10) [(Akram & Mannan, 2020) ; (Banerjee *et al.*, 2020) ; (Cheng *et al.*, 2020) ; (Dhar Chowdhury & Oommen, 2020)].**

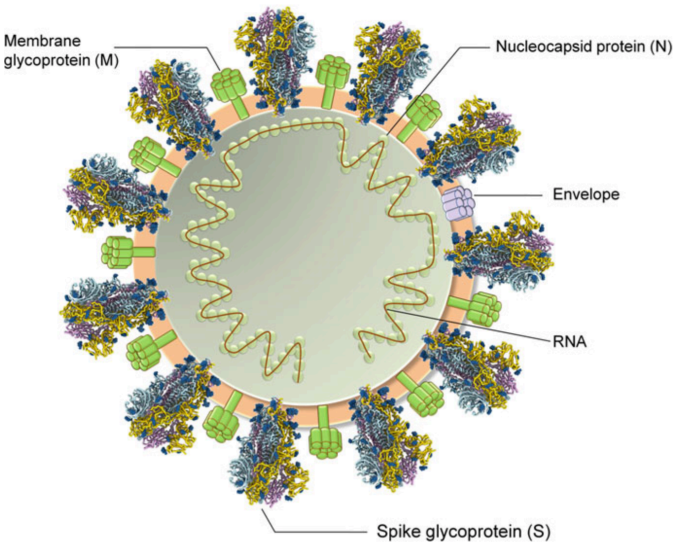


Figure 10: Structure of SARS-CoV-2 (Kumar *et al.*, 2020).

III.5. Genome

SARS-CoV-2 has a non-segmented, positive sense, single-stranded RNA (+ss RNA), containing a 30 kb genome with 14 open reading frames (ORFs) and 38% G+C content, encoding 9,860 amino acids (AA), among the largest known RNA genomes (**figure 11**) **[(Anastasopoulou & Mouzaki, 2020) ; (Caly *et al.*, 2020) ; (Jiang *et al.*, 2020) ; (Kumar *et al.*, 2020) ; (Lai *et al.*, 2020) ; (Oberemok *et al.*, 2020) ; (Romano *et al.*, 2020) ; (Talluri, 2020)].** The genome encodes for both structural and non-structural proteins (Nsp) with different functions **[(Akram & Mannan, 2020) ; (Anastasopoulou & Mouzaki, 2020) ; (Banerjee *et al.*, 2020) ; (Bhowmik *et al.*, 2020) ; (Jogalekar *et al.*, 2020) ; (Wu, 2020)].**

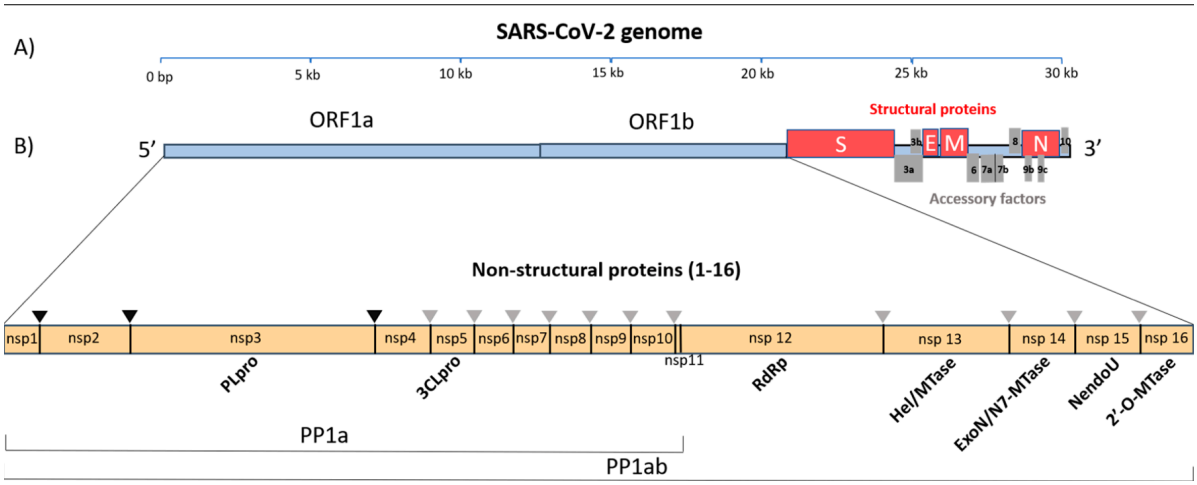


Figure 11: Schematic diagram of SARS-CoV-2 polycistronic genome (A) genome of SARS-COV-2 organized in individual ORFs (black/grey triangles = cleavage sites) (B) (Romano *et al.*, 2020).

The genomic RNA has a 5' cap and a poly-A 3' tail with genome characterization showing two flanking untranslated regions, the 5'UTR -265 nucleotides and the 3'UTR -358 nucleotides-long **[(Anastasopoulou & Mouzaki, 2020) ; (Romano *et al.*, 2020)].**

Structural proteins encoded by the 3'-terminus include spike glycoprotein (S; consists of 2 domains—S1 and S2), envelope protein (E), membrane protein (M), and nucleocapsid protein (N) **[(Akram & Mannan, 2020) ; (Banerjee *et al.*, 2020) ; (Jogalekar *et al.*, 2020) ; (Wu, 2020)],** and the 5'-terminal of the genome consists of accessory genes that are species-specific and encode polyproteins pp1a and pp1b, where pp1a is further divided into nonstructural proteins (Nsps) that participate in genome transcription and replication **[(Anastasopoulou & Mouzaki, 2020) ; (Bhowmik *et al.*, 2020)].**

ORF1ab is a large polyprotein encoding sixteen non-structural proteins: nsp1 (suppresses the antiviral host response), nsp2, nsp3 (a papain-like protease), nsp4, nsp5 (3C-like proteinase), nsp6, nsp7 and nsp8 makes a complex to form a primase, nsp9 (responsible for RNA/DNA binding activity), nsp10, nsp12 (RNA-dependent RNA polymerase) (RdRp), nsp13 (helicase), nsp14 (3'-to 5' exonuclease), nsp15 (endoribonuclease), and nsp11 **(figure 12) [(Bhowmik *et al.*, 2020) ; (Helmy *et al.*, 2020) ; (Romano *et al.*, 2020) ; (Wu, 2020) ; (Yang *et al.*, 2020)].** Namely, ORF1ab gene which encodes replicase/transcriptase required for viral genome replication, adding to that the incorporation of a polybasic cleavage site in the viral RNA, might be important for viral pathogenesis and transmissibility **[(Akram & Mannan, 2020) ; (Tang *et al.*, 2020)].**

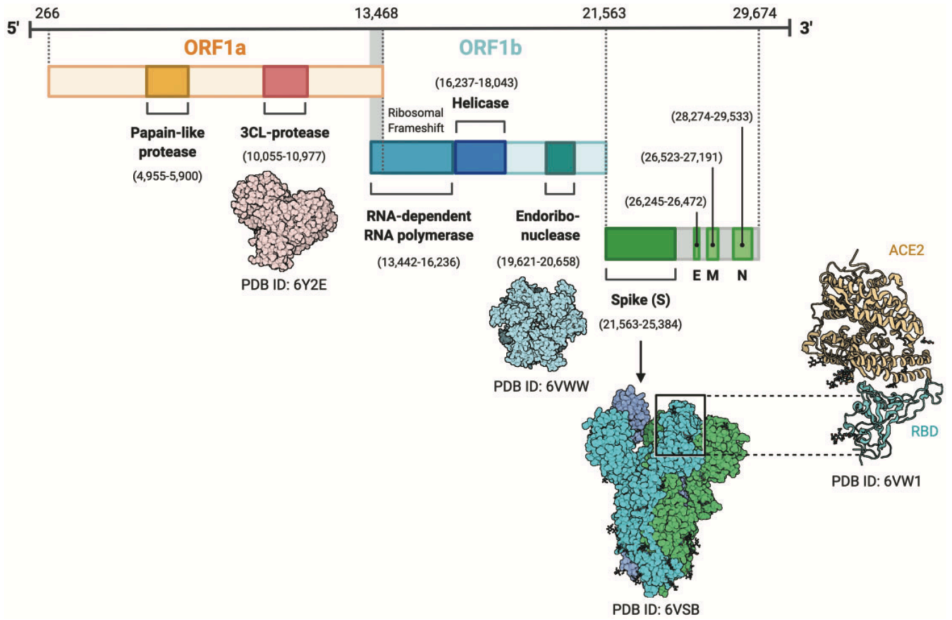


Figure 12: Genomic organization of SARS-CoV-2 (Jogalekar *et al.*, 2020).

III.6. Mutations

As an RNA virus, it was hypothesized that the SARS-CoV-2 mutates faster than DNA viruses **(Banerjee *et al.*, 2020),** with mutations arising during every replication cycle **(Lu *et al.*, 2020).**

At the beginning of the viral spread and based on a population genetic analyses of 103 SARS-CoV-2 genomes, the virus was divided into two major lineages (L and S), these two were well defined by just two tightly linked Single nucleotide polymorphisms (SNPs) that show complete linkage across SARS-CoV-2 strains **(Tang *et al.*, 2020).** Scientists believe, that these changes have enhanced the virulence of the two circulating strains of the virus, indicating that, the L lineage representing the "deadly strain" (~70%) was found to be more prevalent than the S lineage which represented the "less virulent one" (~30%) **[(Alanagreh *et al.*, 2020) ; (Tang *et al.*, 2020)].**

Almost a month after the first study, a phylogenetic network of 160 largely complete SARS-CoV-2 genomes and while using a bat virus as an outgroup, resulting in the root of the network (**figure 13).** Three central variants were found, distinguished by amino acid changes, which were named A, B, and C, with A being the ancestral type, it was found in significant proportions in East Asia, America and Australia. Also, Node B is derived from A by two mutations and B-types were the most common types in East Asia, and lastly, type C which differs from its parent type B by a non-synonymous mutation, was the major European type and it was absent in the mainland China **[(Forster et al., 2020) ; (Majeed & Shajar, 2020)].**

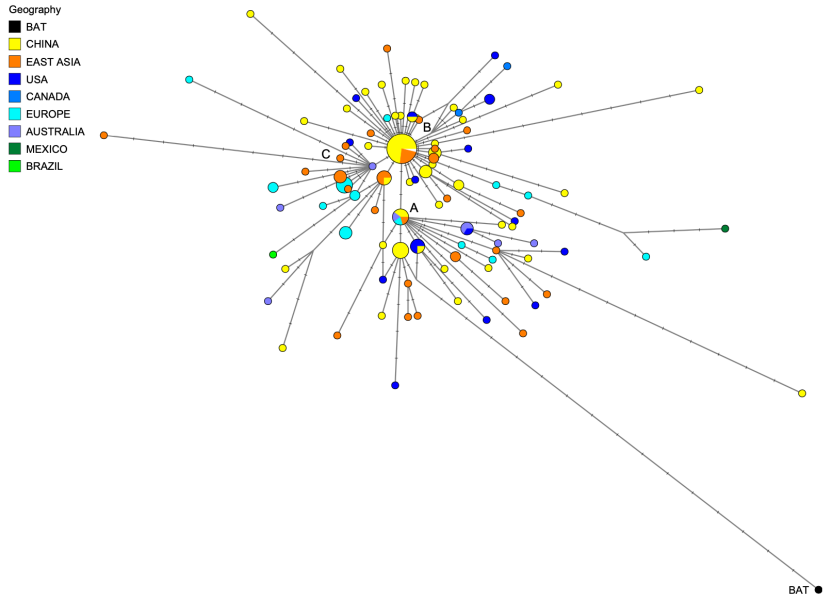


Figure 13: Phylogenetic network of 160 SARS-CoV-2 genomes with node A, the root cluster obtained with a bat coronavirus isolate BatCoVRaTG13 (Forster *et al.*, 2020).

Forster *et al.,* (2020), constructed this viral network to show ancestral viral genomes existing alongside their newly mutated daughter genomes**,** the phylo-geographic patterns in the network are potentially affected by distinctive migratory histories, founder events, and sample size.

More recently, a phylogenetic analysis based on full genomes, characterized the geographic and temporal patterns of aged and new mutations, examined genomic profile and identified frequent mutations, inferred linkage disequilibrium and haplotype structure, constructed the evolutionary paths and correlated phylogenetic clusters with mutations. Six major subgroups of SARS-CoV-2 strains were identified with strong geographic preferences and were characterized by 14 common mutations, most of which occurred in ORF1ab, with exceptions in S, N, ORF3a and ORF8. This classification of six subgroups provides a mutation-based taxonomy of viral strains and explains the heterogeneity of strains within each of L and S types and A, B, C types previously reported **(Yang *et al.,* 2020).**

Mutations may increase the fitness of the virus to the environment, while elevating the risk of drug resistance, altering the case fatality rate, and reducing the efficacy of vaccines **(Yang *et al.,* 2020).** While some mutations are pathogenic, other may be favorable and will undergo positive selection pressure **(Banerjee *et al.,* 2020).**

III.7. Life cycle of the virus

Human coronaviruses utilizes host cellular components to achieve various physiological processes, including viral entry, genomic replication, the assembly and budding of virions, thereby resulting in pathological damage to the host **(Pillaiyar *et al.,* 2020).** SARS-CoV-2 replication has a complex process which involves RNA synthesis, proofreading and capping **(Romano *et al.,* 2020).**

III.7.1.Viral entry

All CoVs encode a surface glycoprotein, a spike anchored in the viral envelope which binds to the host-cell receptor and mediates viral entry, since cell entry is an essential action for cross-species transmission **[(Letko *et al.,* 2020) ; (Walls *et al.,* 2020) ; (Wang *et al.,* 2020)].** CoVs S proteins (S) are (~1200 aa long) typical class I viral fusion proteins, that contributes to the recognition and binding to the cell receptor, tissue tropism and pathogenesis **[(Coutard *et al.,* 2020) ; (Ou *et al.,* 2020) ; (Shang *et al.,* 2020) ; (Walls *et al.,***

2020) ; (Wang *et al.,* 2020)]. They consist of three domains: an extracellular domain (EC), a transmembrane anchor domain and a short intra-cellular tail.

EC has two functional subunits, a receptor-binding subunit S1 (it contains two independent domains, an N-terminal domain (S1-NTD) and a receptor binding domain (RBD), which plays a key role in receptor recognition and binding and a membrane-fusion subunit S2 (C-terminal S2-membrane-anchored protein at the S2' site), with a protease cleavage required for activation of the fusion potential, of the S protein **[(Banerjee *et al.,* 2020) ; (Coutard *et al.,* 2020) ; (Hoffmann *et al.,* 2020) ; (Lan *et al.,* 2020) ; (Letko *et al.,* 2020) ; (Ou *et al.,* 2020) ; (Romano *et al.,* 2020) ; (Wang *et al.,* 2020)].**

SARS-CoV-2 gets into the cell through the recognition of the Angiotensin Converting Enzyme 2 (ACE2) receptors by the spike glycoprotein **[(Romano *et al.,* 2020) ; (Sungnak *et al.,* 2020) ; (Valencia, 2020)].** These receptors belong to the ACE family that consists of an N-terminal PD (Peptidase domain) and a C-terminal collectrin-like domain (CLD) **(Yan *et al.,* 2020),** it inactivates angiotensin II while generating angiotensin, having a physiological role in controlling vasoconstriction and blood pressure **[(Gurwitz, 2020) ; (Yan *et al.,* 2020)].** SARS-CoV-2 S-protein-RBD and ACE2-PD have identified key residues involved in their higher affinity interaction **[(Andersen *et al.,* 2020) ; (Stawiski *et al.,* 2020) ; (Yan *et al.,* 2020)],** owing to, the receptor binding motif (RBM) region, in the carboxy-terminal half of the RBD **[(Lan *et al.,* 2020) ; (Letko *et al.,* 2020)].**

Structural and computational analyses predict that SARS-CoV-2 not only uses human ACE2 as its host receptor, but uses it more efficiently and that the interaction RBD-ACE2 is not ideal but more of optimized **[(Andersen *et al.,* 2020) ; (Letko *et al.,* 2020) ; (Ma & Holt, 2020) ; (Oberemok *et al.,* 2020) ; (Ou *et al.,* 2020) ; (Shang *et al.,* 2020) ; (Xiao *et al.,* 2020) ; (Yeo *et al.,* 2020) ; (Zhou *et al.,* 2020)].** The binding affinity alone is unlikely to explain the unusual transmissibility of SARS-CoV-2, as though, the unique '-RRAR-' furin cleavage site (FCS) at the S1–S2 boundary of the SARS-CoV-2 spike protein, that may have a role in facilitating the rapid human-to-human transmission **[(Andersen *et al.,* 2020) ; (Lan *et al.,* 2020) ; (Wang *et al.,* 2020)].** However, a recent study by **Xia *et al.,* (2020)**, showed that FCS may be not as critical as previously thought for the high fusion capacity of SARS-CoV-2.

Transmembrane serine protease 2 (TMPRSS2) priming is important for SARS-CoV-2 S protein activation **(Ou *et al.*, 2020)**, it cleavages the C-terminal segment of ACE2 and enhances the S protein–driven viral entry **[(Hoffmann *et al.*, 2020) ; (Yan *et al.*, 2020)].** ACE2 and TMPRSS especially TMPRSS2 are co-localized in the same host cells, the latter exerts hydrolytic effects responsible for S-protein priming and viral entry into target cells (**figure 14)** [**(Gu *et al.*, 2020) ; (Hoffmann *et al.*, 2020)].** But TMPRSS2 was only expressed in a subset of ACE2+ cells, suggesting that the virus might use alternative pathways, especially cathepsin B, which was expressed in more than 70–90% of ACE2+/TMPRSS2- cells **(Sungnak *et al.*, 2020).** Yet another human receptor, CD147 (also known as Basigin or extracellular matrix metalloproteinase inducer (EMMPRIN)), has recently been identified as a possible route of viral entrance **[(Akram & Mannan, 2020) ; (Romano *et al.*, 2020) ; (Su *et al.*, 2020) ; (Ulrich & Pillat, 2020)].**

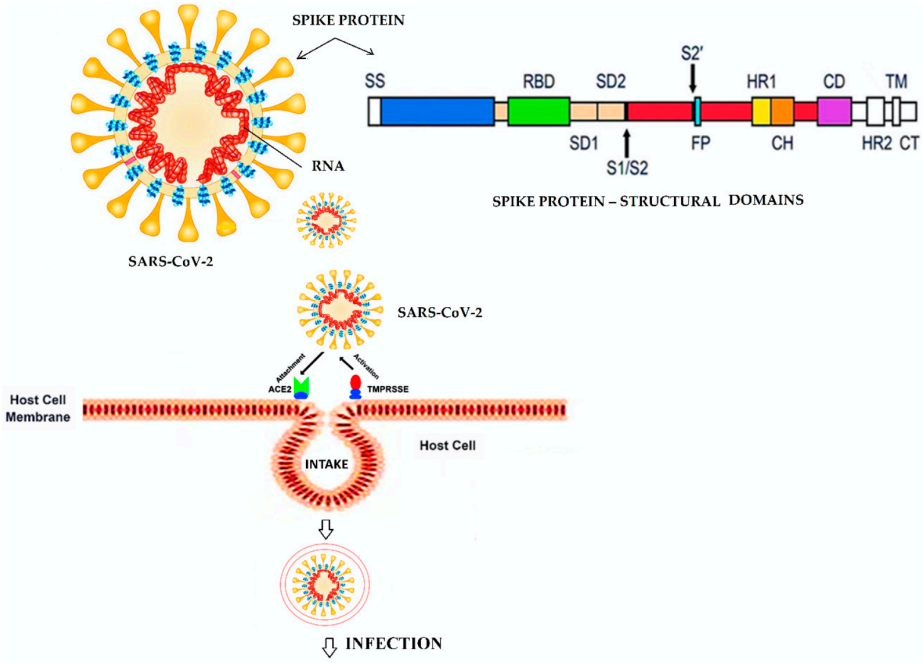


Figure 14: The interaction of the viral S-protein with ACE2 (Nadeem *et al.*, 2020).

III.7.2.Replication

The replication of the novel virus begins after the binding of its spike protein, on the cell surface ACE2 of the host **[(Pillaiyar *et al.*, 2020) ; (Zhang *et al.*, 2020)].** Primary viral replication is presumed to occur in mucosal epithelium of upper respiratory tract (nasal cavity and pharynx), with further multiplication in lower respiratory tract and gastrointestinal mucosa **(Jin *et al.*, 2020).** Once inside the cell, the infecting RNA acts as a messenger RNA

(mRNA), then will be translated by host ribosomes to produce the viral replicative enzymes, in which the viral RdRp, generates new RNA genomes and the mRNAs for the synthesis of the components necessary to assemble the new viral particles inside the cytoplasm of the cell (as shows **figure 15) [(Abdulamir & Hafidh, 2020) ; (Romano *et al.,* 2020)].**

III.7.3.Assembly and release

Following translation and production of structural proteins, nucleocapsids are assembled in the cytoplasm and followed by budding into the lumen of the endoplasmic reticulum (ER)–Golgi intermediate compartment. Virions are then released from infected cell through exocytosis, where they acquire their new envelopes from the cell membrane **[(Abdulamir & Hafidh, 2020) ; (Alanagreh *et al.,* 2020) ; (Azkur *et al.,* 2020)].**

III.7.4.Viral dissemination

Viruses spread from infected cells into viral-specific target uninfected cells and organs **(Xiao *et al.,* 2020).** It is important to report that, the novel feature setting this virus apart from previous HCoVs is the furin cleavage site '–PRRA–' at the S1/S2 boundary of SARS-CoV-2 S, which is processed during biosynthesis **(Walls *et al.,* 2020).** This ubiquitous expression of furin-like proteases could participate in expanding SARS-CoV-2 cell and tissue tropism **[(Walls *et al.,* 2020) ; (Wang *et al.,* 2020)].** Since, furin is expressed in a variety of organs and tissues, including brain, lung, gastrointestinal tract, liver, pancreas and reproductive tissues, therefore, gives the ability to infect organs or tissues insensitive to other coronaviruses **(Wang *et al.,* 2020).** Likewise, it is speculated that SARS-CoV-2 S protein is capable of triggering protease-independent and receptor-dependent syncytium formation, such a mechanism might enhance virus spreading through cell–cell fusion and this might partially explain rapid progress of disease **(Ou *et al.,* 2020).**

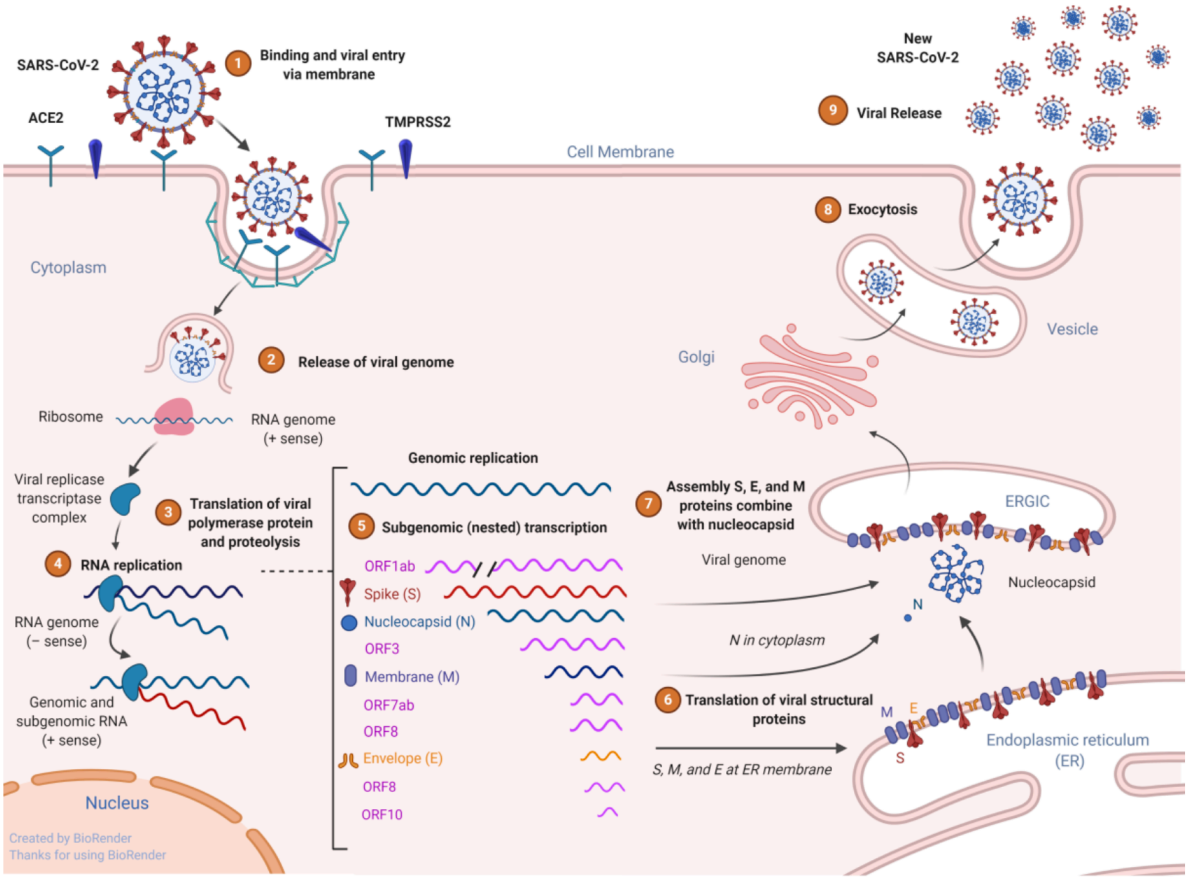


Figure 15: Schematic representation of the genomic and subgenomic organizations and replication of SARS-CoV-2 (Azkur *et al.*, 2020).

III.8. Transmission

On January 25th, Human-to-human transmission of SARS-CoV-2 has been confirmed by the WHO **[(Anastasopoulou & Mouzaki, 2020) ; (Li *et al.*, 2020) ; (Lu *et al.*, 2020) ; (Xia *et al.*, 2020) ; (Xiao *et al.*, 2020) ; (Zhou *et al.*, 2020)],** and it is now apparent that the current novel coronavirus has an accelerated rate of human-to-human transmission than SARS and MERS CoVs **(Bhowmik *et al.*, 2020),** but it also appears that it is less pathogenic than its predecessors too **(Chen, 2020),** according to the case fatality rate, which is the proportion of deaths attributed to a certain disease among all individuals diagnosed with that disease over a specified period of time **(Randolph & Barreiro, 2020).** Although the fatality rate will continue to change until all infected people recover, the high transmissibility is estimated with a basic reproduction number R0, which is the average number of people who will catch a disease from a contagious person, of approximately between 1.4 and 5.5 (**table 2**) **[(Chen, 2020) ; (Howard *et al.*, 2020)].**

Table 2: Case fatality rate and R0 value of known emerging virus infections (Chen, 2020).

Virus	Case Fatality Rate %	R0
2019-nCoV	3	1.4-5.5
SARS-CoV	10	2-5
MERS-CoV	40	<1
Avian H7N9	40	<1
Ebola	70	1.5-2.5
HIV	80	2-4

The latency period of the novel virus may be less than its incubation period there by meaning, people may be contagious even before being symptomatic, meaning that the virus can spread from asymptomatic carriers **[(De Soto *et al.,* 2020) ; (Lai *et al.,* 2020) ; (Oberemok *et al.,* 2020) ; (Sahu *et al.,* 2020) ; (To *et al.,* 2020) ; (Valencia, 2020) ; (Wu *et al.,* 2020)].**

As of now, the routes of SARS-CoV-2 transmission seems to be diversified, with a growing concern over the possibility of fecal-oral transmission **[(Gu *et al.,* 2020) ; (Sahu *et al.,* 2020) ; (Xiao *et al.,* 2020)],** but respiratory transmission is still the primary route for SARS-CoV-2 **[(Wu *et al.,* 2020) ; (Wu *et al.,* 2020) ; (Zhang *et al.,* 2020)].** Expectantly, the virus has been detected in different body fluids, secretions like saliva, urine, blood **[(Paoli *et al.,* 2020) ; (To *et al.,* 2020)]**, but no virus particles or viral RNA were detected in tear fluid and conjunctival secretions **(Xia *et al.,* 2020),** nor semen **[(Pan *et al.,* 2020) ; (Paoli *et al.,* 2020)].** However, there were cases of a prolonged detection of viral RNA for 20 days or longer after disappearance of COVID-19 symptoms, suggesting that SARS-CoV-2 might be excreted at low levels despite clinical recovery **(To *et al.,* 2020).**

Although being a respiratory virus, its transmission occurs extremely through close, direct contact, with infected person's secretions, droplets released via speaking, coughing and sneezing but also on fomites/surfaces, anywhere from 4h to three days **[(Banerjee *et al.,* 2020) ; (Chen, 2020) ; (van Doremalen *et al.,* 2020) ; (Gu *et al.,* 2020) ; (Howard *et al.,* 2020) ; (Jogalekar *et al.,* 2020) ; (Lai *et al.,* 2020) ; (Morawska & Cao, 2020) ;**

(Oberemok *et al.,* 2020) ; (Sahu *et al.,* 2020) ; (Valencia, 2020) ; (Wu *et al.,* 2020) ; (Xia *et al.,* 2020)].

Experts in droplet dynamics and airflow, agree that it is highly likely that the SARS-CoV-2 virus also spreads by air **(Morawska & Cao, 2020).** A study showed, that 1min of loud speaking generates at least 1,000 virion-containing droplet nuclei that remain airborne for more than 8 min and the direct visualization by laser light scattering method demonstrated how normal speech generates airborne droplets that can remain suspended for 10 min or longer **(Stadnytskyi *et al.,* 2020).** Nonetheless, The National Health Commission of China stated that airborne transmission "not determined", by reason of the difficulty to directly detect viruses traveling in the air **(Morawska & Cao, 2020).**

Moreover**,** the experimental measurements that tested SARS-CoV-2 in five environmental conditions (aerosols, plastic, stainless steel, copper, and cardboard) **(van Doremalen *et al.,* 2020),** resulted in the viability of the virus in aerosols throughout the duration of 3 hours, with a reduction in infectious titer from 10^3,5 to 10^2,7 TCID50 per liter of air [**TCID= tissue-culture infectious dose].** Also, SARS-CoV-2 was found to be more stable on plastic and stainless steel than on the other materials, and viable virus was detected on them up to 72 hours, though its titer was greatly reduced after 72 hours on plastic and after 48 hours on stainless steel. However, on copper, no viable SARS-CoV-2 was measured after 4 hours and no viable SARS-CoV-2 was measured after 24 hours on cardboard **[(van Doremalen *et al.,* 2020) ; (Valencia, 2020)].**

Furthermore**,** several studies reported that digestive system other than respiratory system may serve as an alternative route of infection, since the viral nucleic acids of several loose stools and both respiratory specimens tested positive (**figure 16) [(Carvalho *et al.,* 2020) ; (Fan *et al.,* 2020) ; (Gu *et al.,* 2020) ; (Xiao *et al.,* 2020) ; (Yeo *et al.,* 2020) ; (Zhang *et al.,* 2020)],** even-more, viral RNA measurements suggest that viral shedding from the digestive system might be greater and last longer than that from the respiratory tract **(Xu *et al.,* 2020),** indicating that, faecal–oral transmission could occur after viral clearance in the respiratory tract **[(Wu *et al.,* 2020) ; (Wu *et al.,* 2020) ; (Yeo *et al.,* 2020) ; (Zhang *et al.,* 2020)].**

Significantly, environmental contamination by patients with SARS-CoV-2 through respiratory droplets and fecal shedding, makes the environment as a potential medium of transmission and supports the need for strict environmental and hand hygiene **[(Ong *et al.,* 2020) ; (Wu *et al.,* 2020)].**

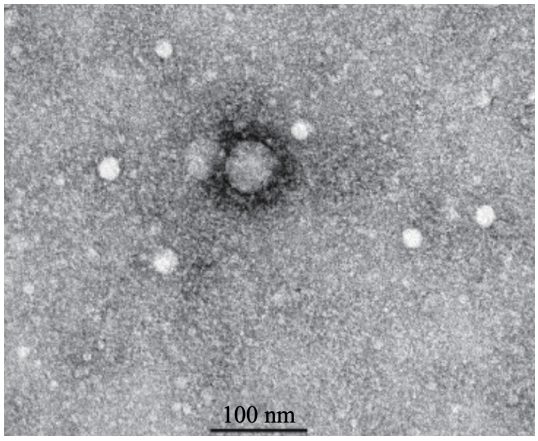


Figure 16: Virus particles with typical morphology of coronavirus were observed using EM after inoculating stool suspension into Vero cells (Zhang *et al.,* 2020).

A very low possibility of vertical transmission was speculated after that, a neonate born to a mother with COVID-19 had elevated antibody levels and abnormal cytokine test results 2 hours after birth, but the infant's repeated negative Real-Time quantitative Reverse-Transcription Polymerase Chain Reaction (RT-qPCR) test results on nasopharyngeal swabs were negative and difficult to explain **(Dong *et al.,* 2020).** As of now, only 11 cases of neonatal infection have been reported, throughout this current pandemic, where only three of which, were presumed cases of vertical transmission **(Gordon *et al.,* 2020).**

III.9. Prevention

Mathematical Models, suggest that public mask wearing is most effective at reducing the spread of the virus, since the most common droplet size threshold has a minimum of 5µm-10µm, that's why a mask may be instrumental in preventing a second wave of infections. In fact, there is currently a global shortage of N95/FFP2 respirators and surgical masks for use in hospitals, that's why, simple cloth masks, present a pragmatic solution for use by the public although the high difference of protection **(Howard *et al.,* 2020).** The use of face masks has become ubiquitous in Asian countries and the WHO currently recommends that people should wear face masks if they have respiratory symptoms or are vulnerable to the disease **(Feng *et al.,* 2020).**

Precautions that include increased ventilation rate, using natural ventilation, avoiding air recirculation, avoiding staying in another person's direct air flow, and minimizing the

number of people sharing the same environment, may help avoid the infection **(Morawska & Cao, 2020).** In addition to**,** home stay obligation**,** avoiding crowdedness, social distancing by maintaining a distance of at least 1 meters or more outdoors and 1.5 to 2 meters indoors and even between family members, as well as hand hygiene practice, either by soap or hand sanitizers, covering coughs and sneezes with disposable tissues and no face-hand contact **[(Chiu *et al.,* 2020) ; (Lai *et al.,* 2020) ; (Morawska & Cao, 2020) ; (Saeed *et al.,* 2020)],** because it has been reported that SARS-CoV-2 is sensitive to 75% ethanol, ether, chloroform, chlorine-containing disinfectant, peracetic acid, and other fatty solvents **(Yi *et al.,* 2020),** some studies also concluded that higher temperature at 56 °C 30 minutes, pressure, and UV may be associated with less SARS-CoV-2 prevalence **(Petrosillo, 2020).**

III.10. Tests and diagnostic

Currently, virus nucleic acid detection of specimen collection (**table 3)**, Computed Tomography (CT) imaging, some hematology parameters and serology are the primary tools for clinical diagnosis of the infection **[(Li *et al.,* 2020) ; (Valencia, 2020)].**

Table 3: Specimen collection and storage (WHO, 2020).

<table>
<tr><th>Specimen type</th><th>Collection materials</th><th>Storage T°</th><th>T°/Time for shipment</th></tr>
<tr><td>Nasopharyngeal and oropharyngeal swab</td><td>Dacron or polyester flocked swabs</td><td rowspan="10">2-8 °C</td><td>2-8 °C if ≤5 days
–70 °C (dry ice) if >5 days</td></tr>
<tr><td>Bronchoalveolar lavage</td><td rowspan="3">Sterile container</td><td rowspan="3">2-8 °C if ≤2 days
–70 °C (dry ice) if >2 days</td></tr>
<tr><td>Endotracheal aspirate, nasopharyngeal wash/aspirate</td></tr>
<tr><td>Sputum</td></tr>
<tr><td>Tissue from Biopsy or Autopsy</td><td>Sterile container with saline or VTM</td><td>2-8 °C if ≤24 hours
–70 °C (dry ice) if >24 hours</td></tr>
<tr><td>Serum</td><td>Serum separator tubes</td><td rowspan="4">2-8 °C if ≤5 days
–70 °C (dry ice) if >5 days</td></tr>
<tr><td>Whole blood</td><td>Collection tube</td></tr>
<tr><td>Stool</td><td>Stool container</td></tr>
<tr><td>Urine</td><td>Urine container</td></tr>
</table>

III.10.1.Nucleic acid detection technology

The two commonly used nucleic acid detection technologies for SARS-CoV-2 are the RT-qPCR and high-throughput sequencing (rarely used due to its complexity and non-accessibility) **[(Li *et al.,* 2020) ; (Valencia, 2020)]**

III.10.1.1.RT-qPCR

Real-Time quantitative Reverse-Transcription Polymerase Chain Reaction (RT-qPCR) is the primarily most common, effective and straight forward method, due to its high sensitivity and specificity for detecting the viral coronavirus RNA from respiratory secretions and blood **[(Li *et al.,* 2020) ; (Sahu *et al.,* 2020) ; (Vellingiri *et al.,* 2020) ; (Xia *et al.,* 2020)],** the CDC proposed specific primers and probes for the ORF1ab, N gene regions, E protein and RdRp for SARS-CoV-2 detection **(Li *et al.,* 2020),** but beyond from the technique high specificity, its false-negative rate cannot be ignored **[(Li *et al.,* 2020) ; (Yi *et al.,* 2020)].**

III.10.1.2.CRISPR-based-testing

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology has promise as a tool for SARS-CoV-2 detection, where CRISPR associated enzymes Cas13 and Cas12 break down strands of RNA, whereas in a test scenario, it is usually measured with a fluorescent signal or activity on a lateral flow strip **(Atzrodt *et al.,* 2020).** A protocol for using the CRISPR-based-Specific High Sensitivity Enzymatic Reporter UnLOCKing (CRISPR-based SHERLOCK) technique to detect SARS- CoV-2 has been approved, which detects synthetic RNA fragments using a dipstick in less than an hour without requiring elaborate instrumentation **(Yi *et al.,* 2020).**

III.10.2.Serology

The antibody profile is vital for timing requests for serological assays and interpretation of antibody test results **(To *et al.,* 2020).** Findings, demonstrate that antibody tests have an important diagnosis value in addition to RNA tests, indicating that it is a good choice for rapid, simple, highly sensitive diagnosis **[(Li *et al.,* 2020) ; (Zhao *et al.,* 2020)].** Many laboratory IgM/IgG and enzyme-linked immunosorbent assay (ELISA) test kits have been developed by public and private companies, to test patients specimens for COVID−19 **(Li *et al.,* 2020).**

III.10.3.Radiological reports

Chest Computed Tomography (CT) scan have also been used in guiding the diagnosis, detecting minor lung lesions in patients at an early stage of disease **[(Li *et al.,* 2020) ; (Xu *et al.,* 2020)].** Early manifestation of bilateral, multifocal, and peripheral posterior distribution, ground glass opacities (GGO) mainly in the lower lung on a chest CT scan might be a sign of the novel coronavirus infection **[(Banerjee *et al.,* 2020) ; (Lai *et al.,* 2020) ; (Sahu *et al.,* 2020) ; (Xu *et al.,* 2020)],** less commonly, septal thickening, bronchiectasis, pleural thickening and sub-pleural involvement have been reported. As disease progression occurs, CT scan may show multifocal consolidations with a paving pattern **(Valencia, 2020).** There were also, a radiographic evidences of an acute stroke in COVID-19 patients **(Avula *et al.,* 2020).**

III.10.3.1.Blood reports

In most cases, blood reports show normal/low white blood cells (WBC), low platelet count whereas pro-calcitonin are mostly normal. Most consistently, C-reactive protein (CRP) and ferritin levels are elevated and similarly Creatine phosphokinase (CPK0), D-dimer, Lactate dehydrogenase (LDH), Alkaline phosphatase (ALK- phos)/Transaminase (AST-ALT) levels were also high **[(Banerjee *et al.,* 2020) ; (Lai *et al.,* 2020) ; (Sahu *et al.,* 2020) ; (Ye *et al.,* 2020)].**

CHAPTER THREE:

CORONAVIRUS DISEASE

2019

"COVID-19"

Chapter Three: COronaVIrus Disease 2019 "COVID-19"

The lethality of COVID-19 is extremely versatile in the world **(Kada *et al.*, 2020).** The virus spreads easily, with some patients experiencing only mild to moderate symptoms, others, suffer from severe ones **(figure 17) (Khailany *et al.*, 2020),** though recovery from the acute phase of the infection is certainly a relief, one must consider the long-term pathological effects of the disease **(Pereira, 2020).** Strangely, another contagion has occurred as a result of COVID-19 spread, involving fear, panic and stress, thereby, resulting anxiety and sleep disturbances **(Ma & Holt, 2020).**

SARS-CoV-2 infection can be roughly divided into three stages **(Shi *et al.*, 2020):**

Stage I, an asymptomatic incubation period / Stage II, a non-severe symptomatic period / Stage III, a severe respiratory symptomatic stage with high viral load.

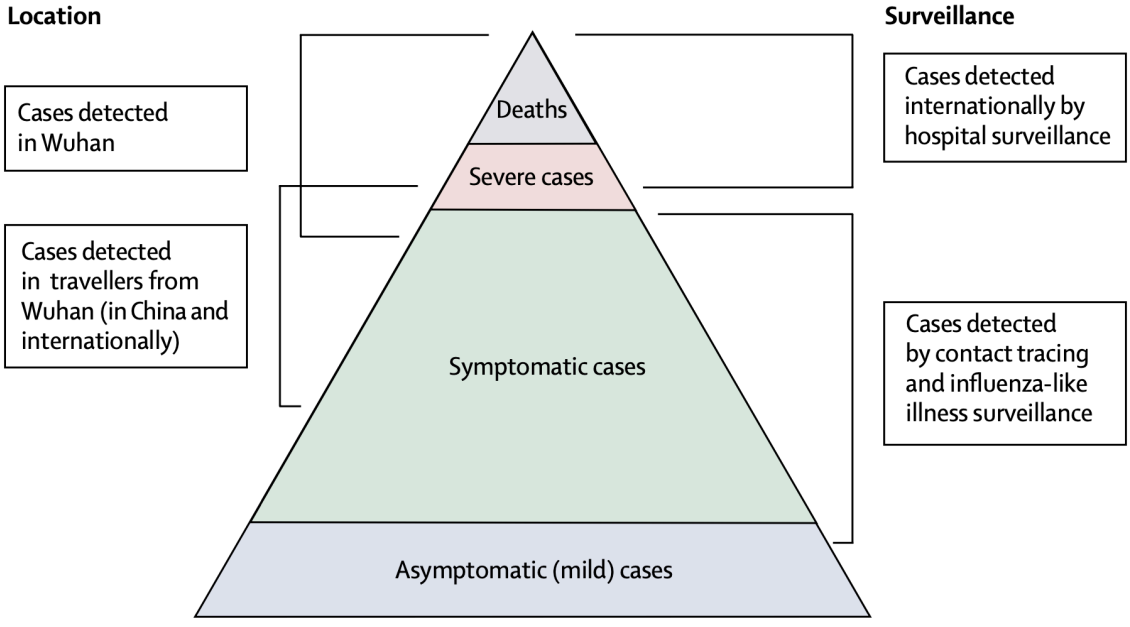


Figure 17: Spectrum of COVID-19 cases (Verity *et al.*, 2020).

I. Incubation

It is important to understand that for any communicable disease, latent period and incubation period which is the time from infection to symptom onset, are two different entities affecting the transmission dynamics **[(Li *et al.*, 2020) ; (Sahu *et al.*, 2020)].**

According to the Centers for Disease Control and Prevention (CDC), the mean incubation period of COVID-2019 virus is approximately 5.1 days (ranging from 2 to 15 days), (most likely 3 to 10 days) **[(Chen, 2020) ; (Li *et al.,* 2020) ; (Oberemok *et al.,* 2020) ; (Sahu *et al.,* 2020) ; (Valencia, 2020) ; (Xu *et al.,* 2020)],** these numbers justify the quarantine period of 14 days set by the WHO **(Sahu *et al.,* 2020).** Many COVID-19 patients are asymptomatic, and nearly all have a pre-symptomatic incubation period **(Howard *et al.,* 2020).** Howbeit, longer incubation periods of up to 24 days were also reported, that might be due to immune evasion properties **(Prompetchara *et al.,* 2020).**

II. Symptoms

Symptoms of COVID-19 are non-specific, dividing the clinical process into three: the viremia phase, the acute phase and the recovery phase **(Lin *et al.,* 2020),** while the disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and acute respiratory distress syndrome (ARDS) **[(Valencia, 2020) ; (Wu *et al.,* 2020)].**

COVID-19 is characterized by flu-like symptom at first, then on around day five, it causes fever, headache, dry cough, myalgia, nausea without vomiting, abdominal discomfort with some diarrhea, loss of smell and taste, after that, around the same time symptoms can worsen leading to shortness of breath and dyspnoea due to bilateral viral pneumonia from direct viral damage to lung parenchyma. Then henceforth day 10, the cytokine storm kicks in, subsequently, ARDS and multi-organ failure ensues **[(Banerjee *et al.,* 2020) ; (Jiang *et al.,* 2020) ; (Lai *et al.,* 2020) ; (Ma & Holt, 2020) ; (Valencia, 2020) ; (Yeo *et al.,* 2020) ; (Zhao *et al.,* 2020)],** septic shock and diarrhea were only noted in a small part of the patients, but severe cases rapidly showed metabolic acidosis, bleeding and coagulation dysfunction **(Zhao *et al.,* 2020).** However, a lot of patients immune system can limit the infection from progression and set out recovery within 2-3 weeks from the beginning of symptoms **(Abdulamir & Hafidh, 2020),** the criteria for recovery showed a disappearance of symptoms and signs, consistent clearance of the virus, and absorption of lung inflammations **(Zeng *et al.*, 2020),** but still, due to the probability of COVID-19 virus recurrence after recovery, a follow-up should be considered regularly **[(Helmy *et al.,* 2020) ; (Lotfi *et al.,* 2020)].**

Severity seems, disproportionately affecting those of advanced age and those with pre-existing chronic medical conditions **(Valencia, 2020),** deducing, that the most vulnerable

group includes the elderly, malnourished, asthmatic, hypertensive, diabetic, immune compromised, cancer and cardiovascular patients, as well as pregnant women **[(Banerjee *et al.,* 2020) ; (Dworakowska & Grossman, 2020) ; (Lai *et al.,* 2020) ; (Zheng *et al.,* 2020)],** excluding autoimmune thyroid disease (AITD) and rheumatoid arthritis (RA) patients from that high-risk group of COVID-19 **(Dworakowska & Grossman, 2020).** Diabetes and conditions like hypertension, have treatments that lead to an increased expression of ACE2, thereby facilitating viral uptake and increasing the risk of severe infection **(Ma & Holt, 2020).** The same way, diabetes mellitus **(**DM) inhibits neutrophil chemotaxis, phagocytosis, and intracellular killing of microbes, making the groups with this disease more and more vulnerable **(Muniyappa & Gubbi, 2020),** as well as active smoking, which has adverse effects on both cardio and pulmonary systems, was also associated with worse composite outcomes **(Cheng *et al.,* 2020).**

In contrast to adults, most infected children appear to have a milder clinical course **(Lu *et al.,* 2020),** probably due to the different immune response to the virus, since aging is associated with a progressive decline in the normal functioning of the immune system, also probably to some COVID-19-cross-reactive antigens, or maybe the presence of other simultaneous viruses in the mucosa of lungs and airways entraining direct virus-to-virus interactions and competition, another theory has been related to the possible difference in the expression of the ACE2 receptor **[(Abdulamir & Hafidh, 2020) ; (Brodin, 2020) ; (Ruggiero *et al.,* 2020)].**

III. The pathophysiology of SARS-CoV-2 infection

ACE2 tissue distribution in organs like the lungs, heart, kidney, liver, endothelium, and intestine, and even on the surface of neurons of the brain, in addition to its vital role in the cardiovascular and immune systems, could explain the multi-organ dysfunction observed in patients **[(Daniel *et al.,* 2020) ; (Richardson *et al.,* 2020) ; (Xiao *et al.,* 2020) ; (Yan *et al.,* 2020) ; (Yi *et al.,* 2020) ; (Zhang *et al.,*2020) ; (Zheng *et al.,* 2020)].**

III.1. Pulmonary pathology

Replication in the upper respiratory tract fits with efficient transmission between hosts, whereas replication in the lower respiratory tract fits with the development of lung disease**.** SARS-CoV-2 replicates efficiently in respiratory epithelial cells throughout the

respiratory tract, including nasal cavity, bronchi, bronchioles, and alveoli (**figure 18) (Rockx *et al.*, 2020),** moreover**,** viral particles were observed in the bronchial and type 2 alveolar epithelial cells **(Li *et al.*, 2020).**

Histological examination and pathologic findings of the lungs showed bilateral diffuse alveolar damage (DAD), pulmonary edma, and hyaline membrane formation, prominent proteinaceous exudates, vascular congestion, and inflammatory clusters with fibrinoid material and multi-nucleated giant cells, indicative of an acute respiratory distress syndrome, as well as characteristic syncytial cells in the alveolar lumen **[(Rockx *et al.*, 2020) ; (Tian *et al.*, 2020)].**

Pneumonia and ARDS are the common immune-pathological event for SARS-CoV-2 **(Li *et al.*, 2020),** since the virus mainly attacks the lungs in the beginning **(Yi *et al.*, 2020),** they're characterized by the rapid onset of widespread inflammation in the lungs and subsequent short/rapid breathing, hypoxia and cyanosis, causing a respiratory failure **[(Daniel *et al.*, 2020) ; (Shi *et al.*, 2020) ; (Taherzadeh *et al.*, 2020) ; (Tay *et al.*, 2020)].**

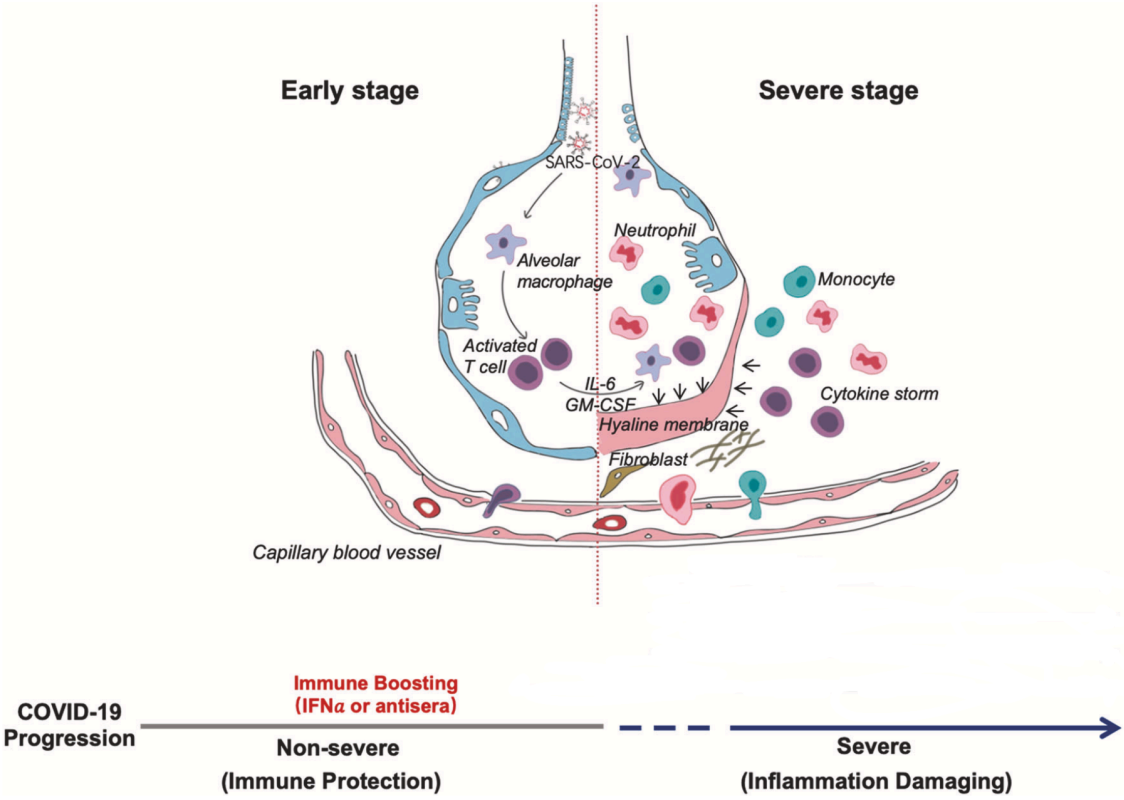


Figure 18: Schematic representation of the progression of COVID-19 infection (Shi *et al.*, 2020).

Lung inflammation was the main cause of life-threatening respiratory disorders at the severe stage **(Shi *et al.*, 2020),** including, a scenario of multisite pulmonary vascular thrombosis with progressive myocardial ischaemia, in which **McGonagle *et al.*, (2020),** believe that pulmonary intravascular coagulopathy is the best explanation for the COVID-19 pneumonia risk factors for poor survival, and suggests an explanation for the increased cardiovascular mortality due to the disseminated intravascular coagulation that has also been reported in COVID-19 pneumonia, but usually as a pre-terminal event **(Ronco *et al.*, 2020).**

III.2. Cardiac pathology

This novel virus disease might theoretically cause chronic damage to the cardiovascular system (**Zheng *et al.*, 2020),** where an acute myocardial injury was the most described cardiovascular complication, in addition to both tachycardia and bradycardia arrhythmia **(Bansal, 2020).** Reports and small case series have suggested an increased risk of myocardial injury, coronary vascular involvement, and heart failure as a sequelae to the disease **(figure 19),** relatively, according to the high levels of ACE2 protein expression on cardiomyocytes **[(Cheng *et al.*, 2020) ; (Zheng *et al.*, 2020)].**

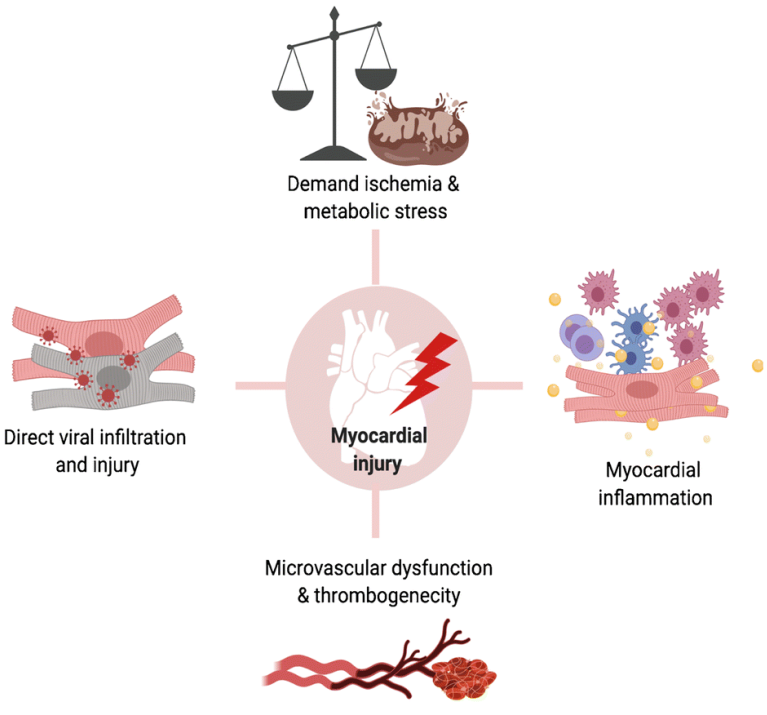


Figure 19:Potential mechanisms for myocardial injury caused by COVID-19 (Cheng *et al.*, 2020).

III.3. Nephropathology

Hematuria and proteinuria as albumin in the urine are the two common symptoms in COVID-19 patients with renal failure, meanwhile the major issue is impaired renal function **[(Lotfi *et al.*, 2020) ; (Staico *et al.*, 2020)].**

Immunohistochemistry (IHC) results indicated that the expression level of the ACE2 protein is significantly higher in the kidney, especially in the renal tubular cells, subsequently, their injury causes a renal tubular atrophy **(Staico *et al.*, 2020).** Along with, kidney histopathologic, ultrastructural, and immunostaining findings, that cited a range of abnormalities, like a significant acute tubular injury (ATI), the occlusion of microvascular lumens mainly by erythrocytes with ensuing endothelial damage, as well as glomerular and vascular changes indicative of underlying diabetic or hypertensive disease **[(Cheng *et al.*, 2020) ; (Su *et al.*, 2020)],** while an observed diffuse acute proximal tubular injury with loss of brush border and non-isometric vacuolation, may be partially caused by the direct virulence of SARS-CoV- 2 **(Su *et al.*, 2020).**

Acute kidney injury (AKI) is common among critically ill patients with COVID-19, likely to be multifactorial, with cardiovascular comorbidity, damage in the kidney or a dysregulated immune response (as shown on **figure 20) (Ronco *et al.*, 2020).**

Based on meta-analysis, it was stated that Chronic Renal Pathology would appear to be associated with an increased risk of severe COVID-19 infection but the viral infection would not aggravate pre-existing chronic renal failure **(Staico *et al.*, 2020).**

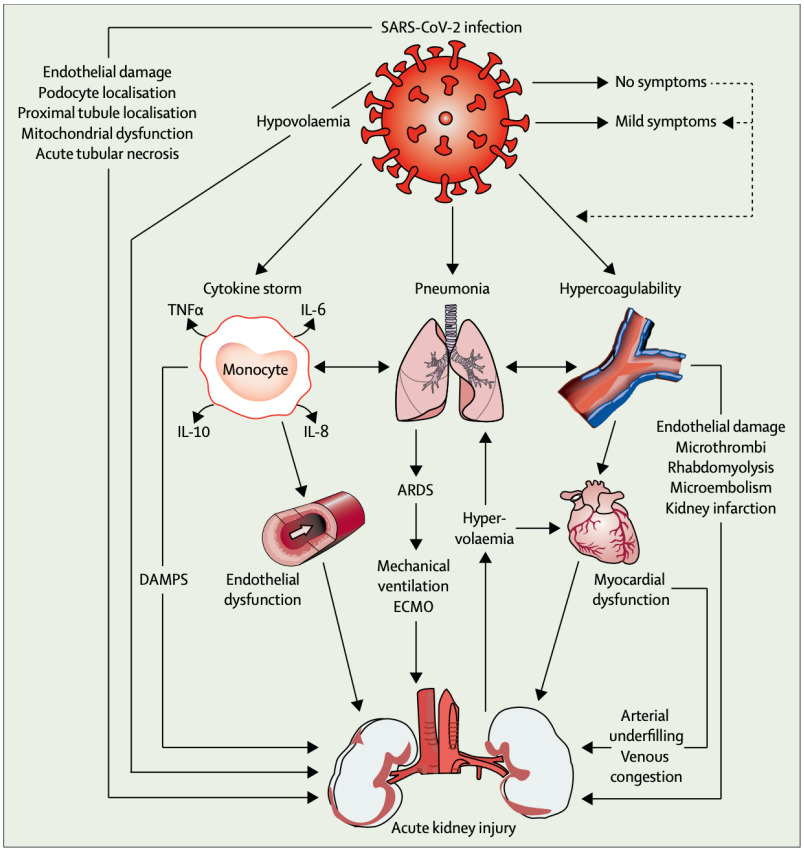


Figure 20: Acute kidney injury in COVID-19 (Ronco *et al.*, 2020).

III.4. Hepathopathology

Liver injury in COVID-19 patients mainly manifests as abnormal liver biochemical indicators, such as an increased Alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin (TBIL) levels and decreased albumin (ALB) levels **(Tian & Ye, 2020).**

An increasing number of COVID-19 patients with liver injury have been reported **(Tian & Ye, 2020),** either by direct virus infection, immune injury, drug-induced liver injury, ischemia, hypoxia, and recurrence or exacerbation of an underlying liver disease **[(Sun *et al.,* 2020) ; (Tian & Ye, 2020)].**

Hepatic dysfunction in severe COVID-19 is accompanied by greater activation of coagulative and fibrinolytic pathways, relatively depressed platelet counts, climbing neutrophil counts, and high ferritin levels **(Bangash *et al.,* 2020).** Moreover, liver biopsy specimens of severe COVID-19 patients, showed moderate microvascular steatosis and mild lobular and portal activity, while autopsy showed a mild zone 3 sinusoidal dilatation, patchy hepatic necrosis and a mild increase in sinusoidal lymphocytes, indicating that the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury **[(Sun *et al.,* 2020) ; (Tian & Ye, 2020)].**

Tian & Ye, (2020), examined foci of hepatic necrosis in adjacent to terminal hepatic veins and periportal area, with no significant surrounding inflammatory cellular infiltration, surprisingly consistent with the pattern of acute liver injury, that may indicate a direct viral attack on the liver.

III.5. Gastrointestinal pathology

Gastrointestinal involvement is present with diarrhea, abdominal pain, vomiting or nausea, these symptoms can exist independently of respiratory symptoms **[(Amarapurkar *et al.,* 2020) ;** (**Suresh Kumar *et al.,* 2020)].**

Carvalho *et al.,* (2020) and **Amarapurkar *et al.,* (2020),** firstly reported a SARS-CoV-2 gastrointestinal infection causing hemorrhagic colitis demonstrated endoscopically and haemorrhagic enteritis, respectively.

III.6. Neuropathology

The COVID-19 is not always confined to the respiratory tract, but also the Central Nervous System (CNS), where it probably invades peripheral nerves and enters the CNS via the synaptic route and induces neurological diseases **(Vellingiri *et al.*, 2020).** Although, it is clear that the pulmonary, renal, and cardiac damage are the primary causes of fatalities in COVID-19 patients, but cerebrovascular or neuronal damage that occurs during the disease could contribute **(Richardson *et al.*, 2020).** The latency period is enough for the virus to enter and destroy the medullary neurons **[(Taherizadeh *et al.*, 2020) ; (Vellingiri *et al.*, 2020)].**

It has been proposed that SARS-CoV-2 gains entry to the CNS by one of three ways: by systemic vascular dissemination through the hematogenous route, peripheral neurons and cerebrospinal fluid (CSF) via a synapse−connected route or more locally across the cribriform plate of the ethmoid bone **[(Prabhakar *et al.*, 2020) ; (Whittaker *et al.*, 2020)],** where the virus possibly attaches to the olfactory epithelium (OE) via ACE2 receptor and gains entry **(figure 21) (Baig & Sanders, 2020).** Most patients also complained of impairment of both olfactory and gustatory perception suggesting that the gastrointestinal system might be a possible route of invasion and transmission to the enteric nervous system (ENS) **(Pereira, 2020).**

Matthew, (2020), stated that the symptoms that might attribute to the respiratory disease are due to the inability of air to get into the lungs, which might actually be a defect in respiration controlled by the nervous system **(Vellingiri *et al.*, 2020).**

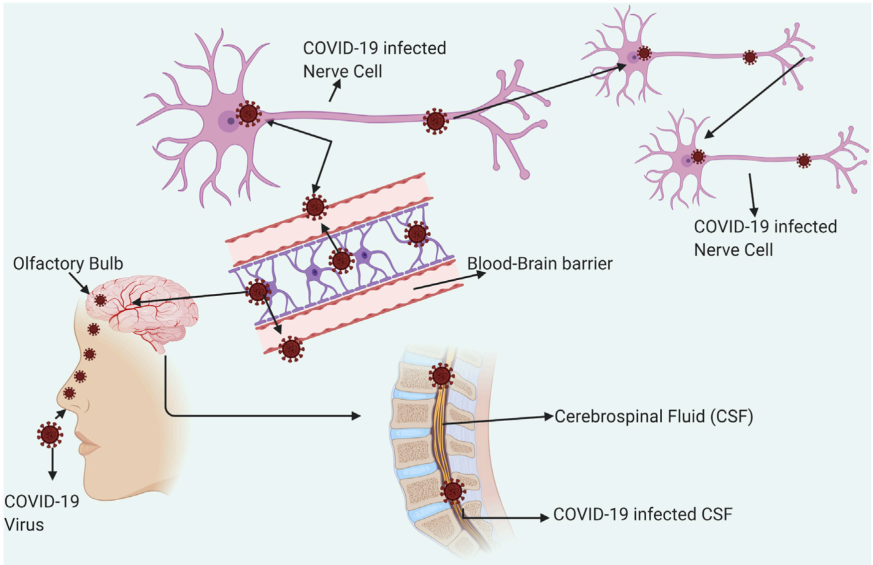


Figure 21: COVID-19 entry into the CNS (Vellingiri *et al.*, 2020).

Reports of neurological manifestations of SARS-CoV-2 are emerging, ranging from milder presentations such as headache, nausea and vomiting, to severe complications such as acute cerebrovascular diseases, impaired consciousness, epilepsy, seizures and strokes **[(Avula *et al.,* 2020) ; (Baig & Sanders, 2020) ; (Prabhakar *et al.,* 2020) ; (Richardson *et al.,* 2020) ; (Vellingiri *et al.,* 2020) ; (Whittaker *et al.,* 2020)],** consistent with the cases of encephalitis that have been officially reported to be a clinical manifestation in patients with COVID-19 **[(Prabhakar *et al.,* 2020) ; (Richardson *et al.,* 2020) ; (Ye *et al.,* 2020)].** Therefore, these reports show that SARS-CoV-2 may have the potency of being neuroinvasive **[(Richardson *et al.,* 2020) ; (Vellingiri *et al.,* 2020)].** Confirmed cases, also reported Guillain-Barre syndrome (GBS) and multi-system inflammatory syndrome in children (MIS-C), altered mental status (AMS) & cardiorespiratory failure as being a significant neurological sequels of SARS-CoV-2 **[(Baig & Sanders, 2020) ; (Whittaker *et al.,* 2020)].**

III.7. Viral sepsis

Patients with severe COVID-19 who met the diagnostic criteria for sepsis and septic shock, had clinical manifestations of shock, cold extremities and weak peripheral pulses and showed severe metabolic acidosis, indicating possible microcirculation dysfunction. Moreover some patients had impaired liver and kidney function in addition to severe lung injury and scattered degeneration of the neurons in the brain **(Li *et al.,* 2020).** The hypercytokinaemia with extreme hyperferritinaemia that is typically seen with haemophagocytic lymphohistiocytosis (HLH) is also evident in some patients with COVID-19 pneumonia and occurs in 3,7–4,3% of sepsis case **[(Mehta *et al.,* 2020) ; (Ronco *et al.,* 2020)].** Blood and lower respiratory tract specimen cultures turned out to be negative for bacteria and fungus in sepsis COVID-19 patients, which indicated a viral sepsis **(figure 22) (Li *et al.,* 2020).**

Li *et al.,* 2020 hypothesize that, the process of viral sepsis is crucial to the disease mechanism of COVID-19.

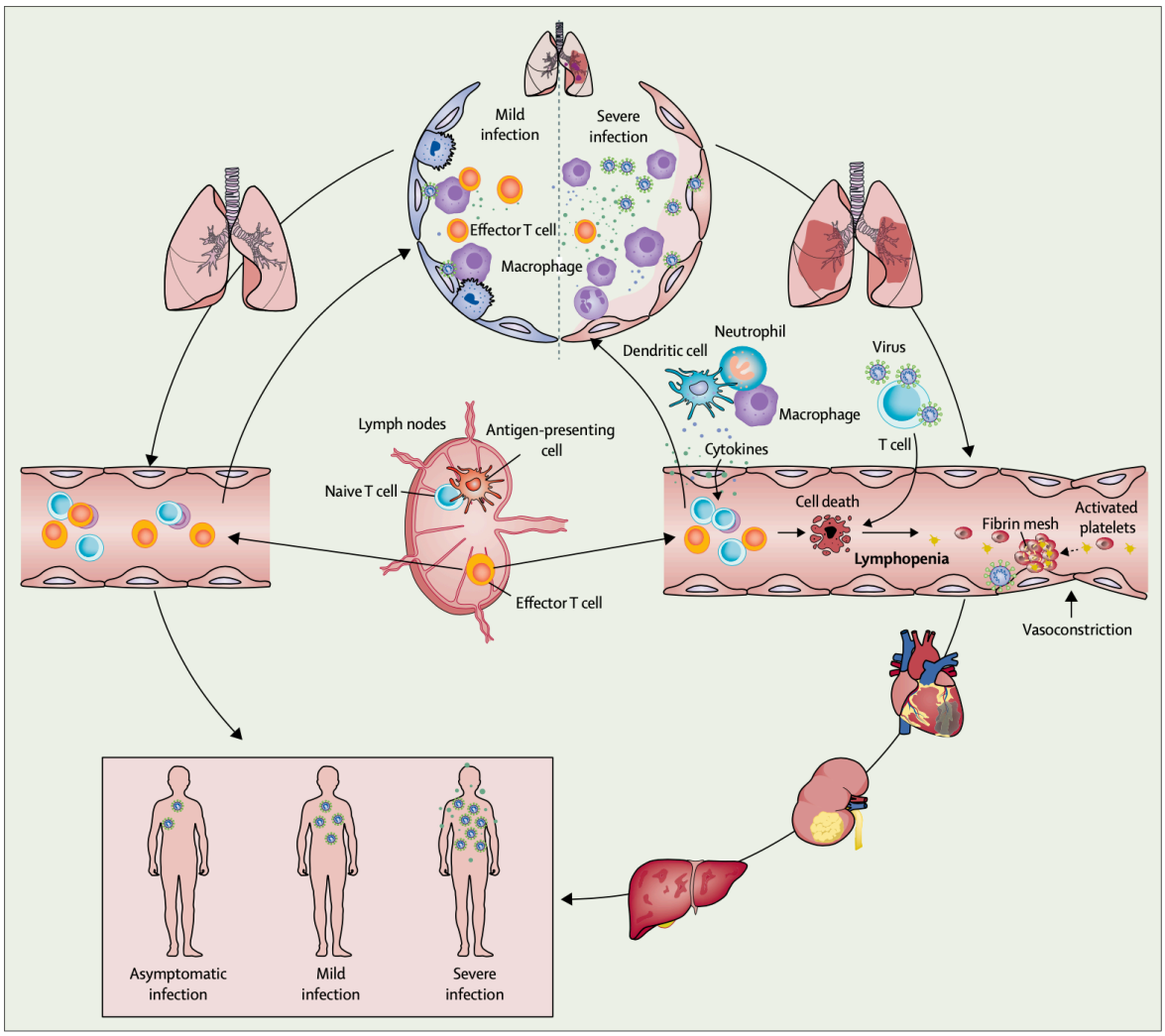


Figure 22: Occurrence and outcome of SARS-CoV-2 viral sepsis (Li *et al.*, 2020).

III.8. Haemoglobin attack

Recent findings, suggest that SARS-CoV-2 can bind to the human haemoglobin (Hb) beta chain, damaging the Heme (composed of iron and porphyrin) structure of erythrocytes, rendering the human Hb deoxygenated **(Majeed & Shajar, 2020),** and suggest also, that red blood cells can probably be infected by Spike-CD147 pathway **[(Abrahams, 2020) ; (Liu & Li, 2020)].**

Autopsy of COVID-19 patients, found that spleens were significantly reduced in size, suggesting that there might be an impact of SARS-CoV-2 targeting the Hb **(Abrahams, 2020),** in addition to the mild anaemia and decreased Hb content that have been reported **(Daniel *et al.*, 2020).**

Through molecular docking, certain proteins of the novel coronavirus 'ORFs' showed binding to porphyrin **(Majeed & Shajar, 2020),** predicting that these ORF proteins can interact with haemoglobin to reduce both oxygen (O2) affinity and total haemoglobin content **(Daniel *et al.,* 2020).**

More recently genetic study, held by **Ellinghaus *et al.,* (2020),** there was the detection of a novel locus, indicating a susceptibility in the involvement of the ABO blood-group system, favoring the platform for the SARS-CoV-2 infection, confirming that blood group O is associated with a lower risk of acquiring COVID-19, whereas blood group A was associated with a higher risk. Is or has these notions been the missing link of COVID-19… maybe!

III.9. Kawasaki disease

In the last two months, a small number of children have developed a more severe inflammatory syndrome associated with COVID-19 **(Pruc *et al.,* 2020),** showing signs of chronic fever, conjunctivitis, erythema in oral mucosa, cervical lymphadenopathy, and polymorphic rash, shock, and multi-organ failure, all characteristics of Kawasaki disease (KD) **[(Pruc *et al.,* 2020) ; (Rodríguez *et al.,* 2020)].** There's an increasing incidence and multiple reports of children diagnosed with KD from different countries like USA, France, England and Italy **[(Chiu *et al.,* 2020) ; (Schroeder *et al.,* 2020) ; (Stower, 2020)].**

Kawasaki disease is an acute, self-limiting vasculitis, that exclusively affects children, mainly boys, it causes an acute inflammation of the blood vessels **[(Jones *et al.,* 2020) ; (Rodríguez *et al.,* 2020) ; (Stower, 2020)],** its etiology is unknown **[(Loomba *et al.,* 2020) ; (Rodríguez *et al.,* 2020)],** but scientists generally associated it with viral respiratory infections **(Jones *et al.,* 2020).**

Misdiagnosis of KD could drive over-treatment, heighten anxiety and even leads to the continuity of school closures **(Schroeder *et al.,* 2020),** and this disease has already been reported with other viruses like Influenza and Epstein-Barr virus (EBV), **Loomba *et al.,* (2020)** questioned**,** should KD with COVID-19 really come as a surprise?!

IV. The Gut Microbiota

The ecosystem of the gut and commensal microbiota can both regulate and be regulated by invading viruses, facilitating either stimulatory or suppressive effects, making SARS-CoV-2-Gut interaction a consideration, with roles in affecting the severity of the the infection, either by direct or non-direct microbiome pathways, specifically, on its impacts on cytokines, and roles in affecting the degree of recovery too **(Kalantar-Zadeh *et al.*, 2020).**

Notably, *Prevotella* has been abundantly seen in the clinical samples of SARS-CoV-2 infected patients, but as of yet, no study has been reported to identify the microbiota species interacting with the virus **(Kalantar-Zadeh *et al.*, 2020).**

So, does *Prevoltella* becomes abundant as a consequence of viral modulation or, conversely, is it the one, modulating the infectious process of SARS-CoV-2**?!** it stays a question of debate and by far important…since in recent years and still, a lot of diseases are being associated with the gut flora, where different interactions occur between the host and these gut microbes, to the point that it was considered to be the second brain of the human body…so immediate researches/data would be helpful in a way!

V. The immune system response to COVID-19

Cytopathic viruses like SARS-CoV-2, induce injury and death of virus-infected cells and tissues as part of their replicative cycle **[(Muniyappa & Gubbi, 2020) ; (Tay *et al.*, 2020)].** It is proposed that, SARS-CoV-2 infection severely compromises the hosts innate immune response, and ability to generate a sufficient adaptive immune response, leading to opportunistic and co-infections **(Yaqinuddin & Kashir, 2020).** Appealingly, virus-induced direct cytopathic effects and viral evasion of host immune responses play major roles in disease severity **(Qin *et al.*, 2020).**

The immune responses induced by SARS-CoV-2 infection are two phased, the first, immune defense-based protective phase during the incubation and the non-severe stages, a specific adaptive immune response is required to eliminate the virus and to preclude disease progression to severe stages and the second, inflammation-driven damaging phase, where the virus will propagate and infect tissues where a protective immune response would be impaired **(Shi *et al.*, 2020).**

V.1. Innate Immunity

SARS-CoV-2 infection and the destruction of lung cells triggers a local immune response, recruiting macrophages and monocytes that respond to the infection, release cytokines and prime adaptive T and B cell immune responses **(Tay *et al.*, 2020).** While using a variety of pattern-recognition receptors (PRRs), alveolar epithelial cells and alveolar macrophages to detect the released pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs), including sensing viral RNA by Toll Like receptors (TLR)3, TLR7, TLR8 and TLR9 **[(Azkur *et al.*, 2020) ; (Tay *et al.*, 2020)].**

Several innate immune signaling proteins are targeted by SARS-CoV-2 viral proteins, which includes the interferon (IFN) pathway that is targeted by Nsp13, Nsp15 and ORF9b, and the NF-κB pathway which is targeted by Nsp13, ORF6 and ORF9c **(Azkur *et al.*, 2020).** The ORF3b may also play a role in the viral pathogenicity by inhibiting the expression of IFNβ **(Yi *et al.*, 2020).** Precisely, an effective innate immune response depends on the interferon type-I responses and downstream cascades resulting in effective induction of an adaptive immune response **[(Prompetchara *et al.*, 2020) ; (Yaqinuddin & Kashir, 2020)].**

V.2. Adaptive immunity

Adaptive immune responses to SARS-CoV-2 could be protective or harmful, or whit both scenarios simultaneously **(Grifoni *et al.*, 2020).**

V.2.1.Cellular-mediated response

Upon entry into the host, the virus is recognized by antigen-presenting cells, mainly, dendritic cells and macrophages, where they hand-over after phagocytosis, viral peptides to CD4+T cells through major histocompatibility complex class 2 (MHC-class 2) molecules**,** but, inside the host cells, viral peptides are presented through (MHC-class 1) proteins to CD8+ cytotoxic T cells, which start to divide and result lysis of the virus-infected tissue cells **(Azkur *et al.*, 2020).** Cytotoxic T-cells (CTLs) and Natural Killer (NK) cells are required to generate an effective immune response against viruses **(Yaqinuddin & Kashir, 2020).** The CD4+ T cells advance the production of viral-specific antibodies by activating T cell-dependent B cells. However, CD8+ T cells are cytotoxic and kill the virus-infected cells **(figure 23) (Vellingiri *et al.*, 2020).**

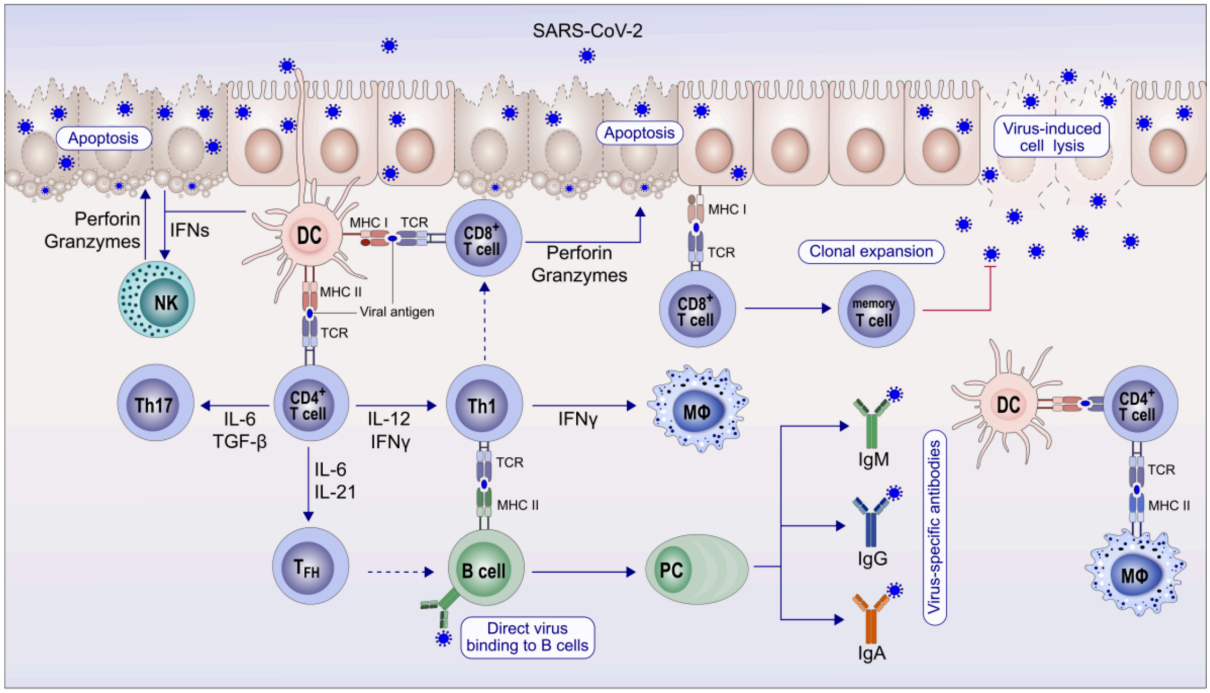


Figure 23: Immune response to SARS-CoV-2 (Azkur *et al.*, 2020).

The overactivation of T cells, manifested by an increase in T-helper (Th)17 and the high cytotoxicity of CD8+ T cells, account for the immune injury **(Azkur *et al.*, 2020).** T-helper cells make pro-inflammatory cytokines via NF-kB signaling, that recruit monocytes and neutrophils to the infection site showing inflammation and activates other downstream cascades of cytokines and chemokines **(Vellingiri *et al.*, 2020).** Pulmonary recruitment of immune cells from the blood and the infiltration of lymphocytes into the airways may explain the lymphopenia seen in most of COVID-19 patients **(Tay *et al.*, 2020).**

The severe infection tends to have a central memory phenotype with a significantly higher frequency of polyfunctional CD4+T and CD8+T cells with cytokine secretion **(Rokni *et al.*, 2020).** Significant CD4+T cell responses were directed against nsp3, nsp4, ORF3s, ORF7a, nsp12, ORF8, and against nsp6, ORF3a, N protein for CD8+ T cell responses. It is most likely that an early CD4+ and CD8+ T cell response against SARS-CoV-2 is protective, but an early response is difficult to generate because of efficient innate immune evasion mechanisms of SARS-CoV-2 in humans **(Grifoni *et al.*, 2020).**

V.2.2.Humoral response

The production of neutralizing antibody (NAbs) plays a protective role in limiting the infection at a later phase and prevents re-infection **[(Prompetchara *et al.*, 2020) ; (Rokni *et***

***al.,* 2020)].** Typical antibody responses to acute viral infection are wildly induced in COVID-19 patients **(Zhao *et al.,* 2020).** Usually, the viral load profile peaks at around the time of symptom onset, at 10 days or later **[(Tay *et al.,* 2020) ; (To *et al.,* 2020)],** and an increase in virus-specific IgM in the acute phase followed by an increase in virus-specific IgG at later phases against SARS-CoV-2 nucleoprotein (NP) or receptor-binding domain (RBD) has been observed **[(Azkur *et al.,* 2020) ; (Rokni *et al.,* 2020)].** B cell responses in patients with COVID-19 occur concomitantly with T follicular helper cell responses, from around 1 week after symptom onset, neutralizing antibody responses, likely to the S protein, begin to develop by the 2nd week **(figure 24) (Tay *et al.,* 2020).**

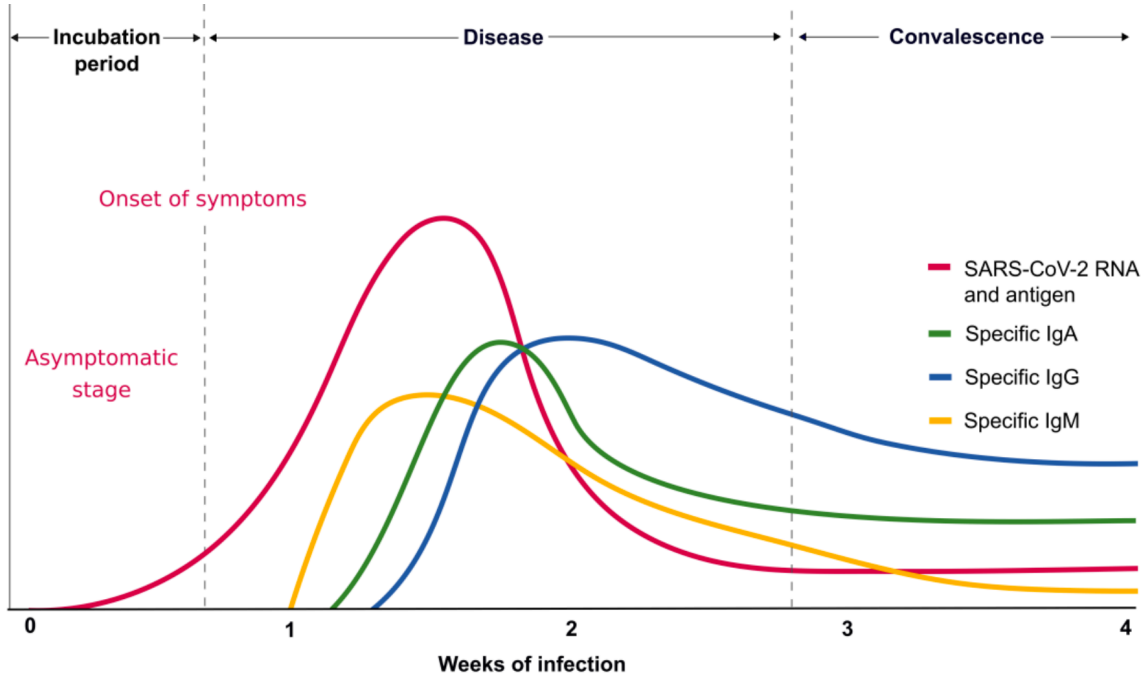


Figure 24: Specific antibody response to SARS-CoV-2 (Azkur *et al.,* 2020).

V.2.3.The cytokine release syndrome (CRS) "Cytokin Storm"

In most COVID-19 patients, recruited cells clear the infection in the lung, the immune response recedes and patients recover. However, in some patients, a dysfunctional immune response occurs **(Tay *et al.,* 2020),** triggering higher expression of pro-inflammatory cytokines and chemokines, including IL-2, IL-7, IL10, IP- 10, TNF-α, G-CSF, MCP-1 and MIP-1A, both and, the consumption of CD4+/CD8+ T/NK cells, and the decrease in regulatory T cells, following an immune suppression stage, resulting in an aggravated inflammatory responses and producing a cytokine storm **[(Li *et al.,* 2020) ; (Qin *et al.,* 2020) ; (Yaqinuddin & Kashir, 2020)].**

This concurrence of a "cytokine storm" that triggers a violent attack by the immune system to the body, with lymphopenia could underlie ARDS, viral sepsis, inflammatory damage of the lung and multi-organ failure and finally lead to death **[(Li *et al.,* 2020) ; (Prompetchara *et al.,* 2020) ; (Shi *et al.,* 2020) ; (Tay *et al.,* 2020) ; (Yaqinuddin & Kashir, 2020)].**

V.3. Immune evasion

Previous studies, suggested that coronaviruses use conformational masking and glycan shielding to limit recognition by the immune response of infected hosts **(Walls *et al.,* 2020).** COVID-19 patients frequently manifest a lymphopenia, suggesting that cellular immune responses may be suppressed **(Raoult *et al.,* 2020).** Accordingly to the increase in Neutrophil-to-Lymphocyte Ratio (NLR) and T lymphopenia and a decrease in CD4+ T cells with no significant change in the number of CD8+ cells and B cells, it was suggested that the COVID-19 virus might damage lymphocytes, especially T lymphocytes, and the immune system is impaired during the period of disease **[(Qin *et al.,* 2020) ; (Rokni *et al.,* 2020)].** Interestingly, it has been shown that SARS-CoV-2 infects human T cell lines by the spike protein via a novel route through CD147, present on the surface of T-cells expressed in many tissues and cells, which plays a role in cell proliferation, apoptosis, tumor cell migration, metastasis and differentiation, especially under hypoxic conditions **[(Azkur *et al.,* 2020) ; (Liu & Li, 2020) ; (Wang *et al.,* 2020)].**

V.4. Immune cross-reactivity

Many coronaviruses cause frequent infections like the common cold. Research on SARS infection showed, that T-cell immunity remained for at least ten years post infection, while antibodies are lost within two years. Therefore, in serological assays cross-reactivity between anti-SARS-2 and other coronaviruses antibodies show up. This cross-reactivity could be mostly attributed to virus proteins that have an amino acid homology that is high enough to allow immunological cross reactivity, like the viral RNA polymerase or structural proteins like the nucleocapsid, and the envelope protein **(Jacobs, 2020).**

Immune response to coronaviruses has led to the detection of SARS-CoV-2-reactive CD4+ T cells in ~40-60% of individuals that were unexposed to SARS-CoV-2, deducing a possibility of cross-reactive T cell recognition between circulating 'common cold'

coronaviruses **(Kwok *et al.,* 2020**), Just like, a case study of six different unexposed donors to SARS-CoV-2 with IgG against 'common cold' coronaviruses had indeed SARS-CoV-2-reactive CD4+ T cells, demonstrating that the cross-reactivity is relatively widely distributed **[(Grifoni *et al.,* 2020) ; (Petrosillo, 2020)].** Although these antibodies may not directly neutralize the virus, they may synergize with the innate immune response to eliminate viral particles and might also offer some protection in children and others that have recently encountered a common cold coronavirus **(Jacobs, 2020).**

Cross reactivity between vaccination and other viral genus has been stated **(Salman & Salem, 2020),** and any degree of cross-protective coronavirus immunity in the population could have a very substantial impact on the overall course of the pandemic **(Grifoni *et al.,* 2020).**

V.5. Herd immunity

Herd immunity is an age-old concept that revolves around an indirect protection conferred by immune individuals to the susceptible ones in a given population against a specific pathogenic infestation. It protects by limiting the spread of the disease **[(Randolph & Barreiro, 2020) ; (Syal, 2020)].** The most relevant measure to evaluate the societal cost of achieving global SARS-CoV-2 herd immunity is the overall infection fatality rate (IFR) defined as the proportion of deaths caused by a certain disease among all infected individuals **(Randolph & Barreiro, 2020).**

Building herd immunity is a possibility. However, there is no straightforward, ethical path to reach this goal, as the societal consequences of achieving it are devastating **(Randolph & Barreiro, 2020).** Indicating that population will continue to remain at risk until, and unless, there is the development of herd immunity either through infection or vaccination (**Dhar Chowdhury & Oommen, 2020).**

VI. Therapeutic and preventive approaches

Potential anti-coronavirus therapies can be divided into two categories depending on the target, one acting on the human immune system or human cells, and another, on the virus itself **(Wu *et al.,* 2020).** Sadly, there is no clear, unified and effective treatment plan, nor definitive therapies or vaccines for COVID-19, but only a variety of potential approaches **(figure 25) [(Ebrahim *et al.,* 2020) ; (Valencia, 2020) ; (Yang *et al.,* 2020)].**

The major druggable targets of SARS-CoV-2 include the 3-chymotrypsin-like protease (3CLpro), papain like protease (PLpro), RNA polymerase ARN dependant (RdRp), and spike (S) proteins **(Mani *et al.*, 2020).** Effective antiviral therapy and measures to modulate the innate immune response and restore the adaptive immune response are essential for breaking the vicious cycle of the disease and improving the outcomes **(Li *et al.*, 2020).**

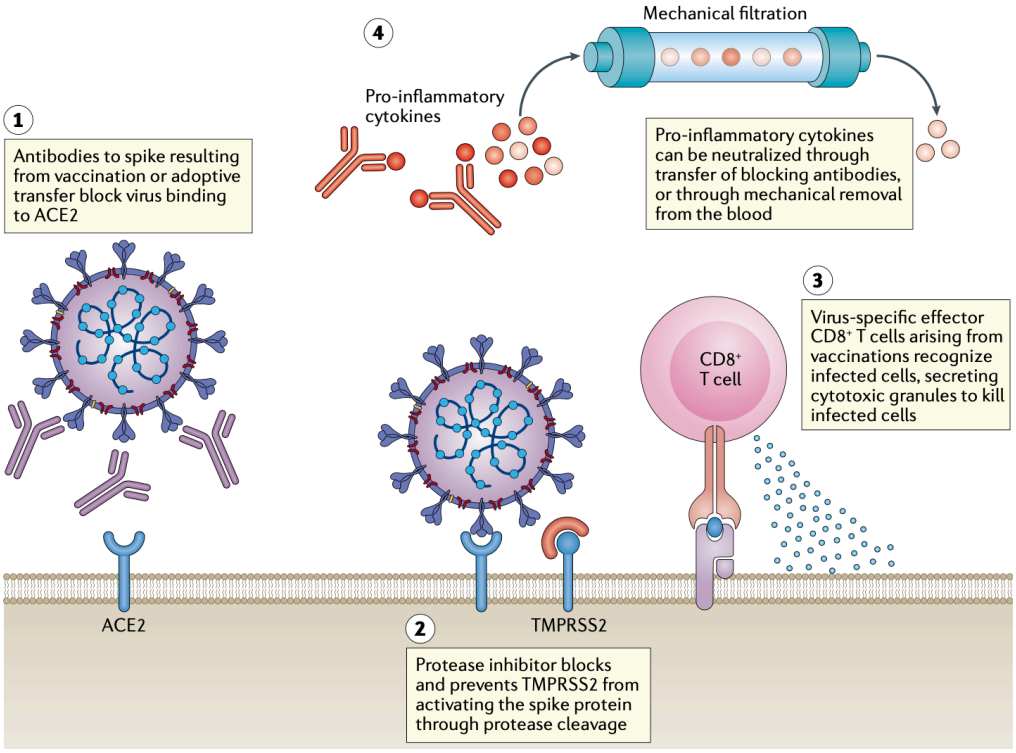


Figure 25: Potential therapeutic approaches against SARS-CoV-2 (Tay *et al.*, 2020).

VI.1. Drugs

Structure-based rational design of binders with enhanced affinities to either ACE2 or the S protein of the coronaviruses may facilitate the development of decoy ligands or neutralizing antibodies (NAbs) for suppression of viral infection **(Yan *et al.*, 2020).** Also, TMPRSS2 is indispensable for the development and homeostasis and thus constitutes an attractive drug target **(Hoffmann *et al.*, 2020).** There are several potential synthetic anti-viral, antibiotic or anti-inflammatory candidates (**table 4) (Alanagreh *et al.*, 2020).**

VI.1.1.Anti-virals

Lopinavir/Ritonavir (Kaletra), nucleoside analogues, neuraminidase inhibitors, Remdesivir, Umifenovir (Arbidol), RNA synthesis inhibitors (such as Tenofovir Disoproxil and Lamivudine), **[(Lai *et al.*, 2020) ; (Mani *et al.*, 2020)].**

VI.1.2.Antibiotics

Azithromycin has been used for the treatment of infectious diseases with a few side effects, it acts as an inhibitor of red blood cells (RBC) invasion, besides of the antibiotic and immunomodulatory effects too **(Ulrich & Pillat, 2020).**

VI.1.3.Anti-parasitics

Ivermectin used for parasitic infections, also showed an anti-viral action against the SARS-CoV-2 **(Caly *et al.,* 2020).**

Chloroquine/hydroxychloroquine used for malaria treatment, with its effects on inhibition of uncoating or alteration of post-translational modifications of newly synthesized proteins and aiding zinc uptake into cells have, been proposed and showed an increase rate of recovery **[(Abrahams, 2020) ; (Lai *et al.,* 2020) ; (Mani *et al.,* 2020)].**

VI.1.4.Anti-inflammatories

Anti-inflammatory drugs especially Janus kinase-signal transducer and activator of transcription (JAK-STAT) inhibitors, used against rheumatoid arthritis, may be effective against elevated levels of cytokines and useful in inhibiting viral entry **[(Mehta *et al.,* 2020) ; (Vellingiri *et al.,* 2020)].** The three best candidates are, Baricitinib, Fedratinib, and Ruxolitinib **(Stebbing *et al.,* 2020),** especially, Baricitinib in combination with direct-acting antivirals like Remidesivir may help fight off the infection **(Anastasopoulou & Mouzaki, 2020).**

VI.1.4.1.Corticoids

Using corticoids as an anti-viral therapy can be a bit risky**,** but Dexamethasone, showed promising results in the early clinical trials against COVID-19, decreasing lung water and reducing its inflammation **(Patel *et al.,* 2020).**

VI.1.5.Immunosuppressive drugs

Developing neutralizing antibodies against the ACE2 or other receptors, comes with a high possibility for reducing the severity of the disease **(Vellingiri *et al.,* 2020).** These drugs, help in reducing the cytokine storm, like Tocilizumab or Sarilumab, which are inhibitors of the Interleukin-6 Receptor (IL-6R) (also known as CD126), that could improve and represses the deterioration of severe COVID-19 patients inflammatory symptoms **[(Valencia, 2020) ;**

(Xu *et al.*, 2020)]. Also, Monalizumab, an inhibitor antibody against NKG2A (also known as CD159, receptors that stimulate or inhibit cytotoxic activity of NK cells), that has been developed and has shown promise to restore the function of CD8+ T and NK cells **(Yaqinuddin & Kashir, 2020).**

Dong *et al.*, (2020), conducted a study about a humanized Llama antibody against SARS-CoV-2, where they found that, these molecules or nano-bodies, would potentially protect against the virus by blocking S-ACE2 interaction and induce antiviral functions, these multi-specific antibodies would be easier to manufacture than polyclonal antibodies, due to the production needs of only one molecule.

Table 4: Common and potent antiviral drugs (Alanagreh *et al.*, 2020).

Drugs	Therapy Strategy	Mechanisms of Therapy	Status
Chloroquine/ hydroxychloroquine	Anti-malaria anti-viral anti-inflammatory	Increasing endosomal pH, interfering with the glycosylation of cellular receptors of SARS-CoV-2, immuno-modulator	FDA approved to be used in an emergency situation
Baricitinib	Rheumatoid arthritis (RA) drug, AP2-associated protein kinase 1 (AAK1) inhibitor	Interfering with viral entry by inhibiting one of the endocytosis regulators	FDA approved
lopinavir/ritonavir	HIV protease inhibitor	Could act by inhibiting SARS-CoV-2 protease for proteins cleavage, interfering with virus replication	
Darunavir			
Ivermectin	Anti-parasite	Inhibits SARS-CoV-2 replication in vitro	
Remdesivir	Antiviral drug (Nucleoside analogue)	Interfering with the viral replication	Investigational
Favipiravir	Nucleoside analog	Binds to the viral RdRp and reduce its reproduction	
Cepharanthie/ Selamectin/ mefloquine	Anti-viral Anti-inflammatory activities	Significantly reduced cytopathic effects of SARS-CoV-2, and decrease the viral load	
Camostat Mesylate	TMPRSS2 inhibitor	Interfering with viral entry	Japan approved

VI.2. Convalescent Plasma therapy

On 24/03/2020 Food and Drug Administration (FDA) has given small basis trial for giving plasma therapy, collected from a recovered patient after proper procedure **(Haque & Akram, 2020),** some reports indicated the use of convalescent serum for therapy of patients with COVID-19 in China, still, it hasn't been widely used, in absence of definitive management protocols **(Cunningham *et al.*, 2020).**

Convalescent plasma (CP) therapy, is a classic adaptive immunotherapy, representing the administration of antibodies against a given agent, it has been applied to the prevention and treatment of many infectious diseases, notably for COVID-19, where it might be a promising therapeutic option **[(Casadevall & Pirofski, 2020) ; (Duan *et al.*, 2020) ; (Syal, 2020)].** It can be used for either prophylaxis of infection, with higher effectiveness or treatment of the disease, which would mostly be effective shortly after the onset of symptoms **(Casadevall & Pirofski, 2020).**

Duan *et al.*, (2020), revealed that one appropriate dose of CP, improved the increase of oxyhemoglobin saturation accompanied by rapid neutralization of viremia and all enrolled COVID-19 patients achieved primary and secondary outcomes**. Zeng *et al.*, (2020)** suggested, that it can even help stop viral shedding**.**

CP therapy can be easily accessible, promising, and safe, but comes with risks too, like the transfusion of a potential pathogen and doses at sub-neutralizing concentrations that could suppress innate antiviral systems, another risk lies within the possibility of attenuating the immune response leaving an individual vulnerable to subsequent re-infection **[(Casadevall & Pirofski, 2020) ; (Duan *et al.*, 2020)].**

VI.3. Mesenchymal Stem Cells therapy

Mesenchymal Stem Cells (MSCs) therapy demonstrates a successful harnessing of natural endogenous pathways with protective immunomodulatory properties in opposing viral infection due to the presence of specific cytokines improved qualities**.** These cells are ACE2-, easily accessible and can be isolated from various tissues such as bone marrow and adipose tissues, including umbilical cord, dental pulp, menstrual-blood, buccal fat pad and fetal liver **[(Golchin *et al.*, 2020) ; (Metcalfe, 2020)].** But immunogenicity, low invasive procedure, limited cell source and ethical issue are the main limitations of this therapeutic approach

(Golchin *et al.,* 2020). However, there's also, synthetic stem cells "LIFNano", in which leukaemia inhibitory factor (LIF) oppose the cytokine storm in the lungs during viral pneumonia **(Metcalfe, 2020).**

China have announced the use of MSCs in severe cases with COVID-19 infection **(Shi *et al.,* 2020),** in addition to USA, Jordan, Iran, and several other countries **(Golchin *et al.,* 2020),** after therapy**,** all of the patients had significantly improved pulmonary function **(Metcalfe, 2020).**

VI.4. Therapeutic BoNTs

Botulinum toxins (BoNTs) are bacterial protein toxins of *Clostridium botulinum,* that naturally induce paralysis of muscle and sudden respiratory failure leading to death in humans. However, there is a therapeutic BoNT with highly diluted injection portions, that appear to elevate immune cell counts and platelet counts in the blood, which might help fight off the SARS-CoV-2, as it can enhance the antigen presentation and the macrophages-mediated phagocytosis to eliminate the virulent factors, improve blood circulation and oxygen supply, adding to those, a neuro-protection against cerebral ischaemic insults with a capacity to migrate from intramuscular injection site to the brain and other organs. It is a relatively safe, beneficial and effective therapy that could easily be neutralized using available antibodies **(Kandasamy, 2020).**

VI.5. New technologies

New technologies have been utilized preemptively to counter the symptoms of SARS-CoV-2 **(Atzrodt *et al.,* 2020).**

VI.5.1.Small interfering RNA therapy

Small interfering RNA (siRNA) are a class of double-stranded non-coding RNA molecules, siRNA-based therapy can be developed against the novel coronavirus, where the siRNAs can hit the highly conserved regions of SARS-CoV-2 RNA like, RdRp, helicase, proteolytic enzymes, and the nucleoprotein and also can act as an inhibitor to suppress the genetic disorders of the lungs **(Ghosh *et al.,* 2020).**

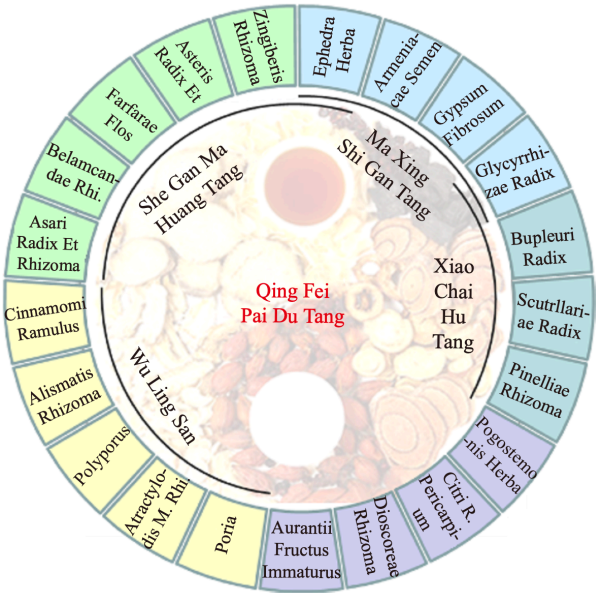
VI.5.2.CRISPR

CRISPR-Cas13 has been utilized to target essential parts of the SARS-CoV-2 virus, through an approach called PACMAN (Prophylactic Antiviral CRISPR in huMAN cells), which has an RNAse activity that can be either used for both the detection as previously mentioned chapter and the destruction of SARS-CoV-2 **(Atzrodt *et al.*, 2020).**

VI.6. Natural medicine

Developing safe, effective, anti-coronavirus therapeutic agents from naturally derived compounds is a hopeful solution **(Mani *et al.*, 2020).** That's why, the search for new molecules with a preservative power of natural origin has an importance, notably by the use of medicinal plants **(Aanouz *et al.*, 2020).** Besides, naturally occurring phytochemicals provide a valuable and powerful resource of chemical compounds displaying antiviral properties **(Mani *et al.*, 2020).**

In Chinese culture, Traditional Chinese Medicine (TCM) played a unique role in the prevention and treatment of emerging infectious diseases, it has also been widely used for the treatment of the novel coronavirus pneumonia, mainly by preventing infection for healthy persons and improving symptoms for patients with mild symptoms, owing to its ability to activate immune cells, improve phagocytosis and induce the production of cytokines **(Du *et al.*, 2020).**



"Qing Fei Pai Du Tang" (QFPDT) is screened out by the National Administration of Traditional Chinese Medicine (NATCM) and widely recommended nationwide **(figure 26) (Du*et al.*, 2020).** Other TCM (such as ShuFeng JieDu or Lianhua Qingwen capsules) were also proposed **(Lai *et al.*, 2020).**

Figure 26: The composition of the prescription Qing Fei Pai Du Tang (Du *et al.*, 2020).

In India, a different matter was the aim to develop an efficient viral inactivation system that has a high preventive potential, by exploiting active compounds from natural Indian medicinal plants renowned for their antiviral and pulmonary protective potentials and infusing them into a nano-fiber-based respiratory masks **(figure 27) (Balachandar *et al.*, 2020).** There's also the Traditional Indian Medicinal Practices like Ayurveda, Siddha and Unani**,** not to forget, their plants/herbs, that have been widely used as a treatment and as a preventive strategy for several diseases, including respiratory viral infections, to create immune-boosting and inflammation-modulating effects to manage the immune system **(Vellingiri *et al.*, 2020).**

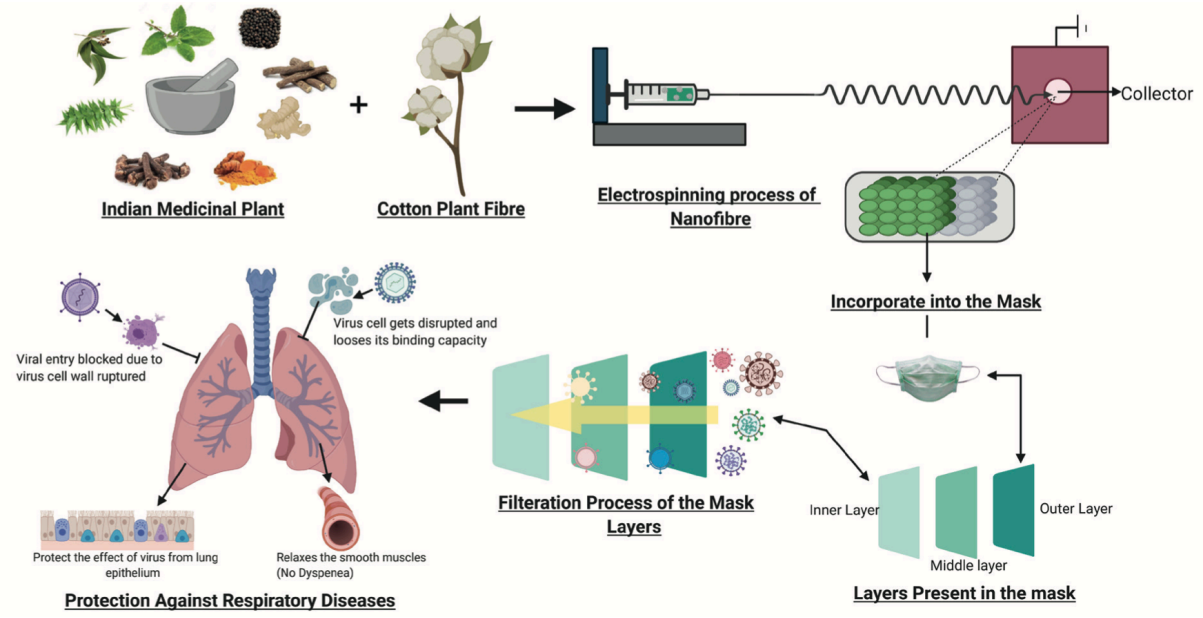


Figure 27: Mask with medicinal plant filter for prevention & deactivation of viruses (Balachandar *et al.*, 2020).

An Egyptian study held by **Elfiky, (2020)**, showed that the Heat Shock Protein A5 (HSPA5) cell-surface is up regulated upon infection, then translocated to the cell membrane where it's subjected to be recognized by the SARS-CoV-2 spike. The author tried to illuminate that some natural product active compounds, may utilize this human cell-surface receptor, having an impact on the virus attachment, like the phytoestrogens and estrogens that showed high affinity through his molecular docking study.

Natural products are known historically for their pharmaceutical properties, especially for the Moroccan medicinal plants, where three molecules of which had a significant antiviral power, B–Eudesmol from *Laurus Nobilis* L, Digitoxigenin from *Nerium Oleander* and

Crocin from *Crocus Sativus L.* These compounds, were interesting as inhibitors of SARS-CoV-2 main protease (3CLpro) **(Aanouz *et al.*, 2020),** which is one of the best-characterized drug targets among coronaviruses that blocks viral replication **(Zhang *et al.*, 2020).**

In Algeria, an *In silico* study by **Abdelli *et al.*, (2020),** showed that multiple compounds from the *Ammoides verticillata* plant harvested from western Algeria targeted the ACE2 receptor, notably, by the Isothymol ligand with high affinity. Along with a molecular docking study by **Cherrak *et al.*, (2020)** that demonstrated how glycosylated flavonoids from natural sources could inhibit the 3CLpro, mainly, the Quercetin-3-O-rhamnoside molecule, which is found in some fruits and vegetables and also in tea infusions.

VI.7. Boosting Immunity

Immunity might be stimulated using vitamin D, C and B3 or low doses of IL-2 **(Jacobs, 2020).** Moreover, Vitamin D appears to have similar modulating effects on IL-6 as Tocilzcumab, as it could offer a realistic alternative treatment **(Silberstein, 2020).**

VI.8. Vaccines

Obviously, the ultimate solution is producing a SARS-CoV-2 vaccine **(Gurwitz, 2020),** since there isn't any effective eradicative treatment for COVID-19 at present **(Anastasopoulou & Mouzaki, 2020).** One of the key components in developing virus neutralizing antibodies or a vaccine design is the CoVs S protein **[(Ou *et al.*, 2020) ; (Wu, 2020)].**

Research institutions and pharmaceutical companies worldwide are stepping up research and development for a coronavirus vaccine **(Yang *et al.*, 2020).** As on 20th of April, there were 5 candidate vaccines under clinical evaluation, guided by a group of experts coordinated by the WHO (**Dhar Chowdhury & Oommen, 2020).** Most of these vaccine would be either as inactivated vaccines, subunit vaccines or viral vectored vaccines (VVV) **(Wu, 2020),** but even once a vaccine is approved for human use, high virus mutation rates, would mean that a new vaccine may be need to be developed for each outbreak **(Gurwitz, 2020).**

CONCLUSION

CONCLUSION

COVID-19 is an infectious disease, posing a massive challenge to the global health, which will probably run a prolonged course until an effective vaccine is found or herd immunity is achieved **(Dhar Chowdhury & Oommen, 2020).**

Highlighting the genome divergence of SARS-CoV-2 would have tremendous importance during this pandemic, providing a better understanding of the genetic and phenotypic characteristics of the virus pathogenesis **(Bhowmik *et al.,* 2020).** Similarly, reliable data for profiles of serial viral load and serum antibody responses are urgently needed to guide anti-viral treatment, infection control, epidemiological measures, and vaccination **(To *et al.,* 2020).**

The host-virus evolutionary arms race over time, leads to natural selection that alters both of the host and the viral proteins, allowing both to increase their fitness **(Stawiski *et al.,* 2020).** Therefore, a detailed understanding of how an animal virus, jumped species boundaries to infect humans so productively, will help in the prevention of future zoonotic events **[(Andersen *et al.,* 2020) ; (Wu *et al.,* 2020)].** Continuous surveillance of coronaviruses in their natural hosts, and in humans, is necessary for rapid control of other new coronaviruses outbreaks, to monitor their future host adaption, viral evolution, infectivity, transmissibility and pathogenicity **(Akram & Mannan, 2020).**

The nature of COVID-19 is revealing itself as the pandemic unfolds, It does not cut through a population uniformly, but has a greater effect on a relatively small fraction of the population, with a possibility of many countries, converging on a marginal level of herd immunity **(McGeoch & McGeoch, 2020).** The mysterious lower rate of fatality in some, could be advocated to the global active viral immunization of children from birth to six years **(Salman & Salem, 2020).** According to the WHO, management of COVID-19 has mainly focused on infection prevention, case detection, and supportive care **(Chen *et al.,* 2020).** Estimations of immunity are also central to epidemiological model calibration of future social distancing pandemic control measures **(Grifoni *et al.,* 2020).** Besides, instead of concentrating efforts on “unlikely” therapies, it would be better to know how the immune

response to this virus develops and how previous exposures to "old" coronavirus can influence the immunity of the population against COVID-19 virus **(Petrosillo, 2020).** Although still, humanity might not get rid easily of COVID-19 as it did with SARS **(Cohen & Kupferschmidt, 2020).**

The resistance of virus transmission to intervention strategies that are not strong enough, resulted in an increased difficulty in designing effective interventions to control the pandemic (**Dai & Locasale, 2020).** «Not testing alone. Not contact tracing alone. Not quarantine alone. Not social distancing alone. Do it all.» WHO Director-General Tedros Adhanom Ghebreyesus stated at a conference **(Cohen & Kupferschmidt, 2020).** We should all be involved to Mask, Test, Trace and Treat…for a better control of the spread.

Since the expansion of the COVID-19 pandemic, rumors, misinformation and falsehood (once a Chemical Gas, or the 5G Network, once a Bacterial Infection, other times the Illuminati and the Deep State conspiracies…), dominated the streets, social networks and the whole media scene, spreading faster than the novel virus itself, corrupting peoples minds, worrying them with unscientifically and unproven facts, detaining their attention from the real problem and making them, not believe that an invisible ultramicroscopic organism can transit easily and kill efficiently its host.

Across the scientific proofs and notions of this modest work, a variety of people might get an insight and draw closer to the reality of things happening to earth in these recent months, understanding what the virus is and what it can do, avoiding it maximally for the sake of the people, the society and for a better future or maybe…for just this year. Yet, in another point of view, has this pandemic had a positive effect on our planet?! does humanity really deserve it, looking at all of our pollution and destructive behavior?! is this pandemic, a way of nature saying i needed a rest?! Maybe, who knows…

To date, there's no certainty nor clarity on how this pandemic will evolve in the coming hours…days…months…and all we can do, is wait, stay safe and pray, in hopes that nature would eradicate this virus by itself and that a second destructive pandemic wave won't be on its way.

In the end, we say, even if was, SRAS-CoV-2…in the name of Nature, in the name of Science or in the name of Politics…Only GOD knows, and time will inevitably sooner or later unveil the ultimate truth of this enigma.

When, How and Will it all really ever be Over?! a question on everyone's mind, remaining a mystery…

"Look deep into nature, and then you will understand everything better"

~ Albert Einstein.

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