

COVID-19: Epidemiology, Pathogenesis and Immunological Basis

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Article Information	Abstract
Received: 05.07.2020 Accepted: 03.10.2020 Published: 09.10.2020	Background: World Health Organisation (WHO) declared COVID-19 as a Public Health Emergency of International Concern (PHEIC). This review presents the geographical distribution of COVID-19 as of 31 st May 2020, the virus pathogenesis, the evolution of total confirmed cases and global death toll of COVID-19 from 31 st December 2019 to 31 st May 2020 on the 5 continents and to display the immunological basis of the disease. Methods: Literatures were found by searching online databases. The evolution of total confirmed cases and total confirmed deaths, every two weeks, were plotted using GraphPad Prism 5.1 software. Results: As of 31 st May 2020 at 10:00 am, WHO reported 218 countries and territories concerned by COVID-19 on the 5 continents, with 5934936 total confirmed cases and 367166 total deaths. SARS-CoV-2 has a spherical shape with some pleomorphism. The infection pathogenesis significantly depends on the binding between spike protein and its receptor (ACE2 principally). Clinical manifestations of the disease vary according to host immunity and range from mild to fulminant. The main mechanism for acute respiratory distress syndrome (ARDS) is the “cytokine storm”. The virus employs many strategies to evade the immune response. Conclusion: COVID-19 has wreaked a lot of havoc. Investigations are still ongoing for the development of treatment and vaccines. In the meantime, measures are being taken to prevent and limit contacts.
Keywords: Covid-19 Epidemiology Pathogenesis Immunological response	

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1. Introduction/Background

SARS-CoV-2 emerged from December 2019 in Hubei, Wuhan, China and is responsible of an international outbreak of respiratory illness called COVID-19 by World Health Organization (WHO) [1]. Highly transmissible from human to human, SARS-CoV-2 causes a wide spectrum of clinical manifestations in patients with COVID-19 [2,3]. The full spectrum of COVID-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure and death [4-7].

Four human coronaviruses (HCoVs), HCoV 229E, NL63, OC43, and HKU1 are known for their endemicity and are responsible of “non-severe acute respiratory syndrome (SARS)-like CoVs” to human. Three novel zoonotic highly pathogenic Coronaviruses, have emerged causing lethal human disease over the past two decades; they are: the SARS coronavirus (SARS-CoV now named SARS-CoV-1) discovered in November, 2002 [8], the

Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV) in June, 2012 [9]; and SARS-CoV-2 [2,10]. Many cases of COVID-19 have been found world widely [11]. On 30th of January 2020, COVID-19 outbreak was declared as a “Public Health Emergency of International Concern” (PHEIC) by WHO and on 11th of March, the disease was characterized by WHO General Director as a pandemic” [12]. COVID-19 has attracted mass news media attention all around the world, more than any other disease. Scientific investigations are still ongoing about the SARS-CoV-2 worldwide, nevertheless some data are available. In view of that, this review presents the geographical distribution of COVID-19 as of 31st May 2020, the virus pathogenesis, the evolution of total confirmed cases and global death toll of COVID-19 from 31st December 2019 to 31st May 2020 on the 5 continents and displays the immunological basis of the disease.

2. Methods

Protocol

The study was carried out on March 2020. Literatures were found by searching online databases such as: Pubmed, Elsevier, Google scholar, and also WHO, European CDC and Our World in Data websites. We searched all English and French scientific publications on the epidemiology, pathogenesis, virus structure, viral replication, total confirmed cases, total confirmed deaths, immune response, immune evasion, immunological characteristics, including “nCoV”/“SARS-CoV-2”/“COVID-19”. The research was done by 2 researchers independently. The sets of literature were compared and discussed with the collaboration of a senior researcher. During this phase, data from articles referenced by some authors have been inserted in our review. Endnote 7.0 (Thomson Reuters) was used to create a bibliography, to collect and manage the selected and cited articles. The process of our literature review is shown on Figure 1.

Data about the total confirmed cases and deaths on the 5 continents (Asia, Europe, America, Africa and Oceania) were collected on precise dates (31st December 2019, 15th January 2020, 31st January 2020, 15th February 2020, 29th February 2020, 15th March 2020, 31st March 2020, 15th April 2020, 30th April 2020, 15st May 2020 and 31st May 2020) on the website <https://ourworldindata.org/coronavirus> edited by Roser *et al* which presents all the data collected between 6:00 am and 10:00 am by European CDC every day since 31st December 2019.

Data analysis

Data/information collected were classified into different domains: geographical distribution of COVID-19 as of 15th April 2020, pathogenesis of SARS-CoV-2, evolution of total confirmed cases and global death toll of Covid-19 from 31st December 2019 to 31st May 2020 on the 5 continents and immunological basis of COVID-19.

Numerical data about the total confirmed cases and confirmed deaths were plotted using the software GraphPad Prism 5.1.

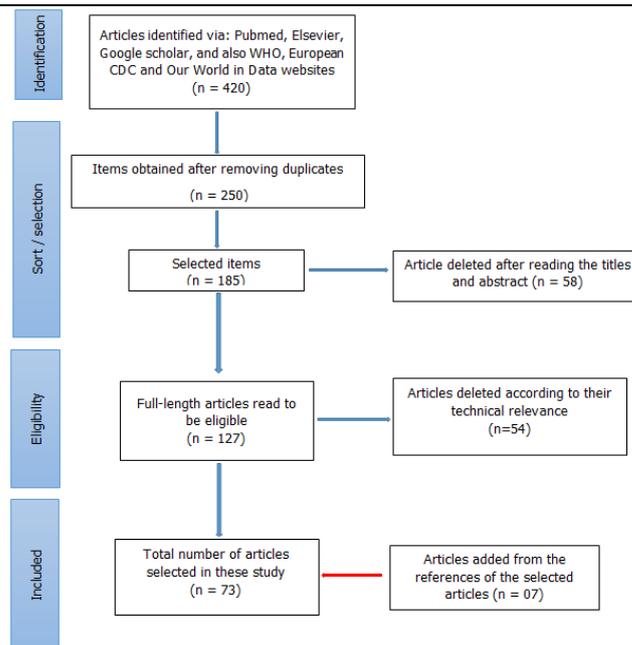


Figure 1: Process of literature review.

Geographical distribution as of 31st May 2020

The first case of SARS-CoV-2 was reported in Hubei (Wuhan, China) and the disease has now spread almost all the countries of the world [13,14]. On 31st December 2019, WHO was alerted about the rising of a pneumonia of unknown etiology in China, on 6th January 2020 Chinese CDC activated level 2 emergency response and on 23rd January, Wuhan was locked down to limit the virus spread [10].

As of 31st May 2020 at 10:00 am, WHO reported 218 countries and territories concerned by COVID-19 on the 5 continents (Figure 2), with 5934936 total confirmed cases and 367166 total deaths [15].

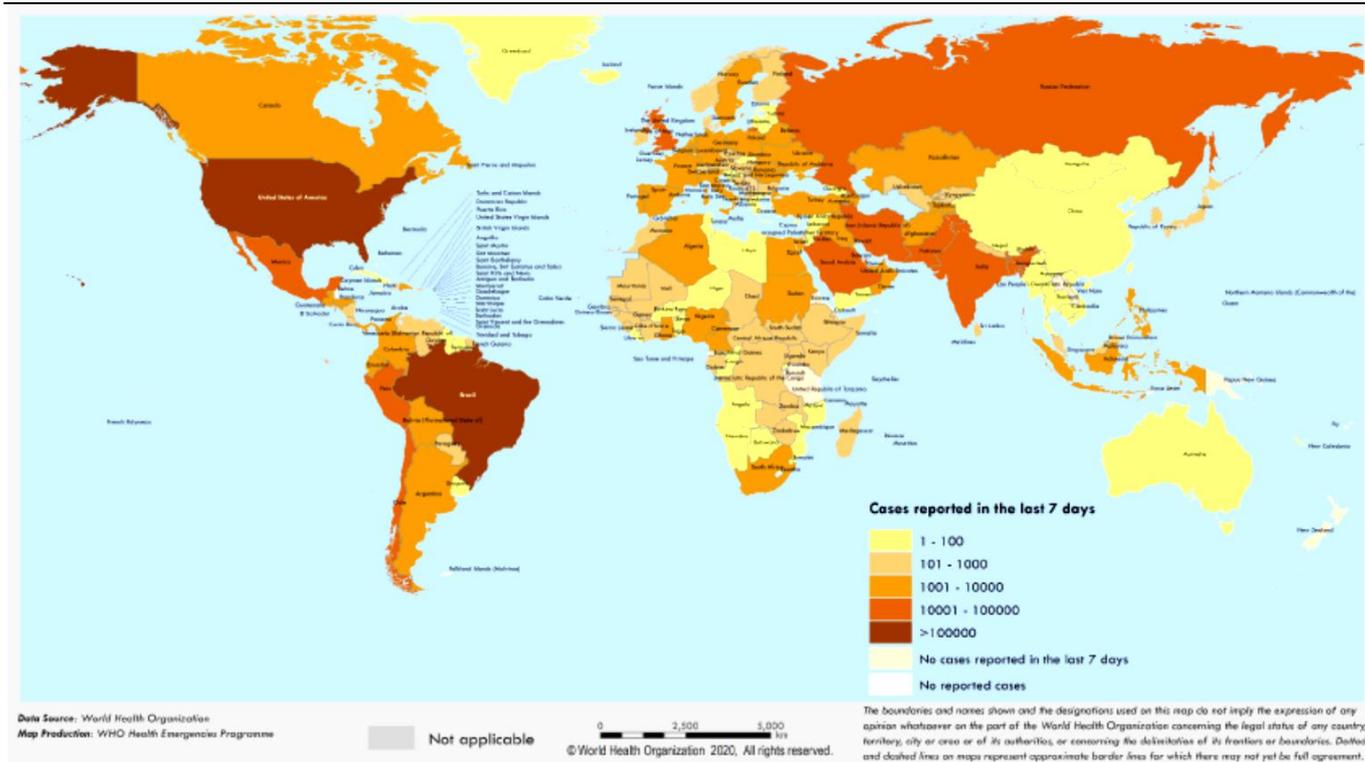


Figure 2: Global distribution of Covid-19 as of 31th May 2020. Source: World Health Organisation [15].

3. Pathogenesis

SARS-CoV-2 can infect people of all ages. Men seems more affected than women [16,17]. No evidence has been found for COVID-19 *in utero* transmission from infected pregnant women to their fetuses [18,19], nevertheless neonatal disease has been described [20-22].

Virus is transmitted through large droplets, and even aerosols, generated by symptomatic or asymptomatic subjects [23]. Those particles can be spread 1 to 2 meters and deposit on surfaces. People can be contaminated when inhaling the droplets/aerosols or by touching contaminated surfaces by SARS-CoV-2 and then touching nose, hand and face [23,24]. The virus can also be transmitted when having direct contact with a symptomatic or asymptomatic carrier. Viral load is higher in the nasal cavity than in throat with no difference between symptomatic and asymptomatic people [14,25]. The virus remain viable on surfaces and certain fabric or paper substrates for days in favorable atmospheric conditions, however can be successfully inactivated by using surface disinfection procedures including ethanol at 62-71%, hydrogen peroxide at 0.5% or sodium hypochlorite 0.1% within 1 minute [26]. The virus mRNA has been found in the faeces, suggesting a faecal-oral transmission [27,28].

• Description of SARS-CoV-2

The pathogen was firstly isolated in China on 7th January 2020. The SARS-CoV-2 virion has the typical structure of coronaviruses. By transmission electronic imaging, the virion looks like a solar corona. The virion shape is

spherical, presenting some pleomorphism. Its diameter range from 60 to 140 nm with quite distinctive spikes (of about 8 to 12 nm in length). The genetic material is a single-stranded RNA measuring 26 to 36 kbs [10,29,30].

The genome of SARS-CoV-2 is around 38% G+C content [30,31] with open reading frames (ORFs) (among which six are common to other coronaviruses) and some other accessory genes [10] (Figure 3). The genome possesses 14 ORFs which encode 27 proteins [32]. ORFs are located at the 5'-terminus of the genome and structural proteins (S,E,M and N) at the 3'-terminus. Also comprised on the viral genome are: 15 nsps (nsp1 to nsp10 and nsp12 to nsp16) and 8 accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and orf14). SARS-CoV-2 seems similar to SARS-CoV at the amino-acid level, but some notable differences exist. For example, present on SARS-CoV, the 8a protein is absent in SARS-CoV-2, on the other hand, 8b protein which is 84 amino-acids in SARS-CoV is 121 amino-acids in SARS-CoV-2; 3b protein also, which is 154 amino-acids in SARS-CoV, is 22 amino-acids in SARS-CoV-2. The functionality and the pathogenesis of SARS-CoV-2 may be affected by those differences on the amino-acid content [32].

Similarities between the structural proteins of SARS-CoV-2, SARS-CoV and MERS-CoV have been checked. It has been 90% genetic similarity between the proteins M, N and E of SARS-CoV-2 and SARS-CoV, while the similarity was reduced but still high concerning the S protein (76,0%). Comparing the similarity between SARS-

CoV-2 and MERS-CoV, it was substantially lower for all proteins (< 50%) [33].

Structural and non-structural proteins play a specific role in viral replication [34]. The most important role belongs to S protein which allows viral attachment, fusion and entry in the host cell [34,35].

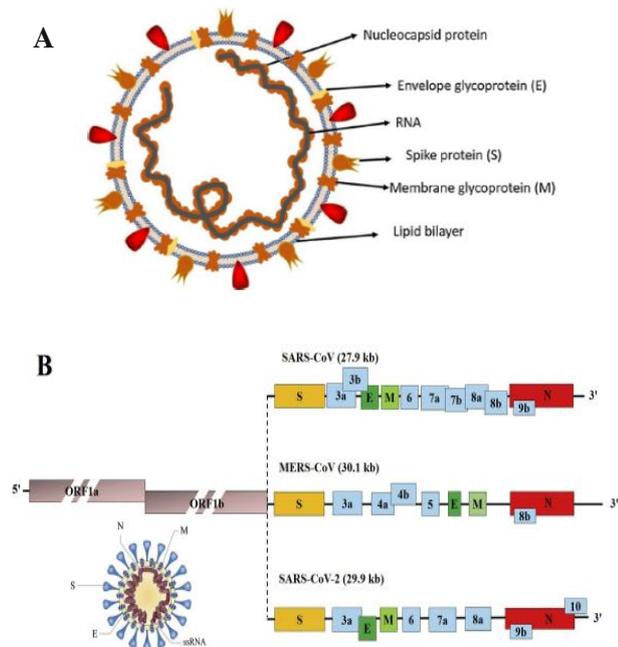


Figure 3: (A) Structure of human respiratory syndrome Coronavirus [29]. (B) Illustration of the complete genome sequences of SARS-CoV, MERS-CoV and SARS-CoV-2. The genetic material of those viruses is a positive sense single stranded RNA (ssRNA) of 26-32 kb in size. The two-thirds of the genome 5'- terminal contains the genome ORF1a/b encoding polyproteins of the viral replicase transcriptase complex. ORFs located on the genome one-third encode four main structural proteins (spike (S), envelope (E), nucleocapsid (N) and membrane (M) proteins) and also several accessory proteins [36].

• Receptors and target cells

It is well known that to understand the pathogenesis of an infectious disease and design the treatment, the infection possible routes should be identified. In COVID-19, the pathogenesis of infection is highly influenced by the virus binding to the receptors of the host cell. Angiotensin converting enzyme 2 (ACE2) is the receptor target required by SARS-CoV-2 as receptor to enter cells [37, 38]. The Coronavirus trimeric S-glycoprotein binds to ACE2 on the host cell via the viral S- receptor-binding domain (RBD) [39, 40].

The tropism and the pathogenesis of Coronavirus are critically determined by host cell proteases. Numerous of those host proteases exhibited proteolyses on the spike protein; among those proteases are endosomal cathepsins, cell surface transmembrane protease serine (TMPRSS) proteases, furin, and trypsin [41].

ACE2, a metallopeptidase, has also been identified as the functional receptor for the spike glycoprotein of the human coronavirus HCoV-NL63 and SARS-CoV [37,42, 43]. According to Qi *et al.*, investigating ACE2 expression profiles across various cell types of organs will allow to visualize the clues of the virus transmission routes and the potential pathogenesis [44]. The interaction between the SARS-CoV-2 spike protein and ACE2 is allowed through a claw like N- terminal peptidase domain on ACE2, made up of α -helical lobes present on outer surface, responsible for interacting with bowl-shaped cavity on S-RBD [11]. The two main access points of the virus residues implicate in the binding process are Lys31 and Lys353 located on ACE2 at the interface of the viral receptor for HCoV-NL63 and SARS [45,46].

Comparing the distribution of ACE2 and SARS-CoV S protein in specific cells and tissues during the autopsy of four SARS patients and a control subject, He *et al* observed that the protein S of SARS-CoV and the ACE2 were both present in: alveolar epithelial cells, bronchial epithelial cells, bronchial serous gland epithelial cells, monocytes/macrophages, gastric parietal cells, small intestinal epithelial cells, hepatocytes, myocardial cells, distal convulated renal tubules, adrenal cortical cells, pancreatic islet cells, acidophilic cells of the parathyroid, sweat gland epithelial cells and acidophilic cells of the pituitary [47].

Sequencing single RNA of 13 human tissues (lung, liver, ileum, rectum, blood, bone marrow, skin, spleen, oesophages, colon, eye, stomach and kidney), Qi *et al* realized that ACE2 is expressed mainly in lung alveolar type II cells (AT-2), liver cholangiocyte, colon colonocytes, oesophagus keratinocytes, ileum enterocytes, rectum enterocytes, stomach epithelial cells and kidney proximal cells. They also revealed some peptidases such as ANPEP, DPP4 and ENPEP, which are co-receptors of SARS-CoV-2 presenting many expression patterns similar with ACE2 [44].

Generally, the surface anchored S-protein of Coronavirus recognizes the receptor ACE2 on the host cell through its subunit S1; that recognition plays un key determinant role in the host specificity [48]. In the sequence of SARS-CoV-2, the receptor binding domain of protein S (S-RBD) residues directly interact with ACE2 receptor, highlighting the central role of ACE2 in SARS-CoV-2 entry into the cell. Phe442, Leu472, Asn479, Asp480 and Thr487, key residues of the SARS-CoV RBD would have been transmitted to SARS-CoV-2 through natural selection and are hypothesized to involve critically in the cross-species transmission of SARS-CoV [48].

On a molecular point of view, the interaction between SARS-CoV-2 and human ACE2 is enhanced principally by the interactions between residues Gln493 and Leu455 of SARS-CoV-2 and the hotspot 31 (Lys31) of ACE2. Other key residues support hotspot 31 on ACE2; they are Leu455, Phe486, Ser494 on S-protein of SARS-CoV-2. Furthermore, the stability of hotspot 353 (Lys353) located

on ACE2 receptor is strengthened by the residue Ser494 of SARS-CoV-2 [45].

• **SARS-CoV-2 replication**

Some authors reported that SARS-CoV-2 cell entry depends on both ACE2 and TMPRSS2, [49-51]. The virus uptake is increased by TMPRSS2 (Figure 4) [51].

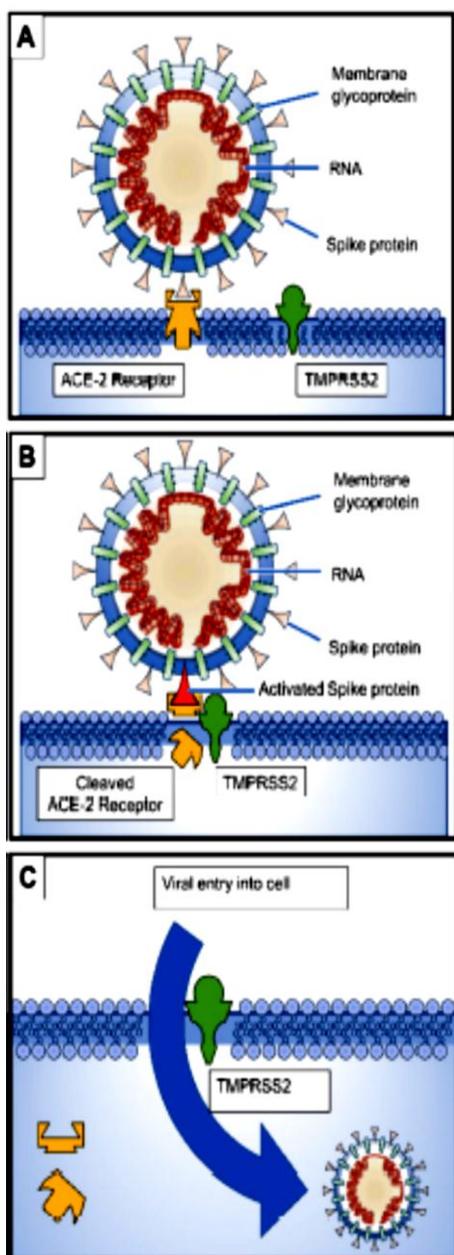


Figure 4: (A) Binding of the spike proteins of Coronavirus bind to ACE-2 receptors of the target cell; (B) TMPRSS2 binding and cleavage of the ACE-2 receptor followed by spike protein inactivation; (C) Viral entry [51].

The viral RBD of the S-protein contains 2 subunits which are necessary for endocytic pathway of the viral

entry; S1 responsible of the binding to the host receptor and S2 subunit implicate in the fusion to the membranes of the host cell [52,53]. The mediators of viral fusion to cell membrane are two tandem domains of S2 called heptad repeats 1 and 2 (HR1 and HR2) [54]

Usually, Coronaviruses enter the target cells via two pathways: the endocytic and the non-endosomal pathway [55]. Because the capacity of SARS-CoV-2 to fuse plasma membrane is higher than that of SARS-CoV, the endocytic pathway has been extensively studied [53,56]. Indeed it has been demonstrated that SARS-CoV-2 S protein entry, precisely on 293/hACE2, is mainly mediated through endocytosis; on that endosomal pathway, except TMPRSS2, other molecules are essential for virus entry, such as PIKfyve, TPC2, and cathepsin [55].

SARS-CoV-2 fusion process seems identical to that of HIV-1, S1 firstly binds to the receptor on the membrane of the target cell, then the fusion peptide located at the S2 N-terminus fits into the cell membrane. Thereafter three HR1s form a trimer attaching to each other and the three HR2s separately bind on the trimer of HR1s and they form a bundle of 6-helix. Finally, virus and cell membrane so close to each other, the fusion is triggered [54].

Once the receptor and the membrane fuse together, the SARS-CoV-2 RNA is released into the host cell cytoplasm. Then the RNA is translated into pp1a and pp1ab which are replicase polyproteins encoding non-structural proteins and the replication-transcription complex (RTC) in double-membrane vesicle is formed. Thereafter the RTC continuously replicates and series of subgenomic RNAs are synthesized, encoding accessory and structural proteins. Virions are formed, by viral proteins and genomic RNA assemblage, in endoplasmic reticulum and Golgi, then transported via vesicles and finally fuse to the plasma membrane and are released out of the cell [29,57].

Evolution of total confirmed cases and global death toll of Covid-19 from 31st December 2019 to 31st May 2020 on the 5 continents

To assess the evolution of total confirmed cases and deaths on the 5 continents (Asia, Europe, America, Africa and Oceania) data were collected on precise dates, on the website <https://ourworldindata.org/coronavirus> edited by Roser *et al* which presents all the data collected between 6:00 am and 10:00 am by European CDC every day since 31st December 2019 (Figure 5). Overall, the data follow the same trend whether it is confirmed cases of COVID-19 or the total number of deaths. It is noted that the first continent affected by the SARS-CoV-2 was Asia where the number of confirmed cases and deaths were higher until around 15th of March, then surprisingly, high numbers of cases were noted in Europe and the trend has remained the same. Followed the case of the American continent where our graph shows an appearance of the first cases between 15th and 29th February and the first deaths between 29th February and 15th March, then quasi-

exponential growth of cases and deaths until April 15th. Finally, according the data registered by the European CDC and reported by Roser *et al.* as of 31st May 2020, America is the most affected continent with 2.8 millions total confirmed cases (TCC) and 161514 total confirmed deaths (TCD), followed by Europe (1.92 millions TCC and 172955 TCD), Asia (1.11 millions TCC and 30265 TCD), Africa (141632 TCC and 4071 TCD) and Oceania (8639 TCC and 132 TCD).

COVID-19 screening strategies differ from one country to another. Some countries screen suspect individuals, subjects coming from a high epidemic area or contact subjects of people already sick or diagnosed positive, while others carry out mass screening strategy.

The new strain of Coronavirus (SARS-CoV-2) is causing more deaths than the MERS-CoV and the SARS-CoV. With MERS-CoV 2494 confirmed cases and 858 confirmed deaths have been registered, and for SARS-CoV 744 deaths have been registered for 8096 confirmed cases [58]. Lockdown strategies have been implemented in several countries to limit the spread of the virus pending the establishment of consistent treatment and vaccine.

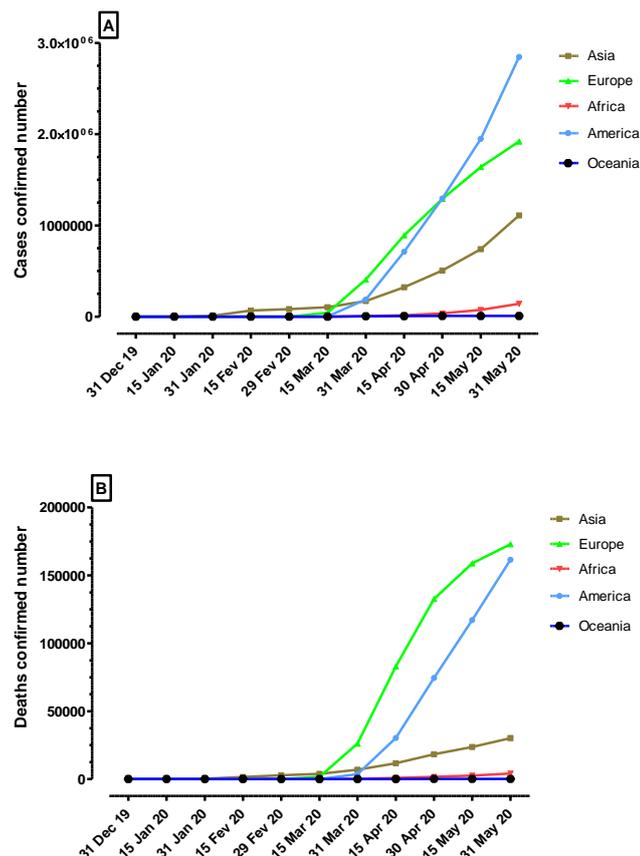


Figure 5: Evolution of total confirmed cases (A) and total confirmed deaths (B) registered on the continents from 31st December to 15th April 2020. Data were collected on specific dates shown on the graphs. Data collected from <https://ourworldindata.org/coronavirus> [59].

4. Immunological Basis of COVID-19

Since the beginning of the COVID-19 outbreak, many investigations have been done by scientific researchers and clinicians. Now, much are learned about this new disease.

Clinical manifestations SARS-CoV-2 patients can be ranged from mild, moderate to severe and rapidly progressive and fulminant disease [60]. The disease becomes frightening when severe respiratory syndrome appears; however not all people exposed to that new virus are infected and not all infected patients reach severe respiratory illness [61-63]. About 80% of COVID-19 patients can present mild or null symptoms [64, 65]. In a total of 72 314 patients recorded, the Novel Coronavirus Pneumonia Emergency Response Epidemiology Team found 61.8% confirmed cases, 22.4% suspected cases, 14.6% clinical diagnosed cases (in Hubei province), and asymptomatic cases 1.2%. Most of the cases confirmed were aged 30-79 years (86.6%) and 80.9% were considered mild. A total of 1 023 deaths occurred among confirmed cases for an overall case-fatality rate of 2.3% [66].

In view of the considerable impact of this epidemic worldwide (see data above), understanding the human immune responses during the SARS-CoV-2 infection is a necessity.

The virus entry in the target cell trigger host's immune response (Figure 5) and antigen-presentation cells (APC) initiate the inflammatory cascade. The APC present the SARS-CoV-2 antigen to Th1 cells (CD4⁺ T helper) and the interleukin-12 (IL-12) is released to stimulate Th1 cells again. Then Th1 cells stimulate cytotoxic T cells (CD8⁺ T killer) involved in targeting and killing any cells containing foreign antigens, here SARS-CoV-2. Furthermore, B-cells involved in antigen-specific antibodies production are stimulated by Th1 cells activated Th1 cells [51].

Lymphopenia and lung damage have been reported in patients with severe cases of COVID-19, showing high levels of pro-inflammatory cytokines [6,61] and level of lymphopenia correlate with the disease severity [67]. Lung damage results in acute respiratory distress syndrome (ARDS) whose the main mechanism of occurrence is the "cytokine storm". Indeed, pro-inflammatory cytokines (such as TNF- α , IL-1 β , IL-6, IL-12, IL-33, IL-18, IFN- α , IFN- γ , etc.) and chemokines (such as CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) are significantly released by effector immune cells [6,64,68,69]. Those cytokine initiate inflammatory responses, attacking violently the immune system, causing ARDS and death can occur [64, 70]. As the immune response is excessively activated, the number of CD4⁺ and CD8⁺ cells in the peripheral blood significantly decrease [70].

Current findings indicate that coronaviruses have the ability to evade the detection by immune cells and so they can subvert the immune response (Figure 7). This partly can explain their longer incubation period (2-11 days on average) compared to influenza viruses (1-4 days) [71].

SARS-CoV-2 immune evasion mechanism seems to be identical to those of other *Betacoronavirus* genus (SARS-CoV and MERS-CoV) [58]. Some scientists reported that the survival of SARS-CoV and MERS-CoV in host cells depends on many strategies they use to subvert immune responses. Pathogen-associated moleculars (PAMPs), the evolutionarily conserved microbial structure, can be recognized by host cells via pattern recognition receptors (PRRs) [36]. SARS-CoV and MERS-CoV can avoid the detection of their dsRNA by the PRRs of the host cell; they are able to induce after fusion to host cell membrane, the production of vesicles with double membrane lacking of PRRs and then replicate in these vesicles [36, 72].

On MERS-CoV particularly, accessory protein 4a, interacting directly with dsRNA, is able to block, at the level of melanoma differentiation-associated protein 5 (MDA5), the induction of interferon [73]. It has been observed also a global down-regulation of the gene of antigen-presentation on cells infected by MERS-CoV [74]. As SARS-CoV, MERS-CoV can inhibit the IFN pathway developing an antagonistic mechanism [75,76].

As illustrated on Figure 7, during initial immune response, Coronavirus can interfere with the steps of RNA sensing, the type I IFN production signaling pathway, and the activation of STAT1/2 downstream of IFN/IFNAR. Delaying or dampening the type I IFN responses, Coronavirus impairs the activation of adaptive immune response. The viral persistence in the cell may lead to heighten inflammatory responses and to exhaust and suppress immune response as a mechanism of regulation feedback. The poor outcome of a Coronavirus disease can be also favor by a biased Th2 type response [58].

Some study, also showed that type I interferon (interferon-alpha, IFN α) induces the expression of ACE2 in nasal cells expressing both the ACE2 receptor and the TMPRSS2 co-receptor. Then, SARS-CoV-2 coronavirus takes advantage of the activation of interferon, the body's first line against a viral attack, to continue its attack on different cell types in the body [77]. Interferon-alpha (IFN α) stimulates the expression of the ACE2 receptor and that the higher the dose of these interferons, the more pronounced the effect. In other words, the presence on the target cells of the viral gateway is reinforced by a mechanism set up by the immune system to normally counter the viral infection [78]. The SARS-CoV-2 coronavirus therefore uses to its advantage an immune defense mechanism to spread throughout the body. In particular, the category of "cup" cells in the human nasal epithelium expressing ACE2 is the one whose genes respond most to stimulation by interferon-alpha (IFN α) [79].

Considering the strategies the virus employs to evade the immune response, destroying the evasion of the immune system by SARS-CoV-2 could be helpful in the treatment of infected patients and the development of specific drug [36]. According to Raoult *et al.*, "current evidence suggests that the most solid predictors of disease severity after infection with SARS-CoV-2 are the patient's age and the concurrence of specific co-morbidities. In contrast, there is no proof (yet) that infection by a pauci-symptomatic person would result in a milder clinical course of immune competent neo-infected person".

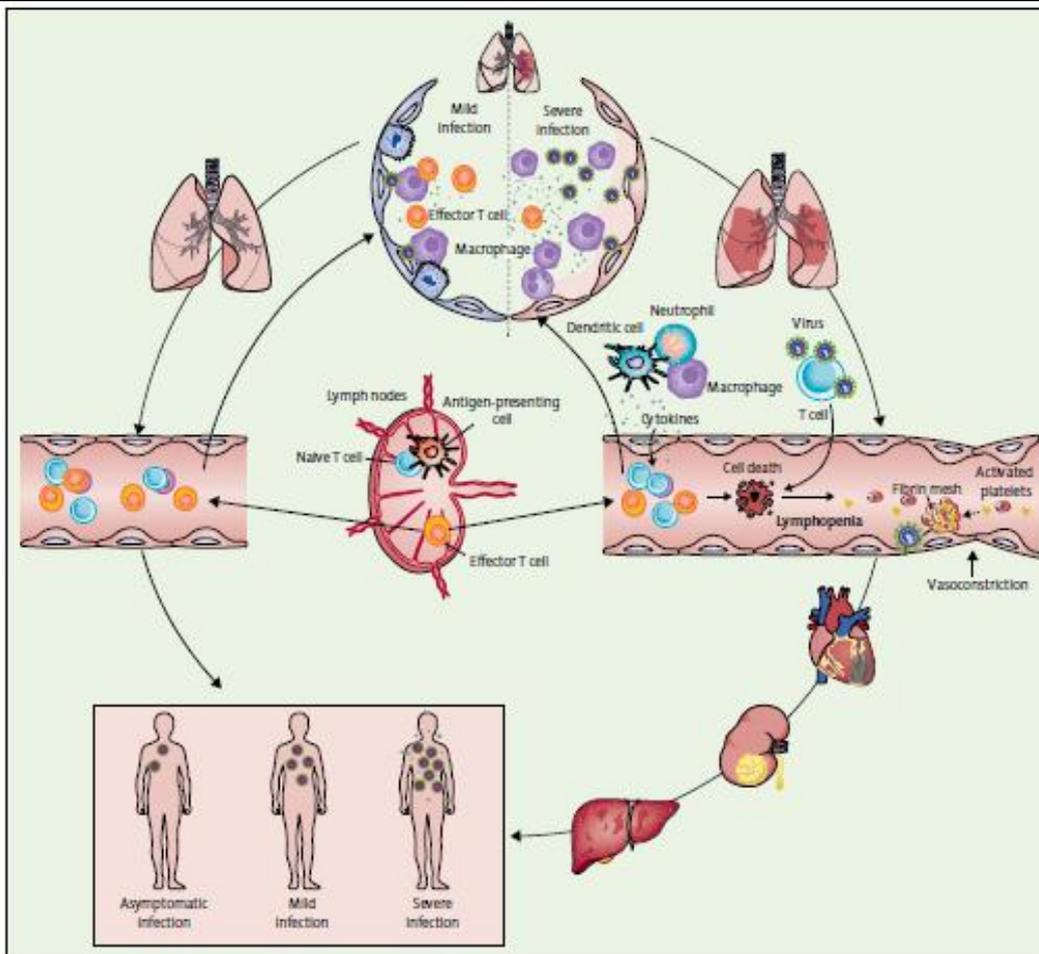


Figure 6: Mechanism of SARS-CoV-2 sepsis occurrence and outcome [80].

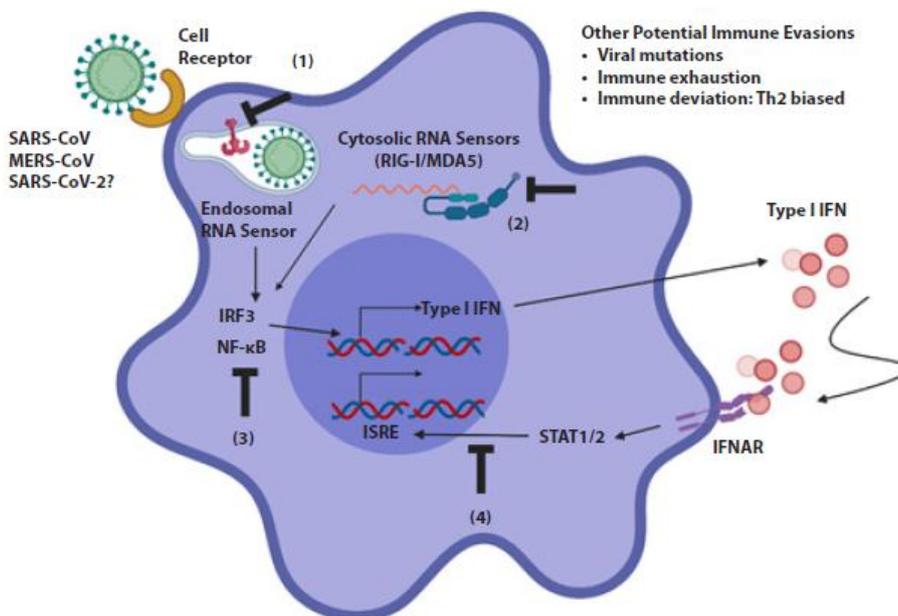


Figure 7: Mechanisms of potential evasion of immune response by human coronaviruses (SARS-CoV, MERS-CoV and SARS-CoV-2). (1 and 2): Blocking of RNA sensing, (3): Inhibition of the signaling pathway of type I IFN, (4): Inference with STAT1/2 activation downstream of IFN/IFNAR [58].

5. Conclusion

COVID-19 is a new disease which has rapidly spread worldwide, from the Chinese province of Wuhan, via human to human contact. The SARS-CoV-2 morphology is similar to that of SARS-CoV and MERS-CoV but it remains some differences which could explain the particularity of the pathogenesis and the severity of the disease. Since 31st December 2019, the total number of cases confirmed and confirmed deaths has increased and grown exponentially (particularly in Europe and America). Despite the fact that the infection can go unnoticed in 80% of cases, this disease scares the world because it can be devastating. This is evidenced by the millions of positive cases detected worldwide, the hundred thousands of deaths registered within 4 months and the economic means already deployed for the management of the disease. This virus, which can be easily eliminated by the body, has an arsenal of mechanisms to bypass the natural immune response. Some of the virus tragedies have been described, and investigations are still ongoing for the development of treatment and vaccines. In the meantime, measures are being taken to prevent and limit contacts.

Conflict of Interest/Competing Interests

The authors declare no conflicts of interest associated with this publication and the outcome of this work has not been influenced by any financial support.

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