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EXTRACT OF CHAPTER 1-
CLINICAL AND IMMUNOPATHOLOGICAL PRESENTATION

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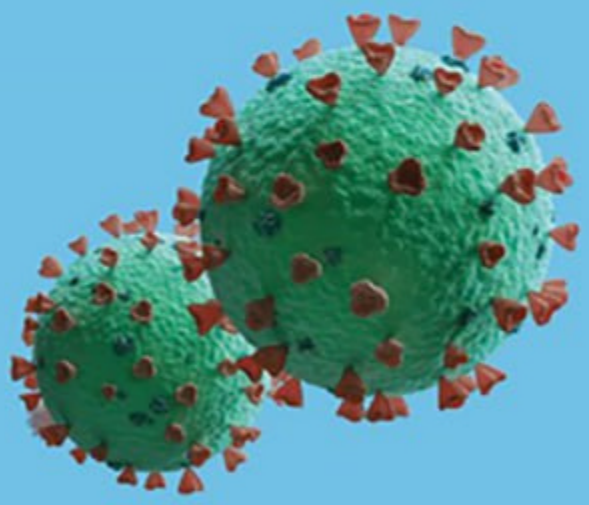

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The 2019/2020 flu season was marked by an abnormal epidemic event that caught much of the world's population organizationally unprepared.
We all know, however, that this event had long been foretold and linked to the 1918 pandemic, infamously known as *"the Spanish flu," which claimed* tens of millions of lives and remained in the collective memory as one of the greatest tragedies caused by a pandemic infectious agent.
In the past 15 years, after the SARS epidemic and the H1N1 pandemic, research centers and pharmaceutical industries have decided to invest heavily in the study of pandemic viruses and for the development of their vaccines,[1] with a crescendo of alert from the scientific world and the media, for the arrival in the very near future, of a Spanish-like pandemic, with devastating global mortality projections (fortunately so far unfulfilled). [2]

After much research work, the pandemic is (almost) here:

On **Dec. 31, 2019**, the Wuhan Municipal Health Commission (China) reported to the World Health Organization a cluster of pneumonia cases of unknown etiology in Wuhan city of China's Hubei province.

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7158580/
Simpson S, Kaufmann MC, Glozman V, Chakrabarti A. Disease X: accelerating the development of medical countermeasures for the next pandemic. Lancet Infect Dis. 2020;20(5):e108-e115. doi:10.1016/S1473-3099(20)30123-7

[2] https://www.centerforhealthsecurity.org/event201/scenario.html

On **January 9, 2020,** the Chinese CDC reported that it had identified a new coronavirus (named by the International Committee on Taxonomy of Viruses SARS-CoV-2: Severe Acute Respiratory Syndrome by Coronavirus 2) as the causative agent of the respiratory disease later named **Covid-19** (COronaVIrus Disease **19**)

On **January 30,** WHO declared the Coronavirus outbreak in China an international public health emergency. WHO subsequently elevated the threat for the coronavirus outbreak to a "**very high**" level on Feb. 28, 2020.
On **March 11, 2020,** WHO Director-General Tedros Adhanom Ghebreyesus called the spread of Covid-19 no longer an epidemic confined to certain geographical areas, but a **pandemic** spread across the globe. [3]

The first two cases of Coronavirus in Italy, a Chinese tourist couple, were confirmed on **Jan. 30** by the L. Spallanzani Institute in Rome, where they were hospitalized in isolation from Jan. 29 and declared cured on Feb. 26. The first case of secondary transmission occurred in Codogno, a town in Lombardy in the province of Lodi, on **Feb. 18, 2020**.

The Italian government declared a **state of emergency** on **Jan. 31**, allocated the first funds and appointed Civil Protection Chief Angelo Borrelli as extraordinary commissioner for the emergency.

A technical-scientific committee to cope with emergency was established by a decree of the Head of the Civil Protection Department on **February 5, 2020,** which was later expanded by an order dated April 18, 2020.

As stipulated in Decree Law 18 of 2020, the Prime Minister by a decree dated **March 18, 2020,** appointed Domenico Arcuri as extraordinary commissioner for the implementation and coordination of measures needed to contain and combat the Covid-19 epidemiological emergency. [4]

[3] https://covid19.who.int/
[4] http://www.salute.gov.it/portale/nuovocoronavirus/homeNuovoCoronavirus.jsp

The clinical presentation

Worldwide there are (June 23, 2020) **473,713 deaths** and about **9 million total cases associated with COVID-19**.
However, it is necessary to emphasize at this time that to date it is not yet possible to have the exact estimate of deaths causally associated with SARS-Cov-2 infection, just as it is not yet known how many asymptomatic (i.e., healthy people who have been found to have the virus) develop the mild to fatal disease, whether asymptomatic people are contagious, and if so, how likely and how they are to become infected.

This lack of basic data clashes with the international case definition according to which "a person with laboratory confirmation of the virus causing COVID-19 is considered a confirmed case regardless of clinical signs and symptoms," in that the laboratory test that allows the presence of the virus to be detected gives no information about the contagiousness of the virus or even whether the person is developing the disease, and therefore also clashes with the containment measures taken (lockdown and quarantine, use of personal protective equipment) which were partly justified only initially when the pathological characteristics of COVID-19 and the dangerousness of the infectious virus were not yet known.

Now, any new containment action must be supported with missing data, otherwise it is no longer justifiable in any way.

The data that are beginning to emerge, however, are that of the Italian sample of people with COVID-19, excluding cured and deceased cases (20,940 cases as of 06/16/2020) about 2% had the condition with a critical clinical picture.
However, this figure is most likely overestimated because we do not know the total number of SARS-Cov2-positive people, and we will have to wait until accurate all-cause mortality data are available to know how many excess deaths were associated with COVID-19 compared with previous influenza seasons.
Another important piece of information is that fatal complications largely affect patients older than 70 years (median age 82 years) and with 2-3 disabling conditions .[5]

[5]h ttps://www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati

This means that **the viral infection alone is not responsible for the severe-fatal complication of the disease,** but rather that the viral phase alone does not cause any major pathology and for much of the population is even asymptomatic.
Instead, urgent consideration should be given in at-risk individuals (the elderly and those with medical conditions) to the secondary phase of symptomatic disease, that is, the complication that manifests itself with a now increasingly well-defined clinical picture, the subject of the chapter presented.

It should be emphasized from the outset that the swab test (RT-PCR) **is not a test to diagnose** the disease, but only detects the presence of the virus; that is, being positive for the virus does not at all mean that the person is sick or will be able to develop the disease, nor that he or she can infect his or her contacts.
Thus, positive subjects are all to be considered cases **with** the virus but not disease, unless an accurate clinical and laboratory diagnosis of COVID- 19 has been made.

The criticality of autopsies

The causes of the deaths **were not confirmed** by the outcome of autopsy and the search for the infectious virus in the tissues for most of the deceased.
To date, there is a lack of biochemical indices that can be used as markers of SARS-Cov-2 infection that correlate with the functions of affected organs, that is, there is a lack of analyses that associate the presence of the virus and viral load in tissues with disease severity.

These studies are critical to understanding how much the virus contributes to the onset of the disease and especially its serious complications. [6]

[6] Sapino A, Facchetti F, Bonoldi E, Gianatti A, Barbareschi M; Italian Society of Pathological Anatomy and Cytology - SIAPEC.
The autopsy debate during the COVID-19 emergency: the Italian experience.
Virchows Arch. 2020;476(6):821-823. doi:10.1007/s00428-020-02828-2
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7190281/

SARS-Cov-2 has been classified as a **class 3 infectious agent** (pathogens that pose a high individual risk and a low collective risk) and requires **biosafety level 3** for conducting autopsies (safety hoods for all procedures, special PPE (personal protective equipment), controlled access, ventilation without recirculation).
Such stringent requirements and the limitations recommended by the Ministry as a precaution to reduce operator infection **delayed the** thorough **diagnosis** of the clinical picture of COVID-19. [7]
Despite these critical operational issues, however, it should be mentioned that COVID-19 has histopathological and clinical course characteristics largely overlapping with those of SARS-Cov and MERS, so it was already known that underlying the complication of infection is an inflammatory response known as **"cytokine storm syndrome**," in which the immune system causes an excessive inflammatory stimulus that attacks the body's structures and leads to multi-organ damage (lungs, intestines, heart, brain, kidneys, liver ect). [8]

As with SARS-Cov, the pathologies for COVID-19 are:

-Injuries of **the respiratory system**: mainly involve the alveoli and mainly consist of desquamative pulmonary alveolitis and bronchitis.
Other lesions include hyaline membrane formation, massive exudation of inflammatory cells in the alveoli, irregular hemorrhage, and focal necrosis

-Damage **to immune organs**: massive necrosis in the spleen and local necrosis in the lymph nodes

-Systemic vasculitis: proliferation, swelling, and apoptosis (programmed cell death) of endothelial cells, with infiltration of monocytes, lymphocytes, and

[7] Pomara C, Li Volti G, Cappello F.
COVID-19 Deaths: Are We Sure It Is Pneumonia? Please, Autopsy, Autopsy, Autopsy!
J Clin Med. 2020;9(5):1259. doi:10.3390/jcm9051259
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287760/

[8] Ye Q, Wang B, Mao J.
The pathogenesis and treatment of the `Cytokine Storm' in COVID-19.
J Infect. 2020;80(6):607-613. doi:10.1016/j.jinf.2020.03.037
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7194613/

plasma cells both around the circumference of small veins and in the vascular walls of the heart, lung, liver, kidney, adrenal gland, and interstitium of striated muscles. Necrosis and fibrinoid thrombosis in small veins.

-reactions of **systemic toxicity**: degeneration and necrosis of parenchyma cells in the lung, liver, kidney, heart, adrenal gland, and nerve cells in the brain.

In addition to respiratory transmission, SARS-CoV can be transmitted through contact with patient excretions and secretions (feces, urine, sweat).
In particular, it has been shown for SARS-CoV that the gastrointestinal tract can be considered a primary target, as the virus present in contaminated food and water, or passed on through direct contact with the secretions and excretions of the sick person, can enter the human body through the epithelial cells lining the surface of the gastrointestinal tract. [9]

A growing number of studies reinforce the hypothesis that the gastrointestinal system plays a preponderant role in the pathogenesis and transmission of SARS-CoV-2 infection, and this is of great relevance both in terms of how to contain and socially distract in the event of an outbreak, and in terms of directing therapy toward enhancing intestinal innate immunity as an effective strategy to overcome the insufficiency of antiviral immunity. [10]

[9] Ding Y, He L, Zhang Q, et al.
Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways.
J Pathol. 2004;203(2):622-630. doi:10.1002/path.1560
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7167761/pdf/PATH-203-622.pdf

[10] Cimolai, Nevio.
Features of enteric disease from human coronaviruses: Implications for COVID-19.
Journal of medical virology, 10.1002/jmv.26066. 28 May. 2020, doi:10.1002/jmv.26066
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7283829/

Immune response to SARS-Cov-2 virus

SARS-Cov-2 is a beta-coronavirus consisting of single-stranded RNA with a lipid envelope containing four structural protein components, the most important of which is the S (Spike) protein.
This protein determines the tropism of the virus and its pathogenicity, as it contains the binding site for the receptor for angiotensin-converting enzyme 2 (ACE2), which facilitates its entry into cells expressing it (particularly gut cells) and is the target of antibodies both produced as a result of natural infection and vaccination. [11]

The following phases can be distinguished during the response to SARS-Cov-2 viral infection:

Virus entry:
initiation of viral replication can cause death of infected cells, vascular leakage, and release of pro-inflammatory mediators with activation of an initial wave of inflammatory mediators.

Cytokines are proteins produced by cells in response to infection and are involved in the formation of an antiviral state as the first line of nonspecific defense and a subsequent specific response against the virus.
This process begins through the recognition of viral molecules by PRRs (pattern recognition receptors - receptors of innate immunity), which are present as transmembrane receptors or in different intracellular compartments.
After binding to the virus, the receptor (in the case of SARS-Cov-2 are TLRs 7 and 9) undergoes a structural change that activates a signaling pathway in the cytoplasm, which in turn promotes the expression of several cytokines.
In the process of inflammation, virus-infected cells produce and secrete proinflammatory cytokines such as IL-1, IL-6, IL-8, TNF and IFN, which are involved in early defense of the body. They can activate cells present at the site of infection and recruit leukocyte cells from the circulating system.

[11]h ttps://www.unisr.it/en/news/2020/3/viaggio-al-centro-del-virus-come-e-fatto-sars-cov-2

Depending on the intensity of this initial inflammatory response, the infection can be Asymptomatic or symptomatic.

Symptomatic phase of the viral infection:

symptoms are similar to flu-like symptoms and last about 7-10 days.
The innate immune system reacts to block virus replication.
If the person has an efficient immune response, the infection resolves without complications.

The clinical presentation of COVID-19 infection is more consistent with subacute rather than acute viral disease.
Compared with H1N1 influenza infections, in which the median incubation time is 2 days and most intensive care unit admissions occur within 24 to 48 h of admission, patients with COVID-19 infection present to the hospital with a median incubation time of 5 to 7 days and are generally admitted to the hospital for another 3 to 4 days before requiring admission to the intensive care unit. [12]

It is important to point out that compared with other respiratory viruses, SARS- CoV-2 infection results in a **lower antiviral response** characterized by low levels of Interferon-I (IFN-I) and IFN-III and **hyperinflammation** due to elevated expression of inflammatory mediators and IL-6.

Immunosuppression may occur at this stage**,** due to both depletion (selective elimination of T lymphocytes that have reacted against the virus) and T-cell depletion, and this may contribute to viral persistence and COVID-19 mortality.
Lymphopenia (absolute or relative decrease in the number of lymphocytes in the circulating blood) is the most consistent laboratory abnormality, and it is important to proceed with

[12] Zhou F, Yu T, Du R, et al.
Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in Lancet. 2020 Mar 28;395(10229):1038]. Lancet. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7270627/

earlier and more urgent intervention in the presence of low T-cell counts, as patients are more vulnerable to secondary infections. [13]

Thus, in a proportion of infected individuals, SARS-CoV2 evades recognition by the immune system through suppression of antiviral mechanisms, promoting complication of the disease.

Complication of the infection:

Onset of pulmonary symptoms. The immune system overreacts to uncontained infection during the first phase with the production of high amounts of inflammatory mediators. If pharmacological intervention is not taken, the complication can rapidly progress to the most severe phase.

Inflammation of the lung is the main cause of life-threatening airway complications in the severe stage, and as could be shown recently, disseminated intravascular coagulation is one of the diseases that leads to death if not treated appropriately in the early stage. [14]

Subsequent to the immunosuppression/hyperinflammation phase, the infected cells undergo cell death and release virus particles along with intracellular components that again trigger the innate inflammatory mechanisms through their recognition by the PRRs present in/on the innate immune cells, resulting in the expression of pro-inflammatory cytokines (including IL-1β, IL-6, TNF-α, etc.), and the activation of adaptive immune cells that are thus involved in host defense.

[13] Front. Immunol. 11:827. (2020) doi: 10.3389/fimmu.2020.00827.
Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19).
Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, Chen L, Li M, Liu Y, Wang G, Yuan Z, Feng Z, Zhang Y, Wu Y and Chen Y
https://www.frontiersin.org/articles/10.3389/fimmu.2020.00827/full

[14] J Clin Virol. 2020 Apr 9;127:104362. doi: 10.1016/j.jcv.2020.104362.
Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past.
Giannis D1, Ziogas IA2, Gianni P3.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7195278/pdf/main.pdf

*When adaptive immune cells (T lymphocytes play a central role in this phase) become activated, they trigger a **"second wave"** of **inflammation** (cytokine storm syndrome and its subtypes), which can be seen in COVID-19 patients who have rapid deterioration after 7-10 days of infection.*

Very severe/fatal phase:

Sudden and rapid clinical deterioration often manifests as an unexpected exacerbation of symptoms (fever, dyspnea) and is correlated with increased levels of acute phase markers (ESR, CRP, ferritin), coagulopathy (elevated titers of D- dimers, disseminated intravascular coagulation) and cell lysis (CK, LDH).

In the most severe patients, clinical and laboratory parameters correlate with increased levels of proinflammatory cytokines (IL-1β, IL-1Ra, IL-6, TNF-α, and sIL2-Rα), suggestive of a cytokine storm. [15]

These manifestations are related to the attack of the body's structures by
Of the immune system.

Cytokine storm can occur due to the combination of a defective, or delayed, IFN I-mediated first line of defense, followed by the production of elevated and persistent levels of cytokines (hypercytokinemia) IL-6, IL-1β, and TNF-α and a dysfunctional T-cell response (usually cytotoxicity).

This results in impaired elimination of dead or infected cells, increased viral replication and spread that further activates macrophages, and culminates in the massive release of multiple cytokines and multiorgan damage.

*During the complication, the person may go through **bacterial co-infections** (especially hospital antibiotic-resistant) that further aggravate the clinical picture.*

Post-infectious phase:

it will be important to monitor patients who have overcome complications, as long-term autoimmune reactions are possible.

[15] Clin Immunol. 2020 Apr 27;215:108448. doi: 10.1016/j.clim.2020.108448.
COVID-19: Immunology and treatment options.
Felsenstein S1, Herbert JA2, McNamara PS2, Hedrich CM3.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7185015/pdf/main.pdf

Immune evasion strategies of SARS-Cov2

As seen above, in **epithelial cells expressing the ACE2 receptor**, suppression of early pro-inflammatory responses mediated by type I interferons (IFNs) and the cytokines IL-1, IL-6, and TNF-α hinders virus containment.
The induction of endothelial and vascular cell damage and cell death following viral replication result in strong and poorly controlled inflammatory responses, leading to tissue damage and systemic inflammation, both of which contribute to the complication of the disease.

In **tissue monocytes/macrophages,** on the other hand, a process known as antibody-dependent enhancement (ADE) occurs in which immune complexes consisting of low-specific antibodies against SARS-Cov-2 and viral particles can be engulfed by macrophages causing their infection.
In infected macrophages, the virus instead of being processed for presentation to other cells of the immune system, on the one hand inhibits type I IFN signaling and on the other hand allows pro-inflammatory expression of IL-1, IL-6, and TNF-α, contributing to the cytokine storm syndrome and fatal potentiation of the disease.
This mechanism occurs when non-neutralizing IgG antibodies are present at the time of infection and in sub-optimal amounts that are formed as a result of previous seasonal coronavirus infections, or following influenza vaccination. [16]

In these cases, the development of acute respiratory disease coincides with antiviral IgG seroconversion.

COVID-19-related inflammatory responses could also be induced by dysregulation of the complement system, a critical component of host innate immunity.
A subgroup of patients with COVID-19 is known to develop **vasculitic lesions, blood vessel occlusion and infarcts**.

[16] Cegolon L, Pichierri J, Mastrangelo G, et al.
Hypothesis to explain the severe form of COVID-19 in Northern Italy.
BMJ Glob Health. 2020;5(6):e002564. doi:10.1136/bmjgh-2020-002564
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7295427/

Histopathologic reports from tissue sections suggest features associated with immune complex-mediated vasculitis, including monocyte and lymphocyte infiltration in and around blood vessels, wall thickening, and focal hemorrhage. [17]

From the perspective of the mechanism of damage induction, **severe/fatal complications associated with SARS-Cov-2 infection can be considered a consequence of ADE**.
The ADE explains why the elderly are at greater risk than healthy children and adults, as they possess a greater amount of nonneutralizing antibodies from coronavirus infections or older vaccinations, and have an inefficient immune system to fight infections.

Also susceptible to the enhancement of the disease are pregnant women and the Infants under one year of age, in case of reinfection.
Hyperimmune serum and IVIGs are effective in treating COVID-19 patients because the transfused antibodies are able to block viral immune complexes from entering immune system cells. [18]

ADE is a major risk factor for vaccination against COVID-19 and influenza because of the high variability of viruses that may predispose to the production of nonneutralizing antibodies.

Immune response, age, and gender difference

Pediatric age

A transient hypogammaglobulinemia that begins at the age of 3-6 months and usually lasts 6-18 months is present in the newborn, caused by a transient deficit in the production of

[17] Xu Z, Shi L, Wang Y, et al.
Pathological findings of COVID-19 associated with acute respiratory distress syndrome [published correction appears in Lancet Respir Med. 2020 Feb 25]. Lancet Respir Med. 2020;8(4):420-422. doi:10.1016/S2213- 2600(20)30076-X
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164771/pdf/main.pdf
[18] Rojas M, et al.
Convalescent plasma in Covid-19: Possible mechanisms of action
Autoimmun Rev. 2020;102554. doi:10.1016/j.autrev.2020.102554
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7198427/

antibodies, due to a physiological delay in the onset of antibody synthesis and the decline in maternal antibodies.
The time window in which transient hypogammaglobulinemia occurs is also called the "window of vulnerability" because the infant could be exposed to infectious diseases and especially the risk of complications without adequate support from the immune system.

During this period, any attack on the immune system by toxic substances (environmental contaminants, in food, drugs, vaccines, ect) and infectious agents can lead to an increased risk of later development of chronic infectious diseases, cancer, allergy, autoimmunity, and diseases of the neurological, reproductive, and endocrine systems. [19]

Maternal antibodies are very effective in protecting infants and children from most infectious diseases during the first 6-12 months of life, however, inhibition of vaccine antibody production is known to occur in infants who still have maternal antibodies due to a blockage of B-cell activation.
[20]

In addition, maternal nonneutralizing antibodies of natural origin (i.e., from infections contracted prior to pregnancy by the mother), or of vaccine origin if the mother was vaccinated during pregnancy, have been implicated in the enhancement of the disease that occurs in children younger than 1 year old born to immune mothers exposed to the infection. [21]

[19] J Toxicol Environ Health B Crit Rev. 2008;11(8):660-680. doi:10.1080/10937400802370923
Potential for early-life immune insult including developmental immunotoxicity in autism and autism spectrum disorders: focus on critical windows of immune vulnerability.
Dietert RR, Dietert JM.
[20] Niewiesk S.
Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies.
Front Immunol. 2014;5:446. doi:10.3389/fimmu.2014.00446
https://academic.oup.com/tropej/article/49/5/302/1690003

[21] Virology. 2016 Apr;491:79-88. doi: 10.1016/j.virol.2016.01.015.
Heterologous challenge in the presence of maternally-derived antibodies results in vaccine-associated enhanced respiratory disease in weaned piglets.
Rajao DS, Sandbulte MR, Gauger PC, Kitikoon P, Platt R, Roth JA, Perez DR, Loving CL, Vincent AL.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4825855/

Mass vaccinations have greatly reduced the transmission of protective antibodies and created a much wider window of vulnerability in infants.
This unnatural, man-made phenomenon may in fact be considered a **very serious adverse vaccine reaction**, the consequences of which in industrialized countries may be mitigated by the fact that infectious diseases are a negligible risk factor compared to other diseases, but may have a major impact in developing countries where, on the other hand, infant mortality from infectious diseases is still very high.

Regarding **pregnant women**, based on the knowledge that they exhibit a pro-inflammatory state in their first and third trimesters, it should be kept in mind that the cytokine storm induced by infections (such as COVID-19[22]) and vaccinations[23] can further potentiate the inflammatory state with very serious consequences in both mother and fetus[24] , and later in the newborn.

Pregnant women may show remissions of autoimmune diseases, but become more susceptible to serious complications of influenza and other infections,[25] and for

[22] Liu H, Wang LL, Zhao SJ, Kwak-Kim J, Mor G, Liao AH.
Why are pregnant women susceptible to COVID-19? An immunological viewpoint.
J Reprod Immunol. 2020;139:103122. doi:10.1016/j.jri.2020.103122
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7156163/

[23] Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F.
The how's and what's of vaccine reactogenicity.
NPJ Vaccines. 2019;4:39. doi:10.1038/s41541-019-0132-6
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6760227/

[24] Garcia-Flores V, et al.
Inflammation-Induced Adverse Pregnancy and Neonatal Outcomes Can Be Improved by the Immunomodulatory Peptide Exendin-4.
Front Immunol. 2018;9:1291. doi:10.3389/fimmu.2018.01291
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6015905/

[25] Influenza Other Respir. Viruses 2013. 7, 1033-1039. 10.1111/irv.12055
Influenza in pregnancy.
Memoli MJ, Harvey H, Morens DM, Taubenberger JK
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3582707/

the same reason, the serological response to vaccines (e.g., inactivated influenza vaccine
[26]) is particularly small.
As for the risks of vaccinations, they are related to disease enhancement in the case of postvaccinal infection and adverse reactions to the vaccine-induced cytokine storm inflammatory response.

Advanced age

As we age, the immune system undergoes profound remodeling and decline, greatly impacting health and survival. [27]
This immune senescence predisposes the elderly to a higher risk of acute viral and bacterial infections. Mortality rates of these infections are three times higher in elderly patients than in younger adults.

During a normal flu season, about 90% of excess deaths occur in people older than 65 years. In addition, poor immune responses explain the reduced effectiveness of vaccines. [28]
The most critical aging-related change in the innate immune system is the increase in the pro-inflammatory cytokines IL-1ß, IL-6 (the geriatric cytokine), IL- 18 and TNFα, which leads to the onset of a low-grade inflammatory state that likely contributes to atherosclerosis, dementia and cancer. [29]

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[26] PLoS One. 2013;8(4):e56700. doi:10.1371/journal.pone.0056700
Altered response to A(H1N1)pnd09 vaccination in pregnant women: a single blinded randomized controlled trial.
Bischoff AL et al.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3630160/

[27] Transpl Int. 2009;22(11):1041-1050. doi:10.1111/j.1432-2277.2009.00927.x.
The aging of the immune system
Weiskopf D, Weinberger B, Grubeck-Loebenstein B.
https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1432-2277.2009.00927.x

[28] Sci Transl Med. 2013;5(171):171ra19. doi:10.1126/scitranslmed.3004794 [published correction appears in Sci Transl Med. 2013 Jul 10;5(193):193er8].
Lineage structure of the human antibody repertoire in response to influenza vaccination
Jiang N, He J, Weinstein JA, et al.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3699344/

[29] Mech Ageing Dev. 2007;128(1):92-105. doi:10.1016/j.mad.2006.11.016
Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans.

"The phenotype of aging," including immunosenescence is the result of an imbalance between inflammatory and anti-inflammatory mechanisms resulting in a state referred to as "inflamm-aging."
Inflamm-aging is due to chronic antigenic stimulation that occurs throughout life and oxidative stress involving the production of oxygen free radicals and toxic products. Harmful agents are produced by the body as a consequence of normal (unavoidable) metabolic processes (e.g., reactive oxygen species, ROS, from oxidative metabolism) or resulting from exposure to a variety of physical factors (e.g., UV rays from sun exposure) or biological agents (viruses, bacteria, parasites).

The elderly are less likely to benefit from vaccinations as preventive measures against infectious diseases because of the immune system's inability to activate an effective defense.
Therefore, aging is believed to reduce vaccine efficacy as a result of an age-associated decline in vaccination-induced immunogenicity, and to predispose more to antibody-mediated disease enhancement from previous infections or vaccinations.

The older segment of the population is more susceptible to complications from COVID-19 also due to a higher frequency of gut dysbiosis due to aging and/or continued use of microbiota-modifying drugs and improper diet[30] , particularly in the community-dwelling long-term elderly.

Gender difference
Data to date show that the entire population with SARS-CoV-2 is 58% male subjects. Higher lethality is in favor of male subjects in all age groups.

Franceschi C, et al.
https://pubmed.ncbi.nlm.nih.gov/17116321/

[30] Nagpal R, et al.
Gut microbiome and aging: Physiological and mechanistic insights.
Nutr Healthy Aging. 2018;4(4):267-285. doi:10.3233/NHA-170030
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6004897/

A higher male risk predisposition occurs when weak immune responses underlie significant tissue damage by viral infection, while a higher female risk predisposition occurs when strong immune responses promote tissue damage.

It has been seen that in the case of coronavirus infections, estrogens have a protective effect, as they increase the initial production of type I interferons with antiviral activity necessary to block virus replication, and stimulate repair activity, while androgens have immunosuppressive effects.

It follows that in men the poor immune response results in greater severe tissue damage.

Immune regulatory genes encoded by the X chromosome in the female gender cause lower viral load levels and less inflammation than in men, while CD4 T cells^{+} are higher with a better immune response.
In addition, women generally produce higher levels of antibodies that remain longer in the circulation. In women, inflammatory IL-6 production after viral infection is lower than in men and is often correlated with better longevity.

Sex differences in the gut microbiome are partially driven by sex hormones, which in turn contribute to sex differences in immunity and susceptibility to a multitude of infections and chronic diseases. [31]
The **microgenderome** defines the interplay between microbiota, sex hormones, and the immune system and involves bidirectional interactions between microbiota, hormones, immunity, and disease susceptibility. [32]

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The autoimmune/inflammatory syndrome

An immune system can only be considered effective when it can identify and destroy pathogen-infected cells while distinguishing those cells from healthy ones.
When immune tolerance is broken, the immune system fails to discriminate between self-antigens and foreign antigens, and the manifestation of autoimmune disease, i.e., unwanted destruction of healthy cells, occurs.

The presence of autoantibodies in patients who have developed Covid-19 caused by sequence similarity (molecular mimicry) between autoantigens and SARS-CoV-2 proteins may suggest that an autoimmune/inflammatory mechanism may be an additional event determining the severity of the disease. [33]

"In light of the information discussed above on the cross-reactivity of SARS-CoV-2 proteins with human tissues and the possibility of inducing autoimmunity, either exacerbating existing conditions of poor health or leading to unforeseen consequences, it would be very prudent to do more in-depth research on the ability of SARS-CoV-2 antigens to induce autoimmune reactions.

"The promotion and implementation of such an aggressive 'immune passport' program worldwide in the absence of thorough and meticulous safety studies may come at a monumental cost to humanity in the form of another epidemic, this time of a rising tide of autoimmune diseases and the increased years of suffering that will accompany them." (Vojdani A, Kharrazianb D) [34]

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