Accademia Nazionale dei Lincei

Commissione Salute

COVID-19: An executive report

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in alphabetical order

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1. Introduction

Italy and the entire world are currently facing the dramatic challenge of the SARS-Cov-2 virus. In the face of this unexpected pandemic, which is putting many aspects of human civilization in great difficulty, the Commissione Salute of the Accademia Nazionale dei Lincei felt that it was its social responsibility to provide the society at large with an Executive Summary of the current knowledge on the origin, mechanisms and and treatment available to tackle this new COVID-19 virus.

This Report does not intend to provide a comprehensive the state-of-the-art review, but rather a snapshot of this rapid evolving situation, a field undergoing rapid evolution, with a daily flood of scientific publications and non-peer reviewed reports. The preparation of a COVID-9 report in this context is therefore a risky undertaking and the extensors of this document are well aware of their limits.

With the limits of the metaphor, we are experiencing *wartime medicine* and *wartime scientific research*. We are too often to respond to plight of patients with empirical approaches. Despite these conditions, a rigorous assessment of the data remains and increasingly becomes an absolute obligation. Finding a balance between emergency and methodological rigour represents a major challenge [1].
Hopefully, with the above mentioned cautionary remarks, this report will provide for the moment the tools to better understand and respond to the unprecedented challenge we are facing.

2. SARS-CoV-2

The virus. Coronavirus disease 2019 (COVID-19) is caused by the infection of the SARS-CoV-2 virus, a coronavirus. Coronaviruses are a large family of viruses that cause illness ranging from the winter common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV), Severe Acute Respiratory Syndrome (SARS) and COVID-19. The SARS-CoV-2 capsid is made up by four structural proteins known as Spike, Envelope, Membrane and Nucleocapsid. The Spike protein that forms a sort of crown on the surface of the viral particles acts as an *anchor* allowing virus attachment, fusion and entry inside the host cells through the binding of Angiotensin-Converting Enzyme 2 (ACE2) receptors [2].

Virus infection. COVID-19 starts whit the arrival of SARS-CoV-2 virions on respiratory mucosal surfaces. Epithelial cells that line the mucous membranes and the mucus secreted by goblet cells form a first effective barrier. When the virus manages to overcome it, a rapid release of danger signals activates the reaction of innate immunity. We do not know yet if and how many SARS-CoV-2 viruses are eliminated by this initial inflammatory reaction, however it is reasonable to assume that the effectiveness of the immune reaction mechanism may play a crucial role in determining whether the infection will be benign or will have major consequences. Once the virus has entered the target cell, viral RNA is immediately translated by the host cell that die by releasing millions of new viruses.

Virus spreading and containment. Coronaviruses are zoonotic, meaning they are transmitted between animals and humans. In the past twenty years a coronavirus has made the so-called "inter-species jumps" three times, passing from its natural host to humans: in 2003 in China the SARS virus; in 2015 the MERS virus in the Middle East; in late 2019 in Wuhan, again in China, the SARS-CoV-2. It is likely that, as already happened for the other coronaviruses, even in the case of SARS-CoV-2 the original host was the bat. There are more than 1,200 worldwide, which account for 20% of the mammalian species: a huge virus reservoir. The passage to humans is believed to require an intermediate host: in the case of SARS it was the civet, for MERS the camel, for the SARS-CoV-2 unknown, but probably the pangolin. Pangolins are an endangered species commercialized for its keratin scales, which are an important ingredient in traditional Chinese medicine while the meat is considered a delicacy in China and Viet Nam [3].

In the fall of 2019 fall, a pneumonia of unknown etiology was diagnosed in individuals connected with the seafood and live animals in the city of Wuhan, in the province of Hubei, China. The new variant beta-coronavirus (SARS-CoV-2) was then isolated from the bronchoalveolar lavage fluid from these patients and the virus genome was quickly sequenced and made public by Chinese scientist [4]. SARS-CoV-2 outbreak was declared a Public Health Emergency of International Concern on 30 January 2020 [5].

On 20 February, a patient in his late thirties with no risk factors for SARS-CoV-2 was found positive to the virus while already admitted in an Intensive Care Unit in Codogno, Lodi, Italy. The following day, 36 other cases with no link to the first patient were found in Codogno. The identification of this second cluster of infected persons marked the beginning of the largest SARS-CoV-2 outbreak outside China. In the following weeks clusters emerged in most Western Countries.

On March 11 2020, the World Health Organization (WHO) upgraded the state of SARS-CoV-2 infection from epidemic to pandemic. To try to limit COVID-19 spread, first China, then South Korea, Italy and, progressively many countries around the world have imposed lockdowns and closed borders [5, 6]. The largest quarantine in the history of mankind is taking place.

Currently Europe appears to be the epicenter of this pandemic: Case counts and deaths are soaring in Italy, Spain, France, and Germany. The estimation of the prevalence of COVID-19 is made difficult due to the rapid spread of the infection and the different methods by which countries detect the disease. However, despite these uncertainties, it is undeniable that Italy has been affected by COVID-19 with particular intensity.

3. Strategies to control COVID-19 spread.

On 23 January 2020, with some delay since the initial COVID19 spread, the Chinese government isolated and locked down tens millions people of Hubei province. People were banned from working, going to school and all forms of aggregation, while shops were closed with the exception of those selling food or medicine. As a result of the lockdown, new cases started to slow down. On 19 March 2020, no new cases were reported in Hubei province [5].

Following Chinese experience, lockdowns of various degree of population mobility are currently being carried out in in several Asian and European countries, in United Kingdom and in the United States. The purpose of lockdowns is to reduce the R_t number, i.e. the number of healthy people contaminated by each SARS-CoV-2 infected person. The Hubei experience shows that it is possible to block the spread of the virus in a relatively short period of time[7]. Effective reduction of infection is crucial to enable more effective patient care and a reorganization of the healthcare system, which has been put in great difficulty by an unexpected high number of patients. As we will illustrate in this report, in a significant proportion of cases SARS-CoV-2 infection can give rise to a serious acute respiratory syndrome, requiring hospitalization in Intensive Care Units (ICU). In most countries around the world ICU beds are a limited resource.

In Italy there were roughly 5,000 ICU beds available before the outbreak. Recent data shows that 12% of SARS-CoV-2 positive cases require ICU admission. In practice, if 42,000 people are infected at the same time the total ICU capacity of the country would be saturated. While the availability of beds in ICU varies from country to country, no healthcare system in the world could withstand an unlimited increase in patients in need of intensive care. For this reason, faced with the outbreak of COVID-19, it is not possible to think only of increasing the number of beds in ICU, but becomes absolutely necessary to put in place measures to contain the spread of the infection, so as to avoid overloading the healthcare system.

However, what can be expected to happen when the lockdowns are lifted? The rebound of new cases that may arise when lockdowns are relaxed may impose the reintroduction of subsequent and perhaps periodical lockdowns. The political and economic cost of a prolonged and repeated lockdowns is very high and opens complex social problems [7,8].

The prospect of less drastic measures to mitigate the probability of person to person virus spread has also been evaluated in UK and other countries [7,8]. In this context, the high-tech approach adopted by South Korea to limits the spread of infection is quite interesting since a particularly well-organized South Korean testing program to isolate infected people and trace and quarantine those who came in contact with them, has prevented the lockdown of entire cities or the whole country. While new clusters of infection may emerge, so far, the South Korean lesson is that high tech preparedness may play a central role in the control of COVID-19 spread [9].

In summary, as of today, three scenarios can be envisioned for the containment of COVID-19: complete lockdown (suppression), mitigation or a combination the two scenarios. Complete lockdown is the current approach taking place in Italy and elsewhere. Mitigation consists of milder containment interventions, such as those initially implemented in UK and other countries. These interventions reflect different stages of the epidemic spread.

Following the resolution of the current dramatic emergency situation in northern Italy, a stop-and-go suppression and mitigation may be required to address societal needs and monitor the possible successive waves of the epidemic.

4. Immunity

Innate immunity. Innate immunity represents a first line of resistance against microbes and evidence suggests that it can block over 90% of encounters with pathogens. Information on innate immunity in COVID-19 is scanty. After infection, the number of lymphocytes decreases (lymphopenia) while the number of neutrophils increases. Inflammatory cytokines (e.g. IL-6, TNF, chemokines) generally increase. SARS-CoV and MERS-CoV infect macrophages and lymphocytes, but this may not be the case with SARS-CoV-2. These viruses suppress the production of interferons, a group of anti-viral cytokines of crucial importance [11]. These findings, as shown below, have clinical implications.

Adaptive immunity. As far as adaptive immunity is concerned, although results are scanty and mainly based on SARS and MERS [12], evidence suggests that, as generally is the case for antiviral resistance, a T helper 1 orchestrated protective immunity [13]. Antibody responses were identified in SARS, MERS and COVID-19 patients and there is evidence for antibody-mediated neutralization of the virus[12].

Coronaviruses are professionals at suppressing various mechanisms in immune response[14]. They do so by suppressing interferon production in macrophages and by downregulating antigen presentation via Class I and Class II HLA glycoproteins.
A key issue with policy and public health implications, is the occurrence and duration of immunological memory. Evidence suggests that coronavirus infections, including SARS-CoV-2, elicits memory. Ralph Baric recently stated that immune response and resistance should last at least 6-12 months [15]. The urgent need for more data on COVID-19 is quite evident.

5. Clinical aspects

SARS-CoV-2 infection presents with a variety of symptoms: It can be completely asymptomatic or present severe symptoms. In Italy, while the country has the highest daily incidence of new cases, about 67% of patients show mild symptoms and about 30% have symptoms that require hospital admission.

The most common symptoms are fever and cough. A small percentage of cases reports gastrointestinal symptoms before the onset of the respiratory symptoms [16].
The first reports from China showed that only 5% of infected patients required ICU admission, while less than 3% needed mechanical ventilation[15]. Recent data from Lombardy region in Italy showed that the rate of ICU admissions is much higher, in the range of 12% of all positive cases, or 16% of all hospital cases[17].

Case fatality rate (CFR) varies in countries across the world. In Italy, the overall CFR is 8.5%. CFR varies significantly among age groups. With almost no reported death in people aged 29 or younger, CFR goes from 0.3 % to 24.1% in the over 90 years old. Patients with comorbidities are more likely to be severely affected and die [17].

6. Diagnostics tests: Virus and Antibodies

SWABS. The milestone in diagnostic tests is represented by by Polymerase Chain Reaction (PCR) based assays that detect viral RNA in nasal swabs. The tests currently used must be carried out by specialized personnel and take approximately 4 hours. The tests have serious limitations, e.g. in advanced patients, nasal swabs may be negative while bronchoalveolar lavages are positive and the frequency of false negatives in asymptomatic patients may be higer[18]. In addition, at present time swabs which inactivate the virus are no longer available, at least in the Lombardy region.

A one hour PCR-based assay (DiaSorin, Italy) has just been approved by the USA Food and Drug Administration (FDA) and this may improve the diagnostic output [19].
In the US "home tests" have been approved by FDA: Kits are shipped to homes along with detailed instructions. The swab is inserted into a protective vial and subsequently mailed to one of the Everlywell diagnostic laboratories for PCR analysis [20].

Antibodies. The search for antibodies is an invaluable source for both individual diagnosis of an infectious disease and epidemiological studies. At present, commercially available antibody assays have not been validated and compared with the PCR assays. However, a recent non-peer reviewed report from academic institutions provides encouraging results [21].

The development of validated and reliable tests that detect SARS-CoV-2 antibodies will be of paramount importance for diagnosis, epidemiology, assessment of immunological memory and provision of information to individuals returning to work following the suppression approaches described above.

7. Therapy

General introduction. A wide range of therapeutic approaches have been tested under uncontrolled conditions. These range from anti-retroviral and anti-viral agents, to Chinese traditional medicine preparations. A detailed discussion of all compounds and strategies goes beyond the purpose of this executive report. As stated in the Introduction, while we understand the challenge posed by emergency medicine, we concur with the New England Journal of Medicine ("…rapidly initiated high quality clinical trials are possible in epidemic situations, even in the trying circumstances that prevailed in Wuhan") and Journal of American Medical Association editorials calling for high quality rigorous clinical trials [1, 22].
Since several drugs are claimed to be effective without high quality clinical trials, recently the WHO announced the launch of a large global trial called SOLIDARITY, which is designed to determine whether any of the drugs to be administered do COVID-19 patients are really effective. This is an unprecedented effort to collect robust scientific data including many thousands of patients in dozens of countries [23].

The pillar of treatment: respiratory support and management of organ failure. Currently, there is no specific treatment for SARS-CoV-2. Supportive therapy is what can make time for patients to regain their basic function. In the context of Severe Acute Respiratory Failure, supportive therapy could

mean invasive mechanical ventilation and or non-invasive support (in the form of high flow oxygen, continuous positive airway pressure or non-invasive ventilation).

Patients that require invasive mechanical ventilation usually are very sick and in need of intense care resources, both in terms of nursing and medical time and technology. Many of these patients develop a form of acute respiratory failure called ARDS (Acute Respiratory Distress Syndrome). One of the cornerstones of ARDS treatment is the so-called "protective lung strategy". This method of treatment consists of using the lowest possible ventilation pressures and volume required to oxygenate the blood without causing harm to the lungs with the ventilator itself.
In some cases, prone positioning is used as a therapy to maximise the gravity effect of blood flow towards the better-aerated parts of the lungs.

While protecting the lungs and allowing them time to heal, particular attention should be paid to supporting the other organs too. Vasopressors may be required to maintain adequate perfusion pressure; fluids have to be carefully titrated to avoid both hypovolemia and fluid overload. In some cases, acute kidney injury develops, and renal replacement therapy may be necessary.
In the most severe cases of ARDS, extracorporeal membrane oxygenation (ECMO) can be used to temporarily substitute the gas exchange function of the diseased lungs. This technique is very invasive, resource intense and particularly challenging to perform during a pandemic in which the volume of critically ill patients to treat is particularly high.

While there is currently no convincing evidence as to the efficacy of any other drug for COVID-19 patients with acute respiratory failure, several clinical protocols based on antivirals, chloroquine, anti-inflammatory drugs, to name a few, have been developed. The rationale and clinical evidence of some of these treatment is reported in this document.

<u>Selected antivirals</u>

- Lopinavir/ritonavir. This is a combination of agents used in the treatment of HIV and has been widely used. However, a recent randomized study in advanced patients showed no benefit [24]. Further carefully controlled adequately powered studies are needed to assess the potential of this combination in early disease.
- Remdesivir. This agent has potent antiviral activity in vitro and in animal model of MERS. Its potential in COVID-19 is undergoing clinical evaluation[25].
- Chloroquine and hydroxychloroquine. Chloroquine and hydroxy- derivative have anti-viral activity as well as the capacity to suppress inflammation (see below). Its potential for the treatment of COVID-19 needs to be investigated.
- Interferons. The rational for considering interferon therapy, systemic or via lung aerosol, is mentioned under 3. It has been used in Ebola and SARS[26, 27]. It will be important to assess its potential in COVID-19 in subsets of patients based on cytokine and immune cell profiles.

The four therapies that seem to be the most promising and will be included in the above mentioned WHO SOLIDARITY global trial are remdesivir; cloroquine and hydroxychloroquine; lopinavir and the same combination plus interferon-beta [23].

Inhibition of excessive inflammation. There is a strong rationale that an uncontrolled immune response and excessive inflammation may play a role in amplifying tissue damage in SARS and possibly in COVID-19. The high levels of inflammatory cytokines (e.g. IL-6, TNF, IL-1, chemokines) and the prognostic significance of IL-6 levels provide a rational for these strategies [28]. These include monoclonal antibodies anti-IL-6 or anti-IL-16R (e.g. tocilizumab), anti-IL-1 (e.g. canakinumab); a recombinant IL-1 receptor antagonist (anakinra); complement targeting strategies; inhibitors of cytokine signaling pathways (JAK1,2) (e.g. baricitinib).

It worth mentioning that chloroquine, proposed as antiviral drug, has immunosuppressive and anti-inflammatory properties. Incidentally, the speculation that usage of chloroquine as an antimalarial drug underlies the apparent resistance of Africa to COVID-19 does not take into account the fact that this agent has long and largely been abandoned in malaria.

Tocilizumab, an anti-IL-6 receptor humanized monoclonal antibody is, to the best of our knowledge, the one agent in this field for which there is more available data. The rational stems from its limited use in rheumatoid arthritis and, most important, in controlling the cytokine release syndrome in CAR-T cell therapy. To the best of our knowledge, Professor Haiming Wei in Hefei conducted the first experimental administration of tocilizumab in a limited series of patients followed by widespread use of this drug following the recommendations included in guidelines issued on 13/02/2020 in China[29]. It should be noted that studies are now ongoing in China and elsewhere, including Italy under the auspices of Agenzia Italiana del Farmaco (AIFA).

Therapeutic Antibodies. Since the early days of immunology, plasma from recovered patients has been used as a source of antibodies. Plasma from recovered patients has been used in China and elsewhere, including Italy, as a source of antibodies, as already done for Ebola although the therapeutic efficacy of this approach remains to be established.

Several academic and industrial laboratories are at various stages of development of human monoclonal antibodies against components of SARS-CoV-2 virions, such as the Spike protein [30, 31]. It should be noted that both with SARS and with other viral infections, under particular conditions, the antibodies can enhance viral entry (Antibody-Dependent Enhancement, ADE) [32] and tissue damage [33]. Therefore, as emphasized above, rigorous clinical evaluation will be mandatory also for antibody-mediated therapies.

8. Anti SARS-CoV-2 vaccines

Rationale. The hope and hype that the media and ordinary people are placing on having as soon as possible a vaccine that protects against COVID-19 is the result of the great triumphs that vaccines have had and are having in the control of infectious diseases[12].

Caveats Vaccines do not always protect well. We still have a long series of serious infectious diseases to which vaccines are only partially effective and we have a series of sensational defeats. Indeed, each disease is an immunological problem in itself: even today, with all the data in over

possessions, it is difficult to predict what vaccine can be truly effective. This difficulty is accentuated in the case of COVID-19, a young disease on which ongoing studies in laboratories worldwide are bringing new data. In addition, RNA viruses generally have a high mutation rate. This is one reason why it is difficult to make effective vaccines to prevent diseases caused by RNA viruses.

Preliminary issues.

- As far as a COVID-19 vaccine is concerned, it is essential to know if the patients who have recovered from COVID-19 are protected against a second infection.
- If these patients develop immunity, for how long? [34]
- It is fundamental to establish whether the immune protection against COVID-19 mainly rests on the anti-virus antibodies or on the reaction of the killer T cells.

In many cases, recovery from a viral disease depends on the combined action of antibodies in the biological fluids that neutralize viral particles and the killer activity of lymphocytes that track down and kill the body's cells infected with the virus, which are turning into factories of millions of new viral particles. However, there are viral diseases whose healing depends mainly, if not exclusively, on the antibody response and others where the destructive action of the killer lymphocytes is fundamental. What is the case with COVID-19?

Role of CEPI. On January 2017, during the World Economy Forum in Davos, Coalition for Epidemic Preparedness Innovations (CEPI) was established, an international organization aimed at promoting the development and storage of vaccines against those microbes that could cause new frightening epidemics: a substantial funding was provided by the Bill & Melinda Gates Foundation, the Welcome Trust and the governments of numerous countries. The major multinational pharmaceutical companies have announced their collaboration. And it was precisely CEPI that, together with numerous other private and public initiatives, already at the very early stages of the epidemic, activated and coordinated numerous and different programs for the preparation of vaccines against COVID-19, following very different conceptual and technological strategies. This diversification appeared essential precisely because, for many diseases, but mainly in the case of a new disease as COVD-19, it is difficult to predict which type of immune response and therefore vaccine will be more effective [35].

RNA vaccines. On 17 March 2020, Dr. Michael Witte administered to volunteers the first shot of an RNA vaccine against the SARS-CoV-2 virus prepared by Moderna, a biotech company from Cambridge, MA [36]. RNA vaccines have been developed precisely to be produced in a very short time. The RNA specific for a particular protein is brought into cells by virus-like particles or into liposomes or bound to nanoparticles. Once the RNA has penetrated the cells of the organism, the cells use its genetic information to produce the target protein.

DNA vaccines. Other biotech companies, including TAKIS Biotech, from Castel Romano, Italy, are experimenting DNA vaccines against SARS-CoV-2 on animals. DNA vaccines are also based on the

possibility of inducing the body cells to temporarily produce the protein against which an immune response should be induced. DNA vaccination stimulate the production of antibodies but can lead to the activation of killer T cells. RNA and DNA vaccines have not yet specifically tested on elderly people, the population with the greater need for an efficient vaccine for COVID-19 [37].

Protein vaccines. In addition to RNA and DNA innovative vaccines that are faster and cheaper to produce, other laboratories, for example the one at Queensland University in Australia, are preparing COVID-19 vaccines using the "reverse vaccinology technique" developed by Rino Rappuoli, GSK in Siena. Starting from the virus RNA sequence, the proteins of the surface of the SARS-CoV-2 virions are identified. Crucial fragments of these proteins, produced in the laboratory with recombinant DNA technology, associated with new adjuvants of synthetic origin that most effectively induce an optimal immune response in the elderly.
Other laboratories are following more traditional strategies, which take longer to develop.

Vaccine assessment. The administration of the new vaccine on a limited number of volunteers, as is already the case with the vaccine developed by Moderna, makes it possible to understand whether the vaccine induces a good antibody response and / or a response of the T killer cells and whether its administration causes clear adverse events. Subsequently, the real evaluation of the effectiveness of the new vaccine will be based on randomized controlled trials that will compare the incidence of COVID-19 in groups of vaccinated and non-vaccinated people. Only the extension of this evaluation to progressively larger groups and for longer periods will determine whether one, several or none of the new COVID-19 vaccines protects effectively or only marginally and if its administration is associated with important collateral events. However, there is so much urgency for the vaccine that in order to quickly verify its efficacy a human "vaccine – SARS-CoV-2 challenge study" has been proposed [38].

Caveats associated to fast track vaccine evaluations. It is likely that in the view of the enormous pressure exerted by the COVID-19 pandemic, surrogate markers are initially used, such as the evaluation of the amount of antibodies or the intensity of the reaction of the T killer cells induced by the vaccine on the volunteers to decide whether initially the new vaccine could reasonably be used for vaccination. However, the administration of the new vaccine must always be carefully associated with a rigorous study of its safety. This is particularly important because a vaccine is not a drug sick people at risk of dying, but rather a treatment that is given to those who are well to prevent the risk of falling ill [39].

The race to develop a COVID-19 vaccine is not only justified but absolutely necessary. However, the time necessary to evaluate the dangers and risks that may arise from a new vaccine must be included in its development. In some cases, vaccines prepared against other coronaviruses or other viruses have worsened the disease[39] and inducing T helper 2-type immunopathology [40].
These issues must be carefully evaluated and excluded before new COVID-19 vaccines is distributed to combat the pandemic or its subsequent outbreak.

Production and economic issues. Once the new vaccine has been validated, subsequent problems will be related to produce and distribute the vaccines. Technological, organizational, regulatory and economic problems will have to be overcome. The production of hundreds of millions of doses of a RNA or DNA vaccine can be complicated, and each dose may be relatively expensive as it may require a fair amount of RNA, in particular to immunize an elderly person [37].
Hence the consideration that vaccines for COVID-19, if effective, will be very difficult to be generally available before a few years. This long interval raises another problem of crucial importance: what if in one or two years the new COVID-19 vaccines no longer crucial or will be exploited by only a small population in a particular area of the world? In fact, today we cannot predict what the evolution of COVID-19 will be, if the pandemic will end, if the epidemic will continue to hit massively, if it will only spread in some areas of the world or if there will be periodic outbreaks of new epidemics.

Recommended vaccines and BCG. At present, no reliable data are available concerning the impact of seasonal influenza vaccination and anti-pneumococcus vaccines on the incidence and clinical progression of COVID-19. However, it should be underlined that we agree with the general recommendation of anti-pneumococcal vaccination in the elderly because of its effectiveness in protecting against super-infection by pneumococcus in the course of viral infections and in reducing the appearance of bacteria resistant to antibiotics.

Lastly, somewhat connect with vaccines, is worth mentioning the hypothesis that the old anti-tuberculosis Bacillus Calmette Guerin (BCG) vaccine may reduce the risk of SARS-CoV-2 infection. A team in the Netherlands is launching a clinical trial with 1,000 health care workers. Similar trials in other countries will evaluate whether BCG vaccine increases resistance to SARS-CoV-2 in elderly people[41]. As discussed above (see point 4, Innate Immunity) innate immunity plays a key role in controlling the first stage of SARS-CoV-2 infection. Therefore, strategies which increase innate immunity ("training strategies") need to be carefully evaluated by epidemiologists and in carefully controlled clinical studies.

8. Preparedness

In the face of the enormous tragedy of death, suffering and social disaster caused by COVID-19 pandemic, it is inevitable to ask how much the world as a whole, and Italy in particular were or should have been prepared.

According to the "2010 Global Health Security Index ranking" [42,43], Italy was not particularly aware of the problems posed by the spread of infectious diseases. Is this justified? In Italy, in just a few weeks over 50 doctors and nurses lost their lives because of to the pandemic and even a greater number has been placed in isolation because they are infected. This is a very serious loss that Italy can never afford to have again. Certainly, much more could have been done in many aspects and a few of them even relatively simple [44,45]. On the other hand, many other countries and even international agencies have taken action in an uncoordinated and sometimes contradictory manner.

We must consider, however, that only a few months ago the assumption to dedicate energy and resources to be better prepared for a possible, but still hypothetical pandemic would have lack the necessary force to overcome indifference, skepticism, anti-scientific attitudes and suspicions of unclear interests and corruption. Italy, a country that has difficulty in convincing a high portion of its population on the importance of basic childhood vaccinations, would not be willing to devote a significant share of resources for measures to face an unprecedent such as a new pandemic. Almost all countries in the world would face the same difficulty, declining it differently on the basis of their own culture [46,47].

An assessment of how Italy and the world could be better prepared can only be made when the pandemic is over. In the future, preparedness is likely to be much more in the center of public health policy [43].

The lesson on the dangers of anti-scientific attitudes and errors in the allocation of resources that Italy and the world are experiencing is complex and very hard, so hard that today we cannot even have a clear idea of the *after* that is waiting for us.

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