Accademia Nazionale dei Lincei

Commissione Salute

COVID-19: An executive report

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in alphabetical order

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1. Premise

At a time when Italy and all world is dramatically faced with the challenge of the SARS-Cov-2 infection, hitting many aspects of human civilization, Commissione Salute of the Accademia Nazionale dei Lincei felt that it is part of its social responsibility to provide the society at large with an Executive Summary of the current status of understanding of origin, pathogenesis, and treatment of COVID-19 pandemic.

This Report is not a comprehensive review of the state-of-the-art of the field but rather snapshot of a field undergoing rapid evolution, with a daily flood of scientific publications and non-peer reviewed reports. Preparing a digest is per se a risky endeavor and the extensors of this report are well aware of their own limitations.

With the limits of the metaphor, we are experiencing *wartime medicine* and *wartime scientific research*. We are called to respond to the drama of patients at times with empiric approaches. Yet rigorous assessment remains a must and striking a balance between emergency and methodological stringency represents a major challenge [1].
Hopefully, with the above mentioned cautionary notes, this report will provide provisional tools to understand and cope with 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 capside of SARS-CoV-2 is made by four structural proteins: 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 people. 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, back in China, the SARS-CoV-2. It is probable that, as already happened for the other coronaviruses, even in the case of SARS-CoV-2 the original host was the bat. There are 1,200 species of bats which are the 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, unknown, but probably the pangolin for the SARS-CoV-2. Pangolins are an endangered species commercialized for its keratin scales used as an ingredient in traditional Chinese medicine while the meat is considered a delicacy in China and Viet Nam [3].

During 2019 fall, a pneumonia of unknown cause was diagnosed in individuals connected with the seafood and wet market in the city of Wuhan, Hubei province, 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 February 20th 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 cases with no link to an index case were found. The discovery of this secondary transmission cluster 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 status of the disease caused by SARS-CoV-2 infection (COVID-19) from epidemic to pandemic. To try to limit COVID-19 spread, first China, then South Corea, Italy and, progressively many countries of 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. While the quick pace of the progression of the pandemia along with different approaches adopted by the various countries to detect the disease limit a real comparison, Italy appears to be hardly hit by COVID-19.

3. Strategies to control COVID-19 spread.

With some delay compared with the initiation of COVID19 spread, on January 23, 2020, Chinese government isolated and locked tens millions people of Hubei province. People were barred from working or going to school and all shops were closed except those selling food or medicine. Following lockdown, new cases began to slow down. On March 19, 2020, no new cases were reported in Hubei province [5].

Following Chinese experience, lockdowns of various degree are currently applied in several Asian and European countries, UK and US. The purpose of lockdown is to reduce the Rt number, i.e. the number of healthy people contaminated by each SARS-CoV-2 infected person. The Hubei experience shows that in this way the suppression of virus spread is obtained in a short term [7]. The effective case reduction obtained through the lockdown allows a better care of the patients and a reorganization of the health care system. As we will report later, COVID-19 can present in a significant percentage of cases as a very severe acute respiratory syndrome, requiring Intensive Care Unit (ICU) admissions. In most countries in the world ICU beds are a limited resource.

In Italy there were roughly 5,000 ICU beds open 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 ICU beds availability varies between countries, no healthcare system in the World could sustain an unlimited surge in ICU patients. For this reason, in order to get ready for a COVID-19 outbreak increasing surge of the ICU capacity alone would not be sufficient and containment manoeuvres must be in place not to overwhelm the capacity of the healthcare system.

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

The perspective 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 South Korea approach appears quite interesting since an effective control of COVID-19 spread was obtained without locking down entire cities or the whole country. The particularly well-organized Korean testing and tracing programs allowed to isolate infected people and quarantine their contacts. 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 containment scenarios can be envisaged, complete lockdown (suppression), mitigation or a mix of the two. Suppression is the current approach, currently underway in Italy and elsewhere. Mitigation consists of milder interventions such as those initially adopted UK and others 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 foreseen to address societal needs and face future waves of the epidemic.

4. Immunity

Innate immunity. Innate immunity represents a first line of resistance against microbes and evidence suggests that it handles over 90% of encounters with pathogens. Information on innate immunity in COVID-19 is scanty. Lymphocyte number decreases (lymphopenia) while neutrophils

number 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 have clinical implications as discussed below.

Adaptive immunity. As far as adaptive immunity is concerned, although results are scanty and largely based on SARS and MERS [12], evidence suggests that, as generally true for antiviral resistance, a Th1 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 of immunity protective against viruses[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 infection with coronaviruses including SARS-CoV-2 elicits memory. Ralph Baric recently stated that immunity and resistance should cover at least 6-12 months [15]. Hard data on COVID-19 are badly needed.

5. Clinical presentation

SARS-CoV-2 infection presents with a variety of symptoms. It can be completely asymptomatic or present with severe symptoms. Data from Italy, the country with the highest daily incidence of cases while we write this report, shows that about 67% of the infected persons present with mild symptoms. About 30% of the infected persons show more severe symptoms, requiring hospital admission.

The most common symptoms are fever and cough. A minority of cases reports gastrointestinal symptoms before the beginning of the respiratory symptoms [16].
Initial reports from China showed a rate of ICU Admissions of about 5% with invasive mechanical ventilation rates being below 3% [15]. Recent data from Lombardy 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 hospitalized cases[17].

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

6. Diagnostics tests: Virus and Antibodies

SWABS. The cornerstone of diagnostic tests is represented by PCR-based assays to detect viral RNA in nasal swabs. The current test requires specialized personnel and approximately 4 hours. It suffers from serious limitations with for instance negative nasal swabs and positive

bronchoalveolar lavages in advanced patients, false negatives in non-symptomatic patients etc [18]. In addition, at the time of writing swabs which inactivate the virus are not anymore available at least in Lombardy.

A 1 hour PCR-based assay (DiaSorin, Italy) has just been approved by US FDA and this may improve the diagnostic output [19].
In the US "home tests" have been approved by FDA: Kits are shipped at home along with detailed instructions. Then the swab inserted it into a protective vial is mailed to one Everlywell diagnostic lab for PCR analysis [20].

Antibodies. The search for antibodies is an invaluable source for the diagnostics of infectious diseases at the level of individuals and for accurate epidemiological studies. At the time of writing, commercially available antibody assays have not been validated and compared with the PCR assays. A recent non-peer reviewed report from academic institutions provides encouraging results [21].

Generation of reliable, validated assessments of the occurrence and significance of 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 antiretroviral and antiviral agents, to Chinese traditional medicine preparations. A detailed discussion of all compounds and strategies is beyond the scope of this executive report. As stated in the Introduction, while we understand the challenge of 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, quite recently the WHO announced a large global trial, called SOLIDARITY, to find out whether any of those can be 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 organ failure. Currently, there are no SARS-CoV-2 specific therapies. Supportive therapy is what can buy time for patients to recover their baseline 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 are usually very sick, require resource-intense care, both in terms of nursing and doctor's 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 strategy consists of using the least possible ventilator's pressures and volumes necessary 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 has to be made to support 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.

Currently, there is no convincing evidence for any other drug in COVID-19 patients with acute respiratory failure. Despite this, several clinical protocols have been developed using antivirals, chloroquine, anti-inflammatory drugs just to name a few. We will review rationale and evidence.

<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 most promising therapies that 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].

<u>Inhibition of excessive inflammation.</u> 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 should be mentioned that chloroquine, proposed as antiviral drug, has immunosuppressive and anti-inflammatory activity. Incidentally, the speculation that usage of chloroquine as an antimalarial 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 usage and recommendation 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 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 selected conditions, antibodies can enhance viral entry (Antibody-Dependent Enhancement, ADE) [32] and tissue damage [33]. Therefore, as emphasized above, rigorous clinical assessments will also be mandatory 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 arise from 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 towards which vaccines are only partially effective and we then have a series of sensational defeats. In effect, each disease is an immunological problem in itself: even today, with all the data we have, it is difficult to predict whether and which vaccine can be truly effective. This difficulty is accentuated in the case of COVID-19, a young disease on which studies implemented in labs all over the world are leading new data day by day. 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 for 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, how long does it persists? [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 lymphocytes.

In many cases, healing from a viral disease is the result of 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. But there are viral diseases whose healing depends mainly, if not exclusively on the antibody response and others in which the destructive action of the killer lymphocytes is fundamental. Which 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 to promote the development and storage of vaccines against those microbes that could cause new frightening epidemics: a significant amount of funds was paid by the Bill & Melinda Gates Foundation, the Welcome Trust and the governments of numerous countries. The major multinational drug companies have announced their collaboration. And it was precisely CEPI that, together with numerous other private and public initiatives, during 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 March 17, 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 firm from Cambridge, MA [36]. RNA vaccines have been developed precisely in order 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 is inside the body's cells, the cells use its genetic information to produce the target protein.

DNA vaccines. Other companies, including TAKIS Biotech, from Castel Romano, are experimenting DNA vaccines against SARS-CoV-2 on animals. DNA vaccines, too, are based on the possibility of making the body cells to temporarily produce the protein against which an immune response should be induced. DNA vaccination induces the production of antibodies but can also favor the development of killer T lymphocytes. RNA and DNA vaccines have not yet specifically tested in elderly persons who are the ones who need them the most [37].

Protein vaccines. In addition to RNA and DNA innovative vaccines that are faster and cheaper to produce, other laboratories as those of Queensland Univ. 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 recombined 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 happening with the vaccine developed by Moderna, allows us to understand if the vaccine induces a good antibody response and / or a response of the T killer lymphocytes and if its administration is associated with evident adverse events. Subsequently, the true assessment 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 unvaccinated people. Only the extension of this evaluation to larger and larger groups and for longer periods will show whether one, all 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 of 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 face of the enormous pressure made 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 lymphocytes 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 should always be carefully associated with the study of its safety. Since a vaccine is not a drug for people at risk of dying but a treatment given to those who are well to prevent the risk of getting sick, the evaluation of its safety assumes particular importance [39].

The race for a COVID-19 vaccine is not only justified but absolutely necessary. However, it must not push to tak e the necessary time to evaluate the dangers and risks that may arise from a new vaccine. In some cases, vaccines prepared against other coronaviruses or other viruses have accentuated the dangerousness of the disease[39] and inducing Th2-type immunopathology [40]. These issues must be carefully evaluated and excluded before new COVID-19 vaccines are employed to combat the pandemic or its subsequent reappearances.

Production and economic issues. Subsequent problems will be related to the production and distribution of millions of doses of the new COVID-19 vaccine. Complex technological, organizational, regulatory and economic problems will have to be addressed to produce and distribute million doses of new COVID-19 vaccines. It may be difficult to create hundred million

doses of a RNA vaccine, 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 indications that the COVID-19 vaccines, if effective, will be very difficult to be commonly 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, periodically, it will give rise to 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 emphasized that we concur with the general recommendation of anti-pneumococcal vaccination in the elderly because of its own merit, its protection against super-infection by pneumococcus in the course of viral infections and its impact on reducing the appearance of bacteria resistant to antibiotics.

Lastly, somewhat connect with vaccines, it is of interest to mention the hypothesis that the old anti- tuberculosis the Bacillus Calmette Guerin (BCG) vaccine may reduces the risk of SARS-CoV-2 infection. A team in the Netherlands will start 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]. A discussed above (see 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 brought 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 does not appear to have been particularly aware of the problems posed by the spread of infectious diseases. Is this judgement justified? In Italy, in a few weeks over 50 doctors and 50 nurses have lost their lives due to the pandemic and even a greater number have been placed in isolation because they are infected. This is a very serious loss that Italy will never have to afford 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 took action in a little coordinated and sometimes contradictory way.

We must consider, however, that only a few months ago the allocation of energy and resources in order to be better prepared for a possible, but still hypothetical pandemic would not have a chance to overcome indifference, skepticism, anti-scientific attitudes and suspicions of hidden

obscure interests and bribery. Italy, a country where it is difficult even to convince a high portion of its population of the importance of basic childhood vaccinations, would not take into consideration to allocate a significant share of resources in order to be prepared for a never seen event such as a new pandemic.
Almost all countries in the world are facing this kind of difficulty, declining it differently on the basis of their own culture [46,47].

An assessment of how Italy and the world could have been better prepared can only be made when the pandemic is over. In the future, preparedness is likely to be much more in the focus 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 facing 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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