In Clinical Practice

Flavio Tangianu · Ombretta Para
Fabio Capello *Editors*

COVID-19 in Clinical Practice

Lessons Learned and Future Perspectives

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In loving memory of Prof. Marco Spissu, and all the Italian medics and health workers that lost their lives to Covid-19 fulfilling their duty in the spring of 2020 and in the following months.

Preface

When the 2020 pandemic of COVID19 struck the world, no one could count on relevant information able to actively affect the outcomes both of the epidemics and of the management of single patient's cases. Because SARS-CoV-2 was a new virus and COVID19 was a new disease, scientists all over the world had to work with whatever knowledge they already possessed, based on what they knew about coronaviruses and broadly on viral infections and viral epidemics.

However, when it became clear that the original outbreak was going to spread around the world and that there were no given answers to the many questions that arose during those tragic months of the first half of 2020, human beings had to act and produce workable models aimed to solve the problem on behalf of the same human species. During the first response, some countries have been hit more than others. Pharmacological and non-pharmacological intervention aimed to reduce the impact and the burden of this unknown disease produced at the time some effects, whose efficacy also in terms of costs and burden for the whole population was not known and difficult to evaluate.

Those first countries that experienced a massive increase in the number of cases, hospital admissions, and death had to fight with blunt weapons made more unharmful by the fact that no one knew at the time how the epidemic would have progressed and what kind of medium- and long-term effect it would have been on the single patients and on the communities.

Whilst medical workforce and decision-makers struggled to find useful solutions, the rest of the world tried to prepare itself to impact the emerging disease with strategies based on no evidences and on no previous experiences.

The worst scenario the world had to face indeed in the recent years had been the 2013 epidemic of Ebola, whose characteristics however made the disease completely different and the models produced to contain a similar infection unable to fit for the COVID19's management purposes.

The world was simply not prepared to face a new worldwide disease.

Yet, because there were no given solutions, and because the long-term effects of this disease are still unknown by the time we are writing this preface, the only possible methodology to mitigate the impact of COVID19 was to rely on preparedness and readiness schemes. Those territories that at the time were unaffected by the disease should have observed what was happening in the world before the wave of the infection could strike them, in order to produce effective plans to contain the infection.

However, this approach needed for coordination and for a plan already shared among nations that would improve the level of communication, optimizing the resources and the response of the different actors involved in the fight against the virus.

Without shared agreements—before, during, and after the first wave of infection—and with no direction aimed to the production of scientific knowledge able to increase the awareness of the disease and the proper sharing of reliable scientific-based information, the study of the diseases and of those measures able to contain the epidemics were strongly constrained. The prompt and relevant requests for action, coming from international health organizations, were by themselves incapable of producing results because those seemed more the voice of the man crying in the desert, whose interlocutor is not given or unknown.

In addition, political decisions aimed to prevent those setbacks that inevitably came with the implementation of measures needed to reduce the spread of the virus (like the impact of these same measures on economy), delayed of weeks and sometimes of months the employment of useful procedures. This had an impact

also on the public opinion reducing the efficacy of some interventions that were loosely applied or that were simply left to the good will of the single individuals or communities.

In spite of the incredible amount of data potentially collected from the field, scientific trials and studies have been conducted with a general direction that focused only on the gathering and processing of the bigger possible amount of information. What happened instead was a collection of hypothesis and thesis based on ideas that often bypassed the system. This produced a number of sometimes unreliable publications, whose scientific content was debatable, and that did not lead to the creation of new and more effective models. What happened in fact was that most strategies were designed following schemes designed for very different diseases and for different and outdated scenarios, ignoring the complexity of the world we and the virus live in.

The result has been a Darwinian approach that produced a number of contentment measures and of clinical methods aimed to reduce the impact of the disease on the communities and on the individual patients. Without a proper methodology however, those strategies able to produce results have partially survived, and the others have succumbed to their fate.

But in a complex world, where simple organisms follow the schemes of the natural evolution, a Darwinian model is more the game field of the virus, rather than the one of the human species. In a match played according to these rules, thus, we were the designed losers.

This book is about that.

We tried to explore some relevant aspects of this new disease, focusing on what we have learnt so far, and on what we still need to understand of this infection. We did not expect in fact to produce a clinical handbook that could be the risk of becoming obsolete at the same time of its writing. Our hope, indeed, is that by the time you read these words more effective models have already been discovered and most solutions actually able to reduce the impact on the different populations of this world are already in place everywhere.

The aim of the book is more to explore the clinical aspects of the disease from a different standpoint, able to show us what has

really happened starting from those first weeks of the pandemics, when we found ourselves in that dreamlike or rather nightmarish scenario that we have experienced mainly in disaster movies before.

And above all to learn from what we have experienced during that time, from the voices of those that have fought the virus at different levels—in the hospitals, in the communities, in the control room—aware that every decision took was often not supported by scientific evidences. And from those lessons, given mostly in the beginning of the epidemic, but that are still taking place, we understand the opponent we are currently fighting, and above all how to fight those enemies that inevitably will have to face in the future.

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1 Introduction

Fabio Capello, Flavio Tangianu, and Ombretta Para

The 2020 COVID-19 pandemic has proven to be one of the most challenging events of our era. Although the surge of a new disease has been broadly foreseen, no one of the plans already in place—in terms of preparedness, readiness, and global health management—was able to produce workable models. This is not surprising: in the last decades, the world has experienced deep modifications in the way people interact and travel around. Moreover, lifestyles have changed globally affecting social, economic, cultural, and behavioral features of both high- and low-income countries.

As a result, geographical boundaries are fading out, in a global, dynamic, and fluid condition, where people are no longer bound to grow, live, and die in a same location, building their lives following the imprint of the older generations.

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In this scenario, the onset of a new disease should not be considered as an extraordinary event. On the contrary, the continuous interaction among cultures, often balanced between ancient traditions and practices and a modern way of life, is likely to produce new pathogens and therefore new pathologies. The advent of HIV-AIDS in the 1980s possibly represents the first example in recent history of the coming of a new disease able to deeply modify the way people related and lived their lives. Pest, cholera, and flu epidemics, to say a few, in the past produced devastating effects on the humankind. Yet, these catastrophic events were part of a world with relatively simple relationships in place and with no scientific solutions available to cure or to stop the spreading of the infections.

Our world, instead, is today a huge clockwork where everything somehow depends on umpteen variables, bound in turn to other conditions. Similarly, as for a butterfly effect, the modification of this fine equilibrium might produce unforeseeable consequences able to distort the reality and to produce unmanageable crisis.

When the first cases of coronavirus struck the world, in the first weeks of 2020, human communities, although aware, were simply not prepared to face an invisible enemy no one knew a thing about. No other diseases, in the history of modern medicine, spread in the population with such a speed and with such a violence. Because everything about the disease was new, and there were no ready solutions in place to fight it, there was no right or wrong moves to do.

Medical doctors and healthcare workers had to rely merely on their theoretical knowledge and on their intuitions, translating what they knew from other diseases and trying to produce results. Yet, the medium- and long-term outcomes were, and are still, unpredictable. Because the disease was so new, most of the information in the first phase of the pandemic referred to few weeks' data gathering and statistics.

In spite of the global, although uncoordinated, effort to produce scientific evidences on how to recognize, treat, and prevent the disease, data were simply not enough, and usual scientific pathways were not always practicable.

Meanwhile, people continued to die in an unprecedented way, with most of the strategies used to manage the most severe cases unable to get the outcomes expected. On the contrary, some of the medical procedures used, following the traditional schemes normally applied to other pathologies, caused more harms than benefits.

As the WHO and top-rated medical journals pointed out at that time, the efforts made to contain the virus came too late and were simply too little, with some Western countries denying the problem as a whole, or other underestimating the risk, avoiding to put in place strategies able to stop the pandemic, because it was considered at the time non-cost-effective.

History proved that approach wrong.

In these circumstances, when the first cases of novel coronavirus infections hit the northern part of Italy, Europe was simply not prepared. The consequences today are clear, but as a matter of fact, no one was ready to face such a sly enemy. Paradoxically, modern medicine relies on a number of procedures, often based on high-tech solutions that are simply unable to work with high volumes of events. The same principles of disaster medicine were simply not applicable because a catastrophic event is considered—sometime wrongly—mainly limited in time and place, with possibly a given start and end time and a known number of people (with predictable features) potentially involved.

COVID-19 was something different, because no one could and can still predict how it would and will evolve, with every single human being potentially involved, despite his or her social and economic state or his or her cultural background or origin.

The overwhelming number of cases that in few days clogged state-of-the-art hospitals in Italy first, and in other European countries later, was simply not controllable. Other countries outside Europe simply didn't learn from was just already happened elsewhere, dening the problem or trasforming it in an internal struggle aimed to resolve unrelated pending political issues. Irrealistic models designed to solve other kind of problems were simply unoperable at this level, at at that scale. Healthcare as a whole stopped to work in its usual way, with thousands of patients affected with COVID-19 and other pathologies, as well, neglected.

Moreover, the same epidemiological and therapeutic strategies used, based on the experience and the evidences gathered in fighting other infection, did not produce useful results or in some cases produced in adverse effects.

That was something no one could do anything about. And this is how frustrating it was.

For the first time in modern history, mankind had to face an invisible and totally unknown enemy: an enemy to fight with no weapons, able to undermine the whole integrity of our societies.

Medicine had to become an "art" again.

Although it is clear and widely acknowledged that medicine is guided by a scientific thrust, medical doctors in the past had to use all their knowledge, experience, and senses to understand and solve a medical problem. Medical devices were few and medical technology still modest. High-tech solutions are now considered essential in modern medicine, and their use in medical practice is often given for granted. Yet, there is no device that can bypass the epistemological process that leads a clinician to a diagnosis and to the formulation of a specific treatment, tailored on a single patient and the uniqueness of his or her condition. Modern procedures, driven by ready-to-use guidelines, have drifted the work of the physician, who today is often afraid (because of lack of experience, lack of confidence in his or her knowledge, or for legal reasons) to try new although reasonable and physiopathologically sound solutions. Problem-solving abilities of doctors have been put on standby, with some medics more afraid to go against the guidelines in place, even when these agreed procedures may reasonably harm the patient.

COVID-19, yet, reset all that.

With dozens of people accessing the hospitals, and most of them dying in any case, there was no time anymore to rely on procedures thought for completely different situations. And because everything was new about this disease, solutions have to be innovative and should depend on the knowledge of the fine physiological and pathological processes that take place in the human body in singular and given conditions.

This is probably the most precious lesson that we have learned in dealing with this novel disease. The human being as well as the

contexts it lives in is complex. The number of variables is so impressively high that no reliable models can produce or predict with relevant accuracy the complexity of this biological system.

However, knowledge coming from science cannot be static. This is in fact a fluid process, where any fact—no matter how certain it may appear—can be proven wrong or falsified at any time. This implies that scientists cannot protect a theory at any cost. On the contrary, they must be ready to give it away as soon as a better one comes next, even if that means rewriting everything they thought they knew. This is the scientific method and the lesson learned from Galileo Galilei and his peers some centuries ago.

Thus, COVID-19 should be considered the Galilean revolution of our era, in terms of how we consider and face diseases.

In this book, therefore, we would not like to offer ready solutions or protocols that have to be schematically used. We would like instead to show the state of the art in fighting COVID-19 in terms of methods and approaches, underlining at the same time that these are mutable solutions: we have reached these conclusions because doctors around the world have started to think out-the-box, depending on the thousands of hours spent in learning and fighting diseases that made otherwise the lives of the many unbearable.

We are therefore aware that some of the facts presented in this book will be outdated when new scientific discoveries about this disease will be available. And we are confident and hopeful that this is going to happen, because it would mean that COVID-19 is not a novel and an unknown enemy anymore.

However, the methodological approach that helped medical doctors to produce workable models and ultimately to save lives must remain and should be always kept in mind, when hopefully in a far future, a new enemy will be at the door threatening the same existence of the humankind.

COVID-19: A Novel Disease

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Flavio Tangianu and Alberto Batticciotto

COVID-19, whose name came from the acronym **CO**rona**VI**rus **D**isease 20**19,** is a novel disease caused by the SARS-CoV-2 virus, discovered after the onset of a previously unknown clinical respiratory syndrome whose cause has been identified at first in the city of Wuhan in China on December 2019.

The onset of this disease represented a major challenge for the whole world of research as for the first time in recent history scientists had to deal with a catastrophic biological event, able to disrupt societies worldwide and to undermine the same structure healthcare nowadays is based upon.

While the fine and labile balance that rules modern society was in jeopardy, researchers were called to study and understand complex new scenarios, building a previously inexistent knowledge from scratches.

Because the disease was so new, the evolution and the way of transmission and onset and progression of the same infection, in

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asymptomatic, symptomatic, and severely affected patients, plus the complications, consequences, and the side effect of both the disease and the experimental treatments were completely unknown and mostly impossible to predict.

In a very short time, yet, scientists from all over the world produced valuable information, able to show a little bit of light at the end of the tunnel. Although a more coordinated action and connection among research institutions and independent researchers would have been desirable, the progress and the contributions of the most lead to major disclosures in a relatively small amount of time.

In this chapter, we will highlight some of the most interesting findings related to what we knew of the pathogenesis of the disease during the first phases of the pandemic, starting from the SARS-CoV-2 infection to the cell and tissue damage that eventually lead to the symptoms and in an unfortunately but considerable number of cases to the decease of the patient. This overview represents the metodological paradigm scientists had to deal with at the beginning of the epidemic, underlying how those discoveries prompted some solutions used today to deal with the disease and its consequences. Besides the understanding of these biological mechanisms and markers was the first step for the development of an effective vaccine.

Understanding how the virus works, in fact, is the first step to develop a cure or to reduce the chance of long-term consequences in severely affected patients.

In addition, these findings helped clinicians to better define therapeutic strategies able to enhance the treatment options, avoiding the use of those medical and nonmedical actions that might result in more harm without significantly increasing the chance of healing or of surviving the disease.

The Pathogenesis of COVID-19

SARS-CoV-2 and Host

Coronaviruses are enveloped viruses with a positive sense single-stranded RNA genome (26–32 kb) [1]. Four genera (α, β, γ, δ) were identified up to now, but only α coronavirus (HCoV-229E

and NL63) and β coronavirus (MERS-CoV, SARS-CoV-1, SARS-CoV-2, HCoV-OC43, and HCoV-HKU1) are able to infect humans [2, 3].

Four structural proteins compose coronaviruses: spike (S), membrane (M), envelop (E), and nucleocapsid (N). Spike, a transmembrane trimetric glycoprotein, protrudes from the virus' surface and allows host cell receptor binding (S1 subunit) and host cell membrane fusion (S2 subunit). For this reason, S-protein is considered responsible of coronavirus diversity and host tropism [4].

Several groups analyzing SARS-CoV-2 S-protein, structurally and functionally, understood that, like SARS-CoV, it requires angiotensin converting enzyme 2 (ACE2) as functional receptor (expressed in the lung, heart, ileum, kidney, and bladder) to enter in human cells. After S1 subunit binding, SARS-CoV-2 probably employs host cell surface proteases and lysosomal proteases (e.g., cellular serine protease TMPRSS2) for protein S cleavage at the S1/S2 cleavage site. After the cleavage, S1 and S2 subunits remain non-covalently bound, distal S1 subunit stabilizes the membrane anchorage, and S2 subunit enters in the pre-fusion state. A second cleavage at the S2 site presumably activates irreversible conformational changes in S2 subunit causing the fusion with cell membrane. Furthermore, SARS-CoV-2 is the only coronavirus that presents a furin cleavage site at S1/S2 site. The ubiquitous expression of furin in human cells easily pre-activates S1/S2 cleavage sites making SARS-CoV-2 the most dangerous coronavirus [5–9].

After cell penetration, viral RNA genome is firstly released into cytoplasm, later translated into two polyproteins and structural proteins, and secondly starts to replicate itself. The envelope glycoproteins of the virus insert into the membrane of the endoplasmic reticulum or Golgi apparatus where it combines with the genomic RNA and nucleocapsid protein forming the new virus nucleocapsid.

The newly formed viral particles germinate into the endoplasmic reticulum-Golgi intermediate compartment. Vesicles containing viruses move toward cell membrane, and, after fusion, they release outside their infective contents [10].

Host Immune System and SARS-CoV-2

As explained above, SARS-CoV-2 can easily interact with his receptor ACE2, highly expressed on the epithelial cells covering the alveolar space [11, 12]. The main consequence of the infection is the destruction of these cells causing the typical lung injury of this disease. It is now clear that the epithelial damage is not merely an effect of the virus itself but rather the consequence of the interaction between the host immune system and the novel coronavirus, with the activation of the host immune system that causes part of the damage.

Lung epithelial cells infected by the virus produce IL-8 that is a well-known chemoattractant for neutrophils and T cells [13]. Infiltration of a large number of innate and adaptive immune cells was observed in the lungs from severe COVID-19 patients [14–17].

The first reaction of the host is to activate innate immunity with his main actors: epithelial cells, alveolar macrophages, and dendritic cells (DCs) [13]. These cells are able to phagocytose the virus-infected apoptotic epithelial cells in order to act as antigen presentation cells (APCs). APC presents viral peptides by major histocompatibility complex (MHC; or human leukocyte antigen (HLA) in humans) to virus-specific cytotoxic T lymphocytes (CTLs). Previous researches on SARS-CoV and MERS-CoV report that the presentation of these coronaviruses mainly depends on MHC I molecules [18], with little information about MHC II functions. HLA-B*4601, HLA-B*0703, HLA-DR B1*1202, and HLA-Cw*0801 [19, 20] are polymorphisms correlated to the susceptibility of SARS-CoV, whereas the HLA-DR0301, HLA-Cw1502, and HLA-A*0201 alleles are related to the protection from SARS infection [21]. HLA-DRB1*11:01 and HLA-DQB1*02:0 (MHC II molecules) are associated with the susceptibility to MERS-CoV infection [22].

However, the main task of APCs is to move to lymphnodes in order to present viral antigens to CD4+ and CD8+ T cells and activate the body's humoral and cellular immunity. CD4+ T cells activate B cells to promote the production of virus-specific antibodies, while CD8+ T cells can kill viral infected cells.

The profile of the production of SARS-specific antibodies was extensively studied for SARS-CoV-1. The first antibodies are IgM produced in 4–6 weeks that disappear at the end of week 12, while the IgG antibody can last for a long time providing a protective role [23]. Regarding SARS-CoV-2, few specific studies are available during the first months of the pandemic. Zhao et al. collected plasma samples from 173 patients with SARS-CoV-2 infection admitted in Chinese hospital. IgM were detected in 82.7% of the study population and IgG in 64.7% with a mean time for seroconversion similar between IgM (12 days) and IgG (14 days). It is interesting to underline how critical patients presented significantly higher antibody titers. Similar results are reported by another case series published by Long et al. Early observations showed no proof about the neutralizing ability of the antibodies detected in these case series [24, 25].

Analyzing peripheral blood of SARS-CoV-2-infected patients, a significant reduction of T cell number is reported [26–28]. Despite the reduction, initially there are no consequences on cell activities because it's compensated by an increased activation of the present T cells as underlined by high proportions of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) double positive fractions [29]. But long term, this overactivation can induce a T cell functional exhaustion that can be related with organ damage [30].

In large part of patients, this effective immune response is able to neutralize or contain virus in order to optimize the viral clearance limiting the disease progression.

Studies focused in COVID-19 patients with severe disease found that an aberrant CD4+ T cell population was found in the serum. These cells co-express interferon (IFN)-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF) [27]. GM-CSF production from T cells is a typical response to virus infection, but if it is excessive, it can activate circulating monocytes able to determine systemic tissue damage [31, 32]. In fact, in patients affected by a severe form of COVID-19 serum, the presence of CD14+ and CD16+ inflammatory monocyte subsets (able to produce high amount of IL-6) and an increased concentrations of pro-inflammatory cytokines, including interleukin (IL)-6, IL-1, IL-12, IFN-a, monocyte chemoattractant protein 1 (MCP1),

macrophage inflammatory protein (MIP)1α, and tumor necrosis factor (TNF)-α were reported [27, 28]. This hyperproduction defines the so-called cytokine storm that can trigger a violent attack by the immune system to the body causing ARDS and multiple organ failure, the main cause of death from COVID-19.

SARS-CoV-2 and Coagulopathy

In addition to respiratory symptoms, thrombosis and pulmonary embolism have been observed in severe forms.

Histopathological analysis of COVID-19 patients showed immune cell infiltration at the vessel wall level with hyaline thrombosis and infarction, while lung necropsy revealed a diffuse alveolar damage and small vessel thrombosis [33].

It is well known that endothelium plays a significant role in thrombotic regulation, so endothelial injury can determine hypercoagulability. An early paper demonstrated that SARS-CoV-2 can induce an endotheliitis at the level of the ACE2 expressing endothelial cell with a massive release of plasminogen activator [34–37].

Furthermore, it is well known that high levels of pro-inflammatory cytokines (e.g., TNF-α and IL-6) are able to activate coagulation cascade and suppress endogenous anticoagulant pathways [38].

An evocative hypothesis suggested that SARS-CoV could be able to interfere with the neutrophil extracellular traps (NET) inducing coagulation's contact pathway and pulmonary megakaryocytes. These interesting hypotheses could bridge the aspect of infection and inflammation with COVID-19 thrombosis pathogenesis [39].

A Probable Difference Between Infection by H1N1 and SARS-CoV-2 in Pulmonary Pathobiology

An early but methodologically interesting hypothesis in pulmonary pathobiology is shown in a little study based on the observations that came from a number of German hospitals. Researchers

examined the morphologic and molecular features of seven lungs obtained during autopsy from patients who died from SARS-CoV-2 infection. The lungs from these patients were compared with those obtained during autopsy from patients who had died from ARDS secondary to influenza A (H1N1) infection and from uninfected controls [40].

The lungs from the patients with COVID-19 and the patients with influenza shared a common morphologic pattern of diffuse alveolar damage and infiltrating perivascular lymphocytes. COVID-19 showed three distinctive angiocentric characteristics.

The first refers to severe endothelial injury associated with the finding of intracellular SARS-CoV-2 virus, and it is associated with disruption of the membranes of the endothelial cells.

A second feature is the observation of widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries in the lungs of patients affected by COVID-19 [41, 42].

A third peculiar characteristic is the finding of the formation of new vessels secondary to intussusceptive angiogenesis seen in the lungs of these same patients who died after COVID-19. These vascular features are so distinctive that even if the sample considered in the study was limited, those represents a fingerprint of the damage caused by the SARS-CoV-2 infection and can be considered as specific and representative of some form of COVID-19. Besides these same findings, and in particular the last one (namely, the intussusceptive angiogenesis) was unexpected; intussusceptive angiogenesis is defined by the presence of a pillar crossing the lumen of the vessel [43], commonly known as intussusceptive pillar, and it can be observed only by scanning electron microscopy [44]. One of the possible explanations is that patients with COVID-19 present a greater level of endotheliosis and thrombosis in the lungs when compared with other group of patients and in particular with those affected by influenza. Although in both groups, in fact, tissue hypoxia was present, the damages of the endothelium caused by inflammation or directly by the virus could lead to the observed intussusceptive angiogenesis.

Even if the observations of this research represent a major disclosure, it is clear that a major limitation of the German study is that the sample was small as it accounted only for 7 subjects out

of more than 320,000 people who have died from COVID-19 at the time of the research; besides, data coming from the autopsy represent only information that come from the final picture of the process. On the basis of the available data, in fact, they cannot reconstruct the timing of death in the context of an evolving disease process. Moreover, there could be other factors that could explain the differences that had been observed between patients with COVID-19 and those with influenza. For example, none of the patients enrolled in the German study and who died from COVID-19 had been treated with standard mechanical ventilation, whereas five of the seven patients who died from influenza had received pressure-controlled ventilation. Similarly, it is possible that differences in detectable intussusceptive angiogenesis could be due to the different time courses of COVID-19 and influenza [45]. Another relevant finding was that the degree of intussusceptive angiogenesis in those who have died because of COVID-19 was deeply affected by the length of the stay in a hospital facility and was proportional with the length of stay. This is in contrast with what has been observed in patients who died from influenza, where the level of intussusceptive angiogenesis was stable at a lower level. This is also consistent with other findings, as long as intussusceptive angiogenesis is one of the most common mechanisms of angiogenesis even in chronic lung injury, representing a predominant process in the final stage of the disease [44].

Another interesting finding is that the number of ACE2-positive cells in the lungs of patients affected by COVID-19 and the number of ACE2-positive cells in subjects affected by influenza were significantly higher than those from the cells in the lungs of the uninfected patients that were used as controls. In particular, the number of ACE2-positive endothelial cells was meaningfully higher and comes together with noteworthy modification of the endothelial morphology. This discovery is representative of the function of endothelial cells in the vascular phase of COVID-19 that appears to have a central role in the pathogenesis of this disease, especially when it comes to the pulmonary involvement of the infection. In the specimens collected and analyzed from patients affected by COVID-19, the endothelial cells presented a clear disruption of the intercellular junctions, showing as well a

swelling of the whole cell, and alteration of their connection with the basal membrane, with a plainly identifiable loss of contact between the two structures.

The role of SARS-CoV-2 is highlighted by the fact that the virus was found within the endothelium [46]. This observation is consistent with the hypothesis that the virus is directly responsible for the damage on the same endothelium enhancing or promoting the effect of the perivascular inflammation.

Conclusions

Although the mechanisms that lead from the infection of SARS-CoV-2 and the development of the different grades of diseases (that can range from a very mild form to a life-threatening one) are still under investigation, it appears evident by now that COVID-19 is caused both by a direct damage of the virus and the one that came from the response of the infected organism to the infection.

This is not unusual in viral infection, but this information is methodologically crucial to understand how the system coronavirus-human body works, so to better develop useful therapeutic solutions.

The findings that came at an early stage from the analysis of the affected patients, in fact, casted some light on the way the virus worked and on how effective some of the remedies adopted at the time were. Clinicians faced the first cases of the disease often relying on treatment options that although very useful in other clinical scenarios could have led to more damage and harm in COVID-19 affected patients.

From this standpoint, the gathering of new information on how the virus works and on how the human body responds to its aggression is paramount. The lesson learned is that we can fight a new enemy with old weapons, if we are able to understand the battlefield we are fighting on. At the same time, we have to be ready to face new challenges that may prove that what we thought we knew about infections might be wrong. Keeping the mind open, it would be possible then to develop new strategies to fight new and old rivals.

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3 COVID-19: Epidemiology and Transmission Methods

Alessia Abenante

Epidemiology

On the 31st of December 2019, Chinese health authorities reported a recent cluster of atypical unspecified pneumonia in the city of Wuhan (Hubei, China). Many of these patients had a common history: the recent exposure to Wuhan's South China Seafood City market. During the second week of 2020, the Chinese Centers for Disease Control and Prevention identified the agent of this unknown pneumonia as a novel human-infecting coronavirus. The intermediate host of the virus might be the bat, one of the non-water animals sold at the market in Wuhan. This beta-coronavirus is able to bind to the angiotensin-converting enzyme 2 receptor in humans, allowing the transmission.

Soon, several similar cases have come up without a history of exposure to the market, suggesting that human-to-human transmission was possible.

In February 2020, the WHO officially named the respiratory disease caused by 2019-nCoV as COVID-19 (coronavirus disease 2019). The virus was eventually classified and designated as SARS-CoV-2 and formally associated with severe acute respiratory syndrome coronaviruses.

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The infection tremendously spread within China and rapidly flied outside the country, with small clusters in France, Germany, and the UK. On the 21st of February 2020, the first case of locally acquired SARS-CoV-2 infection was diagnosed in Northern Italy in a young Italian man with no travel history to known areas of viral circulation or link to a probable or confirmed COVID-19 case. Prior to this date, only three cases of COVID-19 had been reported in Central Italy, a couple of Chinese tourists and a man who returned from a business trip to China.

On the 11th of March 2020, following the alarming levels of spread and severity of the disease, and by the stunning levels of countries' inaction, the WHO made the assessment that COVID-19 had to be characterized as a pandemic. Since the first reports of cases from Wuhan, the infection reached all continents, except for Antarctica.

There are proven concerns that the reported case counts underestimated the real number of people infected by SARS-CoV-2, as only a fraction of acute infections has been diagnosed and reported, especially in the first months. Seroprevalence surveys in the USA and Europe have suggested that the rate of prior exposure to SARS-CoV-2, as reflected by seropositivity, exceeds the incidence of reported cases by approximately tenfold or more.

At the beginning of August 2020, the cases of COVID-19 reached over 21 million, with more than 750 thousand deaths. The most afflicted continent is America, with a weekly report for the USA that counts more than 350,000 new COVID-19 patients and a rapidly increasing diffusion in South America (in Peru, the number of death increased of 220% in the second week of August, compared to the previous weeks), and it is also affecting indigenous people. Southeast Asia is the second most hit area, with 26% of the world's cases registered in the first week of August 2020 (see Fig. 3.1).

Moreover, the numbers reported in Europe during summer 2020 have gradually increased as well. Starting with clusters in meat processing and packaging facilities in Belgium, Denmark, and Germany, the number of cases all over Europe has been growing consistently.

A good statistical instrument used to forecast the trend is the reproductive number "Rn." This indicator represents the average

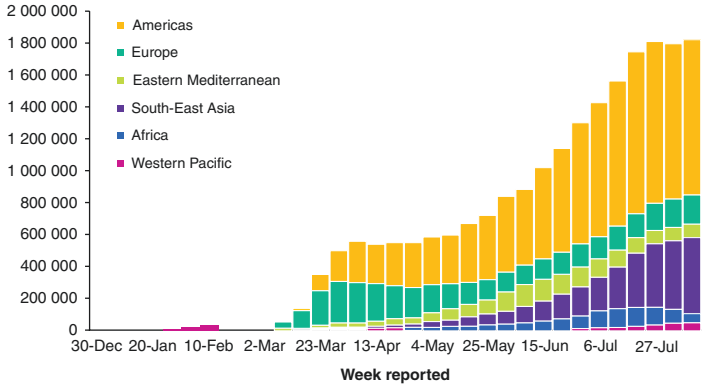

Fig. 3.1 Distribution of COVID-19 cases worldwide, from December 2019 to August 2020. WHO epidemiological update (Reproduced under open access, license CC BY-NC-SA 3.0 IGO)

number of possible secondary infections produced by the exposition to a single infectious case. Applied to time zero, we call it "R0." The calculation considers the time between the onset of symptoms in the infector and in the infected. When the control interventions start and the population cannot be considered as fully susceptible, transmission potential at a given time can be estimated by the effective reproductive number "Rt." When this value is <1, we face a decrease of the epidemiologic curve of transmission. The more the value is >1, the more the disease is spreading. That's a good wake-up call, especially when it is high while the global case number seems steady.

In the most affected region of Italy, at the end of February 2020, the estimated "R0" was 2.96. At the end of March 2020, it was still >1, but gradually decreasing, especially after the national lockdown.

Analyzing the condition in our country that quite reflects the international situation, the median age of COVID-19 patients is now lowering. At the beginning of the pandemic, it was around 61 years old, while, in August 2020, it went down reaching 35 years old (see Fig. 3.2). Prevalence is quite the same for both sexes, slightly more for women (52% vs. 48%).

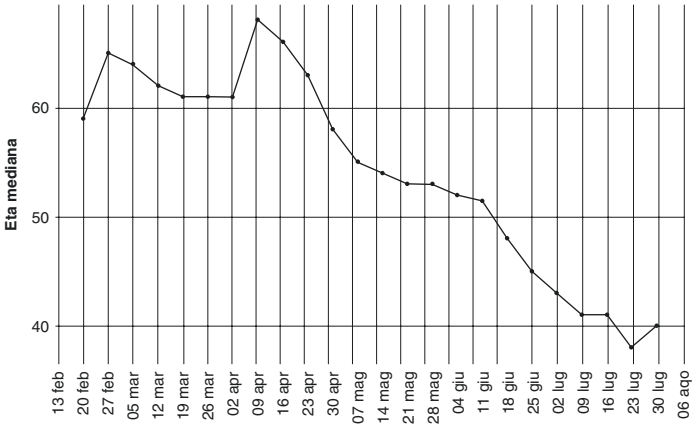

Fig. 3.2 Median age of COVID-19 patients. Epidemia COVID-19, Istituto Superiore Sanità, Rome, www.epicentro.iss.it/coronavirus, updated 08/04/2020 (Reproduced under open access, license CC BY-NC-ND 2.5)

During the first months, most of the positive cases were Italian natives who got sick in Italy.

On the other hand, after the reopening of the borders, which coincided with the beginning of summer holidays, we assisted to equal numbers of native and imported cases (from both Italians as tourists outside the country and from foreign tourists on holiday in Italy).

At the beginning of the outbreak, when the health system was caught rather unprepared, there was a high incidence of severe respiratory diseases and deaths. This was mainly the consequence of the long amount of time elapsed from the onset of symptoms and the diagnosis. Currently, a lot of asymptomatic or paucisymptomatic cases are being registered, with an important reduction of the worst cases.

Among the Italian healthcare workers, about 30.122 cases have been diagnosed (12.1% of the total). The median age is 47 years old and 70.1% of them are women. Compared with the rest of the population, the mortality rate at a given age is lower, probably due to the higher number of individuals tested, even if asymptomatic.

Transmission

SARS-CoV-2 is an RNA virus that affects the respiratory tract and may lead to an acute respiratory distress syndrome. Commonly, respiratory infections are transmitted by air, which means through droplets or aerosol.

Droplets are defined as particles bigger than 5–10 μm in diameter that enclose the bacteria/virus. Transmission by droplets occurs when a person is within 1 meter from someone who has respiratory symptoms (e.g., coughing or sneezing) and his/her mucosae (mouth, nose, or conjunctiva) are exposed. It may also happen through direct contact with infected people (e.g., shaking hands) or indirect contact with surfaces in the immediate environment, soon after the deposition by gravity of the infectious droplets.

Instead, aerosol transmission refers to the presence of microbes within droplet nuclei, which are generally considered to be particles of less than 5 μm in diameter. They can remain in the air for longer periods of time and be transmitted over distances much greater than 1 m.

According to current evidence, SARS-CoV-2 is primarily transmitted between people through respiratory droplets and direct contact. In an analysis of 75.465 COVID-19 cases in China (February 2020), airborne transmission was not reported, but there are strong concerns that the virus may be aerosolized during certain procedures (e.g., intubation, the use of nebulizers, turning the patient to the prone position) or activities (e.g., singing). Moreover, in a recent paper based on laboratory experiments, *van Doremalen* compared the aerosol stability in the air of SARS-CoV-1 vs. SARS-CoV-2, finding that the latter remains viable and infectious in aerosol for hours.

In 2016, *Scharfman et al.* analyzed the fragmentation processes of muco-salivary fluids through sneeze and coughs with fast photography application, showing the distribution of droplets and trying to determine the distance they can reach. The study continued in 2020 when *Bourouiba* displayed how peak exhalation speeds can reach up to 10–30 m/s, creating a cloud that can reach approximately 7–8 m.

Moreover, based on the available knowledge, *Morawska and Cao* showed how small particles with viral content travel in indoor environments, covering distances up to 10 m from the emission sources, just like SARS-CoV-1. The spread by air of its predecessor has been already reported in several studies, which retrospectively explained the pathway of transmission in some indoor environments. Once the droplets arrive in the air, the liquid content starts to evaporate, and some of them become so small that transport by air is more effective than by gravitation. These small droplets are then free to travel and carry their viral content meters and meters away from the source. The presence of SARS-COV-2 on airborne particles was also pointed out by on-field studies carried out by *Liu et al.* inside Wuhan's hospitals: RNA was detected in air samples collected inside the buildings and the surroundings. Similar findings are also reported in the study of *Santarpia et al.*, where the presence of SARS-COV-2 was identified in air samples collected at the Nebraska University Hospital. Hence, according to these evidences, the propagation of the disease through aerosol could be possible in some specific situations, while it seems unlikely in the everyday setting. In few reports of healthcare workers using only contact and droplet precautions while being exposed to patients with undiagnosed infection, no secondary infections were identified despite the absence of airborne precautions. Furthermore, if aerosol transmission of such a virulent pathogen were possible just through speech or cough, the safe distance needed would be much higher and containing the diffusion would not be possible.

At the end of July 2003, after 8 months, SARS-CoV-1 had infected approximately 8.100 people in limited geographic areas. At the beginning of August 2020, in the same period of time, SARS-CoV-2 had reached more than 20.6 million people and continues to spread all around the world. Despite the use of similar control interventions, the development of the two epidemics turned radically different. An important distinction between the two coronaviruses is the high level of viral shedding in the upper respiratory tract for SARS-CoV-2, even among presymptomatic patients. Also, for SARS-CoV-1, the peak of the shedding was associated with the symptom onset and occurred on average

5 days later than with SARS-CoV-2, making symptom-based detection more effective and timelier.

Clearly, the spread of the disease is higher when the infector is symptomatic (sneezing and coughing in the environment). However, when there are no symptoms, it is difficult to detect and isolate the source. *Li et al.* estimated that in China a large proportion of transmission cases (79%) were from individuals who had not been tested because apparently asymptomatic. In addition, *Wei et al.* investigated all 243 cases of COVID-19 reported in Singapore between January 23 and March 16 2020 and identified presymptomatic transmission as the most likely explanation in seven clusters of cases. A presymptomatic person develops symptoms while already transmitting the virus to another person, with a median time between 1 and 3 days of exposition before the source patient developed symptoms.

Another relevant issue for the evaluation of transmission is to identify the virus viability conditions in the atmosphere. In 2011 and 2012, *Yang et al.* examined the association between Influenza A virus viability and environmental factors such as relative humidity and aerosol composition (e.g., salt, proteins, mucus) introducing a possible explanation for influenza's seasonal patterns in different regions. In the same years, *Quin et al.* investigated the microbiome adsorbed onto airborne particulate matter (PM2.5 and PM10) over a period of 6 months between 2012 and 2013 in Beijing City, showing the variability of microbiome composition depending on the examined month. The analysis showed the highest abundance of viruses in January and February, concurrently with the greatest pollution. Furthermore, other studies dealt with the association between PM and infectious disease incidence (e.g., influenza, hemorrhagic fever with renal syndrome) confirming that the inhalation of these particles may promote virus penetration into the deepest parts of the lungs, supporting the induction of respiratory infections. This combination between droplets' nuclei and particulate matter is considered plausible, especially under favorable environmental conditions. The best stabilization of aerosols in the atmosphere requires temperature around 0–5 °C and high relative humidity. Also, it is generally assumed that the inactivation rate of viruses is promoted by an increase in tempera-

ture and solar radiation. On the contrary, high levels of relative humidity may play a key role in viral spread, resulting in an increased virulence. In this regard, *Ficetola et al.* showed how the spread of SARS-CoV-2 peaked in temperate regions of the northern hemisphere with a mean temperature of 5 °C and a mean humidity of 0.6–1.0 kPa, while it decreased in warmer and colder regions. All these data could help explaining the massive spread during winter in Northern Italy, one of the most polluted areas in Europe.

Speaking of droplets' nuclei transmission, *van Doremalen et al.* investigated the stability of SARS-CoV-2 after generating aerosol on various surfaces and compared it with SARS-CoV-1. It was found that one of the predominant mechanisms for SARS-CoV-2 to be contagious is the self-inoculation from contaminated fomites. This analysis demonstrated that the virus is more stable on plastic and stainless steel than on copper and cardboard, especially compared with SARS-CoV-1. Viable virus was detected up to 72 h after application to these surfaces, although the virus titer was greatly reduced. On copper, no viable SARS-CoV-2 was measured after 4 h, while on cardboard it took 24 h. The longest viability was on stainless steel and plastic, with an estimated median half-life of approximately 5.6 h.

During the last months of pandemic panic, almost every human fluid has been tested, searching for new transmission routes (see Fig. 3.3). The non-respiratory specimens included stool, blood, ocular secretions, urine, and semen, but the role of these sites in transmission is still uncertain. However, the likelihood of blood-borne transmission (e.g., through blood products or needlesticks) appears low because respiratory viruses are generally not transmitted through the blood, and transfusion-transmitted infection has not been reported yet for SARS-CoV-2 or for the other coronaviruses.

Actually, a case study of a man presenting bilateral conjunctivitis in the 13th day of the disease suggested that viral shedding may also occur in the eyes. RT-PCR of conjunctival samples was found until day 19. Another case report about the first patient diagnosed with COVID-19 in Italy showed the same. The patient presented bilateral conjunctivitis, fever, respiratory symptoms,

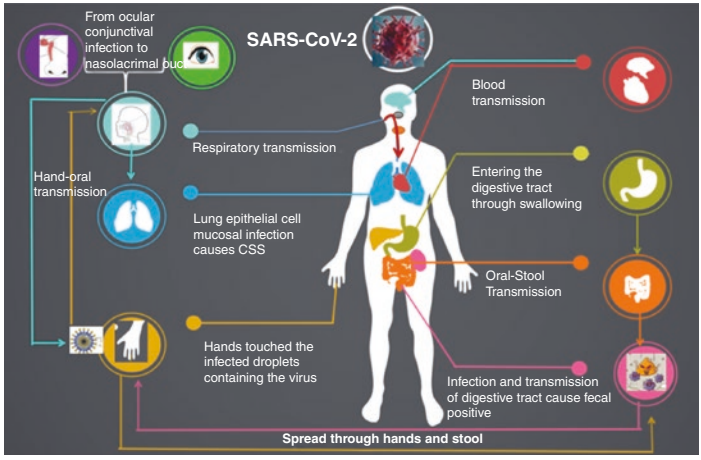

Fig. 3.3 Possible ways of human-to-human transmission of SARS-CoV-2. (Image from Li H, Wang Y, Ji M, et al. Transmission Routes Analysis of SARS-CoV-2: A Systematic Review and Case Report. Front Cell Dev Biol. (Copyright © 2020 Li, Wang, Ji, Pei, Zhao, Zhou, Hong, Han, Wang, Wang, Li and Wang. Open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice)

nausea, and vomiting. SARS-CoV-2's RNA was detected via conjunctival swab on day 3 of hospitalization and continued to be positive until day 27, while conjunctivitis resolved on day 20. An RNA-positive ocular sample was inoculated in Vero cells obtaining a cytopathic effect after 5 days, demonstrating that the virus found was infectious. Although, the evidence of ocular transmission as an effective contagious route is limited. In fact, a prospective study in Singapore showed how the tears of 17 COVID-19 patients resulted negative for the presence of SARS-CoV-2, while nasopharyngeal samples were positive: this might mean that transmission through tears is unlikely or very rare.

Another route of transmission that has several investigations is the fecal-oral one. *Yifei et al.* enrolled 42 COVID-19 patients with or without gastrointestinal symptoms and tested their stool

specimens for SARS-CoV-2. 66.6% of them resulted positive, without correlation with the type of symptoms or the severity of the disease. 64.3% remained positive for viral RNA in fecal samples even after the nasopharyngeal swabs turned negative. Therefore, it seems that viral shedding in stool lasts 6–10 days longer than the negative conversion of the pharyngeal swab. Other evidence was found by *Wang et al.* investigating 1070 specimens collected from 205 infected patients at 3 hospitals in the Hubei and Shandong provinces, confirming the presence of viral RNA in a not negligible part. The possibility that the RNA found belonged to vital virus has been also investigated and confirmed in a small review of case reports performed by Sehmi and Cheruiyot. However, in these experimental data, fecal-oral transmission has not been clinically described, and according to a joint WHO-China report, did not appear to be a significant factor in the spread of the infection.

Vertical transmission is another alarming way of transmission that has been studied. Several cases have been reported, mostly in the third trimester of pregnancy. Congenital infection may be possible but uncommon (<3% of maternal infections), while it's also likely that most of the neonatal infections are the result of the exposure of the babies to mothers or other caregivers with SARS-CoV-2 infection. In a systematic review performed by *Kotlyar et al.*, neonates born from 936 COVID-19-infected mothers had positive nasopharyngeal swab in 3.2% within 48 h from birth.

Suggested Readings

Epidemiology

Bollettino di Sorveglianza COVID-19 dell'Istituto Superiore di Sanità (updated 08/04/2020).
https://www.ecdc.europa.eu/en/covid-19/latest-evidence/epidemiology
https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-international-outbreak
https://www.uptodate.com/contents/coronavirus-disease-2019
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

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Transmission

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4 Diagnosis of Severe Acute Respiratory Syndrome-Related Coronavirus-2 Disease

Benedetta Pennella and Paola Sterpone

The Role of Diagnostic During the COVID-19 Pandemic

As of the first half of 2021, the COVID-19 pandemic due to the coronavirus SARS-CoV-2 reached more than 200 countries worldwide with more than 15 million confirmed cases (and probably a much higher number of infected) and over 3 million deaths [1].

The primary aim of epidemic containment is to reduce disease transmission by decreasing the number of susceptible persons in the population or by decreasing the basic reproductive number (R0). After the surge of a new disease, like the COVID-19 in 2020, given the lack of effective vaccines or specific treatments, the most effective way to reduce SARS-CoV-2 transmission is to identify and isolate contagious person [2].

Testing patients for SARS-CoV-2 has the purpose of identifying those who are infected, which is necessary for individual

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patient management, as well as for implementation of strategies to prevent the spread in healthcare facilities and in the community.

To detect this novel coronavirus, molecular-based approaches have been the first line of methods to confirm suspected cases. Nucleic acid testing is the main technique for laboratory diagnosis [3]. As with other emerging viruses, the development of methods to detect antibodies and viral antigens is started after the identification of the viral genome.

In Italy, early in February 2020, the Laboratory of Virology at the National Institute for Infectious Diseases "Lazzaro Spallanzani" (INMI) in Rome and the Regional Reference Centre for Emerging Infections, following the announcement of the emerging outbreak, established the diagnostic capability sequencing SARS-CoV2 genome and provided support to other Italian regions.

Nucleic Acid-Based Methods

Real-time reverse-transcriptase polymerase chain reaction (RT-PCR) is considered the gold standard for direct detection of SARS-CoV-2 [2]. RT-PCR is used to detect the virus in the specimens collected through swabs, as recommended by the World Health Organization, for clinical management and outbreak control purposes [4].

The most common sample types being tested are swabs taken from the nasopharynx and/or oropharynx, with the former considered more sensitive than the latter [5]. Following collection, swabs are placed into a liquid to release virus/viral RNA from the swab into solution. Then, viral RNA is extracted and subsequently amplified by reverse transcription-PCR [6].

For patients with pneumonia, lower respiratory tract secretions, such as sputum and bronchoalveolar lavage fluid, are tested. It should not be assumed that each of these (e.g., nasopharyngeal swab specimen, sputum, bronchoalveolar lavage fluid) will have the same chance of identifying SARS-CoV-2; detection rates in each sample type vary from patient to patient and may change over the course of individual patient's illness.

In a first study on 1070 specimens, collected from 205 patients with COVID-19, bronchoalveolar lavage fluid specimens showed the highest positive rates (93%), followed by sputum (72%), nasal swabs (63%), fibrobronchoscopy brush biopsy (46%), and pharyngeal swabs (32%). Collecting specimens from multiple sites may increase the sensitivity and reduce false-negative test results [7].

Positive results indicate the presence of the virus, which must be correlated with other diagnostic tests and the clinical history in order to confirm the SARS-CoV-2 disease. Also, we note that viral RNA does not equate to live virus, and therefore, detection of viral RNA does not necessarily mean that the virus can be transmitted from that patient [6]. Moreover positive test does not rule out a possible bacterial or other virus coinfection. False-positive results are rare but have been reported with certain platforms [8]. Above all, a negative result does not exclude an infection from SARS-CoV-2 and therefore should not be used alone to make clinical decisions but must always be integrated with laboratory, instrumental, and epidemiological information. Repeating the test, days later in a suspected case, increases the chance of confirming the presence of the virus [9].

The accuracy and predictive values of SARS-CoV-2 nucleic acid amplification tests have not been systematically evaluated. They are highly specific tests. Even if nucleic acid amplification test has high sensitivity in ideal settings (i.e., they are able to accurately detect low levels of viral RNA in test samples known to contain viral RNA), clinical performance in real life is more variable [10]. In the literature, sensitivity of the RT-PCR test between 30 and 70% is described [10]. This means that a significant proportion of patients with SARS-CoV-2 pneumonia can be falsely negative and their hospitalization in non-isolated areas could represent a serious source of infection. Lippi et al. described potential RT-PCR vulnerabilities that may bias the diagnostic accuracy of this assay, including both general pre-analytical issues (collection, handling, transport and storage of the swabs, quality and volume of the collected material, interference from other substances) and analytical issues (choosing the right diagnostic window, validation of assays, harmonization, instrument func-

tioning). Procedures to minimize the risk of diagnostic errors include repeated collection of specimens in patients with suspicion of infection, training on swab collection, quality assurance for analytical procedures, and combination of clinical evidence with RT-PCR results [11]. These molecular-based approaches present other known limits: long turnaround times, potential shortage of reagents, and the need for certified laboratories, expensive equipment, and trained personnel [12].

The public health emergency requires an unprecedented global effort to increase testing capacity. The large demand for RT-PCR tests due to the worldwide extension of the virus is highlighting the limitations of this type of diagnosis. In Italy, mostly in the first phase of pandemic, the lack of reagents and specialized laboratories forced the government to limit swab testing to patients who clearly showed symptoms of severe respiratory syndrome, thus leading to a number of infected people and a contagion rate that were largely underestimated.

Immunoassays

Immunoassay is another established diagnostic method. This method detects viral protein antigens or serum antibodies in patients who have been exposed to SARS-CoV-2 [13].

Using recombinant viral proteins, it could detect antibodies as early as 3 days after the development of the first symptom. The accuracy of the ELISA for IgG and IgM antibodies was more than 80% [14]. The efficacy of these tests also depends on the specificity of the antigens used to capture the antibodies from the patients. Between the spike (S) proteins and nucleocapsid (N) proteins, the sensitivity of the S proteins is higher for the antibody capture. In a comparative study, both ELISA and colloidal gold immunochromatographic kits showed equal sensitivity with 100% specificity for the SARS-CoV-2 detection [15].

Several immunoassay kits are already on the market for emergency detection of COVID-19. However, one of the notable problem of this method is that it works in patients who must have an immune response to SARS-CoV-2. Other drawbacks include changes in viral load over the course of illness, potential cross-

reactivity (less specific), and low sensitivity compared with nucleic acid-based methods. Nevertheless, immunoassays are faster and cheaper than the RT-PCR methods [16]. They can be used for rapid screening of previous SARS-CoV-2 infections. This is particularly useful in the reopening stages of lockdown at which people restored from previous COVID-19 infections, and therefore immune to the virus, can safely re-engage with society.

Point-of-Care Molecular Diagnostics and Emerging Techniques

Point-of-care (POC) testing refers to a wide category of diagnostic tests that can be performed wherever patient care occurs. Functionally, these tests have a rapid turnaround time and can potentially be performed by various non-laboratory clinical personnel. These assays can be molecular or serologic.

Some are 10-min lateral flow immunoassays that detect IgM and IgG antibodies directed against SARS-CoV-2 [Xiamen AmonMed Biotechnology, Sugentech, and Cellex]. Biotech developed a similar test called Wondfo SARS-CoV-2 antibody test. Other similar tests promoted by Jiangsu Medomics Medical Technologies (Nanjing, China) and Innovita Biological Technology are now in shipping. Abbott produced the POC PCR isothermal test that delivers a positive result in 5 minutes and a negative result in 13 minutes. Some of these tests are already approved by the Food and Drug Administration (FDA) for emergency use (EU). The available POC tests need to be studied in the current emergency setting. The WHO proposed a protocol to assess the effectiveness of serology testing; however, it is currently impossible to evaluate and compare all the different POC tests because of the lack of reliable data. With the now available data, the WHO does not recommend the use of POC for the purpose of clinical diagnosis, although research on their performance is encouraged and their use would lead to a reduction in the high costs of molecular confirmation tests [17].Given the variety of problems associated with current clinical diagnosis for the SARS-CoV-2, as above, we discuss below some promising available emerging techniques.

Isothermal Amplification for Nucleic Acid Targets

One of the isothermal nucleic acid amplification approaches is *reverse transcription loop-mediated isothermal amplification (RT-LAMP)*. In this method, the RNA genome of SARS-CoV-2 is first reverse transcribed to cDNA and is then amplified using four to six target-specific primers [18]. Some commercial COVID-19 diagnostic kits based on this technique are already on the market . Abbott ID Now is such an example. This method only requires 5 min to give positive results. Recently, however, issues on false negativity have been raised for the Abbott ID Now [19]. This may be attributed to the compromised performance of the RdRP target (one of gene sequenced from SARS-CoV-2 genome) used in this assay, which is supposed to be mutating and evolving.

Rolling circle amplification (RCA) is another isothermal amplification method, in which a segment of the target genome is circularized and amplified by a highly processive strand-displacing DNA polymerase [20]. Compared to the LAMP assay, the RCA method is simpler since it requires fewer steps and can be performed at room temperature. This method offers higher sensitivity than RT-PCR since it amplifies the target sequence by ∼10,000. In addition, it presents high specificity, thus reducing false-positive results often encountered in PCR-based assays [21]. However, this method requires a circular template whose preparation is dependent on the length of a linear template and the ligation efficiency of the DNA circularization; inappropriate design of complementary sequences therefore results in failure of amplifications [13].

Lateral Flow-Based Detection on Nucleic Acids and Protein

The nucleic acid-based isothermal amplifications discussed above partially overcome the limitations of conventional RT-PCR methods, as they do not require elaborate laboratory facilities while their turnaround time is short. However, these methods still

demand trained staff to perform different sample collection and processing steps [13]. To give a solve to these issues, paper-based lateral flow assays (LFAs) have gained interest due to their low cost, easy manufacture, and full compatibility with POCT, which allow them to be easily performed by anyone at home. In LFAs, both nucleic acid detection methods and immunoassays can be utilized. The device is often made of papers with immobilized capture probes. Upon binding with nucleic acid targets, the probes give a visible signal.

IgM/IgG rapid test kits are available for qualitative antibody testing of COVID-19. Weak signal is one of the significant problems associated with the immunoassay-based lateral flow assay, which results in reduced sensitivity [22]. Different signal enhancement strategies thereafter have been proposed, such as the use of colloidal gold nanoparticles conjugated with the probes. Upon binding with the target, the gold nanoparticles linked to the capture probe aggregate to change the color, enhancing the signal [23].

At the Department of Medicine and Surgery ASST Settelaghi (University of Insubria), in the north of Italy, a diagnostic accuracy study to validate the use of a rapid salivary test (RST) as a point-of-need antigen test suitable for a mass screening program has been conducted. The RST consisted of an antigen test based on a customized lateral flow assay (LFA) kit which was used to detect the presence of the virus in the saliva by identifying the viral spike protein.

A total number of 122 patients were recruited in this study. The sensitivity of the RST was 0.93 (95% CI: 0.77–0.99), while its specificity was apparently low, i.e., 0.42 (95% CI: 0.32–0.53). These results were explained by two reasons. Firstly, specificity was reduced probably because most of the suspected false positives with RST were also quite positive from salivary RT-PCR, giving reason to the index test. Therefore, their nasopharyngeal swab provided a false-negative result. Secondly, observers reported some difficulty reading the strip, particularly for low-intensity signals. In these cases, the observers tended to overestimate the positivity of the test, and this would explain most of the remaining false-positive cases [24].

In our clinical practice during the pandemic, within the High Intensity Medicine Department dedicated to the care of patients with SARS-CoV-2 infection (ASST Settelaghi Hospital in Varese, north of Italy), the rapid salivary test became useful for identifying patients with negative SARS-CoV2 swab but with high clinical suspicion, concretely demonstrating its high sensitivity and its usefulness as a complementary test.

Clinical Criteria

The possibility of COVID-19 should be considered primarily in patients with new-onset fever and/or respiratory tract symptoms. The clinical manifestations ranged from mild nonspecific symptoms to severe pneumonia with organ function damage. The common symptoms are fever, cough, fatigue, dyspnea, myalgia, and smell and taste disturbances [25]. One study showed 39.6% of 140 confirmed COVID-19 patients had gastrointestinal symptoms [26] and 10.1% presented with gastrointestinal discomfort at onset in Wang's study [27].

Although it may be difficult to accurately distinguish COVID-19 from other viral respiratory infections, development of acute dyspnea several days after the onset of the initial symptoms is suggestive of COVID-19 [28], as well as the presence of anosmia and dysgeusia, hallmarks of this virus infection. The likelihood of COVID-19 is increased if the patient resides in or has traveled within the prior 14 days to a location where there is community transmission of SARS-CoV-2. Residence in congregations or participation in events where groups of cases have been reported represents a high risk of exposure and likewise all people working in health facilities where outbreaks have occurred.

Close contact includes being within approximately 2 m of the affected individual for more than a few minutes while not wearing personal protective equipment or having direct contact with infectious secretions while not wearing protective equipment.

Who Needs to Be Tested?

In response to the rapidly evolving COVID-19 pandemic, countries used different testing approaches depending on testing capacity, public health resources, and the spread of the virus in the community.

When the first cases in Italy began to appear, the criteria for carrying out molecular tests were very limited; the Ministry of Public Health had defined the following criteria [29]. *A suspected case of infection is defined as a person with acute respiratory desease of any degree of severity that, within 14 days preceding the onset of symptoms, has one of the following exposures:*

1. *close contact with a confirmed symptomatic case of SARS-CoV-2 infection*
2. *visited or worked in a healthcare facility in a country where nosocomial infections have been reported from novel coronavirus (e.g. Codogno, in Lodi, at that time)*
3. *visited or worked in a live animal market in Wuhan (China) or close contact with animals in countires where novel coronavirus it is known to circulate in animal populations or where human infections have occurred for presumed zoonotic transmission.*

As the number of suspect cases increased, it became immediately clear how these criteria were too restrictive, and did not allow the diagnosis to be made correctly, and furthermore made it difficult to isolate suspect patients. This had led to a silent spread of infection in hospitals facilities, involving hospitalized patients and healthcare personnel.

On March 2020, the WHO and the Centers for Disease Control and Prevention (CDC) removed restrictive testing criteria, recommending that clinicians use their judgment to determine whether a test should be performed.

On March 2020, the Minister of Public Health has issued a new circular defining the new criteria, in accordance with WHO indications [30]:

1. A person with acute respiratory infection (sudden onset of at least one of the following signs and symptoms: fever, cough, and difficulty breathing) and without another etiology that fully explains the clinical presentation and who has a travel history or residence in a country/area where local transmission is reported during the 14 days preceding the onset of symptoms
2. A person with any acute respiratory infection and who has been in close contact with a probable or confirmed case of COVID-19 in the 14 days preceding the onset of symptoms;
3. A person with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease—e.g., cough, difficulty breathing) and that requires hospitalization (SARI) and without another etiology that fully explains the clinical presentation
   - In the CDC (Centers of Disease Control and Prevention) recommendation document, updated on July 2020, five populations for which SARS-CoV-2 testing is appropriate are described:
   - Individuals with signs or symptoms consistent with COVID-19
   - Asymptomatic individuals with recent known or suspected exposure to SARS-CoV-2 to control transmission
   - Asymptomatic individuals without known or suspected exposure to SARS-CoV-2 for early identification in special settings
   - Individuals being tested to determine resolution of infection
   - Individuals being tested for purposes of public health surveillance for SARS-CoV-2

   Generally, viral testing for SARS-CoV-2 is considered to be diagnostic when conducted among individuals with symptoms consistent with COVID-19 or among asymptomatic individuals with known or suspected recent exposure to SARS-CoV-2 to control transmission or to determine resolution of infection. Viral testing is screening when conducted among asymptomatic individuals without known or suspected exposure to SARS-CoV-2 for early identification and surveillance when conducted among asymptomatic individuals to detect transmission hot spots or characterize disease trends [31].

Symptomatic Patients

If possible, all symptomatic patients with suspected infection should undergo testing; the diagnosis cannot be definitively made without microbiologic testing. However, during the emergency, the shortness of reagents may not make the molecular test available to everyone with suspected COVID-19. IDSA [32] has suggested priorities when testing capacity is limited; high-priority individuals include hospitalized patients (especially critically ill patients with unexplained respiratory illness) and symptomatic individuals who are healthcare workers or first responders, work or reside in congregate living settings, or have risk factors for severe disease.

In many cases, when the availability of testing is limited, the diagnosis was made presumptively based on a compatible clinical presentation in the setting of an exposure risk, particularly when no other cause of the symptoms was evident.

Asymptomatic Individuals

Testing certain asymptomatic individuals may also be important for public health or infection control purposes. Potential indications for testing asymptomatic individuals include [33]:

- Early identification of infection in congregate living facilities that house individuals at risk for severe disease (e.g., long-term care facilities, correctional and detention facilities, homeless shelters)
- Screening hospitalized patients at locations where prevalence is high (e.g., ≥10 percent PCR positivity in the community)
- Prior to time-sensitive surgical procedures or aerosol-generating procedures
- Prior to receiving immunosuppressive therapy (including prior to transplantation)
- Following close contact with an individual with COVID-19 (this includes neonates born to mothers with COVID-19)

However, the time to detectable RNA following exposure is unknown, so the optimal time to test for COVID-19 following exposure is uncertain; 5–7 days postexposure is recommended based on the average incubation period. Even if a contact has a negative viral test following exposure, quarantine is still suggested in most cases.

Routinely Blood Test

The currently available data suggest that laboratory test results are often altered in COVID-19-affected patients, and some of these may also be considered significant predictors of adverse clinical outcomes. The most frequent abnormalities observed in SARS-CoV-2 infection are lymphopenia; increased values of CRP, LDH, ESR (erythrocyte sedimentation rate), and D-dimer; and low concentrations of serum albumin and hemoglobin [34]. Many laboratory abnormalities were instead predictive of adverse outcome, as summarized in Table 4.1.

Procalcitonin does not appear substantially altered in patients with COVID-19 at admission, but the progressive increase of its value seems to correlate with a worse prognosis. Serum procalci-

Table 4.1 Main laboratory abnormalities in patients affected by SARS-CoV-2 infection with unfavorable progression

Main laboratory abnormalities in patients affected by SARS-CoV-2 infection with unfavorable progression
– Increased white blood cell count
– Increased neutrophil count
– Decreased lymphocyte count
– Decreased albumin
– Increased creatinine
– Increased lactate dehydrogenase
– Increased alanine aminotransferase (ALT)
– Increased aspartate aminotransferase (AST)
– Increased total bilirubin
– Increased D-dimer
– Increased C-reactive protein
– Increased ferritin

tonin levels are typically normal in patients with viral infections, whereas its gradual increase is probably due to bacterial superinfection, which could precipitate the clinical course of the illness.

Thus, a simple blood test helped us in identifying false-positive/false-negative RT-PCR tests, playing a crucial role in the mass screening of potential COVID-19-infected individuals, especially in the first phase of pandemic when large shortage of RT-PCR reagents and specialized laboratory did not allow early detection of the infection.

The Role of Imaging

As already said, COVID-19 is highly contagious; thus, early detection is of paramount importance to isolate suspected cases and contacts to control its outbreak.

Chest imaging (in particular high-resolution chest CT) has shown to have an irreplaceable role in the diagnosis of COVID-19, mainly in the context of typical clinical presentation with negative results of first RT-PCR. Typical chest CT imaging includes multiple, peripheral, bilateral, patchy, subsegmental, or segmental ground-glass opacities and areas of consolidation which are mostly distributed along bronchovascular bundles and subpleural space; air bronchograms with area of consolidation and bronchial wall thickening are often present (Fig. 4.1).

In a report of 51 patients with chest CT and RT-PCR performed within 3 days, the sensitivity of chest CT was greater in comparison with RT-PCR assay at initial presentation (98% vs. 71%, respectively). These patients whose nucleic acids tests were initially negative for SARS-CoV-2 infection but have suggestive imaging features on chest CT did test positive later with repeat swab test. Thus, it has been recommended that patient with positive imaging findings but negative RT-PCR test should be isolated and molecular test repeated to avoid misdiagnosis.

However, the need for an early diagnostic definition could in some cases make the waiting of the molecular test result prohibitive; in addition there were many patients with false-negative test results (even after repeating the test). Thus, some hospitals in the

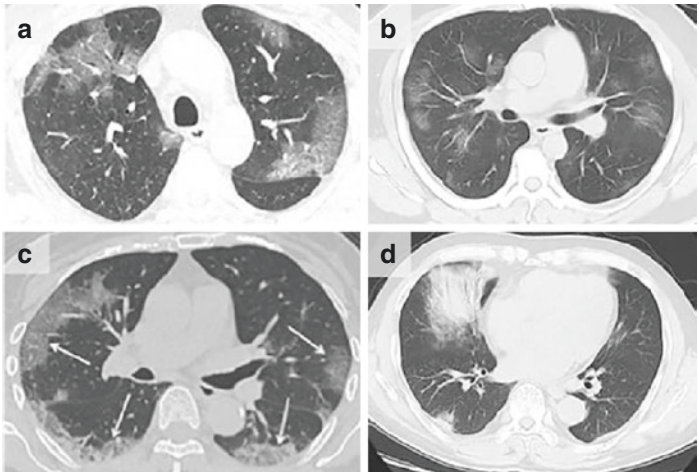

Fig. 4.1 Typical CT findings of COVID-19: (**a**) multiple patchy areas of pure ground-glass opacity (GGO) and GGO with reticular and/or interlobular septal thickening; (**b**) multiple patches, grid-like lobule, and thickening of interlobular septa, typical "paving stone-like" signs; (**c**) bilateral ground-glass and consolidative opacities with a striking peripheral distribution; and (**d**) large consolidation in the right middle lobe, patchy consolidation in the posterior and basal segment of the right lower lobe, with air bronchogram inside*. *Imaging from Wenjing Yang, Arlene Sirajuddin, Xiaochun Zhang, The role of imaging in 2019 novel coronavirus pneumonia (COVID-19), Eur Radiol 2020 (Copyright © European Society of Radiology 2020: This article is made available via the PMC Open Access Subset for unrestricted research re-use and secondary analysis in any form or by any means with acknowledgement of the original source. These permissions are granted for the duration of the World Health Organization (WHO) declaration of COVID-19 as a global pandemic)

north of Italy, given its high sensitivity, have established the diagnosis of COVID-19 in patients with high clinical suspect based only on chest HRCT.

The main issue of using chest CT for COVID-19 diagnosis is due to its low specificity (25%): differential diagnosis with other viral/atypical pneumonia is necessary.

Although chest CT represents a valid screening tool, identification of viral RNA remains the gold standard.

What About Serology?

Development of antibody response takes time and can be host dependent; moreover, the duration of the immune response is still unknown, as there is still no certainty about its real protection from a second infection.

Early study suggests that the majority of patients seroconvert between 7 and 11 days postexposure to virus; as a result of this natural delay, serologic test is not useful in the setting of acute illness, and a negative results would not exclude SARS-CoV-2 infection, particularly among those with recent exposure to the virus.

Differently from the traditional hallmark of humoral immune response characterized by early IgM expression and subsequent maturation into IgG, some reports of SARS-CoV-2 patients indicate that IgM expression is observed concurrently with IgG expression. Thus, dating infection as recent/acute or past on the basis of Ig isotype is not a reliable test.

Another potential issue is due to the cross-reactivity of antibody to non-SARS-CoV-2 coronavirus protein: positive results may be the hallmark of past infection with other coronaviruses.

In conclusion, the gold standard for the diagnosis of COVID-19 is the identification of the virus with nucleic acid-based methods, despite their sensibility and specificity are not 100%. Thus, early identification of epidemiologic risk factors and suspect clinical symptoms is helpful in defining whom to test and in reducing the number of false positive.

Chest imaging (mainly HRCT) has been proven to be very sensitive in detecting viral pneumonia and represents a valid and essential tools in the diagnostic flow chart, mainly in patient with negative nasopharyngeal swab but with high clinical suspicion.

In the pandemic scenario, rapid and noninvasive test would be desirable: antigenic tests have been developed, but their sensitivity and reliability is not well established and clinical trials are needed.

The role of serology test is actually uncertain [35]; serologic assay that accurately assesses prior infection will be essential for epidemiological study, but the role of human immunity response to COVID-19 is still undefined.

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5 Isolation Measures for COVID-19 Patient

Tiziana Ciarambino

Introduction

On December 2019, China notified the outbreak to the World Health Organization and on January 1 the Huanan Seafood Market was closed. On January 7, the virus was identified as a coronavirus that had >95% homology with the bat coronavirus and >70% similarity with the SARS-CoV. The 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) as it is now called is rapidly spreading from its origin in Wuhan City of Hubei Province of China to the rest of the world [1]. While COVID-19 transmits as a droplet pathogen and is placed in Category B of infectious agents (highly pathogenic H5N1 and SARS), by the China National Health Commission, infection control measures recommended are those for category A agents (cholera, plague). Several properties of this virus make prevention difficult, namely, nonspecific features of the disease, the infectivity even before onset of symptoms in the incubation period, transmission from asymptomatic people, long incubation period, tropism for mucosal surfaces such as the conjunctiva, prolonged duration of the illness, and transmission even after clinical recovery. In the absence of vaccines and specific

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therapy, the prevention is crucial. In this report, we describe the isolation measure for COVID-19 patients.

Isolation Measures

The only public health tools to control person to person transmittable diseases are isolation and quarantine, social distancing, and community containment measures [2].

Isolation

Isolation of confirmed or suspected cases with mild illness at home is recommended. Isolation is the separation of ill people from non-infected people and usually occurs in hospital settings but could also be done at home for mild infections [3]. For isolation to be successful in preventing transmission, case detection should be earlier, before the onset of viral shedding or at least before the onset of peak viral shedding. For SARS-CoV-2, a highly sensitive case definition was used with a focus on fever or respiratory symptoms and an epidemiological link (contact or travel history). All suspected patients were isolated until SARS-CoV-2 was ruled out. Patients should be placed in separate rooms. Patients should be asked to wear a simple surgical mask and practice cough hygiene. The rooms, surfaces, and equipment should undergo regular decontamination preferably with sodium hypochlorite. All contacts, including healthcare workers, should be monitored for the development of symptoms of COVID-19. Caregivers should be asked to wear a surgical mask when in the same room as patient and use hand hygiene every 15–20 min. Patients can be discharged from isolation once they are afebrile for at least 3 days and have two consecutive negative molecular tests at 1-day sampling interval [4].

Quarantine

This procedure involves movement restriction, ideally combined with medical observation during the quarantine period, of close contacts of infected patients during the incubation period [5]. The premise for successful quarantine is prompt and comprehensive contact tracing of each and every confirmed patient. Quarantine can take place at home or in designated places such as hotels, and both of these options were used during the SARS-CoV-2 pandemic. Quarantined contacts had to record their temperatures and were visited or telephoned, daily, by a member of the public healthcare team. If the contact developed symptoms, they were investigated at a designated healthcare facility. The principle is that if the person under quarantine developed illness, that person would not have any close contacts to spread the disease, effectively reducing the R0 of the outbreak to less than 1. Once it is no longer feasible to identify all infectious individuals and their contacts in the attempt to slow the spread of disease, a possible next step is to apply community-wide containment measures.

Community-Wide Containment

Community-wide containment is an intervention that is applied to an entire community, city, or region, designed to reduce personal interactions [2]. These interventions range from measures to encourage personal responsibility to identify disease, increase social distancing among community members including cancellation of public gatherings, and finally implement community quarantine [3]. Enforcement of community-wide containment measures is far more complex than isolation or quarantine because of the larger number of people involved. The control measures, in China, during 2003 SARS epidemic, and

applicated in different countries, during this pandemia, included school closures and closures of all universities and public places, as well as the cancellation of the public holiday. Immediately, the R0 decreased greatly and consistently [6].

Hospital-Based Measures

These procedures included isolation rooms with barrier nursing techniques, strict enforcement of personal protective equipment for staff, and restriction of visitors and movement of staff. Infection control precautions were enhanced in all hospitals and included the provision of separate triage facilities for patients with fever or respiratory symptoms. Healthcare workers should be provided with fit tested N95 respirators and protective suits and goggles. Airborne transmission precautions should be taken during aerosol generating procedures such as intubation, suction, and tracheostomies. To reduce within hospital spread, hospitals banned all visitors to patients with SARS-CoV-2, as reported for SARS infection [7]. In Italy, temperature screening was mandated once daily for all healthcare workers [8]. Healthcare workers who developed fever had to report to a designated healthcare facility and were isolated until SARS-CoV-2 was ruled out. To accommodate the large number of patients with SARS-CoV-2 (both probable and suspect), in Italy, rapidly constructed Unit Covid-Hospital within few weeks.

Prevention of Global Spread

Following the WHO global alert, and a stronger emergency travel advisory issued by the WHO on March 11, 2020, almost all countries with imported cases were able to either prevent any further transmission or keep the number of additional cases small. Exit screening via thermal scanners was done for all departing passengers at all airports of affected countries. Many countries also implemented entry screening for all passengers arriving from affected areas. No travel bans were implemented at any time, but

travel advisories to avoid nonessential travel to countries affected by SARS were issued by several governments.

Conclusions

Containment of COVID-19 should remain the focus at the moment. The short-term cost of containment will be far lower than the long-term cost of non-containment. However, closures of institutions and public places, and restrictions in travel and trade, cannot be maintained indefinitely. Countries have to face the reality that individual case containment might not be possible in the long run, and there might be the need to move from containment to mitigation, balancing the costs and benefits of public health measures. Even if our public health measures are not able to fully contain the spread of COVID-19 because of the virus characteristics, they will still be effective in delaying the onset of widespread community transmission, reducing peak incidence and its impact on public services, and decreasing the overall attack rate. In addition, minimizing the size of the outbreak or suppressing its peak can reduce global deaths by providing health systems with the opportunity to scale up and respond and to slow down the global spread until effective vaccines become available.

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6 COVID-19 and Facial Masks: How, Where, When, and Why

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Although, as of summer 2021, it was a year that the COVID-19 age has started, despite research in the field of vaccine and medications, nothing has been done to improve antiviral mask and, overall, the inadequate way they are usually used.

It is necessary to obtain and produce mask *with a determinist effect* and the power to guarantee the absolute virus isolation (or a destruction which aims asymptotically to 100%). Nevertheless, it might be sufficient to limit the pandemic, in some circumstances, obtaining masks with a lowered efficiency but able to reduce the contagion and that are helpful for the sanitary authority.

Rational and balanced are the keywords for an appropriate use of mask. Unfortunately, sanitary institution indications vary from a country to another one: online guidelines are available, but detail and clarity differed. As example, by the end of 2020 (after several months since the beginning of the pandemics) nine countries and regions recommended surgical, medical, or unspecified masks in public and poorly ventilated places; 16 recommended against people wearing masks in public; and two explicitly recommended against fabric masks. In addition, 12 failed to outline the minimum basic World Health Organization guidance for masks [1].

In conclusion, "online guidelines for face mask use to prevent Covid-19 in the general public are currently inconsistent across nations and regions" [1]. At the beginning of the pandemic, as example, also the drastic use of military gas mask to protect surgeon during tracheotomies could be acceptable [2] as well as the project with 3D printer [3] and all the attempts with cardiopulmonary resuscitation mask [4].

O'Kelly et al. tested common fabric (as denim jeans and cotton flannel) with particle, demonstrating a performance of 40–45% in filter particle of the same size of virus [5]. Another article suggests the use of homemade three-layer nonwoven fabric plus granular tea towel or nonwoven shopping bag [6]. Debatable, the article influenced the choice to liberalize the production and use of antiviral masks that no respect EN rules. However, some authors emphasize the important psychological role of whatever mask for preserving mental health [7]; certainly an advantage, although not efficacy in protection.

In war, everything is accepted but *everything* cannot be the final resolution of mask battle. The problem hides different parameters which should be examined case by case. As example, put on and take off the mask during computer working [8] or mask-wearing plus instant hand hygiene to slow the exponential spread of the virus [9] and the side effect, as the alterations of cerebral hemodynamics because of NK95 mask [10] and moreover.

Eventually, the more the mask will be effective, the better operators can use it and better the result will be. The picture below (Fig. 6.1) stresses the idea.

The main aim of this chapter is to rationally suggest and analyze in a scientific manner the enormous antiviral mask problem. Some parameters as the Bacterial Filtration efficiency BFE) or the Particulate Filtration Efficiency (PFE), born to preserve patients during surgery operation or worker to pollutants, are not suitable as prevention devices for general population during viral pandemics.

Banalization and lack of preparation cannot be accepted anymore. Masks, as medications, vaccine, and other devices, need to be studied and tested.

Masks: What Is Their Application?

It is essential to define the adequate use of correct device in the specific setting. The aims of using a mask are numerous:

(a) The reduction of chance of interhuman contagion (in other words, R_0)[1] for all people
   1. Reduction of R_0 in specific subgroup of people
   2. Reduction of probability of contagion in confined setting

[1]We speculate that R_0 is not adequate to indicate the spreading of pandemic and it could not be used as a predictor.

The approximate use of model R_0 is unrealistic. We consider R_0 only for a clearer explanation. A predictive pandemic model is indeed necessary.

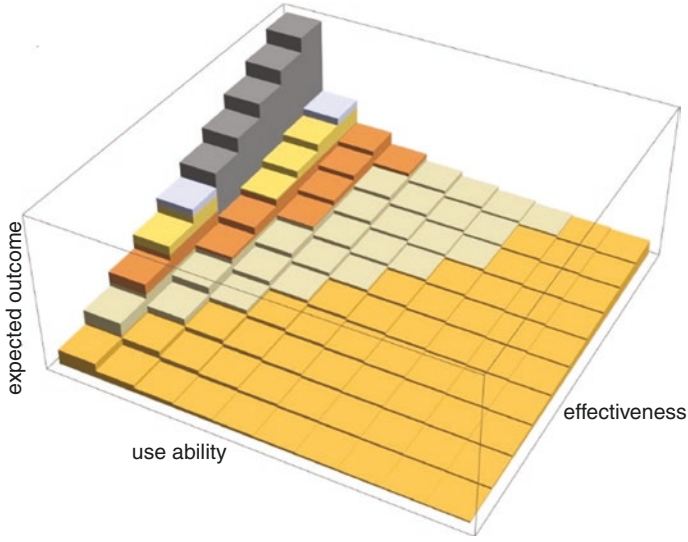

Fig. 6.1 The scale is calibrated from 1 to 10 where 1 is the worst value and 10 the best achievable. *Use ability:* operator or patient who wears mask appropriately, in the right position, and knows which mask is necessary, when it is necessary to wear and the way to preserve and change it. The use ability depends on who uses the mask, the final beneficiary. *Effectiveness:* objective mask features as the power of filter. It depends on the mask producer. *Expected outcome*: decrease of infection. The values of independent variables are arbitrary; however, they depend on the setting, on the site (hospital, street, market…), on the population sample, on social distancing, and so on. So, a lot of different parameters should be evaluated to explain the final effect of device and human behavior on infection. At the moment, European situation is included between orange and brown area, in other words, on lower levels than optimal ones to take advantages of protection mask power

3. Reduction of infection probability by other reservoir: animals, surfaces, polluted air, etc.

(b) Decrease inhalation probability together with virus and of other factors which can simplify virus transmission or increase pulmonary and other organ damage (as PM 3 and PM 2.5)

(c) Avoiding infection in determinist way (in all classes as above)

(d) Determining other healthy effect (as the need of safety and protection)
(e) Avoiding physical and psychological side effects

Take-home Messages

Mask must satisfy at least one or more of the features listed above. For each goal, a different mask is needed. How, when, and where to use mask must be explained to the population and doctors

The features to opt for the right choice of mask change case by case: a positive, infected person must wear a different mask which should avoid transmission to other negative people. On the other hand, a negative case should wear a mask which protects himself from the infection.

Mask Aim in Different Settings: A Pragmatic Approach

As already said above, analyzing all the possible events in the different environmental setting, results are extremely complex. In literature [11–16], some instances are present: mathematic models have been developed ad hoc to examine mask filter and leakage rate, models on how air allows scattering of aerosol with high risk of virus transmission, or on social distancing.

However, the actual studies are not decisive, probably for the different research which forbids the born of real model, able to explain the complexity of problem.

Figure 6.1 suggests some main cluster of parameters (use ability, mask filtering effectiveness); from each parameter, it is possible to obtain more and more variables to quantify and elaborate. However, a correct method should guarantee the use of representation and calculus with more dimensions (including as example social distancing, different indoor/outdoor settings, etc.). In the following figures, our aim is to explain with simple graphical shapes this complex problem.

PPE Basic Features in Different Settings

Figure 6.2 aims to explain the PPE indispensable features to reduce the probability of interhuman infection, according to the setting of use.

Usually, masks with a high breath capacity have a lower filter efficacy. For this reason, it is essential to define the correct device according to adequate trade-off between considered variables. Indoors and crowd setting are at high risk of infection, as it is seen in Fig. 6.2, and high-performance filter device might be necessary. However, the duration time of exposition affects the choice of the right device (the breath necessary for 5 h in school is different from that of 30 min of bus).

Appropriate Use to Enhance Mask Efficacy

This section aims to describe the increase in the effectiveness of individual protection against contagion through the adoption of complementary measures. This scenario has different effectiveness according to the context in which it is found and represents only an additional increase to the minimum standard, which must be guaranteed by the use of appropriate protection devices.

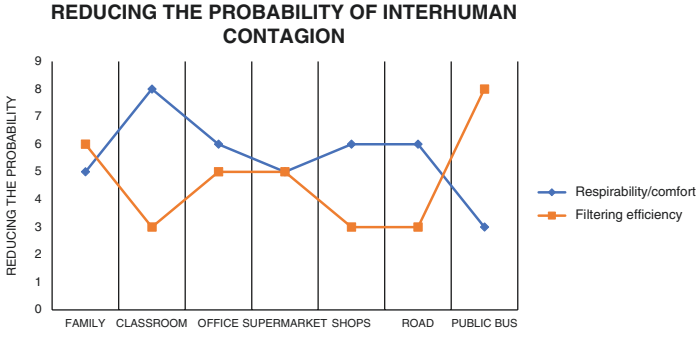

Fig. 6.2 The classes represented (respirability/comfort–filtering efficiency) consider duration time of exposition, numerousness of people, and the supposed risk grade associated to the individual presented scenario

The idea is to give correct information and advices to people. Jones NR et al. [17] suggest a similar method of operation, based on colorful tactic to emphasize the risk of viral transmission from a positive asymptomatic change according to the setting, the activity conducted (e.g., speaking or being quiet), and the presence or absence of masks. Increasing social distances, the infection rate should be lowered about 30–40% [18]: this conclusion is relevant in the choice of a mask, which must be more protective when social distances cannot be maintained, as in a crowded public transport (Figs. 6.2 and 6.3).

In some specific settings, e.g., the healthcare workers (HCW), the problem of mask choice has been deeply analyzed [19]: we speculate that the right choice of different mask type depends on the specific task of HCW and on the type of virus-spreading particles. However, some relevant aspects (e.g., leakage due to improper mask use) have not been studied sufficiently, as a consequence of the difficulties of an experiential nature.

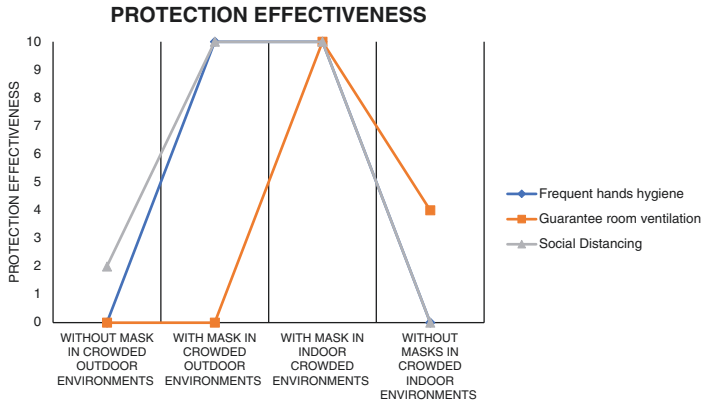

Fig. 6.3 The protection effectiveness strongly depends on the environmental context. Frequent hand hygiene, room ventilation, and social distancing do not perform an alternative function to the presence of the required PPE. Adequate spacing, hand hygiene, and indoor good ventilation can increase the level of protection provided by masks toward more solid and performing standards

In other more complex settings (e.g., some types of urban transport, supermarkets, etc.) there are insufficient studies to draw conclusions. Several articles have studied the schools, in particular for the impact of school closure on mortality or contagions [20, 21], or discussed aspects relating to social distancing, the use of masks, hygiene rules, the possibility of using tracking systems, and other topics [12, 22–24]. We believe that the differences in the approach of these studies and the highly different ethnocultural settings do not allow us to draw specific conclusions applicable to the PPE sector.

It is evident that for the different environmental conditions and different degrees of risk exposure, very different protection tools are needed, and any DIY mask (home "do-it-yourself mask") can not only prove useless but can even worsen the risk of exposure by making the person and his neighbors feel protected while in fact they are not or are not sufficiently.

How the Masks Should Be Used and What Level of Empowerment Is Required for the Various Situations of Use

This aspect is strategic. For each type of use and for each type of grinder, the citizen must have clear and easily understandable explanations on the following:

- How to wear the mask and for how long
- What risks he runs wearing it incorrectly
- How he can change the use of the mask according to other measures taken at home or in public places
- When to change it according to the type of setting in which it is located
- How to store and dispose it
- On possible side effects, use or nonuse in the presence of other possible contaminants or pathogens (pollen, bacteria, other viruses, pollutants)

They should also be familiar with the general characteristics of the masks available on the market and be able to read the package leaflet. This should be mandatory, and very clear, with explanatory images.

Furthermore, every citizen, every employer, and every magistrate have the right to know how much that mask protects him, if the protection is absolute or not, for how long it lasts, and other parameters that allow him to make informed choices about the behavior to be adopted and on the risks, proper to their family members.

These rules might seem too difficult, but they are much easier to explain than the use of drugs (definitely more complex) that everyone can use.

Take-home Messages

If the masks are our first and most effective line of defense against contagion, we cannot use them in a nonspecific and uncritical way. Citizen empowerment is essential.

Doctors and healthcare personnel should have reference manuals for the choice of masks, to give advice to citizens and the sick, and in some cases they could prescribe differentiated uses of masks or other shielding systems (e.g., air cleaner) in particular in the presence of symptomatic patients at home or outside the hospital setting.

Side Effects

Warning: the most serious and frequent side effect paradoxically is contracting a viral disease. It happens when the mask is not protective, and thus the wearer is exposed to a greater risks not adopting more effective safety measures as, for example, staying at home or going to places with very high social interactions *Caveat*.

Side Effects and the Correlation Risk/Benefit

The masks can have high or low filtering efficiency according to their physical structure; filtering efficiency can change from batch to batch within different confidence intervals (low only for high-quality masks). Finally, individual masks may have manufacturing defects or be related to improper maintenance. Furthermore, the user can use the mask in an ideal way (the right mask, well-worn and held on the face for the right time, in the right environment) or in a nonideal way. Furthermore, it must be considered that the efficiency filters and the rules of use can be strongly influenced by other variables, for example, the ambient humidity, the presence of pollutants in the air, the type of circulation of the air itself, and others.

The sum of these factors contributes to influencing the results in terms of contagion prevention, but, since they are not measurable and are usually unknown to the citizen, it will cause an incorrect (or random) assessment of the real risk of exposure to the infection. We consider this as a side effect of use, like taking a drug whose useful dose (whether too high or low) and the interval between doses cannot be defined.

Unlike the obvious and measurable errors of use that are obviated through appropriate empowerment (e.g., the very common error of the mask worn without covering the nose can be corrected easily by informing the citizen), it must be admitted that there are a series of "unknowable" stochastic factors intrinsically linked to the use of masks.

Figure 6.4 summarizes this particular side effects in different setting; it is highly probable that the negative effects of this factor depend on other parameters, such as the different setting (outdoors or indoors, crowded or not) as well as the coexistence of more trivial errors, as in the cases analyzed in the previous paragraphs. Therefore, Fig. 6.4 does not refer to specific side effects of masks, briefly described in the next paragraph. In fact, where there are side effects such as those described in Sect. 3.2, the problem will be to carry out specific treatments or to change the mask.

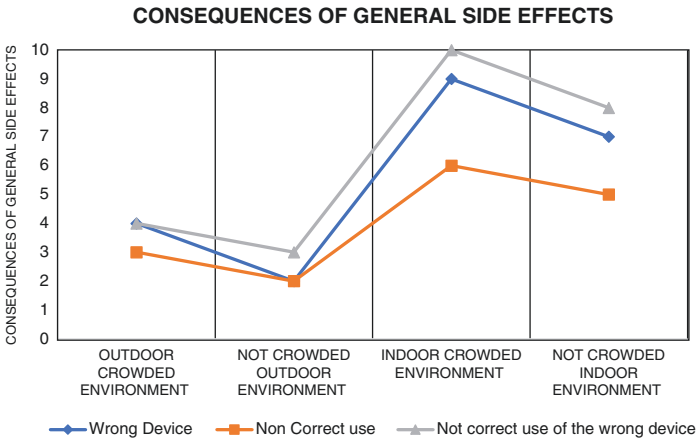

Fig. 6.4 The consequences of general side effects derived from a wrong device, a not correct use, or lastly not correct use of the wrong device in different setting, crowded or not, indoor or outdoor. In indoor environment, the risk of general side effects is enormous, especially when the wrong device is used in uncorrected way

It is also clear from the table that the most critical situation is present in case of a closed and crowded environment, situation in which it is necessary to adopt extreme care not only in the choice of the device to be used but also in the time and method of use. In other words, the higher benefit from a correct use of mask will be obtained in indoor crowded place. In this setting, the use of ventilation systems and air cleaners with HEPA 14 or filters of similar effectiveness can be strongly suggested.

Specific Side Effects

The possible side effects should be classified: (a) in relation to the different pathophysiological effect that a mask can produce but also (b) in function of the completely wrong use by unpredictable or inexperienced users, which is always possible due to the very large diffusion.

This second category can include all cases of improper use even by children, people with pisco motor coordination difficulties, and numerous others (in analogy with what is described for plastic bags, which can suffocate those who use them to play). Fire resistance must also be considered, along with the facilitating effect on domestic accidents (e.g., a nearsighted elderly person with glasses may trip over a carpet if the glasses fog up from a misused or unsuitable mask).

The detailed analysis of these aspects is not within the scope of this chapter. Regarding specific side effects (a), we underline the possible effects associated with low breathability of many models of masks, particularly in fragile patients with COPD and/or SARS-CoV-2 pneumonia, who present a respiratory cycle with very low DP, or people who engage in physical activity at work or for leisure and numerous others. The masks can facilitate the accumulation of CO_2 in the anterior chamber (in particular, cup masks with low breathability), or they can require more work of the respiratory system. These effects may be greater in some categories of patients, particularly children and the elderly.

Finally, there is the problem of the sense of discomfort and the psychological implications, both favorable (feeling protected) and unfavorable, associated with intolerance and a sense of dyspnea or real induction of dyspnea.

Mask and Biohazard: How to Reuse and Wash Mask

Masks are composed of different polymers or nonwoven fabric, derived from industrial processes of melt blown or spun bond and other; these are highly polluting compounds, which, together with those used for nappies and diapers, have an unfavorable ecological impact. Moreover, each mask is a repository of viruses and bacteria [25].

The correct management of masks depends on the specific type of mask used. As example, common single-used surgical mask should not be reused or disinfected. People should wear and take off mask without touching the external surface. It is necessary to clean hands before putting mask on, as well as before and after

taking it off, and then the mask should cover the nose, mouth, and chin. Then the single-used mask should be disposed in undifferentiated container. Surgical masks are intended to protect the patient: they adapt to the face of the user and can be worn for not more than 8 h but should be changed earlier when damaged or visibly wet [19]. Respirator masks available in Europe are FFP (filtering face piece) masks (Standard EN 149) and in the USA an N95 mask. According to the filter performance of particles >0.3 μm, there are three categories: FFP1 (>80%), FFP2 (>94%), and FFP3 (>99%). FFP2 masks are intended to protect the carrier from the inhalation of airborne particles, and if they have masks with expiratory valves, they are not indicated in the COVID-19 setting because they do not protect others. More complete explanations on the classification and basic characteristics of PPE masks are reported in the literature [26].

Still Open Problems and Questions to Be Solved

1. Variolation [27] is another virus feature to consider. The reduction of variolation could be obtained with PEE, stimulating adaptive immunity. Without a doubt, the last circumstance is worse than the possibility of not being infected and, also if true, it cannot rely on fate, such as the use of mask, more or less capable of an effective virus filtering.
   This problem should be analyzed, also considering low, incessant, risk exposition. We consider it fundamental in this phase to conduct research to understand what happens for small, repeated inspections and/or expositions by different routes (through different mucous membranes or through the conjunctiva or through the gastrointestinal apparatus). In fact, the extremely high dissemination of virus makes extremely probable phenomena of repeated exposures by different contact routes, in different periods of life and to different viral strains.
2. Eventually, legal and ethics implications should be evaluated as penal and civil responsibility. This is a significant critical issue, considering the main and probably most important role of PPE at the moment.

3. Mask sterilization and reuse. Few studies report different results about this topics suggesting or not different methods of mask decontamination or sterilization [28–30]. A definitive conclusion cannot be reached, even if a mild sterilization with ethyl alcohol at 70°, for a few minutes and not for 2 hours as carried out in some tests, is easy to carry out even in the home environment, can be suggested in many cases.
4. Mask chemistry and their interactions with viral particles
   Many woven fabrics were found to form fiber-webs resulting in an increase of material disorder, thereby disrupting flowing gas streamlines and providing more surfaces with which the aerosols can interact. Viral particles present electric charges by which different types of physical chemical interactions can occur between virus and mask components [31]. When particles interact with a filter, they are collected and retained by a fiber through van Der Waals forces so that the particle may no longer follow a flowing gas streamline remaining entrapped. Electrostatic deposition, occurring due to a charge difference between a fiber and a particle, can also be important in some materials. Synthetic materials act in different ways. For example, cationic polymers have shown high affinity for virus binding, and hydrophobic polycationic surfaces have been reported to inactivate influenza viruses owing to irreversible attachment on the surface followed by the damage of viral structure with a loss of infectivity. Hydrophobic and non-charged oleophilic materials have been shown to destroy virus envelope, whereas anionic copolymers may alter surface protein structure by changing the environmental pH or directing interact with proteins causing denaturation.

   Surgical masks are made in nonwoven fabric. Productive processes involving TNT allow us to obtain a random layout of fibers which can guarantee high filtration levels. For external layers, which perform a protective function towards the face, are more suitable TNT in Spunbound; otherwise, for the internal layer, deputed to the filtration function, microfibers smaller than TNTs in Meltblown technology are required. Microfibers that spun with Spunbound technology are thicker than those produced with MeltBlown technology, which confers a higher

robustness and cheapness compared to the others. TNT produced via MeltBlown technology, instead, confers higher filtration levels due to microfibers' dimensions, resulting less resistant than the previous. Facial filtering FFP1, FFP2, and FFP3 are made with nonwoven fabrics having different properties and functionalities. The external layer protects from the bigger particles, and the intermediate one is usually made in MeltBlown tissue and filters smaller particles. The internal layer, in contact with the face, has a double functionality: maintain the shape of the mask and protect the latter from the humidity produced by human breath, cough, or sneezes. The discriminant in terms of effectiveness for each device is represented by the filter. Ultimately, the difference through filtering structures determines its usage. Thanks to the filter layers, obtained with different technologies, as MeltBlown, we can have truly remarkable differences in filtering and global quality.

In summary, individual insulation can be achieved with masks, as long as it can filter a significant proportion of the infectious material [32]. It should also be considered that, given the resistance characteristics of SARS-CoV-2, the virus contaminating masks can be transmitted from different particles, (a) like the virus or just wider and then with size $\geq$0.1 μm, (b) aerosols created by droplet desiccation (droplet nuclei) possibly associated with air pollutants of very variable sizes anyway with an order of a μm, (c) from very large and flashiest droplets (5 μm upto 50 μm), and (d) from submillimeter or millimetric droplets containing potentially infecting organic material (saliva, mucus, etc.).

In our opinion, it is a serious mistake to focus only on the points c and d and even worse if one does it to justify the use of totally inefficient or do-it-yourself PPE. Several investigations demonstrated that also an aerosol virus (b) transmission occurs, especially in confined settings (school and hospital rooms, dental clinic, etc.), although with a secondary efficiency in comparison with droplets. However, in intensive care units where respirators generate high levels of humidity, this transmission modality may have a significant impact.

More subtle particles, which can spread the virus, can be suspended in the air for undefined time because of their micron, aerodynamic size, and their low sedimentation speed (millimeters of seconds). Probably particles are diluted in the ambient and then the viral load is proportionally reduced but particle remains transmissible playing an important role in determining infection for the small but repeated viral loads in the absence of adequate air environmental filter.

Through cough or sneeze, particles can be spread at a distance of few meters, with a speed of about 150 km/h. Particles usually (except for class d) don't drop off immediately. It is a common mistake to focus only on class c. It becomes a serious mistake if it is done to justify handmade PPE, not very efficient also for class c. In some studies, it was demonstrated the presence of viral particles near the ill patients although he or she wears a surgical high-quality mask.

It is necessary to specify that we limit to mention only simple elements, but the list of parameters to consider is vast. We are trying to develop predictive models and means of measure, investigating in a sector where almost all (research institutional corporation, authority, and enterprises) are trivializing in a way that will remain in the scientific history as a negative example. Understanding how particles spread in the air is difficult, but it is more arduous for virus.

Conclusion

Warning: at present, we can estimate that the defensive potential of masks against the pandemic is reduced by about half, due both to the presence of many inefficient masks and to the frequent errors of use by the population.

The current laws about the use of masks do not include adequate distinctions according to the different environmental settings and the different grades of risk. The rules limit to stress the fact that devices with a higher filtering capacity should be used by people at high risk of exposure. In addition, the use of homemade masks can increase unconsciously the risk for who wears the mask and his neighbor for the wrong feeling of protection.

Although COVID-19 age pushed the accelerator on scientific research, likewise a correct scientific approach to develop and improve PPE missed. The main problems remain the appropriateness of guidelines who often are inadequate, not clear because not clear and unanimous are scientific evidence. This causes confusion between common people and more over healthy workers who go to front as martyr rather than a hero. The aim of this section is voluntarily provocative, suggesting the minimum standard necessary to guarantee adequate protection. The foundations descend from the modern medicine which has in primary prevention its strength.

Appendix. A Possible Modeling Strategy for the Mask Filtering

Masks can be considered in first approximation in a porous medium: in this situation, the Fick's second law for the diffusion in the presence of absorption of a solute (the viral particles) may be given as

$$\varepsilon \frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} - \rho \frac{\partial Q}{\partial t}$$

where C is the concentration, D the Brownian diffusion, and ε the porosity, while $\rho \frac{\partial Q}{\partial t}$ is an attractor term due to the absorption of the solute. It is to be noted that bulk density is bound to porosity by the equation $\rho = (1 - \varepsilon)d$, being d the density of the solid.

Yi et al. [33], for a mask with a layer having coordinate $x \in [0, L]$, wrote the balance equation for the virus in liquid water in the form

$$\frac{\partial(\varepsilon_W C)}{\partial t} = \frac{\partial}{\partial x}\left(\varepsilon_W D \frac{\partial C}{\partial x}\right) - \frac{\partial(\varepsilon_W v C)}{\partial x} - \frac{\partial(\rho \varepsilon_V)}{\partial t},$$

in which C is the viral concentration, ε_W the volume fraction of the liquid water, ε_V the volume fraction of viruses, D the Brownian

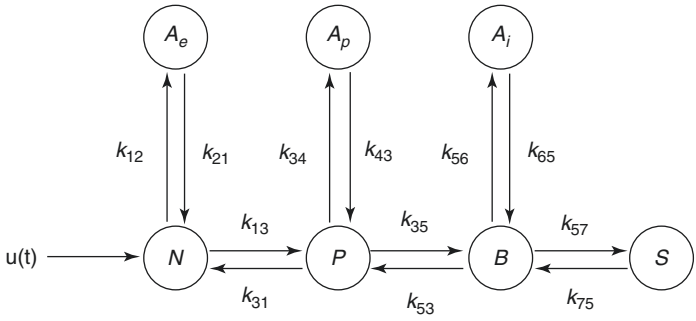

Fig. 6.5 A simple compartmental model for the virus spread across a face mask. N is the compartment "near" the external surface of the mask, P the pore, B the breath, and S the subject, while A_e, A_p, and A_i, respectively, represent the absorbed viral particles on the external layer of the mask, on the inner pore surface, and on the internal layer. The k_{ij} coefficients are assumed to be nonnegative real numbers

diffusion, and v the intrinsic velocity of water. Such a travel of the viruses through the mask could be simplified and basically represented in terms of compartments as given in Fig. 6.5.

It is assumed a supply of virus from the environment defined by the nonnegative real-valued time function $u(t)$. The viral particles spread among the various compartments assumed in the model, e.g., N (the space near the mask external surface), P (the pore channel), B (the breath of the subject), and S (the subject's own body), whereas A_e, A_p, and A_i are the compartments where the viral particles are stored when absorbed on the external surface of the mask, on the surface of the pores, and on the internal surface of the mask.

The kinetic parameters $k_{ij} \geq 0$ governing the transitions from a compartment to another one are assumed to be constant; however, the dynamics of the viral diffusion across the mask can also be generalized by taking the parameters as function of time $k_{ij}(t)$: this last assessment could be useful, by hypothesis, if the absorption capability of the mask fabric can be saturated, e.g., if there is

some carrying capacity for the absorption, so that a given $k(t)$ may have, for example, a logistic curve shape. At present, indeed, we may assume that the mask turnover in the same subject will be much more rapid than the mask saturation, so that, at this approximation level, a constant value for the k_{ij} parameters will be sufficient to describe the system.

From what above, one may evolve the following system of differential equations:

$$\begin{cases} \dfrac{\partial N}{\partial t} = u(t) + k_{31}P + k_{21}A_e - (k_{13} + k_{12})N \\ \dfrac{\partial A_e}{\partial t} = k_{12}N - k_{21}A_e \\ \dfrac{\partial P}{\partial t} = k_{13}N + k_{43}A_p + k_{53}B - (k_{31} + k_{34} + k_{35})P \\ \dfrac{\partial A_p}{\partial t} = k_{34}P - k_{43}A_p \\ \dfrac{\partial B}{\partial t} = k_{35}P + k_{65}A_i + k_{75}S - (k_{53} + k_{56} + k_{57})B \\ \dfrac{\partial A_i}{\partial t} = k_{56}B - k_{65}A_i \\ \dfrac{\partial S}{\partial t} = k_{57}B - k_{75}S \end{cases}$$

which in general matrix notation becomes

$$\frac{\partial \boldsymbol{q}}{\partial t} = \boldsymbol{K}\boldsymbol{q} + \boldsymbol{u}$$

with $\boldsymbol{K}$ being the coefficient matrix, while $\boldsymbol{q}$ and $\boldsymbol{u}$, respectively, are the virus compartment and the virus supply vectors. This basic and somehow coarse-grained phenomenological model can be generalized or else simplified by adding new compartments or compacting some compartments among the present ones.

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7 Clinical Pictures of COVID-19

Davide Carrara, Francesco Regoli, and Luigi Venturini

Coronaviruses are very common pathogens that in most cases cause flulike symptoms. Two beta-coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), can cause severe pneumonia with respiratory distress syndromes and death.

At the end of 2019, a new coronavirus, named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was identified for the first time in China (Wuhan). This virus spread rapidly causing a disease called COVID-19, which led to a global pandemic.

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This virus is typically transmitted through respiratory droplets and has an average incubation time of 4–5 days with a maximum of 14 days; more than 95% of patients who develop symptoms became symptomatic within 11.5 days.

Clinical spectrum is very heterogeneous, with a wide range of symptoms reported. It varies from an asymptomatic form to severe life-threatening disease [1, 2]. The respiratory tract is the principal target of SARS-CoV-2; however, many other organs and systems could be involved.

Asymptomatic infections are estimated to be about 20% of the total, reaching in some reports the 30–40%. A study performed on the passengers of the Diamond Princess (the cruise ship where a first major outbreak has been reported, becoming a model of the spread of the infection inside a close community) showed that about 19% of them were positive at the time of the screening test and 58% of them were asymptomatic at the time of diagnosis [3, 4].

COVID-19 is a pathology that mainly affects the respiratory system with variable manifestations, including in the mildest cases like dry cough (50% of patients), dyspnea (40%), and sore throat and fever (in 50% of patients and in about 90% of hospitalized patients) up to more serious cases with the appearance of a clinical picture characterized by hypoxemia, bilateral pneumonia, acute respiratory distress syndrome (ARDS), or septic shock (5% of overall patients and in 20% of the hospitalized ones). Fortunately, most infections are not serious (about 80%). Severe cases typically evolve in a two-step pattern, with a mild to moderate severity presentation in the first 8–10 days and a severe evolution thereafter [5].

COVID-19 can manifest itself with a wide clinical spectrum, and therefore it is important to identify various clinical phenotypes to optimize therapy. In a cohort of 44.500 confirmed infections, 81% was a mild form of infection, severe disease was reported in 14% of cases, critical form in 5%, and the overall case fatality rate was 2.3%. Among hospitalized patients, the proportion of critical or fatal disease is higher, with 27% of these requiring intensive care [6–8].

Some patients with an initially not serious illness can get worse, and this usually happens within a week. In a study of 138 patients hospitalized in Wuhan for COVID-19, dyspnea occurred on average 5 days after the onset of symptoms, and hospitalization occurred after an average of about 7 days [9].

The mildest and most common phenotype is characterized by fever, headache, and/or mild respiratory symptoms, such as cough (70% of patients) and sore throat, as well as asthenia; in this case, the X-ray is normal and there is no hypoxemia. The second phenotype is found in 80% of hospitalized patients, and it is characterized by the presence of hypoxemia and small opacity at chest X-ray compatible with pneumonia, the most important manifestation of this infection ($PaO_2 > 60$ mmHg with FiO_2 21%); these patients need monitoring. The third phenotype is less common (about 15–20% of hospitalized patients); the patient presents fever, marked hypoxemia with increased respiratory frequency ($PaO_2 < 60$ mmHg with FiO_2 21%), and multiple opacities at chest X-ray. This phenotype may be the evolution of the second one, or it may be the clinical manifestation of onset. Phenotypes 2 and 3 have good lung compliance and can avoid intubation. Phenotype 4 is characterized by severe hypoxemia and respiratory distress requiring intubation. At radiological evaluation, there are multiple bilateral opacities with interstitial involvement. This phenotype still has normal lung compliance. The patient generally presents a picture of "hyperinflammation," with hyperpyrexia and systemic symptoms. Phenotype 5, representing only a small percentage of cases, represents an advanced stage with overt ARDS, shock, and multi-organ dysfunction. ARDS can occur rapidly during the course of the disease (in 20% of cases within 8 days of the onset of symptoms) [10, 11].

About lung compliance, COVID-19 often shows a clinical picture of normal lung compliance associated with severe hypoxemia, a picture that is rarely found in ARDS by other causes. Gattinoni et al. postulated a different classification with two primary phenotypes, which differ on the basis of pulmonary compliance: type L, characterized by a high compliance (i.e., low elastance), with a low ventilation-perfusion ratio, and type H, characterized by a high elastance with a high right to left shunt. In

addition, in the first phenotype, lung weight and recruitability are low, while they are high in the second phenotype.

Generally, COVID-19 pneumonia has, at the beginning, the typical characteristics of the phenotype L; normal compliance indicates the presence of normal amounts of gas in the lung, so hypoxemia is due to hypoxic vasoconstriction—lung thickening is absent or present with ground-glass type, and therefore the weight of the lung is normal or slightly increased—and the non-aerated tissue is low and therefore there is only low recruitability.

This phenotype can remain unchanged, regress, or progress to the next phenotype. When pneumonia progresses or intrathoracic pressures increase (that can per se cause ventilatory stress), non-cardiogenic pulmonary edema is induced. The phenotype H is characterized by a reduced volume of gas inside the lung due to increased edema, a right to left shunt with perfusion of non-ventilated tissue, and an increase in lung weight due to the presence of lung opacity. The unventilated tissue is therefore increased, and, as in severe ARDS, there is high recruitability. The type H pattern has all criteria of severe ARDS [12].

Risk factors for the development of a serious pathology include cardiovascular comorbidity, diabetes mellitus, chronic lung diseases, malignancy (particularly hematological, lung borne, or metastatic), chronic kidney disease, obesity, and cigarette smoking; another risk factor is the male sex. Only 3% of patients have none of these risk factors. At blood testing, the following parameters are associated with a severe course: lymphopenia, thrombocytopenia, increased transaminases, LDH and inflammation indexes (e.g., PCR and ferritin), D-dimer, PT, troponin, CPK, and worsening renal function [13, 14].

Cardiovascular involvement can be a severe complication, associated with the possibility of developing arrhythmias, cardiac ischemia and shock, or thromboembolic complications, such as pulmonary embolism or cerebral ischemia [15–17].

Acute myocardial injury, defined by elevated levels of cardiac biomarkers or electrocardiogram abnormalities, is a common manifestation of COVID-19, and it's associated with an increased risk of mechanical invasive ventilation and mortality. Early data

in Chinese patients showed acute myocardial injury in 7–20% of patients with COVID-19.

Although various case reports have described myocarditis during the COVID-19 outbreak [18], few studies have included echocardiography or MRI; therefore, the real incidence of myocarditis remains unclear [19].

In a small cohort with 112 patients with COVID-19, 14 of these showed myocardial injury without the typical signs of myocarditis such segmental wall motion abnormalities of depressed left ventricular ejection fraction, suggesting a secondary genesis to the systemic condition rather than a myocardial infection [20].

Approximately 25% of patients hospitalized for COVID-19 developed heart failure [21, 22]. Heart failure with preserved ejection fraction can be triggered, especially in elderly, by fever, tachycardia, fluid overload, and impaired renal function [23]. Severe left heart failure is relatively uncommon [24].

Patients affected with COVID-19 are at an increased risk of arrhythmias due to underlying comorbidities, polypharmacy, and disease progression. Several studies have concluded that the prevalence of cardiac arrhythmias is higher in critically ill patients compared to noncritically ill patients.

Acute coronary syndrome (ACS) is a recognized complication of infectious disease. SARS-CoV-2 potentially triggers ACS through systemic inflammation that causes pro-thrombotic state or direct endothelial injury, which can result in plaque rupture, micro thrombosis, or coronary spasm. However, the exact incidence of ACS in COVID-19 patients is unknown, because during outbreaks in several countries, like Italy and the USA, the global number of hospitalization for ACS or percutaneous revascularizations is reduced [25–27], but there has been an increase in out-of-hospital cardiac arrest [28].

Venous thromboembolism is a well-known complication of COVID-19. Incidence of pulmonary embolism (PE) in hospitalized patients has been reported to be around 1.9–8.9%. Furthermore, the incidence of symptomatic venous thromboembolic events is significantly higher in ICU (27%) patients than in patients admitted in medical ward (3%) [29].

Deep vein thrombosis (DVT) is mainly localized in the distal district, with an incidence of about 12% in non-ICU patients. However, most of these events are asymptomatic and can occur despite adequate thromboprophylaxis [30].

The hypercoagulability condition that occurs in severe form of COVID-19 can manifest itself not only with major thromboembolic events but also with microvascular thrombotic angiopathy, which can worsen organ dysfunction, mainly in the lungs but also in other organs [31, 32].

Coagulopathy is frequently observed in severe COVID-19, characterized by elevations in fibrinogen and D-dimer levels, mild prolongation of PT/aPTT, and mild thrombocytopenia, which differ from the classic disseminated intravascular coagulopathy (DIC) seen in bacterial sepsis or trauma. These alterations in coagulation markers generally correlate with a parallel rise in markers of inflammation [33, 34].

Although less frequent, arterial thrombosis (AT) can also occur. In a significant systematic review, AT occurs in approximately 4% of ICU patients. Most patients were elderly male with comorbidities, and the anatomical localization included various districts with different prevalence (limb arteries 39%, cerebral arteries 24%, great vessel 19%, coronary arteries 9%, and superior mesenteric artery 8%) [35].

Stroke seems to be relatively uncommon in the setting of COVID-19 [36]. The frequency of ischemic stroke related to COVID-19 in hospitalized patients has ranged from 0.4 to 2.7%, while the incidence of intracranial haemorrhage has ranged from 0.3 to 0.9% [37] [38]. Stroke risk may differ according to the severity of COVID-19. Early case series suggest that for patients with mild illness, the risk is <1%, while for patients in intensive care, the risk may be as high as 6% [39]. Limited data suggest that ischemic stroke associated with COVID-19 occurs primarily in older patients with vascular risk factors [37].

Ischemic stroke is the most reported cerebrovascular event complicating COVID-19. The cause is often cryptogenic or attributed to large vessel thrombosis/occlusion, cardiogenic embolism, or arterial dissection [40].

Preliminary data suggest that COVID-19 is associated with a higher risk of ischemic stroke compared with influenza. In a retrospective cohort study comparing patients with emergency department visits or hospitalizations for COVID-19 (n = 1916) or influenza (n = 1486), the incidence of ischemic stroke was higher among patients with COVID-19 (1.6% versus 0.2% with influenza, adjusted odds ratio 7.6, 95% CI 2.3–25.2) [41].

While several mechanisms of stroke related to COVID-19 have been postulated, thrombophilia associated with the virus or the host immune response appears to be one important mechanism, as suggested by elevated markers of hypercoagulability and inflammation; in fact, a pro-inflammatory state may be associated with thrombophilia ("thromboinflammation"), increasing risk of stroke and other thrombotic events [42].

Cardiac dysfunction associated with SARS-CoV-2 infection may also serve as a potential embolic stroke mechanism.

Other neurologic complications—such as disorders of smell and taste, headache, dizziness, myalgia, alteration of consciousness, weakness, and seizures—are found in approximately half of hospitalized patients with COVID-19. Critically ill patients have a higher possibility of neurologic complications than patients with less acute illness [39].

By now, it is not possible to determine which of these neurologic problems are linked to COVID-19. Studies have reported that anosmia and dysgeusia (olfactory (OD) and gustatory dysfunctions (GD)) are common early symptoms in patients with COVID-19, occurring in more than 80% of patients [43]. Furthermore, they may be an initial manifestation of COVID-19 and can occur in the absence of nasal congestion, but rarely they are the only clinical manifestation of COVID-19. It has been documented that magnetic resonance imaging (MRI) signal abnormalities in one or both olfactory bulbs in patients with COVID-19 can resolve on follow-up imaging [44]. The study led by Meini et al. aims to investigate the timing of recovery from olfactory (OD) and gustatory dysfunctions (GD) in a population of 100 hospitalized patients for COVID-19 and discharged a month earlier from three Italian nonintensive care wards. Recovery from OD or GD was fast, occurring within 4 weeks in most patients.

Chemosensory dysfunctions in women were less common, but longer lasting [45]. What makes this study valuable is that it focuses on a population of hospitalized patients significantly older than those previously reported and adds data on gender differences. The damages that SARS-CoV-2 causes on taste and smell must be different from other viruses, but the pathophysiological mechanisms are largely unknown. It is reasonable to hypothesize that the OD is not related to definitive damage on neuronal cells but probably involved other cell types. In case of SARS-CoV-2-induced anosmia, magnetic resonance imaging of the olfactory bulb did not show irregular findings concerning its volume or signal intensity [46].

Encephalopathy is frequent in critically ill patients with COVID-19. In a group of 58 patients with COVID-19-related ARDS, encephalopathy was present in about two-thirds of patients [47]. It is probable that hypoxemia, especially found in patients with severe COVID-19, plays a role in many patients, like metabolic derangements due to organ failure and medication effects. The etiology is often multifactorial. A neuropathologic case series of 18 patients, who deceased for COVID-19 and who were encephalopathic before dying, has shown in all patients acute hypoxic ischemic damage and chronic neuropathology (e.g., arteriosclerosis, Alzheimer pathology) in most of them [48]. In other patients with encephalopathy, a dysregulated systemic immune response to SARS-CoV-2 may be implicated. Patients with COVID-19 may develop prominent delirium and agitation requiring sedation; others manifest encephalopathy with somnolence and a decreased level of consciousness [39].

A few cases of Guillain-Barré syndrome (GBS) have been described in patients with COVID-19. GBS is an infrequent complication of COVID-19. Among approximately 1200 patients with COVID-19 admitted over a 1-month period to 3 northern Italy hospitals, 5 cases of GBS were identified, presented with progressive, ascending limb weakness evolving over 1 to 4 days, and 3 of these required mechanical ventilation [49]. The interval between the onset of viral illness and the development of muscle weakness is 5–10 days, like that observed for other viral infections associated with GBS.

Isolated case reports have described the following syndromes in patients with COVID-19:

Meningoencephalitis—both viral and apparent autoimmune meningoencephalitis have been reported in patients with COVID-19. These complications are rare [50].

Acute disseminated encephalomyelitis (ADEM) and acute hemorrhagic necrotizing encephalopathy—a few case reports have described patients with clinical and neuroimaging findings consistent with ADEM [51]. Some patients have had myelitis with or without brain involvement [52].

Generalized myoclonus—one report has described three patients (ages 63–88 years) who have developed generalized myoclonus as an apparent postinfectious complication of COVID-19 [53].

Posterior reversible encephalopathy syndrome (PRES)—PRES has been reported in a few patients with COVID-19 [54].

Rhabdomyolysis—in Wuhan, 11% of patients were reported to have evidence of muscle injury with elevated creatine kinase (CK) (>200 U/L) and/or myalgia [39]. Myalgia was a common complaint in a series from Italy [55].

The gastrointestinal manifestations of COVID-19 are quite common but often underestimated. The first evidence of gastrointestinal involvement in patients with COVID-19 comes from a study conducted in China. It is increasingly evident that the gastrointestinal tract and the liver, where the enzyme ACE2 is expressed, are targets of SARS-CoV-2; the viral RNA was found in the stool of patients, implying a possible fecal-gold transmission, of great importance for public health.

In some studies, up to 61% of patients hospitalized with COVID-19 showed digestive symptoms, mainly anorexia (35%), diarrhea (34%), and nausea (26%). In some cases isolated gastrointestinal symptoms may precede the onset of respiratory symptoms [56, 57].

In some cases, the clinical presentation may be with asymptomatic rise of the enzymes of hepatocyte necrosis (14–58%); generally, the increase in transaminases is slight (<5 times the maximum values), with an increase in AST greater than ALT. Rarely, however, hepatitis has also been reported. Some

symptoms related to liver involvement may therefore appear, such as asthenia, abdominal pain, and anorexia, up to the typical manifestations of decompensated liver disease. In patients with known liver disease, acute worsening of liver function may occur [58, 59].

Kidney involvement is also possible during SARS-CoV-2 infection and can manifest as acute kidney injury (AKI), proteinuria, and/or hematuria [60, 61]. In a large cohort of COVID-19 hospitalized patients in New York, AKI was diagnosed in one-third of these (47% mild, 22% moderate, 31% severe), while hematuria and proteinuria were found in 46% and 42%, respectively [62].

It is still not clear if AKI is due to hemodynamic alterations, cytokines storm, or direct cytotoxicity of the virus.

COVID-19 patients have shown multiple skin manifestations, such as morbilliform rash; urticaria; pernio-like, acral lesions; livedo-like, vascular lesions; and vesicular, varicella-like eruptions. In children and adolescents with COVID-19, a severe multisystem inflammatory syndrome with mucocutaneous, systemic, laboratory, and imaging findings of atypical, severe Kawasaki-like disease has also been reported. Case series from around the world have documented a range of potential dermatologic manifestations of COVID-19 [63].

The incidence (ranging from 0.2 to 20.4% of cases) and timing of cutaneous manifestations of COVID-19 are difficult to determine [64]. Also unclear is the association of certain skin manifestations with the illness severity [65].

Moreover, it cannot be excluded that in some patients, the observed skin findings may represent cutaneous reactions to the numerous treatments used for COVID-19. Among 171 laboratory-confirmed COVID-19 patients with cutaneous manifestations from the registry, the most commonly reported were morbilliform rash (22%), pernio-like acral lesions (18%), urticaria (16%), macular erythema (13%), vesicular eruption (11%), papulosquamous eruption (9.9%), and retiform purpura (6.4%) [66].

Exanthematous (morbilliform) rash—in several case series, a morbilliform rash predominantly involving the trunk has been described as the most common cutaneous manifestation of

COVID-19 [67]. The rash has been noted either at the disease onset or, more often, after hospital discharge or recovery [64].

Pernio (chilblain)-like lesions of acral surfaces ("COVID toes") present as erythematous-violaceous or purpuric macules on the fingers, elbows, toes, and the lateral aspect of the feet, with or without accompanying edema and pruritus. They have been described across the age spectrum in patients with confirmed or suspected COVID-19, in the absence of cold exposure or underlying conditions associated with pernio [68]. Resolution may occur in 2–8 weeks. The understanding of the pathogenesis of these lesions is still under evolution, though it seems to be a primarily inflammatory process [69]. Pernio-like lesions may represent a post-viral or delayed-onset process, with 80 out of 318 cases in the American Academy of Dermatology/International League of Dermatologic Societies registry developing lesions after the onset of other COVID-19 symptoms [68]. Moreover, there are several case reports and case series of patients with pernio-like lesions testing positive for either immunoglobulin M (IgM) or immunoglobulin G (IgG) for SARS-CoV-2 infection and negative for polymerase chain reaction (PCR), possibly indicating a later stage in the disease process [70]. However, pernio-like lesions can, in some cases, appear while patients are still PCR-positive for the virus, which has potential implications for infectivity and viral spread: in fact in an Italian study that screened 22 patients presenting with pernio-like lesions, 6 (26%) were PCR positive for SARS-CoV-2 [71].

Livedo reticularis-like vascular lesions have been reported in a few patients with COVID-19 [72]. In a series of 171 laboratory-confirmed cases, these vascular lesions were noted in 5.3 and 2.3% of patients, respectively [66].

Retiform purpura and necrotic vascular lesions seem to be associated with severe COVID-19; in a series of 11 patients with retiform purpura and laboratory-confirmed COVID-19, all were hospitalized and 9 had acute respiratory distress syndrome [66].

In three patients with SARS-CoV-2 infection and severe respiratory failure who had retiform purpura or livedo racemosa, histologic and immunohistochemistry studies of skin biopsies revealed a pattern of complement-mediated microvascular injury in both

involved and normally appearing skin [31]. Acute urticaria with or without concomitant fever has been reported as a presenting sign of COVID-19 infection [73]. There are several reports describing a vesicular-pustular, varicella-like eruption associated with COVID-19 [74]. In a series of 24 patients, an eruption of small papules, vesicles, and pustules appeared 4–30 days after the onset of COVID symptoms and resolved in a median of 10 days [75]. A real-time PCR for SARS-CoV-2 from vesicle content performed in four patients yielded negative results. Seventeen of 24 patients were not taking any medications, ruling out a drug reaction. An erythematous, polymorphic rash, erythema and/or firm induration of hands and feet, oral mucositis, and conjunctivitis, along with systemic, laboratory, and imaging findings of atypical, severe Kawasaki disease, have been described in a cohort of ten Italian children during the COVID-19 pandemic [76]. Similar cases have been reported in the UK [77].

Secondary infections, particularly bacterial and fungal infections, are also possible, despite frequent prescription of empiric antimicrobial therapy in these patients [78].

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8 Radiological Pictures of COVID-19

Chiara Recaldini, Federico Fontana, Giada Zorzetto, and Massimo Venturini

Introduction

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the etiological agent of the coronavirus disease (COVID-19), resulting in viral pneumonia as the most frequent complication.

The real-time reverse transcription-polymerase chain reaction (RT-PCR) detection method for COVID-19 has been developed and applied in clinics.

At present, RT-PCR remains the reference standard for the final diagnosis of COVID-19 infection; however—especially in

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the early stage of the outbreak in some countries—the high false-negative rate and the lack of RT-PCR assay limited the timely diagnosis of infected patients [1].

Radiology plays a key role in the early detection and treatment of patients affected by COVID-19. Radiological exams are relatively easy to perform, can produce fast diagnosis, and facilitate larger public health surveillance and response systems [2–6].

In this chapter, we highlight the role of thoracic imaging during the COVID-19 pandemic.

Imaging Findings

Chest X-Ray

Chest X-ray (CXR) may represent a low-cost and widely available tool in detecting lung involvement in patients with possible COVID-19 pneumonia [7].

Lung involvement appears initially as reticular opacities and vague hazy densities which correspond to ground-glass opacities described at computed tomography (CT), but in the early stage, CXR can be of little diagnostic value because the reported baseline sensitivity compared to CT is less than 70% [8] (Fig. 8.1).

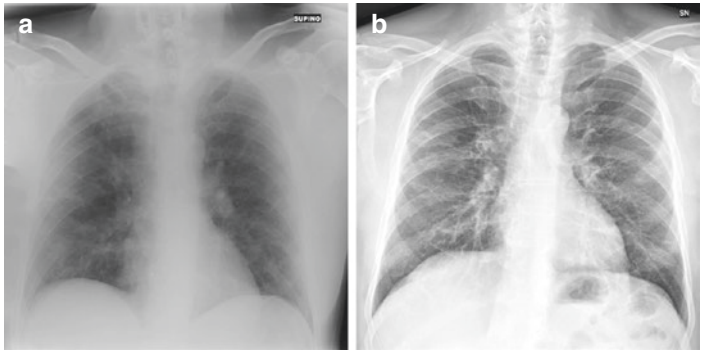

Fig. 8.1 A 60 year-old patient with mild respiratory symptoms and positive RT-PCR test. (**a**) Bedside anteroposterior CXR shows fine reticular opacities and no other significant abnormalities. (**b**) At 1-month follow-up, CXR is negative and no complications have occurred

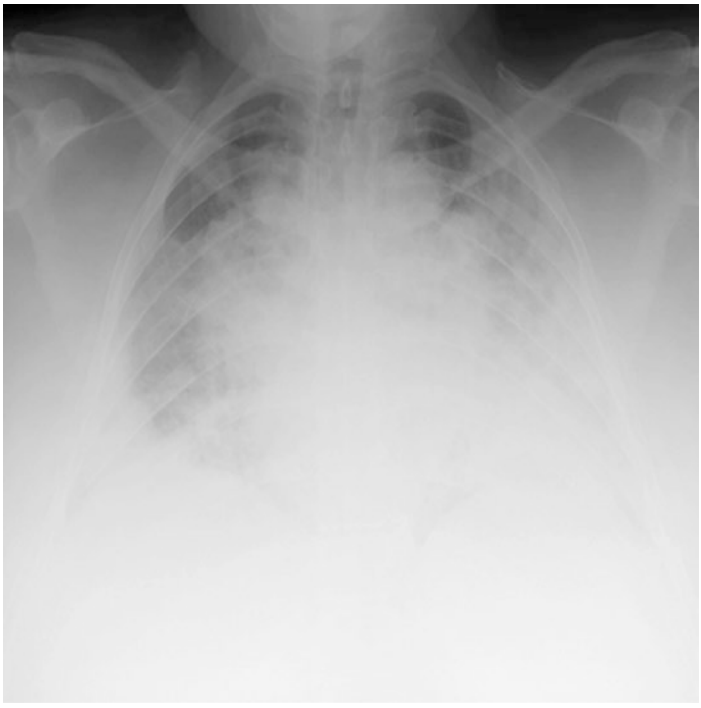

Fig. 8.2 A 78-year-old woman. "White lung" CXR. Bilateral diffuse patchy consolidations at the middle and inferior zones of both lungs; increased cardiac diameter; no pleural effusion

Consolidation occurs when air in the alveolar air spaces is repleted with exudate or product of disease. This renders the lung solid [9]. As consolidation is radiographically denser than the air, this results in a "white" image on CXR. As the disease progresses, patchy consolidations become extensive and widespread to both lungs. In contrast to acquired bacterial pneumonia, viral pneumonias typically produce patchy consolidations that are predominantly bilateral, peripheral, and basal. However, these manifestations are not specific for COVID-19 (Fig. 8.2).

Pleural effusions are rare on CXR and are identified late in the course of the disease. Lung cavitation is rare too.

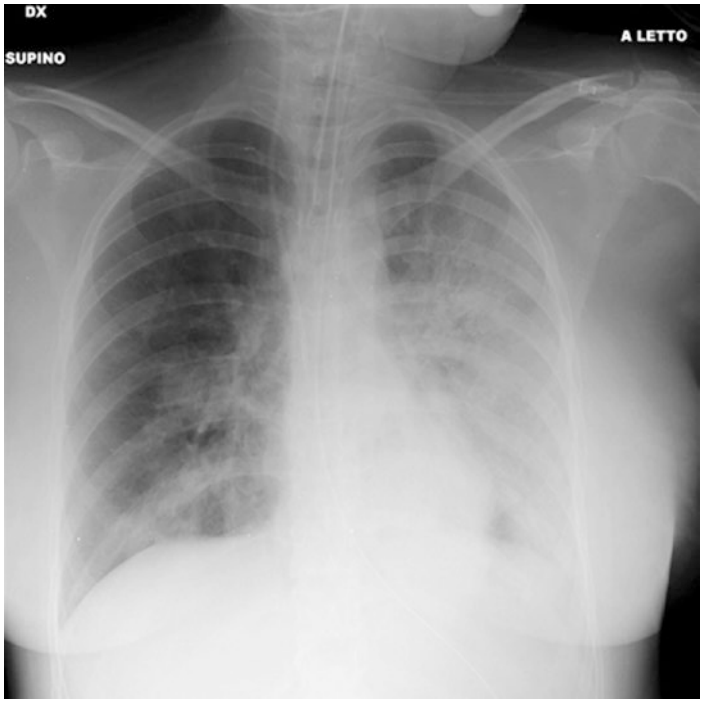

Fig. 8.3 A 22-year-old girl with ketoacidosis coma, clinically ARDS, intubated. CXR on admission. Diffuse lung opacities totally occupied left lung and partially right lung

When lung disease involves the majority of the lungs, CXR can be sufficient to identify acute respiratory distress syndrome (ARDS) requiring mechanical ventilation (Fig. 8.3).

According to the Fleischner Society Consensus Statement, CXR is not routinely indicated in stable intubated patients with COVID-19 [10].

CXR can be useful in monitoring progression and complications of the disease [10]. Diffuse chest wall subcutaneous emphysema, pneumomediastinum, and pneumothorax after intubation can occur due to alveolar rupture leading to interstitial emphy-

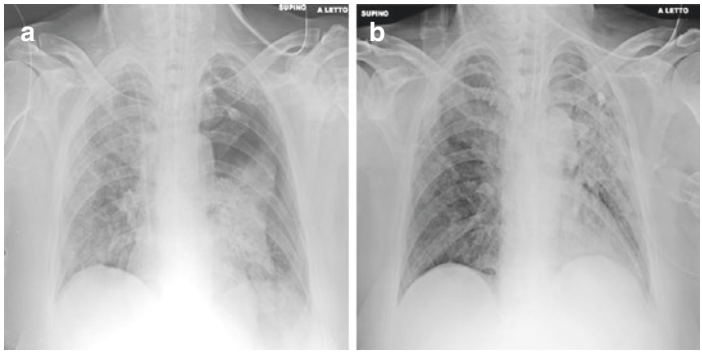

Fig. 8.4 Bedside CXR in intensive care unit. (**a**) Worsening of respiratory condition in severe pneumonia. Diffuse lung opacities peripherally and bilaterally and massive left pneumothorax with lung collapse. (**b**) After chest tube placement, the lung re-expanded

sema; spontaneous pneumomediastinum or pneumothorax may occur too, and although the precise mechanism is unknown, the diffuse alveolar damage itself can contribute to alveolar rupture [11] (Fig. 8.4).

CXR can be obtained with portable equipment, with the advantage to be performed in isolated room in wards and intensive care unit in order to minimize patient transportation, thus reducing the risks of transmission of infection. Portable equipment can be used outside hospitals in nursing homes as part of projects of "home radiology" to examine patients in quarantine or to reduce transportation in hospital, with equal level of diagnostic performance [12].

Furthermore, they are easy to clean and disinfect.

Sensitivity of CXR is dependent on the extent of COVID-19 infection. In a context of high pretest probability and high disease severity, bedside CXR diagnostic performance can be higher than previously reported, and it can be considered a useful first-line examination and sufficient for monitoring the evolution of the disease [2].

Computed Tomography

High-resolution computed tomography (HR-CT) is a non-contrast thin slice volume CT (0.625–2 mm) with a specific algorithm to study lung parenchyma and especially interstitial diseases. In case of suspicion of vascular complications, such as pulmonary embolism, intravenous iodinated contrast agent administration is indicated.

The radiological imaging pattern of respiratory infection depends on the pathogenesis of pneumonia. Viruses in the same viral family share a similar pathogenesis and subsequently a typical imaging picture. SARS-COV-2, similar to severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome (MERS), shows a "ground-glass" pattern.

CT Features of COVID-19 Pneumonia

Ground-Glass Opacity

Ground glass (GG) is defined as "hazy increase opacity of the lung, with preservation of bronchial and vascular margins." It is caused by partial filling of airspaces, interstitial thickening (due to fluid, cells, and/or fibrosis), partial collapse of alveoli, increased capillary blood volume, or a combination of these, the common factor being the partial displacement of air. GG opacity (GGO) is less opaque than consolidation, in which bronchovascular margins are obscured and the air is completely absorbed [4, 9].

GGO is the radiological manifestation of a pathology of the secondary lobule, the smallest pulmonary unit surrounded by interstitium. The target of SARS-COV-2 is the alveolum and the alveolar-capillary membrane. The lung responds to this damage with a stereotype answer that is diffuse acute lung injury (ALI). On histology, alveolum is filled with hyaline membranes, necrotic cells, exudate, and hemorrhage. GGO is the expression of thickening of interstitium as well as partial filling of airspaces. As ALI worsens, GGOs are more extended.

The characteristic patterns and distribution of GGO is a bilateral involvement (87.5%), peripheral distribution (76.0%), and

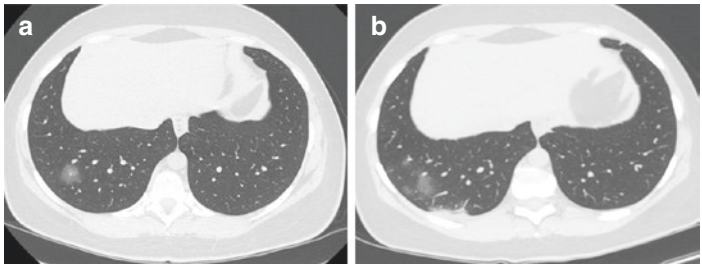

Fig. 8.5 HRCT. (**a**) Monolateral focal rounded GGO with vessel enlargement in a 33-year-old woman, mild symptomatic, with professional exposure. Three subsequent nasopharyngeal swabs negative. (**b**) HRCT 1 week after: monolateral multifocal GGO and pleural reaction; RT-PCR turned positive

multilobar involvement (78.8%). GGO can be round in shape, and occasionally at the early stage of the disease, it may be monolateral and monofocal [13] (Fig. 8.5).

Crazy Paving

Crazy paving (CP) is defined as interlobular septal thickening and intralobular lines superimposed on a GGO background, resembling irregular paving stones. This sign may result from the alveolar edema and interstitial inflammatory of ALI: lymphocytes accumulate in septa together with septal edema. The endothelial damage causes vascular dilatation of little veins in interlobular septa and capillaries in intralobular septa. This can be a sign of COVID-19 entering progressive or peak stage [14] (Fig. 8.6).

Consolidation

Consolidations are multifocal, patchy, or segmental, distributed in subpleural areas or along bronchovascular bundles. Lung involvement gradually increases to consolidation up to 2 weeks after disease onset (Fig. 8.7).

Air Bronchogram

Air bronchogram is defined as a pattern of air-filled (low attenuation) bronchi on a background of opaque airless lung. It may be

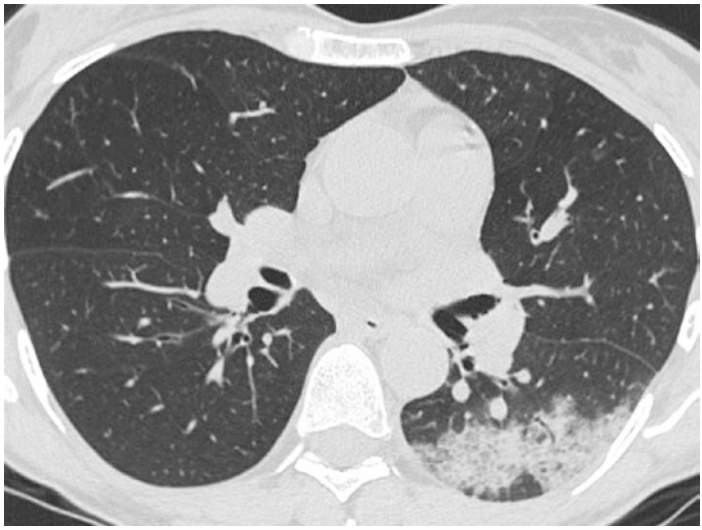

Fig. 8.6 A 50-year-old woman presenting with fever and worsening dyspnea. a) Focal subpleural opacity at the left lobe with thickening of inter- and intralobular septa (CP pattern)

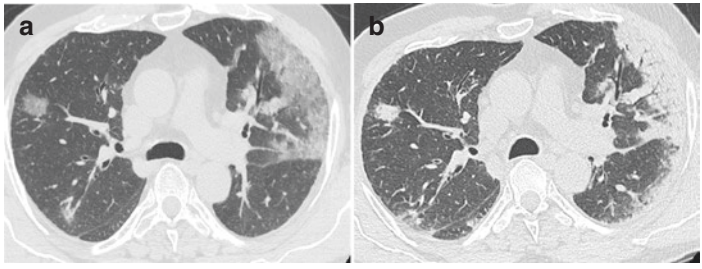

Fig. 8.7 A 56-year-old patient presenting with fever and asthenia. (**a**) Round GGO in the right lobe and subpleural GGO and CP in the left lobe in the early phase; (**b**) after 1 week (peak phase), the same lesions have a consolidative appearance with air bronchogram

due to a partial bronchiolar dilatation filled with gelatinous mucus attached to the bronchial wall [14].

Bronchiectasis and bronchial wall thickening can be the result of inflammatory damage of the bronchial wall.

Vascular Enlargement

Vascular enlargement is defined as luminal dilatation/engorgement or mural thickening of pulmonary vessels (>3 mm) inside the GGO. This sign is still under debate as it may be attributed to a damage and swelling of the capillary wall caused by pro-inflammatory factors, or it may be the result of phenomena of focal microthrombosis [15, 16].

Reversed Halo Sign

It represents a focal rounded GGO surrounded by a more or less complete ringlike consolidation. It was initially reported to be specific for cryptogenic organizing pneumonia but was described in other conditions. This may be a transitory sign from GGO to consolidation and may correspond to an early phase of organizing pneumonia [13, 16].

Lymphadenopathy

Lymphadenopathies occur late in the disease, and according to some authors, they have got a bad prognostic value [17]. Occurring with pleural effusion and extensive lung nodules may suggest bacterial superinfection (Fig. 8.8a).

Striplike (Reticular) Opacities

In the late phase, peripheral radiopaque bands appear with an arcade morphology.

Others

Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, and nodules are less common or rare.

Table 8.1 lists the frequent typical and relatively atypical CT signs of COVID-19.

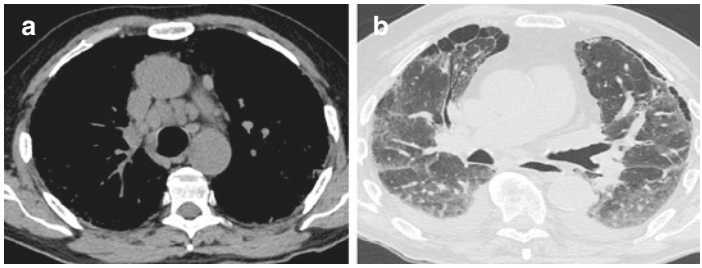

Fig. 8.8 (**a**) HRCT mediastinal window shows multiple mediastinal lymphadenopathies. (**b**) Parenchymal window: bilateral reticular subpleural opacities and bilateral pleural effusion in a preexisting chronic obstructive pulmonary disease in a 73-year-old man

Table 8.1 Common CT findings of COVID-19 pneumonia

COVID-19	
Typical findings	Atypical findings
Multifocal ground-glass opacities	Central or peribronchovascular
Peripheral and basal distribution	More apical distribution
Unsharp demarcation	Lymphadenopathy
Round	**Very atypical**
Vascular thickening	Cavitation-calcification
Crazy paving	Tree-in-bud, bronchiolitis
Ground glass and consolidation	Nodular pattern
Reversed halo sign	Mass
Striplike opacities	Pleural thickening

The most common CT findings are GGO alone or in combination with CP changes and consolidative opacities. The typical mild COVID-19 pneumonia mainly starts as small subpleural, unilateral, or bilateral GGOs in the lower lobes, which then develop into the CP pattern and subsequent consolidations. After more than 2 weeks, the lesions are gradually absorbed with residual GGO and subpleural parenchymal bands.

Jin et al. [18] described the characteristic CT findings of COVID-19 in five temporal stages: *ultra-early*, *early*, *rapid progression*, *consolidation*, *and dissipation stages*. Other authors

simplify with only four temporal stages (stages may overlap) [19, 20]. Interestingly, temporal changes are asynchronous in the same lung as the damage is not uniform in the lung; also, it has been noticed a time discrepancy between clinical features and CT features.

During the *ultra-early stage* (asymptomatic, 1–2 weeks after exposure), CT may show single or multiple focal GGO, patchy consolidative opacities, pulmonary nodules encircled by GGO, and air bronchograms. At this stage, however, CT can also be totally negative.

In the *early stage* (early symptomatic presentation, 0–4 days after onset of symptoms), CT findings include single or multiple GGOs or GGO combined with interlobular septal thickening.

In the *rapid progression* stage (days 3–7 of symptomatic presentation), CT findings include large, light consolidative opacities and air bronchograms.

During the *consolidation stage or peak stage* (second week of symptomatic presentation), the involved area of the lung slowly increased to the peak involvement, and dense consolidations become more prevalent.

About 2–3 weeks after the onset, *the dissipation stage* begins: CT may show dispersed patchy consolidative opacities, reticular opacities (referred to as "striplike opacities"), bronchial wall thickening, and interlobular septal thickening. No CP is present any more. Extensive GGO could be observed as the demonstration of the consolidation absorption.

On average, CT findings are most prominent on day 10 of the disease (Fig. 8.9). After day 14, improvement in imaging findings is reported in 75% of the patients, including decreased number of involved lobes and resolution of CP pattern and consolidative opacities.

Development of pleural effusions and progression to a mixed pattern of GGO and consolidative opacities have been reported in later disease stages. A mixed pattern might suggest the presence of organizing pneumonia that has the potential to progress to fibrosis.

For most of the discharged patients, 2 weeks after discharge, pulmonary damage could be potentially repaired without any

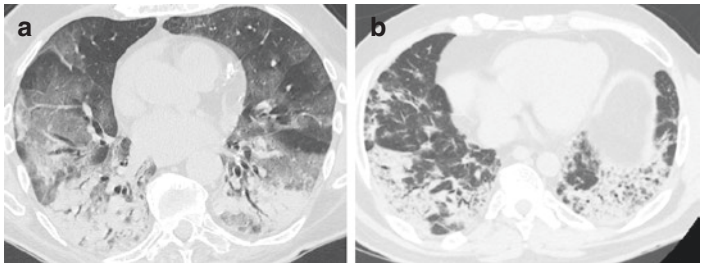

Fig. 8.9 (**a**) Bilateral consolidations with parapneumonic bronchiectasis and GGOs. (**b**) Ten days later, subpleural basal consolidation and reduction of GGOs

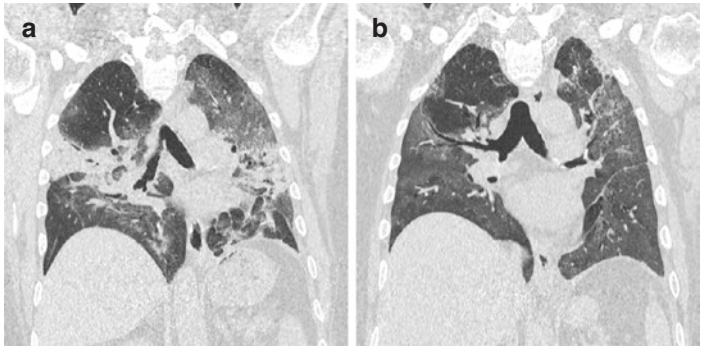

Fig. 8.10 A 67-year-old man with acute respiratory insufficiency. (**a**) Coronal multiplanar reformatted CT. Bilateral consolidations in the middle portion of both lungs, associated with peripheral GGOs. (**b**) After 1 month reduction of consolidations with residual diffuse GG

sequelae. More than 40% of patients demonstrated residual abnormalities including GGO and fibrous stripes (Fig. 8.10). Elderly patients and more severe patients need longer time to recovery [21].

There is concern about the possibility to develop pulmonary fibrosis and functional respiratory decline. Currently, the relation between fibrosis and patients' prognosis is debatable. Some researchers suggested the presence of fibrosis indicates good prognosis of a patient with stabilizing disease status; others thought that fibrosis might indicate a poor outcome, reporting it may progress to interstitial fibrosis disease [11, 22].

Differential Diagnosis

A typical radiological pattern for COVID-19 pneumonia suggests a confidence in diagnosis; however, typical pattern does not mean specific.

As a matter of fact, COVID-19 CT pattern has a wide range of differential diagnosis, as listed in Table 8.2 [23].

Radiologists must be aware of the history, clinics, and laboratory findings to correctly interpret CT pattern.

In addition, COVID-19 can be superimposed on an already existing respiratory pathology, for instance, pulmonary fibrosis or chronic obstructive disease, or can coexist with another infection (bacterial) or aspiration (Fig. 8.8b).

Two groups recently proposed standardized CT reporting guidelines: the Radiological Society of North America (RSNA) and the Dutch Radiological Society [24, 25]. Chest CT findings were classified for COVID-19 pneumonia into four groups: typical appearance, indeterminate appearance, atypical appearance, and negative for pneumonia.

The aims of these reporting guidelines are to familiarize all radiologists with the typical imaging findings of COVID-19 and to decrease inter-radiologist variation in the reporting of cases. The question of whether to include terminology such as "coronavirus" or "COVID-19" in reports remains an area of debate. Although these guidelines do represent important contributions, they should be applied with caution. A typical imaging CT may encourage to repeat a negative RT-PCR. Nevertheless, reporting "atypical finding" may result in a false-negative case with the risk of missing COVID-19 diagnosis with its implications.

Given the presence of CT abnormalities, the probability that CT findings represent COVID-19 depends largely on the pretest probability of infection which is defined by community prevalence of infection. If the disease prevalence is high, even atypical presentations are likely to be COVID-19, but if the disease prevalence is low, even typical CT findings may be caused by another disease. So far, from the literature, we can't correctly establish sensitivity, specificity, and predictive positive and negative value of CT because the diagnostic performance for chest CT is valid only for the study population from which it is calculated. CT has been studied primarily in regions with a high prevalence of

Table 8.2 Chest CT differential diagnosis of COVID-19 pneumonia

Infectious	Pulmonary edema	Interstitial lung diseases	Exposures	Aspiration
Influenza A, B virus Cytomegalovirus Adenovirus Respiratory syncytial virus SARS-COV, MERS Bacterial pneumonia Mycoplasma, chlamydia Pneumocystis	Increased hydrostatic pressure (cardiac edema) Permeability edema with DAD (ARDS) Permeability edema without DAD (drugs) Mixed edema	Nonspecific interstitial pneumonia Desquamative interstitial pneumonia Organizing pneumonia	Hypersensitivity pneumonia Electronic cigarette or vaping use lung injury Drug toxicity	Aspiration Diffuse alveolar hemorrhage Pulmonary alveolar proteinosis Eosinophilic pneumonia

DAD diffuse alveolar damage

COVID-19, but its performance in lower-prevalence environments as the ones we are likely to see in the coming months is not clear. A well designed, cross-sectional study is needed to define the sensitivity of typical CT findings and their specificity when multiple other disease processes are at play.

Application of Artificial Intelligence in COVID-19

It is reported in the literature that artificial intelligence (AI) system has outstanding performance in the detection of subtle GGO, which is the most easily missed typical CT feature of COVID-19. Also, it can precisely segment the lesion region and calculate the lesion volume, volume rates of lesions to total/left/right lung, and each lung lobe. Comparing CT scans of the same patient at several time points, the radiologist can use the system to measure changes in each lesion and track the progression of the disease. Some researchers have tried to apply AI in CT image analysis to differentiate COVID-19 from other viral pneumonia patients. With clinical symptoms, laboratory testing results, and contact or travel history, the AI system can help doctors identify patients with risk of progressing to a more severe disease state at the time of admission, for timely, precise, and effective treatment decisions [26, 27]. However, AI must be used with judgment. The Italian Society of Medical and Interventional Radiology published a statement in which a) it supports the research on the use of AI as a predictive and prognostic decision support system, b) on the other hand it does not support the use of AI for screening as a first-line test for diagnosis, and c) it reiterates that CT with AI cannot replace molecular test with nose-pharyngeal swab (RT-PCR) [28].

The Role of Chest CT and its Relationship with RT-PCR

RT-PCR test obtained on nasopharyngeal swab is widely used to confirm COVID-19 infection, and it is recommended by WHO guidelines [29]. RT-PCR has its own limitations and variability. A number of factors influence the results of the RT-PCR assay including site of specimen (nasal or bronchial), chronicity of ill-

ness (early or late) at the time of sampling, and reliability of the testing kit.

Several studies compared the accuracy of chest CT against RT-PCR with a sensitivity ranging between 72 and 97% [6, 30, 31]. However, according to Raptis et al. [32], this high sensitivity can be explained by a selection bias of the studied population and low threshold for positive disease on chest CT. Using RT-PCR as a reference, specificity of chest CT ranges between 25 and 56% and accuracy between 68 and 72%. The positive predictive value and accuracy of chest CT were higher in patients older than 60 years old. The positive rate of RT-PCR was 32–93% because RT-PCR was obtained through throat swab which has low positive rates as viral pneumonia does not usually produce purulent sputum [6, 30, 31].

In many healthcare settings, such as developing countries, CT imaging may be the only available diagnostic test due to a shortage of diagnostic laboratory kits, while validated.

Although some clinicians have advocated the use of CT as an adjunct to or in lieu of RT-PCR in settings where testing capacity is insufficient, this strategy would probably lead to false-negative results. Imaging can range from normal to typically abnormal for COVID-19. Furthermore, the so-called typical findings have substantial overlap with other infectious and noninfectious entities, as already written.

Several scientific societies have published guidelines and position statement regarding the appropriate use of imaging during the pandemic [33]. They recommended against the routine use of CT for the screening of COVID-19 as a normal chest CT does not effectively exclude COVID-19 and an abnormal CT is not specific for COVID-19.

The Fleischner consensus statement on the role of chest imaging in COVID-19 takes care of disease severity, pretest probability, risk factors, evidence of disease progression, and availability of diagnostic testing. According to Fleischner Society, CT is appropriate in establishing baseline pulmonary status and identifying cardiopulmonary abnormalities in patients with moderate to severe disease. In a resource-constrained environment with high community burden of disease and scarce availability of diagnostic test, CT has been used to rapidly triage patients into non-COVID-19, possibly COVID-19, or most likely COVID-19 [10].

COVID-19 as a Systemic Disease

SARS-COV-2 infection is principally a respiratory illness and pneumonia is the main presentation, but other organs can be affected too.

Among the clinical manifestations that can be investigated with radiological imaging we mention are as follows:

- *Pulmonary embolism*: an increase incidence of acute pulmonary embolism in hospitalized COVID-19 patients has been reported [34], especially when D-dimer is elevated. Preventive anticoagulation has been recommended in severely ill hospitalized patients.
- *Hepatomegaly and splenomegaly.*
- *Myocarditis:* characterized by high levels of highly sensitive cardiac troponin I and NT-proBNP and from mild to severe left ventricular hypertrophy (LVH) leading to left ventricular systolic dysfunction [35].
- *Spontaneous bleeding*: multiple sites of bleeding have been reported (such as lumbar and iliolumbar, inferior epigastric, inferior gluteal arteries); the origin of spontaneous bleeding in these patients remains unclear: a potential explanation for these findings is that the increased levels of pro-inflammatory cytokines can lead to coagulation disorders [36].
- *Neurological involvement*: the virus can reach the central nervous system through the bloodstream and neuronal retrograde route, leading to encephalitis and meningitis; in these patients, the examination of cerebrospinal fluid can confirm the presence of viral RNA [37].

The Role of Interventional Radiology in COVID-9 Disease

Interventional radiology can play a role in the treatment of hospitalized patients with SARS-CoV-2 infection, who have developed a wide range of respiratory and systemic complications during their hospital stay.

Different societies of radiology and vascular interventional radiology, as well as local protocols [38–40], have established a set of standardized recommendations to minimize the risk of contagion among interventional radiologists, nurses, technicians, and aides working together in the Angiographic Suite, based on the selection of procedures for interventional radiology, the correct ventilation of the room (high efficiency particulate air filtration systems), the proper use of personal protective equipment (gowns, masks, gloves, eye protection, shoe covers), the disposal of used and unused materials, and the handling of potentially or certainly infected patients.

The interventional procedures most frequently performed in the angiographic room on COVID-19 patients are endovascular treatment of acute stroke, placement of central venous catheters (CVC), and deployment of inferior vena cava filters in selected patients with massive acute pulmonary embolism (PE) (Fig. 8.11) not responsive to therapeutic anticoagulation or as a prophylactic device in order to prevent acute PE in hypoxic, immobilized

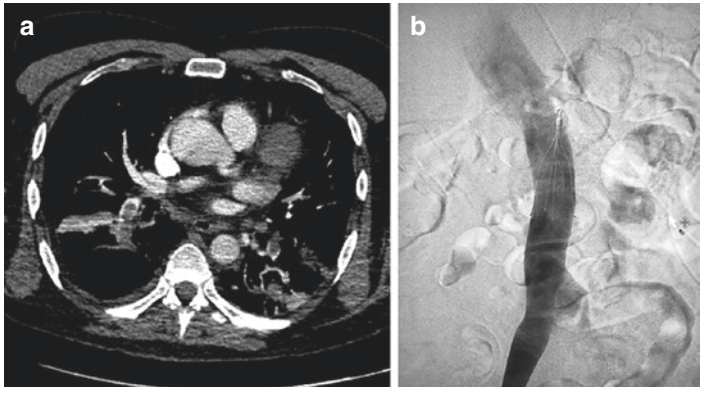

Fig. 8.11 (**a**) CT with endovenous iodinated contrast agent, arterial phase. Patient with SARS-CoV-2 infection with pulmonary bilateral thromboembolism. (**b**) Inferior vena cava venogram of percutaneous image-guided insertion of an inferior vena cava filter

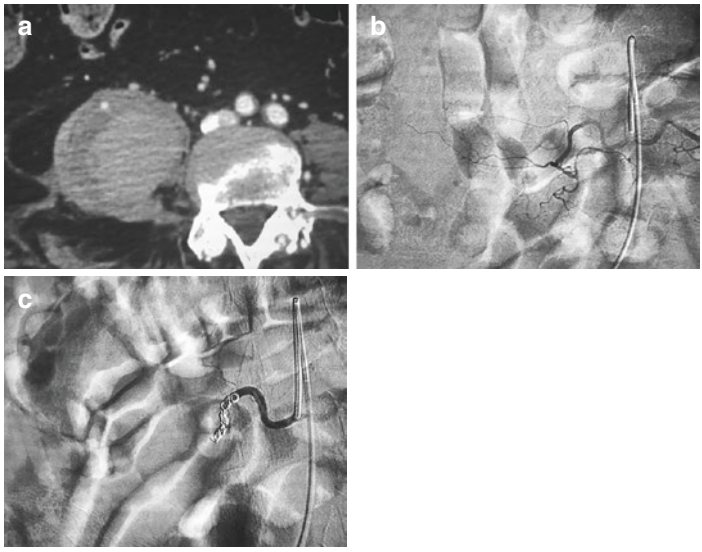

Fig. 8.12 (**a**) Contrast-enhanced CT in a patient with SARS-CoV-2 infection who developed large hematoma of the right psoas muscle with focal spreading of contrast medium (**b**) angiogram during the angioembolization procedure showing the active bleeding. (**c**) Final control after metallic coils positioning

patient [41]. Also, angioembolization of active bleeding has been proven to be an effective alternative in complex patients with many comorbidities (Fig. 8.12).

The placement of pleural drainage to treat conspicuous pleural effusion conditioning breathlessness and respiratory insufficiency, usually in the late stages of hospitalization (Fig. 8.13) and of percutaneous cholecystostomy catheters (Fig. 8.14) to treat patients with symptoms and ultrasonographic features of acute cholecystitis [42], can be carried out under ultrasound guidance on bedside in order to minimize movement of infected patients.

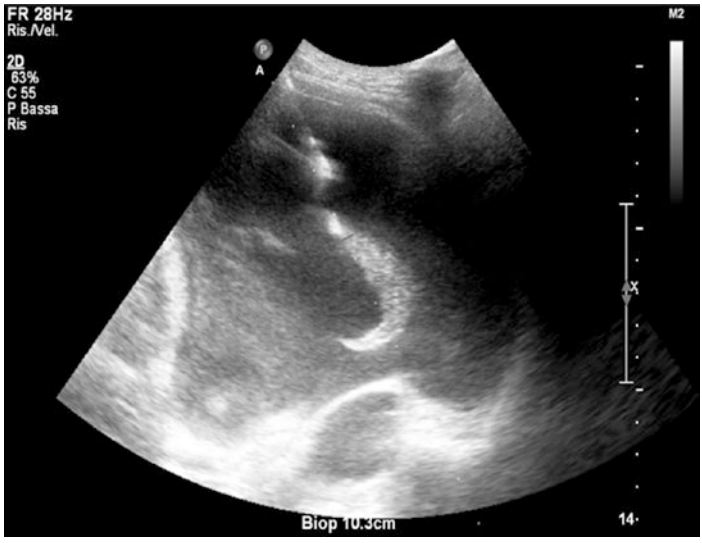

Fig. 8.13 Placement of a drainage catheter on patient's bedside, in order to treat a conspicuous pleural effusion in an elderly patient with SARS-CoV-2 infection

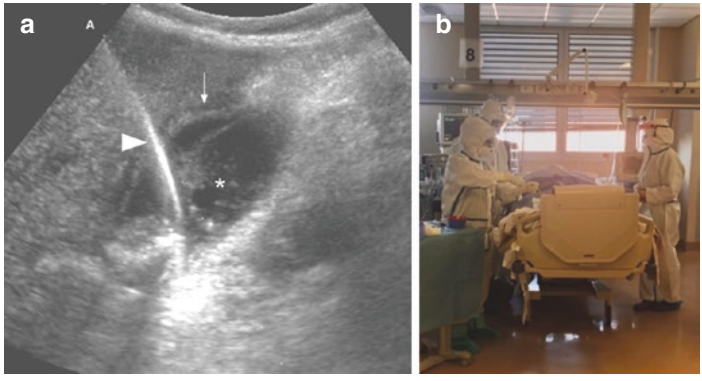

Fig. 8.14 Team of interventional radiologists positioning a percutaneous cholecystostomy catheter at the patient's bedside, in a patient with SARS-CoV-2 infection, with ultrasonographic features of acute cholecystitis, hospitalized in the intensive care unit. (**a**) ultrasound driven procedure showing the echographic mark of the catheter inserted; (**b**) the interventional radiology team in action

Conclusion

Radiology plays a key role in the COVID-19 pandemic, offering the advantages of diagnosis and follow-up for mild and severe patients. Radiologists must be familiar with the typical radiological patterns of COVID-19 and the main differential diagnosis.

Imaging departments must be reorganized to fulfill the request of imaging of COVID-19 patients as well as to guarantee the safety of patients and healthcare staff, by correctly using the right individual protective devices and ensuring that workplaces and equipment are adequately decontaminated in order to minimize the risk of infection transmission.

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9 Management of Patients with SARS-CoV-2 Infection

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Abbreviations

ARDS	Acute respiratory distress syndrome
COVID-19	Coronavirus infection disease 2019

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CRP	C-reactive protein
HFNO	High-flow nasal oxygen
LDH	Lactate dehydrogenase
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SpO2	Saturation of oxygen

COVID-19 is a respiratory disease due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. In general, adults with coronavirus infection disease 2019 (COVID-19) can be categorized based on the severity of their symptoms.

- **Asymptomatic Infection**: individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic or antigen test but have no symptoms. These patients do not need any treatment but may be a source of disease transmission. They should be well educated to take all the preventive measures to curtail transmission especially to family members and close contacts.
- **Mild Illness:** individuals who may have some signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.
- **Patients with Pneumonia:** individuals who have symptoms of low respiratory tract infection and findings of interstitial infiltrates on radiological examination. They can be classified in two subgroups:

  Moderate Illness: individuals who have a saturation of oxygen (SpO2) ≥94% on room air

  Severe Illness: individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%

– **Critical Illness:** individuals who have acute respiratory distress syndrome, septic shock, and/or multiple organ dysfunction.

Management of Patients with Mild Symptoms

Patients with a mild clinical presentation may not initially require hospitalization unless there is concern about rapid clinical deterioration. They should be isolated to contain virus transmission in COVID-19 health facility and community facility or self-isolate at home. This decision should be based on the local COVID-19 care pathway, clinical presentation, requirement for supportive care, and risk factors for progression toward more severe disease and conditions at home, including the presence of vulnerable persons in the household [1].

Patients at home in self-isolation may be followed up and cared for by family members. Patients should be educated about measures to prevent the infection from spreading to household contacts, while family members and caregivers should also be provided with information and education on how to care for these patients without exposing themselves. Given the possible risk of deterioration (such as difficulty breathing, chest pain, dehydration), these patients should be closely monitored and periodically referred to physicians by phone or telemedicine, depending on local care pathway [1, 2]. Risk factors for progressing to severe illness may include older age, underlying chronic medical conditions, and immunosuppression. For these patients at high risk for deterioration, isolation and monitoring in hospital is preferred. In fact, clinical signs and symptoms usually worsen, with progression to lower respiratory tract disease, in the second week of illness.

Patients should be aware about the importance of adequate balanced nutrition and appropriate fluid intake, in order not to be malnourished nor dehydrated as this may have a negative impact on the disease.

Febrile patients can be treated with antipyretic drug like paracetamol. Although there is no evidence to indicate that there

are severe adverse events in patients with COVID-19 and treated with nonsteroidal anti-inflammatory drugs, acetylsalicylic acid should be avoided for the risk of Reye's syndrome [3]. Corticosteroids are not indicated in patients with mild symptoms, and some studies suggest that their use is associated with inhibition of the immune responses and delay in pathogen clearance, particularly in patients with early disease [4]. Their use is indicated only in patients with more severe illness and hypoxaemia [5].

Hydroxychloroquine has in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and it has been proposed as a potentially effective treatment [6]. However, a relevant randomized, double-blind, placebo-controlled trial conducted in 491 outpatients with early SARS-CoV-2 infection and mild symptoms did not show any substantially effects of hydroxychloroquine treatment in reducing symptom severity [7].

Use of antibiotics should be discouraged, unless they are indicated for other reasons, because their use may lead to higher bacterial resistance rates [1, 8].

Self-isolation must be continued until two consecutive SARS-CoV-2 oropharyngeal swab tests are negative or 2 weeks after symptoms resolve in areas where retesting is a challenge [1].

Management of Patients with SARS-CoV-2 Pneumonia

SARS-CoV-2 pneumonia is a condition characterized by symptoms of low respiratory tract infection, findings of interstitial infiltrates on radiological examination, and positive SARS-CoV-2 oropharyngeal swab test. It generally occurs in the second week of infection. Typical laboratory abnormalities include elevated serum C-reactive protein (CRP) and lactate dehydrogenase (LDH). Lymphopenia and mild thrombocytopenia are the most common hematological abnormality described [9]. The most common radiological findings on CT scan are the presence of diffuse, peripheral ground-glass opacities [9]. Prevalent symptoms are fever, dry cough, shortness of breath, fatigue, anosmia, ageusia, nausea/vomiting or diarrhea, and myalgia [9]. Patients with

SARS-CoV-2 pneumonia must be hospitalized and isolated according to local care pathway.

Complications of COVID-19 include myocarditis, ventricular arrhythmias, acute cerebrovascular disease (stroke and encephalitis), venous and arterial thromboembolic events, acute respiratory distress syndrome (ARDS), kidney injury, liver dysfunction, disseminated intravascular coagulation, bleeding, and septic shock [9]. Regular monitoring of vital signs and use of medical early warning scores (e.g., NEWS2, PEWS) facilitate early recognition of these complications and treatments' escalation of the deteriorating patient. Moreover, regularly hematology and biochemistry testing should be obtained to early identify the onset of these complications.

In patients with respiratory failure, oxygen therapy must be started with nasal cannula or Venturi mask, titrating both flow and FiO2 to reach the oxygen saturation target (SpO2 > 90% in non-pregnant adults, SpO2 ≥ 92–95% in pregnant women, and SpO2 ≥ 88–92% in hypercapnic patient) [1, 9]. Adequate nutritional support should be ensured in COVID-19 patients, avoiding parental nutrition unless it is necessary. In order to reduce the incidence of stress ulcers and gastrointestinal bleeding, proton pump inhibitors or histamine-2 receptor blockers should be administered to these patients. General measures of managing SARS-CoV-2 pneumonia also include correction of electrolyte acid-base balance disorders and avoiding administration of hypotonic solutions and overload [1].

Current evidences do not support the discontinuation of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers during hospitalization of COVID-19 patients, but rather a study suggests that their continued use in hypertensive COVID-19 patients yields better clinical outcomes [10]. In patients with hyperglycemia, it is important to improve glucose control targeting blood glucose between 140 and 180 mg/dL and using, respectively, insulin infusion for critically ill patients and subcutaneous insulin with basal bolus schedule for more stable patients [11].

Viral inhibition is the mainstay of the management, and it would be expected to be most effective early in infection.

Remdesivir is an RNA-dependent RNA-polymerase inhibitor with inhibitory activity against SARS-CoV-2 in vitro [12]. This preliminary data was confirmed in a double-blind, randomized, placebo-controlled trial enrolling 1063 hospitalized COVID-19 patients with evidence of lower respiratory tract involvement. Statistical analysis showed that remdesivir was superior to placebo in shortening the time to recovery in these patients [13]. In this study, remdesivir appears to demonstrate the most benefit in those patients with respiratory failure [13]. Another study found no difference in terms of clinical status between patients, who did not require mechanical ventilation, treated with remdesivir for 5 or 10 day [14, 15]. Although the impact of remdesivir on survival remains unknown, it currently appears to be the only antiviral drug with proven positive clinical impact in patients with SARS-CoV-2 pneumonia and respiratory failure. Remdesivir should be administered intravenously by giving a loading dose of 200 mg on the first day, followed by 100 mg daily for 5 days [14, 15]. The main adverse events of remdesivir therapy are elevation of hepatic enzymes, gastrointestinal complications, rash, renal impairment, and hypotension. Other antiviral drugs are currently under investigation, but there is no evidence that their use is effective in the treatment of patients with SARS-CoV-2 pneumonia [1, 9, 15].

Preclinical and clinical studies have shown chloroquine and hydroxychloroquine to inhibit viral entry and endocytosis of SARS-CoV-2 with additional benefit of immunomodulation effects [12]. In a clinical trial of 150 hospitalized patients with mild and moderate COVID-19, administration of hydroxychloroquine did not result in a significantly higher probability of negative conversion than standard of care alone [16]. Other studies did not find any effect of hydroxychloroquine administration in risk of intubation or mortality among patients hospitalized for COVID-19 [17, 18]. QT prolongation, torsades de pointes, and ventricular tachycardia are the most common side effects of both drugs. Current evidences about chloroquine and hydroxychloroquine do not support their use in patients with SARS-CoV-2 pneumonia [9, 15].

Other therapeutic strategies include the modulation of the inflammatory response and the prevention of disease progression. In analogy to other severe respiratory tract infections, the role of

corticosteroids for the management of SARS-CoV-2 pneumonia is interesting and controversial, due to their anti-inflammatory and anti-cytokine effects. A recent Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, which randomized hospitalized COVID-19 patients to receive dexamethasone or usual care, found that dexamethasone reduced 28-day all-cause mortality in those who had respiratory failure [5, 15]. Based on these results, SARS-CoV-2 patients with pneumonia and respiratory failure should be treated with dexamethasone 6 mg daily for 10 days or until discharge if earlier. If dexamethasone is unavailable, equivalent glucocorticoid dose may be used, such as methylprednisolone 32 mg daily or prednisone 40 mg daily [15].

Other drugs that target the overwhelming inflammatory response following SARS-CoV-2 infection are under investigation. To date, there is not enough data to support their use in clinical practice, but only in the context of clinical trial [9, 15]. In case of their use, screening for chronic infectious diseases, such as human immunodeficiency virus, hepatitis B virus, and tuberculosis, should be made before their administration.

Thromboembolic prophylaxis with subcutaneous low-molecular-weight heparin is recommended for all hospitalized patient with COVID-19 [19]. For those with hemorrhagic contraindications, mechanical prophylaxis (intermittent pneumatic compression devices) can be used. Based on clinicopathologic reports demonstrating an association between severe SARS-CoV-2 infection and coagulopathy, parenteral anticoagulants are widely used in the management of these patients. Beyond their primary anticoagulant effects, these drugs have been found to exhibit antiviral, anti-inflammatory, and cytoprotective effects [20]. Studies are ongoing to assess whether certain patients with severe SARS-CoV-2 infection will benefit from therapeutic anticoagulation [9]. Patients with therapeutic anticoagulation for other underlying conditions, such as atrial fibrillation or prevention of venous thromboembolism recurrence, should continue their treatment unless significant bleeding develops or other contraindications are present. Caution should be taken in patients treated with direct oral anticoagulants for the high risk of pharmacological interaction with antiviral or antibiotic treatment.

Despite frequent prescription of broad-spectrum empirical antimicrobials in patients with coronavirus-associated respiratory infections, there is paucity of data to support the association with respiratory bacterial/fungal coinfection [21]. Antibiotic overuse increases the risk of emergence of multidrug-resistant bacteria and *Clostridium difficile* infection. Antibiotics should not be prescribed in patients with moderate illness unless there is clinical suspicion of a bacterial superinfection [1]. However, patients with severe illness should be treated with empiric antimicrobials based on clinical judgment, patient host factors, and local epidemiology [1].

Management of Patients with Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a life-threatening clinical condition characterized by bilateral pulmonary opacities that occur as a complication of SARS-CoV-2 infection [22]. It is due to an acute, diffuse, inflammatory lung injury leading to increased alveolar capillary permeability and loss of aerated lung tissue. Dyspnea is the most common symptom and is associated with impressive hypoxemia. Risk factors associated with progression from pneumonia toward ARDS are older age, male gender, and the presence of significant comorbidities. Laboratory findings associated with the onset of ARDS are hyperferritinemia and elevated levels of CRP, LDH, and D-dimer. PaO2/FiO2 ratio correlates with disease severity and progression. Based on PaO2/FiO2 ratio, ARDS can be classified into three degrees:

- **Mild**: $300 < PaO_2/FiO_2 > 200$ with PEEP $\geq$ 5 cm H_2O
- **Moderate**: $200 < PaO_2/FiO_2 > 100$ with PEEP $\geq$ 5 cm H_2O
- **Severe**: $PaO_2/FiO_2 < 100$ with PEEP $\geq$ 5 cm H_2O

Supportive care remains the mainstay of management. For patients who are unresponsive to conventional oxygen therapy, a trial of heated high-flow nasal oxygen (HFNO) or noninvasive mechanical ventilation (NIMV) should be considered, unlike in

patients with hemodynamic instability, multiorgan failure, or abnormal mental status. In these latter conditions, patients should be evaluated for intubation and invasive mechanical ventilation. Intubation should not be delayed if the patient acutely deteriorates or does not improve after a short trial. For patients requiring invasive mechanical ventilation (see also Chap. 10), lung-protective ventilation with low tidal volumes (4–8 mL/kg, predicted bodyweight) and plateau pressure less than 30 mg Hg is recommended [23].

Prone positioning may facilitate oxygenation probably due to alveolar recruitment, redistribution of trans-pulmonary pressure, ventilation perfusion (V/Q) ratio matching, better secretion management, and positive hemodynamic effects. This hypothesis is supported by two recent studies where self-proning was associated with improved oxygenation parameters in at least two-thirds of adults with COVID-19 with respiratory failure [24, 25]. Further studies are needed to assess the impact of self-proning in patient's outcome.

Empiric antimicrobials should be prescribed based on clinical judgment, patient host factors, and local epidemiology.

Remdesivir is the only antiviral drug with positive clinical impact in COVID-19 patients with ARDS. It should be intravenously administered with a loading dose of 200 mg on the first day and then at dose of 100 mg per day for at least 10 days [13–15].

A retrospective cohort study of 201 patients with SARS-CoV-2 pneumonia admitted to Wuhan Jinyintan Hospital in China showed methylprednisolone treatment decreased the risk of death in patients with ARDS [26]. These results are recently confirmed in a controlled, open-label trial, enrolling hospitalized patients with SARS-CoV-2 infection. In this study, dexamethasone treatment resulted in lower 28-day mortality among COVID-19 patients who were receiving either invasive mechanical ventilation or oxygen alone [5, 15]. Based on these results, COVID-19 patients with ARDS should be treated with dexamethasone 6 mg daily for 10 days or until discharge if earlier [15]. If dexamethasone is unavailable, equivalent glucocorticoid dose may be used.

Anticoagulant prophylaxis is indicated in all patients, unless hemorrhagic contraindications are present [9, 19]. A chest CT scan with contrast should be performed in patients with sudden

worsening of respiratory failure or significant increase of D-dimer level to exclude pulmonary thromboembolism. In this case, parenteral anticoagulants are preferred to oral anticoagulants, given their short half-life and the ready availability of reversal agents.

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10

Respiratory Support in COVID-19 Respiratory Failure

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Introduction

In terms of the pathophysiology of pulmonary infection with SARS-CoV-2, COVID-19 can be divided into three phases. Pulmonary damage in advanced COVID-19 often differs from the known changes in acute respiratory distress syndrome (ARDS). Two types (type L and type H) are differentiated, corresponding probably to an early- and late-stage lung damage. This differentiation should be taken into consideration in the respiratory support of ARF. Personal protective equipment (PPE) should have priority because fear of contagion should not be a primary reason for intubation. Based on the current knowledge, inhalation therapy, nasal high-flow therapy (NHF), continuous positive airway pressure (CPAP),or noninvasive ventilation (NIV) can be performed, without an increased risk of infection to staff if PPE are provided, and a significant portion of patients presents with severe hypoxia that requires high concentrations of inspired oxygen (FiO_2). In this

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situation, the oxygen therapy can be escalated to CPAP or NIV when the criteria for endotracheal intubation are not yet met. In ARF, NIV should be carried out in an intensive care unit or a comparable setting by experienced staff; in fact under CPAP/NIV, a patient can deteriorate rapidly. For this reason, continuous monitoring and readiness for intubation are to be ensured at all times. If the ARF progresses under CPAP/NIV, intubation should be implemented without delay.

The severity of respiratory failure is determined by the interaction of three factors: (1) the severity of infection, the immune response and function, and comorbidities; (2) the patient's ventilatory response to hypoxia (hypoxic drive); and (3) the time between the onset of the initial symptoms and the beginning of clinical treatment.

Pathophysiological Basis of Respiratory Treatment

Different Phenotypes, Different Ventilatory Support

In terms of pathophysiology, respiratory failure is primarily characterized by mild to severe hypoxic respiratory distress. In the course of the disease, however, some patients have considerable recurrent CO_2 increases. Patients intubated and ventilated in this phase of the disease have an increased alveolar-arterial oxygen gradient (also taking into account a high inspired oxygen fraction [FiO_2] and assuming a respiratory quotient of 0.85) and a remarkably large difference between arterial and end-tidal CO_2.

In addition, assessing the patient's cardiovascular condition is extremely important. The first data from China showed a high proportion of cardiac patients (20–30% of hospitalized patients) at an early stage of the pandemic. These numbers were confirmed in the European patient collectives [1]. Analysis of the deceased patients in the Wuhan cohort found cardiac damage in 34% and cardiac failure in 40%, either as the sole cause or in combination with respiratory failure [2, 3]. In this context, the associated

mortality risk of acute cardiac damage was higher than age, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and preexisting cardiac disease. Several factors must be considered as causes of that—because of the administration of a variety of drugs in these patients—and possible drug-related toxic effects cannot be excluded; this in fact has frequently been described. Therefore, we must assume the presence of an increased cardiac stress, particularly that starting early on with the development of hypoxemia.

Hypoxemia with a decrease in oxygen levels requires an increase in cardiac output to maintain adequate oxygen transport. At the same time, the heart can be additionally stressed as a result of hyperventilation due to an increase in right ventricular (RV) afterload. The greater respiratory effort causes an increase in the negative intrathoracic pressure, resulting in an increase in transmural left ventricular (LV) pressure. From a pathophysiology point of view, the development of hypoxemia can induce RV overload, but there is currently no evidence that this is the case in the early phase of the disease.

As in community-acquired pneumonia (CAP), the systemic inflammatory response can foster cardiac complications such as arrhythmia, heart failure, and coronary events. However, the rate of cardiac manifestations is higher than with CAP (approx. 25%).

Another cause of cardiac damage may be myocarditis. So far, however, only a few significant case studies are available.

To what extent the regularly identified elevated D-dimer reflects increased coagulation activity has also not yet been established. Indeed, the disease seems to be associated with an increased risk of thrombotic events and coagulation system disorders. For example, pulmonary embolism was detected in 25% of a series of 81 seriously ill COVID-19 patients [4].

In line with the changes observed in imaging and based on data in Gattinoni et al. [5, 6], two chronological CT manifestations can be distinguished, the so-called type “L” and type “H” COVID-19 pneumonia (see below).

Two types of COVID-19 pneumonia can be distinguished, with different pathologies (type L and type H) corresponding to early- and late-phase pneumonia.

The definition of acute respiratory distress syndrome (ARDS) in accordance with the Berlin definition can be met in both manifestations; however, it has been shown that COVID-19 pneumonia, especially in the early stage (type L), but also in the late stage (type H), differs significantly from the common changes accompanying ARDS, such as those observed in septic shock or bacterial pneumonia.

COVID-19 Pneumonia, Type L

The early phase, which can be compensated by the patient with oxygen support, is described as COVID-19 pneumonia, "type L" , by Gattinoni et al. [5, 6] where "L" stands for:

- Low (low elastance, i.e., high compliance)
- Low ventilation/perfusion mismatch
- Low lung weight with low inflammatory fluid retention

the radiological correlate of ground-glass densities, and no or little consolidation. This type, therefore, also has a low potential for recruitment.

In the early phase, the viral infection leads to moderate local, subpleural inflammation with interstitial fluid accumulation (morphologically corresponding to the ground-glass pattern seen on CT). The greater part of the lungs is not affected, which explains the preserved normal pulmonary elastance. In affected areas, the vessels are maximally dilated with a postulated loss of hypoxic vasoconstriction, and there is thus an increase in shunt volume. It is not clear whether this is the result of endothelial damage or active vascular smooth muscle relaxation regulated by inflammatory mediators. The physiological response to hypoxemia is an increase in ventilation. Due to the preserved lung compliance, however, patients do not perceive this as dyspnea. This explains that no/only minor dyspnea symptoms are felt, despite pronounced hypocapnia with a $PaCO_2$ <22 mmHg and simultaneous significant hypoxemia.

In addition to recording the gas exchange and blood gas parameters, the leading clinical parameter is the respiratory rate and its changes over time, which can be interpreted as a surrogate parameter of respiratory effort. While it would be desirable and helpful to determine the respiratory effort as well as intrathoracic pressure changes by means of esophageal pressure measurement, this approach cannot be easily and routinely applied in the clinical setting, especially since the technology and experience required are not generally available primarily in intensive care units (ICUs) and the outside (i.e., sub-intensive unit). The increased respiratory rate and increased ventilation possibly could lead to further lung damage due to the associated mechanical stress (shear forces and high intrapleural pressure amplitude). This phenomenon was first described experimentally by Barach et al. [7, 8] and Mascheroni et al. [9] and was labeled patient self-inflicted lung injury (P-SILI). The supply of oxygen during this phase can provide ventilatory relief.

COVID-19 Pneumonia, "Type H"

According to current studies, approximately 15–20% of hospitalized patients develop severe lung damage. Accordingly, extensive densifications, similar to those seen in other types of severe pneumonia and patients with extrapulmonary ARDS, are seen on the CT. Such imaging patterns can also be caused by nosocomial infections.

The working group of Gattinoni et al. [5, 6] describes this progressive, critical state as COVID-19 pneumonia, type "H":

- High (high elastance, i.e., low compliance) as a result of increasing edema
- High lung weight
- High share of recruitable lung volume.

This condition reflects the pathophysiology of severe pneumogenic ARDS with signs of DAD. [10] Very similar changes were

seen in patients who died of SARS [11] and MERS [12]. The model of Gattinoni et al. [5, 6] has been shown to provide a good basis to better understand the pathophysiology of COVID-19 pneumonia. Nevertheless, many questions remain unanswered. From a clinical point of view, it is imperative to have comprehensive diagnostic procedures for both spontaneously breathing patients and particularly for postintubation patients.

This differentiation can be taken into consideration in the respiratory support of ARF.

Noninvasive Ventilation (NIV) and Continuous Positive Airway Pressure (CPAP)

From a pathophysiology point of view, mechanical support by means of noninvasive ventilation (NIV) or continuous positive airway pressure (CPAP) via a mask system or helmet could be helpful during phase "L" to prevent possible P-SILI.

The applications of positive end-expiratory pressure (PEEP) during acute HRF secondary to pulmonary edema, atelectasis, or pneumonia have been demonstrated to improve arterial oxygenation by increasing functional residual capacity, shifting the tidal volume to a more compliant part of the pressure-volume curve, thus reducing both the work of breathing and the risk of tidal opening and closure of the airways. Moreover, PEEP recruits non-aerated alveoli independent pulmonary regions, stabilizes the airways, and reduces inhomogeneity of lung volume distribution.

PEEP can be applied to spontaneous breathing patients through CPAP systems. The helmet CPAP applied in patients with severe HRF due to pneumonia demonstrated to reduce the risk of meeting the criteria for endotracheal intubation compared with venture face mask.

The helmet equipment briefly consists of a transparent, latex-free, polyvinylchloride hood joined by a metal or plastic ring to a soft polyvinylchloride collar of different sizes (just measure the patient's neck circumference to choose the size). Generally, the helmet is better tolerated than the face mask, especially for prolonged treatments (in the case of CPAP for COVID-19 ARF

from 4 to 7 days or more of treatment according to our experience); with the helmet, the patient can drink and take drugs without removing the device, and also the risk of developing nasal decubitus is reduced.

In a relevant overview concerning the indication for the protection of healthcare workers from SARS-CoV-2 infection, Ferioli et al. [13] showed how the helmets provided with a tight air cushion around the neck helmet interface have negligible air dispersion during NIV application and represents, with CPAP via oral mask, the noninvasive ventilator support that allows the minimum room air contamination. In any case, in restricted availability of negative pressure rooms, like when there is a large afflux of patients and demand exceeds supply, it is suggested to apply an antiviral filter both on the inspiratory and on the expiratory ports of the helmet. This should maximally reduce the risk of droplet dispersion. The most effective CPAP is achieved when the PEEP level is maintained throughout the respiratory cycle; inspiratory PEEP fluctuations reflect an insufficient gas delivery compared with the patient minute ventilation. Concerning this consideration probably high-flow systems should be preferred for CPAP with helmet when flows are greater than 40/60 L/min to reduce the risk of CO2 rebreathing (CO2 rebreathing depends on two factors: the amount of fresh gas that passes through the helmet and the amount of CO_2 produced by the patient) and to maintain a constant PEEP throughout the respiratory cycle.

Finally, the CPAP systems need an access to a high-flow oxygen source without necessitating electricity. For the risk of accidental gas flow interruption with a dangerous risk in PEEP and in oxygen reduction, the application of helmet CPAP should be always supported by appropriate and dedicated monitoring and alarming systems.

Helmet CPAP is currently being extensively used in Italy during COVID-19 pandemic. Despite the relative simplicity on setting, CPAP application needs careful evaluation of patient's respiratory and hemodynamic status. There are not randomized studies on the use of CPAP in COVID-19 pneumonia; based on several observational studies and on clinical experience with more than 180 patients treated with CPAP outside ICU in Ospedale di

Circolo in Varese from March 1 to May 1, 2020, and as recommended by Vitacca et al. [1], we could suggest indication for CPAP use at 10–12 cmH_2O, without humidification and with helmet (first choice), for CPAP use with a mask (second choice) and for NIV use with an oronasal face mask (third choice), using high-performance ventilators or, if these are lacking, dedicated NIV platforms or home ventilators. HFNC may play a role in the treatment of very early stages of hypoxemia (P/F 200–300) or for weaning from CPAP or VAM. Clearly, for CPAP/NIV, using the maximum available personnel protection is indicated.

Prone Position

The prone position can improve oxygenation and can potentially result in less injurious ventilation. Because of a higher density of pulmonary vessels in the dorsal lung region (independently of gravity), the change of ventilation distribution while prone (i.e., relative increase in ventilation in the dorsal nondependent areas) results in improved $V/\dot{Q}$ matching and oxygenation. This does not necessarily equate to lung protection and better outcome. While prone, the chest wall compliance decreases when the anterior, more flexible part of the chest is facing the bed, explaining in part a more homogeneous distribution of ventilation and regional lung stress and decreasing the risk of ventilation-induced lung injury and possibly pendelluft. It is possible that the contraction of the muscular diaphragm, which faces the open dorsal lung during pronation, exerts a more uniform distribution of stress, whereas the muscular diaphragm exerts a more localized stress when facing the collapsed lung during supination. These mechanisms and the effect of prone positioning on respiratory drive and effort need to be investigated in spontaneously breathing patients. Prone position during invasive mechanical ventilation improved oxygenation in large randomized clinical trials (RCTs) of patients with ARDS [14]. However, better oxygenation was not associated with improved survival in trials with short duration of prone positioning. In an RCT that included 466 patients with moderate and severe ARDS (PaO_2:FIO_2 <150), prone positioning

for at least 16 hours per day with protective mechanical ventilation reduced 90-day mortality [15]. Previously, small case series showed feasibility and improvement in oxygenation in awake patients placed in the prone position during spontaneous or assisted breathing while receiving NIV and oxygen through high-flow nasal cannula.

Elharrar et al. [16] reported a single-center before-after study that included 24 patients with acute hypoxemic respiratory failure and infiltrates on chest computed tomographic scans. Prone positioning was started without changing the system for oxygen supply or fraction of inspired oxygen (FIO_2). Sartini et al. [17] performed a 1-day cross-sectional before-after study that included 15 awake patients with mild and moderate ARDS. Several conclusions can be drawn cautiously from these case series, although the findings cannot be generalized without confirmation in larger trials. The prone position during spontaneous and assisted breathing in patients with acute hypoxemic respiratory failure may become a therapeutic intervention in the near future. Tolerance is sometimes a limitation of the technique, the physiological effects are not clarified, and the benefits of very short sessions may be questionable. Can the prone position prevent intubation? This question is essential, but intubation is a medical decision, not a physiological state. Improvement in oxygenation during prone positioning may prevent clinicians from making decisions about intubation solely based on hypoxemia. This is potentially a good outcome, but clinical assessment of work of breathing is essential in this context to avoid delayed intubation with eventually poor outcome. Clinicians should closely monitor patients for whom prone positioning is used for tolerance and response and aim to prevent delayed intubation and controlled mechanical ventilation when necessary.

One algorithm (see Fig. 10.1) that could summarize the management methods of COVID-19-related respiratory failure is the one proposed, in a recent review, by the multidisciplinary group of Genoa [18].

After all, always remember:

The decision to institute invasive mechanical ventilation (involving an endotracheal tube) is based on physician judgment –

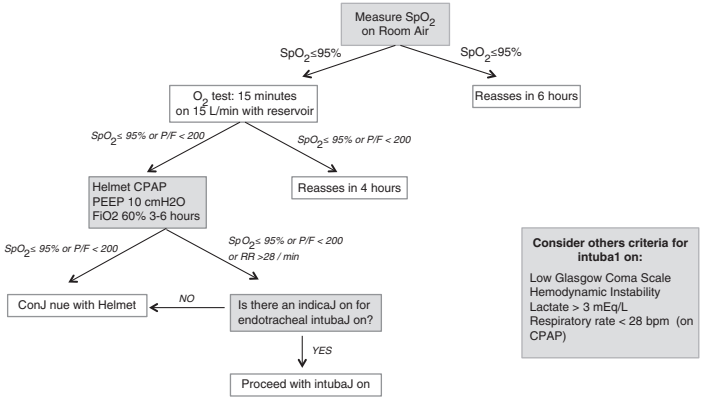

Fig. 10.1 A decisional algorithm to manage ventilator support in patients with SARS-CoV-2-related respiratory failure

clinical gestalt influenced by oxygen saturation, dyspnea, respiratory rate, chest radiograph, and other factors [M. J. Tobin [19, 20]*].*

Invasive Ventilation in SARS-CoV-2 Patients

In the literature, there are different rates of invasive mechanical ventilation in SARS-CoV-2 patients, and currently there is no consensus about better invasive management of these patients but only clinical recommendation-related study. However, mechanical ventilation (MV) is the cornerstone in the management of respiratory failure to guarantee adequate oxygen delivery and to clear carbon dioxide. For patient with respiratory failure, noninvasive ventilation (NIV) at the beginning of respiratory distress has been reported to reduce mortality and the need of intubation in viral pneumonia [21], but MV is recommended to be applied in a timely manner if the oxygen saturation and respiratory distress do not improve or even get worse after NIV. The main clinical indications can show if a sufficiently high arterial O_2 level is achieved or not and if as a consequence of that the patient

develops a respiratory distress; in these cases, MV is the only instrument to save the patients. A study [22] in the New York state found that patients who have received mechanical ventilation were 76% when considering aged patients minor 65 years and 97.2% if we considered an age over 65. This data reveal the magnitude of mechanical ventilation in COVID-19 patients. It is inadvisable to delay tracheal intubation in patients with a low oxygenation index, with a worsening of respiratory distress symptoms or already with multiple organ failure present during administration of noninvasive oxygen therapy. Advanced techniques during invasive mechanical ventilation, such as pressure and limited volume ventilation, the use of PEEP, the use of neuromuscular blocking agents, and the pronation and the use of ECMO (extracorporeal membrane oxygenation) should be considered.

Mechanical Ventilation in COVID-19 Patient: Timing and Management

In a suggestive editorial by Hannah, the author writes about the decision to ventilate a patient with SARS-CoV-2 infection pointing out that "the same debate we are now having regarding early versus late use of mechanical ventilation and when patients need to receive mechanical ventilation has been going on since the birth of intensive care 70 years ago […]," [23] referring to epidemic of polio. We can find a lot of papers that describe a different rate of intubation; for example, in Italy, Grasselli et al. [11] describe a rate of 88% in a patient with pulmonary distress with mechanical ventilation, while a rate of 45% in China was described by Guan et al. [24]. In author's opinion, different resources and clinical strategies could explain these data. Regarding literature about patients without viral pneumonia but with acute respiratory distress, there is an extreme variability between study to define the main criteria to adopt mechanical ventilation [25, 26]. Jin et al. [27] describe that refractory hypoxemia and alterations in clinical parameters must be

considered as indicators to initiate MV, in particular tachypnea (>30 bpm) and hypoxemia ($PaO_2 < 60$ mmHg) with elevated FiO_2 and NIV failure. In COVID-19 patients, the literature is not clear, and during early phase of epidemic peak (March 2020) in Italy, the SIAARTI (Italian Society of Anesthesia and Analgesia and Intensive Care) suggested to start mechanical ventilation in the early clinical manifestation avoiding any delay [28]. This indication was not completely satisfied due to impossibility to maintain an elevated rate of intubation in hospital with resource limited setting, and also, more importantly, during pandemic period, noninvasive ventilation has been demonstrated to be effective and relevant saving intubation in selected cases. Robba et al. [18] have developed a flowchart to candidate to intubation these patients focusing on bedside test and rationing PPE use, and we describe in Table 10.1 a simple score to start mechanical ventilation in patient with suspected or confirmed SARS-CoV-2 infection. Moreover, the mortality rate in patients intubated and ventilated was very high and underestimated, suggesting that ventilation is not the solution but only a "take patient time" to avoid complications and fatal evolution. The ARDS Berlin definition and its implication could be no effective in COVID-19 patients [29], and several authors describe the evidence of different phenotypes of SARS-CoV-2 infection [1, 18]. The main feature is the dissociation between the severity of hypoxemia and the maintenance of relatively respiratory wellness. In effects, the compliance of the respiratory system is generally about 50 mL/

Table 10.1 Intubation and mechanical ventilation in COVID-19 patient: a simple score

PATIENT CHARACTERISTICS with SUSPECTED or CONFIRMED Sars COV-2 Infection:	SCORE
– Moderate or Severe ARDS : Respiratory Index < 150.	1
– Failure of Non Invasive Ventilation (Cpap, HFO, NIV).	2
– Values of Blood Gas Analysis don't improve.	1
– Signs and Symptoms of respiratory distress : Respiratory rate, Tidal Volume, Respiratory drive.	2
– Urgent and emergent complications with neurological and cardiovascular collapse.	2
– Clinicians decisions due to impossibility to continue NIV (low patient compliance, NIV refused. . .).	2
	TOTAL : ____

Score < 1 : Continue monitoring focusing on : respiratory rate, respiratory drive, clinical examination.
Score ≥ 2 : Consider Intubation and Mechanical Ventilation.

cmH_2O (value median) during early phase with a hypoxemia scenario, in particular during modest physical exercise. Therefore, the different phenotypes with which COVID-19 manifests itself are hypothesized to depend on the interaction of three factors:

- Severity of infection, host response, physiological reserve, and presence of comorbidities
- Ventilatory responsiveness of the patient to hypoxemia
- Time of infection onset

The interaction between these factors leads to the development of a spectrum of diseases attributable to evolution of two primary "phenotypes" L and H (see also Chap. 7) in accordance with Gattinoni et al. [1] or 1–2–3 described by Robba et al. [18] The L phenotype is attributable to the fact that viral infection leads to a modest interstitial edema local subpleural (ground-glass lesions) where lung structures have different elastic properties. The normal response to hypoxemia is to increase minute ventilation, firstly by increasing the tidal volume associated with a more negative intrathoracic inspiratory pressure and a consequent decrease in $PaCO_2$. These patients could remain unchanged without any invasive or noninvasive support. They, mainly, manifest desaturation and a moderate respiratory distress during exercise such as "walking test." In many cases, the hospitalization is due to elevated fever or alteration of quality of life. For this reason, they maintain this clinical setting for several days and then improve or worsen their physical status. As revealed by numerous studies, the key that determines the evolution of the disease, in addition to the severity of the disease itself, is how negative is the inspiratory intrathoracic pressure. In fact, a greater negative inspiratory intrathoracic pressure associated with increased lung permeability due to inflammation causes pulmonary edema interstitial "patient self-inflicted lung injury" (P-SILI). Currently, the authors agree that the switch from type L to type H is determined by the evolution of COVID-19-related pneumonia and by the injury attributable to ventilation and high stress. In the type L, the hypoxemia could be corrected through

several noninvasive devices: high-flow nasal cannula (HFNC), continuous positive airway (CPAP), or noninvasive ventilation (NIV), but at this stage should be the mandatory measurement (or the estimation) of inspiratory esophageal pressure fluctuations, and, in the absence, the fluctuations in venous pressure could be a surrogate. The magnitude of the inspiratory pleural pressure fluctuations can determine the transition from type L to type H phenotype, but intubation should be performed as soon as possible in accordance with clinical indicators and P-SILI onset regardless of phenotype manifestation. Once intubated, a deep sedation with curarization is often necessary, and all patients have to be ventilated in accordance with clinical and radiological signs of COVID-19. Initially, a strategy with low tidal volume ventilation (VT 4–8 mL/kg of PBW) instead of higher tidal volumes (VT > 8 mL/kg PBW) is recommended. Additionally, a higher PEEP (>10 cm H_2O) strategy should be preferred over a lower PEEP, and PEEP should be titrated according to FiO_2 to maintain an appropriate SpO_2 [30]. The type L patients, if hypercapnic, can be ventilated with volumes greater than 6 mL/kg (up to 8–9 mL/kg), as the high compliance results in a more tolerable effort without the risk of VILI. Pronation should be used only as a rescue maneuver or in phenotype where atelectasis is distributed nonuniformly. High PEEP values could worsen hemodynamic stability increasing the need for fluids and vasoconstrictor drugs without having important effects on oxygen delivery. In these cases, PEEP should be reduced to 8–10 cmH_2O, as the recruitability is low and the risk of hemodynamic failure increases at higher levels. Type H patients should be treated as severe ARDS according with definition [31], and the higher PEEP, if compatible with hemodynamics, pronation, and extracorporeal support, should be used (Table 10.2).

The weaning process in these patients is not well studied, and therefore there are no guidelines or recommendations [27].

Table 10.2 Mechanical ventilation in COVID-19 patient

Mechanical Ventilation in SUSPECTED or CONFIRMED Sars- Cov2 Infection:

SETTING

Sedation and/or Curarization
Volume Controlled Ventilation
Vt: 4-8 mL/Kg (PBW: Predicted Body Weight)
FR: 18-26/minute (max 32/minute)
PEEP/FiO2:

FiO2:	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9-1.0
	8	10	10	10	12	14	14	16-24

TARGET

SpO2 88-95%
PaO2 55-80 mmHg
Pplat £ 28 cmH2O (In BMI elevated could be higher)
Driiving pressure £ 12-14 cmH2O (In BMI elevated could be higher)

PRONATION

-Early if MV failure (Low Respiratory Index)

Modality:

- period of 12-16 Hours.
- success : if improvement up to 4 hours after pronation
- failure : no improvement of Respiratory Index.
: worsening of Respiratory Index or Cardiovascular Complications

ECMO

- refractory hypoxemia despite:
a) Conventional treatment
b) prone positioning.

veno-venous (VV) extracorporeal membrane oxygenation (ECMO) can be considered as an option.

"used as rescue therapy only. in carefully selected patients."

Currently, the standard local procedure is recommended focusing on the risk of contamination and infection. Therefore, simple considerations could be done:

- Patient has to be well awake with adequate cough reflex.
- Patient must have hemodynamic stability.
- To proceed for weaning patient must have adequate ventilation parameters (low FiO_2, low PEEP, low pressure support, etc.).
- Consider weaning trial: spontaneous breathing for a long period with CPAP or PSV.
- A respiratory physiotherapy in accordance with local resources is necessary.
- Proceed with extubation in patients with SARS-CoV-2 infection active in rooms dedicated.

Disclosure The authors declare that they have no competing interests.

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11 Principles of Pharmacological Therapy

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Information about COVID-19 has evolved so quickly that it can be difficult for clinicians to feel confident that they are staying current.

There is currently no solid evidence from randomised controlled trials (RCT) for specific anti-COVID-19 treatment although many are ongoing. The treatments undertaken are part of clinical trials approved by ethics committees or study protocols. Some pharmacological agents have been described in observational studies or are used based on in vitro efficacy. It is important to emphasize that there are no controlled data to support the use of any of these agents and their efficacy for COVID-19 is unknown [1].

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Remdesivir is the only antiviral drug currently authorized by the US Food and Drug Administration (FDA) and European Medicine Agency (EMA) for the treatment of hospitalized adults with SARS-CoV-2 lower respiratory tract involvement. Remdesivir is a broad-spectrum antiviral drug, acting as an adenosine analog, which incorporates into nascent viral RNA chains and results in premature termination [2]. It has been previously tested for SARS, MERS, and Ebola and recently demonstrated in vitro activity against SARS-CoV-2 [3].

Efficacy and safety of remdesivir for treatment of COVID-19 patients have not been fully disclosed. Preliminary data analysis from the phase 3 adaptive trial (NCT04280705; ACTT-1) in hospitalized adults with COVID-19 and evidence of lower respiratory tract infection indicated a shorter median time to recovery in the remdesivir group in comparison with the placebo group and suggested that remdesivir treatment may provide a survival benefit [4]. Moreover, in patients with severe COVID-19 not requiring mechanical ventilation, significant difference did not emerge between a 5-day course and a 10-day course of treatment [5]. Promising data came from the manufacturer's compassionate use program on children and pregnant women. No safety warnings were identified for the drug in these populations [6].

Chloroquine (CQ) and hydroxychloroquine (HCQ) are 4-aminoquinoline derivatives, which have been widely used in the treatment of malaria and several rheumatologic conditions for over 60 years. Both CQ and HCQ have shown in vitro activity against various viruses, including flaviviruses, retroviruses, and coronaviruses, like SARS-CoV-1 and MERS-CoV [3]. In vitro activity against SARS-CoV-2 was also reported, albeit the exact mechanism of antiviral action is still unclear. It has been suggested that these drugs may interfere with several steps of cellular infection and viral replication. Namely, CQ may counter the glycosylation of ACE-2 receptors, acknowledged as the site of SARS-CoV-2 cell binding; CQ and HCQ increase the pH of acidic cellular organelles, hindering the intermediate stages of endocytosis and virion transport and posttranslational modification of newly synthesized viral proteins; CQ/HCQ can interfere with the process of virion assembly and viral protein synthesis [7].

Moreover, their immunomodulatory activity may theoretically contribute to reduce the hyper-inflammatory response in severe COVID-19 cases [8]. According to in vitro physiologically based pharmacokinetic models, HCQ was reported to be more potent than CQ to inhibit in vitro SARS-CoV-2 infection, while it resulted two to three times less toxic than CQ itself in animal models [9].

CQ and HCQ were introduced in the early stage of the pandemic as a potential treatment for COVID-19 [10]. Promising results were initially obtained by a series of uncontrolled, open-label study performed in France, which suggested that HCQ treatment significantly decreased viral load in COVID-19 patients and its effect was reinforced by azithromycin (AZ) combination [11, 12]. However, subsequent randomized trials comparing HCQ with standard care/placebo suggested that HCQ may not reduce the risk of death, mechanical ventilation, or duration of hospitalization [13]. In particular, the two largest COVID-19 randomized controlled treatment trials (RECOVERY and SOLIDARITY; SRCTN registry: 50189673 and 83,971,151) have stopped recruitment to the HCQ arm because of a lack of evidence for benefit in severe COVID-19 [14, 15]. Combination with AZ has not been supported by any real evidence of benefit, and it resulted independently to be associated with a higher risk of cardiac arrest compared to no drug [16]. On the other hand, several observational studies on large multicenter cohorts reported a positive impact associated with HCQ/CQ treatment, in terms of in-hospital mortality [17, 18].

Prolongation of QTc is a consistent finding with CQ/HCQ, thus requiring electrocardiographic monitoring and correction of modifiable risk factors (i.e., common electrolyte abnormalities, especially in severely impaired renal function, and coadministration of drugs which prolong the QT interval). Many national and international guidelines on COVID-19, as well as some regulatory authorities, have warned against the potential risk associated with the use of CQ and HCQ (alone or in combination with azithromycin) and recommend against the use of these drugs for the treatment of COVID-19, except in the context of a clinical trial [19].

Further data from randomized, controlled clinical trials are warranted, since results available to date are still insufficient to draw conclusions regarding possible role of CQ/HCQ in COVID-19 patients, especially in the early stage of the disease.

The association lopinavir/ritonavir (LPV/r) is used together with other antiretrovirals for the treatment of human immunodeficiency virus since the beginning of the century. LPV/r demonstrated in vitro activity against SARS-CoV-2, as well as against other zoonotic coronavirus [20]. Retrospective data from SARS epidemic suggested that an early antiviral treatment with LPV/r can potentially reduce the incidence of severe and critical cases [21]. However, a first clinical trial in hospitalized adults with severe COVID-19 in China did not show reduction in time to clinical improvement and mortality with LPV/RTV compared with standard of care [22]. Moreover, no significant differences were observed in reduction of viral RNA load, duration of viral RNA detectability, duration of oxygen therapy, duration of hospitalization, or time from randomization to death. These results prompted national and international guidelines to recommend against the use of LPV/RTV or other HIV protease inhibitors for the treatment of COVID-19, except in the context of a clinical trial [23, 24].

Darunavir with cobicistat (DRV/c) had no in vitro activity against SARS-CoV-2 at clinically relevant concentrations [25]. Manufacturer states they have no clinical or pharmacologic evidence to support the use of DRV/c for the treatment of COVID-19. Results of an open-label, controlled study in China indicated that a 5-day regimen of DRV/c was not effective for treatment of COVID-19 [26].

No data to date support the use of atazanavir and other HIV protease inhibitor in the treatment of COVID-19 patients.

Also the optimal dosage and duration of treatment are not known. According to the current Emergency Use Authorization, the recommended dosage of treatment for hospitalized adults is 200 mg by IV infusion on day 1 (loading dose), followed by maintenance doses of 100 mg by IV infusion once daily. Recommended total treatment duration is 5 days and may be extended for up to 5 additional days (total treatment duration of 10 days) for those

requiring invasive mechanical ventilation and/or ECMO and patients who do not demonstrate clinical improvement after the first 5 days.

It is now clear that COVID-19 is a systemic disease; therefore, in addition to antiviral therapy, different pharmacological classes have been tested starting from different physiopathogenetic mechanisms involved in the disease.

A key role is played by the massive activation of the inflammatory system linked to the cytokine storm that occurs in some patients. In these patients, elevated interleukin (IL)-6 levels have been described. During viral infection, IL-6 is released by various cell types, including dendritic cells and macrophages of the innate immune system. IL-6 binds its IL-6R receptor, present on the surface of various cells, involving them in pro-inflammatory actions. In addition to causing excessive permeability of the vessels, the exaggerated action of interleukin-6 can activate the immune system against the body itself, giving rise to a real cytokine storm capable of proving severe pneumonia and ARDS.

Clinical worsening and the increase in values of cytokines often occur around the tenth day in concert with the appearance of the first specific immunoglobulins against SARSCoV-2. It's therefore conceivable that the specific immune response may be partly responsible for the symptoms observed.

In the case of influenza, for example, an exaggerated immune response can lead to diffuse alveolar damage with the formation of hyaline membranes and fibrin exudates and healing with fibrotic outcomes [27].

These physiopathogenetic assumptions have led clinicians to hypothesize a possible therapeutic role of some classes of immunomodulating drugs and in particular of steroids.

In COVID-19 infections, serum levels of IL-6 can rise to as high as 100 pg/mL. A strong correlation between serum levels of IL-6 and serum viral RNA in the blood of patients with SARS-CoV-2 infection has been observed. Moreover, a higher plasma viremia is associated with worsening of general conditions. Similarly with other inflammatory diseases such as CRS and secondary HLH, IL-6 antagonist drugs can be very useful in the treatment of severe cases of COVID-19 [28].

IL-6 inhibitors such as tocilizumab are currently the most studied immunomodulatory drugs and which initially seemed the most promising.

The therapeutic guidelines of the Chinese National Commission published in March 2020 considered the use of tocilizumab for patients with severe COVID-19 and elevated levels of IL-6 [29].

Tocilizumab acts by binding specifically to both soluble and membrane IL-6 receptors (sIL-6R and mIL-6R) by inhibiting the signals mediated by them and consequently inhibiting the pleiotropic pro-inflammatory effects of IL-6. It has shown interesting results, and it is approved by the Chinese National Health Commission as a complementary therapy for severe cases of COVID-19 infection in patients with severe pneumonia and in patients with COVID-19 who require hospitalization in the ICU. In a study on 21 Chinese patients at the beginning of the pandemic, the combination of tocilizumab (in a single administration) with antiviral therapy showed good tolerability and clinical improvement already in the first 24–48 h of treatment.

The posology to be used, according to the first studies, should be that recommended for the treatment of cytokine release syndrome by IV infusion lasting 60 min (4–8 mg/kg in patients weighing 30 kg or more); if after 12 h a significant clinical, radiological, or hematochemical response (including plasma levels of IL6) has not been achieved, a second administration can be performed. A third dose can be administered if the ferritin and D-dimer values are still elevated 24 h after the first administration [29].

Despite the first promising results, some systematic reviews on the use of tocilizumab in SARS-CoV-2 infection have recently been conducted, and in the conclusions they stated that there is insufficient evidence regarding the clinical efficacy and safety of tocilizumab in patients with COVID-19. Its use should be considered experimental, requiring ethical approval and clinical trial oversight [30, 31].

Sarzi-Puttini et al. [32] showed a series of other immunological drugs such as anti-IL1 and anti-TNFα that could play a role in COVID-19, extensively discussing the rationale for their use and

emphasizing the crucial role of impaired innate immunity and storm cytokine in disease progression.

Recent evidence has led to the hypothesis that IL-1 may represent another effective clinical target for the treatment of patients with COVID-19 with a severe course. Different drugs have been developed so far that can block the activity of IL-1, used mainly for the treatment of some diseases, mostly on an autoimmune basis:

- Anakinra, a recombinant version of the endogenous IL-1 antagonist (IL-1Ra), capable of inhibiting cytokine activity by competing with IL-1 for binding to its receptor, without transducing any signal. The drug is approved for the treatment of various diseases characterized by an overproduction of IL-1 including rheumatoid arthritis and periodic fever syndromes.
- Canakinumab, a human monoclonal antibody that binds IL-1β with high affinity, inhibiting its biological activity and preventing the activation of other inflammatory mediators. This drug is indicated in different pathologies with a pronounced inflammatory course, including periodic syndromes associated with cryopyrin, Muckle-Wells syndrome (MWS), and systemic juvenile idiopathic arthritis (SJIA).

IL-1 is recognized as one of the first engines that feeds the cytokine storm in the context of secondary hemophagocytic lymphohistiocytosis (HLHS) or macrophage activation syndrome (MAS), the clinical picture of which is very similar to that found in COVID-19 patients with severe disease [33–35]. IL-1 inhibitors appear to be key therapies in the treatment of MAS or secondary HLH and therefore may be valid therapeutic options also for the treatment of COVID-19, boasting a good safety profile even when used in pregnant women and children [36]. Through the inhibition of IL-1, it is expected that these drugs may also contain the NF-κB-mediated hyperproduction of other cytokines with pro-inflammatory activity, including IL-6. There are reports of an early increase of IL-1 in COVID-19 patients with progression of lung damage; a report of seven cases of COVID-19 patients affected by secondary hemophagocytic lymphohistiocytosis

treated with anakinra has recently been published, in which improved clinical condition was observed [37]. Several clinical trials are currently being recruited for the treatment of COVID-19 through the use of IL-1 inhibitors (in particular anakinra and canakinumab), alone or in combination with other immunomodulatory drugs.

Another class of drugs that has proved extremely promising is JAK inhibitor drugs. A recent study compared three JAK inhibitor molecules, baricitinib (approved for rheumatoid arthritis), fedratinib, and Ruxolitinib (approved for myelofibrosis), suggesting their potential role in inhibiting cytokine storm through inhibition of JAK-STAT pathway. In addition, baricitinib specifically exhibits greater activity against AAK1 (adapter-associated protein Kinase 1), a protein involved in viral endocytosis.

JAK inhibitors can inhibit cytokine storm by blocking the intracellular signal (mediated JAK) of numerous inflammatory cytokines (IL-6, IFN-γ, IL-2). These drugs could also play a pivotal role in the treatment of both moderate and severe COVID-19 patients [37, 38]. Their use could have a rationale even in an earlier stage of the disease since it is also able to reduce viral entry (GAK, mediated AAK1) as well as inflammation (JAK mediated).

Ruxolitinib is a balanced JAK1/JAK2 inhibitor with good selectivity over non-Janus kinases. These differences in selectivity may in turn be responsible for the differentiated safety profiles. For example, fedratinib shows a high incidence of gastrointestinal intolerance and cases of Wernicke's encephalopathy [38], whereas tofacitinib has been associated with an increased risk for lymphomas as well as cardiovascular events in patients 50 years of age and older with at least one cardiovascular risk factor [39].

Emerging data from ongoing investigator-initiated trials suggest a potential benefit of ruxolitinib with a manageable adverse event profile [39, 40].

The key role played by inflammation has led some authors to hypothesize a possible treatment with intravenous immunoglobulins in selected cases. In fact, the inflammatory response induced by the virus appears to be due to the hyperactivation of macrophages, especially in the lungs, through various mechanisms

including the interaction with the receptors for the Fc portion of immunoglobulin (FcR).

Studies conducted on animal models of SARS-CoV indicate that the interaction between the viral surface antigen S (Ag) and host antibodies (anti-Spike IgG) would promote receptor-mediated internalization for the Fc portion in macrophages and this interaction would result in massive release of cytokines [41].

It will be necessary to carry out further studies to identify biochemical markers capable of identifying patients who are candidates for this therapy.

Recently steroids, whose role is extremely debated, have been reconsidered in COVID-19 therapy.

The WHO [42] discouraged the routinely use of systemic corticosteroids for treating SARS-CoV-2, allowing their use for other concurrent conditions such as asthma/acute exacerbation of COPD, sepsis, or septic shock. Recent studies instead encourage the use of dexamethasone in intensive care units, since it reduced the length of intubation and the overall mortality in patients with moderate to severe ARDS.

Corticosteroid use has a phisiopatologic basis since they can reactivate pulmonary macrophage subpopulations toward an anti-inflammatory action and reduce chemokine levels (i.e., IL-8) that contribute to SARS pathogenesis.

About usefulness of steroid treatment in COVID-19, the RECOVERY trial [43] represented a milestone: in patients hospitalized with COVID-19, the use of dexamethasone (oral or i.v., a dose of 6 mg once daily for up to 10 days) resulted in lower 28-day mortality among those receiving other invasive mechanical ventilation or oxygen alone.

The most recent literature highlighted hyperimmune plasma as another promising treatment.

In the past, blood products from healed patients had been used for curing several infectious diseases. However, results from a non-randomized comparative study about Ebola infection, published in 2016 on the *New England Journal of Medicine*, didn't show significant improvement of survival in those patients treated with 500 mL of recovered plasma, compared to the group of conventional treatment. The reason could be that the neutralizing

antibody titer of patients recovering from Ebola infection is not elevated [44].

Several data suggest that using plasma from healed patients could arrest the infection progression and reduce disease severity also with a mechanism that differs from viral neutralization: immunoglobulins found in hyperimmune plasma could down-regulate the pro-inflammatory response through Fc-mediated pathways, as demonstrated in the contexts of autoimmune diseases and viral infections. Some studies suggest using IVIG even from healthy donors to prevent the cytokine storm and so the multiorgan dysfunction that is often seen in COVID-19 severe cases; to date, this approach has been effective in three patients [45]. An American first study about the security profile of plasma in 5000 COVID-19 convalescent patients is in the course of publication: the incidence of severe adverse reactions is 1% and 7-day mortality is 14.9%. However, it is important to underscore that this study comprehends a cohort of hospitalized or intensive care unit patients, whose COVID-19-related mortality is more elevated (15–20% and 57%, respectively) [46]. The FDA has approved its use in patients with serious or immediately life-threatening infection. A small Chinese pilot study [47] about healed plasma reported that its use in severely ill COVID-19 patients raised antibody titers, reduced the viral load, and led to symptom improvement; in other studies, this treatment has not proven to be effective instead. In any case, to demonstrate the efficacy of this kind of passive treatments, it is necessary to align study protocols.

Monoclonal antibodies (mAb) are identical antibodies, produced by one kind of cellular clone. The first cross-neutralizing mAb, specific also for SARS-CoV-2, is 47D11. It was obtained from transgenic mice and then converted into a totally human-shaped Ab with an IgG1 isotype. It is specific for the S1b region containing RBD of SARS-CoV and SARS-CoV-2, and it has a neutralizing activity against pseudovirus VSV-type through a mechanism independent from the inhibition of the bond between RBD and ACE2. Other alternative inhibition mechanisms have been pointed out. Another mAb is S309, which was isolated from the memory B cells of a man who was infected from SARS-CoV

in 2003: it strongly neutralizes both SARS-CoV and SARS-CoV-2 [48].

It is important to begin an adequate thrombosis prophylaxis in every COVID-19 hospitalized patient because of the high thrombotic risk due to the activation of coagulation cascade. To date, there are no supportive data to begin anticoagulant therapy nor to establish a correlation between D-dimer levels and thrombotic risk [49]. It is essential to balance thrombotic and hemorrhagic risk. There are factors that increase the thrombotic risk, like a history of thromboembolism, SIC score ≥4, active neoplasia, use of respiratory helmet with axillary braces, and presence of CVC. In those cases, a higher LMWH dosing compared to prophylaxis is indicated. In older patients with comorbidities, it is important to also evaluate their hemorrhagic risk. For patients who are already orally anticoagulated, it is indicated to suspend TAO/NAO and to shift to LMWH at anticoagulant dosing, due to known pharmacological interactions between oral anticoagulants and antivirals used in COVID-19 treatment.

In conclusion, properly treatment for COVID-19 remains an actual challenge for physicians, and the most successful regimen is probably going to be multidrug therapy with a crucial role of immunomodulatory and anti-inflammatory agents.

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Prognosis of COVID-19

12

Emiliano Panizon

It has been known since the beginning of the COVID-19 pandemic that SARS-CoV-2 infection can express in a wide range of clinical presentations, from the completely asymptomatic to the severe respiratory and multi-organ involvement that can lead to intensive care admission and death.

Estimating the infection's outcome has tremendous implications in matters of healthcare management and public health policies such as the enforcement of social distancing and lockdown measures that have a great impact, both psychosocial and economic, on involved countries and communities. This task comes with great difficulties, as we will see in this chapter.

Fatality

At a global level, case fatality rate (CFR) for SARS-CoV-2 stands at around 4%. This indicator, however, varies widely among different countries and can be as high as 15% (UK) and as low as

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1.6% (Russia)[1]. While such variability may be partly caused by socioeconomic and demographical characteristics and also by health system organization and congestion during the peak of the emergency, the obvious problem with case fatality rate is that its denominator is determined by the number of confirmed diagnosis. If only a portion of cases are discovered, it is likely that they will end to be disproportionally patients with a severe form of the disease, while many of the mildest forms (not to speak about asymptomatic infections) go undiagnosed. For instance, in the first months of the pandemic, South Korea adopted an aggressive strategy of testing and contact tracing, while the Italian Ministry of Health prioritized testing in patients who required hospitalization, and as of March 14, this led to a high proportion (19.3%) of positive test [1]. This discrepancy can at least partially explain the difference between CFR in Italy (14%) and South Korea (2.1%). Even within a single country, CFR may vary greatly. For instance, as reported by the China-WHO joint mission, fatality rate was estimated as 17% in patients who developed symptoms between the 1st and 10th of January, but only 0,7% in patients that became symptomatic after the 1st of february [2].

There have been COVID-19 outbreaks among populations that were systematically tested, making CFR a reasonable approximation of infection fatality rate (IFR) with due corrections. For instance, the IFR among infected crew and passengers of the Diamond Princess cruise ship has been calculated as 1.3% [3].

Estimating the IFR for national populations, however, is a more demanding task. It has been estimated as 0.66% for China, cross-examining individual-case data for COVID-19 patients (to estimate the time between onset of symptoms and outcome), the aggregate distribution of cases to the observed cumulative deaths in China, and the prevalence of PCR-confirmed cases in international residents repatriated from China [4]. A statistic model based on early data has given an IFR of 0.8% for France [5]. A more direct way to estimate IFR is to measure the true prevalence of the disease by way of seroprevalence survey. A study made with these premises on different Spanish autonomous

[1]If not otherwise specified, data from John Hopkins University of Medicine available at coronavirus.jhu.edu are used (updated on the 23th of July 2021).

communities calculated an IFR of 1.15% as a whole; interestingly, this indicator varied between 0.13% and 3.25%. IFR by region was positively associated with SARS-CoV-2 seroprevalence, mortality, and hospitalization rate, strongly hinting that in regions with more extensive and rapid spread of the pandemic, COVID-19 was characterized by higher fatality because hospitals and the health system were overrun [6].

The frequency of severe forms of the disease, which may eventually require hospitalization, has been estimated variously depending on the criteria used for definition of "severe" and the characteristics of the populations examined. In the Chinese Centers for Disease Control report on 72,314 cases (44,500 confirmed infections), mild disease was reported in 81% of patients, severe disease (dyspnea, hypoxia, or >50% lung involvement on imaging within 24–48 h) in 14% of patients, and critical disease (respiratory failure, shock, or multi-organ dysfunction) in 5% [7].

Fatality rate is obviously worse in severe and hospitalized patients. Among COVID-19 patients admitted for pneumonia, carried out between January and February 2020 in Wuhan, 26% required ICU admission (for invasive and noninvasive ventilation or high flux oxygen) and 4.3% died during follow-up [8]. An early retrospective study carried out on critical patients (defined as either requiring mechanical ventilation or a fraction of inspired oxygen of at least 60%), also during the Wuhan outbreak in the same period, showed a really high mortality, 61.5% at 28 days [9]. ICU mortality for COVID-19 has been reported to be as high as 85% [10]; while variability in this indicator unavoidably depends on different criteria for admission in ICU, mortality in critical patients may increase because of hospital overcrowding and decrease, thanks to direct and indirect acquisition of knowledge and experience by health operators [11].

Long-Term Outcome

Because of the novelty of the disease, data on long-term outcome are still lacking. Persistent symptoms after discharge seem to be frequent, with an Italian case series showing 53.1% of patients previously hospitalized for COVID-19 reporting fatigue and 43.4% reporting

dyspnea. Potential long-term consequences may be inferred from prior experiences with serious respiratory illnesses and, in particular, by known long-term sequelae of ARDS and mechanical ventilation such as pulmonary scarring [12]. Persistence impairment of respiratory parameters and exercise capacity have been known to be impaired for months and even years in SARS and MERS patients; an impairment in diffusing capacity, which correlated with previous disease severity, has been documented in discharged COVID-19 patients [13]. Extrapulmonary involvement may also bring long-term sequelae. Neurological symptoms, from the relatively benign such as headaches, anosmia, and ageusia to the possibly life-threatening and invalidating such as ischemic and hemorrhagic stroke, myelitis, and encephalitis, have been well documented and are relatively common [14, 15]. A nationwide surveillance study in the UK documented a consistent number of cerebrovascular events and neuropsychiatric syndromes in COVID-19 patients, while cognitive (dementia-like), psychotic, and affective alterations are common during severe infections in the elderly, and nearly half of those manifestations were experienced by patients younger than 60 years old, suggesting a more direct involvement of the brain [16]. Cardiologic sequelae may be also expected, considering the relatively high prevalence of cardiac injury as clinically defined (including arrhythmias, ventricular function decline, troponin I elevation) [17, 18] and as documented by MRI [19]. All of the former considerations are to be put in the context of the wide range of neuromuscular, cognitive, psychological, and nutritional disorders that are well documented after lengthy stays in intensive care units and that are collectively known as post-intensive care syndrome [12]. Follow-up outpatient facilities are being set around the world and will eventually answer the current doubt and uncertainties [20].

Increased Risk Groups and Special Populations

Old age has been repeatedly confirmed as an independent risk factor for poor outcome in COVID-19, since the beginning of the pandemic [21]. It appears that risk increases proportionally with age; according to the Italian National Institute of Health (Istituto Superiore di Sanità), 59.2% of COVID-19 victims in Italy were

older than 80 years old, and the fatality that was estimated for the 80–89 years age group was more than 3 times greater than in the 60–69 group and 13 times greater than in the 50–59 age group [22]. A study carried out in the UK also found that the risk of death among patients older than 80 years was 20-fold that among individuals 50–59 years old [23].

Comorbidities such as cardiovascular disease, hypertension, diabetes, and obesity are also disproportionally prevalent among severe forms of COVID-19 and COVID-19-related deaths [21, 23, 24], but this observation must be cleared of possible confounding bias such as the association between comorbidities and age and between one comorbidity and the others. For instance, hypertension is highly prevalent in the general population, among elderly patients, and also strongly associated with obesity and diabetes; in some studies, multivariate analysis has found no independent association between this condition and COVID-19-related mortality [23, 25]. In contrast, severe asthma, despite early reports that found asthmatic patients are underrepresented in COVID-19 patient cohorts, seems to be an independent risk factor for poor outcome [23].

According to the limited data available, pregnant women have been suspected of being at increased risk of developing a severe disease during SARS-CoV and MERS-CoV infection [26, 27]. Pregnancy, however, doesn't appear to be a risk factor for increased morbidity and mortality in SARS-CoV-2 infection, unlike what has been observed in SARS and MERS. Most studies show similar rates of mild, moderate, and severe forms of COVID-19 in pregnant and nonpregnant women [28, 29]. Data regarding COVID-19 impact on pregnancy outcome are still scarce, and it is not yet possible to ascertain if the disease increases the rate of preterm delivery. Vertical transmission is possible (unlike in SARS), possibly in utero [28].

Long-Term Immunity

The duration and scope of acquired immunity (humoral as well as cell-mediated) is the object of ongoing investigations. Real-time PCR positivity after two or more repeatedly negative swabs

in a convalescent COVID-19 patient is a relatively common occurrence [30]. In most cases, repeated positivity happens shortly after discharge and/or PCR negativity, and as shown by data collected by the Korean Centers for Disease Control, no new infection was correlated to such patients, neither any infectious virus could be isolated in cell cultures [31], suggesting that the amplification of SARS-CoV-2 RNA depended on low-grade viral persistence or that the genetic material detected was actually part of virus debris. Reinfection, however, has been documented at least in one case in which a young man from Hong Kong first recovered from a mildly symptomatic infection and then tested positive again after several months; whole-genome sequencing (that by chance was carried out also for the first time) showed that the SARS-CoV-2 strain involved the second time was phylogenetically different. The second infection, though, was totally asymptomatic [32].

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Basic Principles of Public Health Measures for the Prevention of the Diffusion of COVID-19

Carlo A. Usai and Fabio Capello

Public health measures refer to a series of actions aimed to reduce the spreading of the SARS-CoV-2 virus in the population. Most of the knowledge related to infectious diseases and to the diffusion of viral infections, locally and globally, is based on well-known models. Yet, this novel coronavirus infection represents a challenge for health policy-makers as long as most of the information related to the virus itself were and are still missing. Vital information as the way of transmission, the persistence of the virus in the environment and on different materials and surfaces, or the viral load needed to produce relevant infections in the human body able to trigger the disease is still under study with no clear data upon which a guidance can be produced.

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Nonetheless, major international health institutions have produced since the onset of the pandemic guidelines and indications that helped decision-makers to deliver contingency plans and instructions to restrain the spreading of the virus [1–7].

Although some of the interventions needed to reduce the impact of the virus on the population and on the health systems are bond to change over the time as the body of evidences on the disease grows and as the pandemic evolves, it is of interest to underline some of the measures produced so far to better understand what can be done with the current level of knowledge to contain the virus and what procedures were not so adequate when considered in the aftermath.

Non-Pharmaceutical Measures

Centers for disease controls worldwide produced guidance aimed to reduce the spreading of the disease and its impact on the different health systems, since the beginning of the epidemic. Because very little information was available at the beginning secondary to the fact that everything was new about this disease, some of the advices provided might have been inaccurate at the beginning or based on transmission models that were adapted from different infections and diseases. However SARS-CoV-2 proved that some of this model (see also Chap. 15) simply did not fit this epidemic and that some of the measures proposed to reduce the spreading of the infection, although useful for other viruses, were inadequate to contain the effect of COVID-19 in single patients and in the population.

This may explain a certain delay in the adoption of what we consider today more appropriate measures. However, most of the advices provided refers to particular phases of the pandemic, and it might explain why some public health measures—as the so-called lockdown—were strictly needed even when the number of infected patients was relatively low and why some others were introduced only later in the evolution of the epidemic.

As long as we know SARS-CoV-2 is mainly transmitted through respiratory droplets. Some other ways of transmissions

are possible, but there are no clear evidences at the moment to support this thesis. Air-borne transmission, however is very likely involved in the spreading of the disease, especially in intensive care settings and secondary to some invasive procedures like thraceal intubation. Another possible way of contagion is the fecal-oral transmission because the shedding of the virus via the gastrointestinal tract has been observed especially in children.

In a first phase of the epidemic, the main goal was to reduce the peak of cases in a given area, so to minimize the impact of the disease on a health system. Because there were and there are no highly effective treatment options, due to the fact that the disease and its short-, medium-, and long-term consequences are still to be determined, the higher the number of cases affecting a population, the higher the sufferance for the healthcare and the economic sector—among others—to face the burden of the infection.

Personal measures play a crucial role, even if they alone are unable to stop the spreading of the disease. Thus, community-based actions are needed to strengthen the effort of the individuals. In the first phases of the pandemic, it implied also the introduction of draconian decisions aimed to reduce the human contacts and therefore the circulation of the virus.

Personal measures include, among others, respiratory and environmental hygiene, social distancing, and the use of personal protective equipment (PPE).

Community-based measures include progressive restrictions of the human activities and produce actions like school closures; local, national, and international travel restrictions; and closure of working places and leisure or entertainment facilities.

The combinations of these two different approaches, modulated according to the phase of the epidemic, can be effective in reducing the number of cases or the growth of the number of people with the disease, balancing the different resources used and the burden for the different sectors of the society [8]. However the real impact of most of the measures introduced in the first year of circulation of the virus are still under evaluation, and the outcomes as well as the cost-effectiveness of some intervention (as the closure of the schools) still unclear.

Personal Protective Measures

As we have seen, personal protective measures refer to those actions that can be adopted by individuals with or without the active involvement of other people and that are aimed to reduce the spreading of the virus or to improve the personal protection against the transmission from infected people.

Although personal protective measures can be effective in mitigating the spreading of most infections as the SARS-CoV-2, because some piece of information is still missing when it comes to COVID-19, we still do not know to which extent a particular action is useful or if more strict procedures are needed.

However, we can summarize the main actions able to contain the transmission [9–14] as per the following list:

(a) Hand hygiene, to be performed properly and according to those procedures proposed by different health authorities as the WHO, with the use of handwashing with soap or via the use of alcohol-based hand sanitizers.
(b) Cough and sneezing etiquette, with the use of disposable paper tissue followed by a correct hand hygiene.
(c) Use of facemasks that have to be accurately selected among the different models available on the market as some masks may not be effective in reducing the shedding or in protecting from infected people (see Chap. 6).
(d) Use of other personal protective equipment, like eye protection (as goggles or face shield), body protection like waterproof gowns and scrubs, and gloves.
(e) Social distancing, aimed to reduce the contact with other people, reducing the exposure to infected secretions. It includes avoiding to touch other people in any exposed part of their body and augmenting the space between two or more people. This may be part of a more community-based procedure (e.g., increasing the spaces among the table in a restaurant or avoiding to seat close to other people during public events or reducing the number of people allowed to access to public transportation) or can be performed by single individuals keeping the distance from other people whenever it is possible.

Environmental Measures

Once a virus is out of the human body, it can linger in the environment and survive on objects and surfaces, enhancing the opportunity of contact with new susceptible subjects [15–20]. The spreading of the virus in confined, indoor and outdoor places can be an important way of transmission between different human beings. Thus, environment should be considered as a possible means of contagion that pair the direct human to human transmission. As long as environmental conditions may vary over the time and in different locations, the way the virus travels among a population can change in different settings, requiring a tuning of those measures needed to contain the infection.

Therefore, it is crucial to properly address the environmental issue, to improve the public health policies aimed to reduce the entity of the epidemic.

Environmental measures refer to those procedures that are aimed to reduce the viral load in the environment or to reduce the secondhand spreading of the virus. Most of the procedures depend on how and how long the virus survives in the atmosphere and on different surfaces and on how effective some substances used for cleaning are in reducing the viral load. The main actions are as follows:

(a) Routine cleaning of frequently used surfaces and places, especially when a single location is shared among different people and especially when these people do not normally live together
(b) Routine cleaning of clothes and objects, especially those that are more likely to get in touch with vulnerable part of the body, like phones, or that are constantly touched like keyboards or door knobs
(c) Minimizing the sharing of objects, even when a routine cleaning of the same is in place
(d) Ensuring appropriate air cleaning via ventilation or via the use of adequate air filters

Social Distancing

As we have seen in the previous paragraph, social distancing may be considered as a personal protective measure, able to ensure the maintenance of a distance able to minimize the risk of transmission from positive people. Because no one knows if the other people in the surrounding are positive for the SARS-CoV-2 virus, constant distancing should be considered always appropriate. However, the risk-benefit ratio and the cost-effectiveness of every measures implemented should be carefully assessed and monitored via continuos feed-back procedures, to avoid to put uncesessary burden on the economy and on the population and on selected cadres of people like the most vulnerable ones—thay might suffer from social distancing developing other types of diseases, like mental illnesses—, and the children, that apparently are not prone to develop the serius form of the disease. From this point of view, social distancing can create long-terms consequences in children that might affect their development, their social lives and their educational and relational skills. Thus, containments measures when adopted for children should be always carefully evaluated in terms of costs and benefits for the same children and fot the population.

However, social distancing is crucial as part of public health measure [21–23] when a case is suspected or when the epidemiological situation requires active action to minimize the spreading of the virus from known foci.

Most of the measures intended to preserve public health and to reduce the spreading of the virus in the population depend on specific indications delivered by local, national, and international healthcare institution. Some affect the population as a whole, while some are addressed to single people or community to contain a specific outbreak.

The most common measures in use are the following:

(a) *Quarantine or self-isolation of SARS-CoV-2 cases and contacts*: there is no shared consensus on the modality and timing of quarantine and isolation and on how to consider

contacts that do not have a clear exposure to a positive person. Most of the policies in place are based on the first reports and observation produced during the first phases of the outbreak. The same directives in place in different countries are based both on epidemiological findings and on economic and political needs and therefore vary in different location. In addition, the observation of new variants, whose infectivity and letality ratio are very difficoult to establish, might lead to the development of different guidelines with different timing in terms of quarantine and isolation's lenght. Moreover, the same exposure to the virus is affected by a number of criteria, like the use of adequate PPE or the vaccination status.

(b) *Contact tracing*: tracing possible contacts of infected people can be challenging as no effective epidemiological models are available (see also Chap. 15) and the same way of transmission is still unclear. The cost-effectiveness during the exponential phase of the epidemic is controversial, especially when the number of daily positives is so high that manual contact tracing cannot be reliable and sustainable, resulting in a time- and resource-consuming operation that might be unable to contain the spreading of the virus in any case. Automatic tracing software able to send alert and to gather useful data is to be fostered, although digital contact tracing has still a number of limitations.

(c) *Mandatory isolation of symptomatic or asymptomatic cases*: as per quarantine and voluntary isolation, there is no shared consensus and most of the protocols in place in the different countries are based on political consideration that takes into account different factors. Because scientific data are not still exhaustive, the right balance on the necessity to preserve health and healthcare resources and the need to protect the economy of a nation depend on local factors. However, the definition of an evidence-based timing for quarantine and isolation and the safety of procedures aimed to define infective cases and potential transmitters should be accurately evaluated by local and international health authorities.

(d) *Voluntary isolation of cases or contact not requiring hospitalization*: potentially exposed people should be aware of their

role in spreading the virus. As long as asymptomatic patients have a role in the circulation of the virus in the population, it is crucial to maintain correct behaviors aimed to reduce the spreading of the disease. Thus, people should always foster and encourage the application of personal protective measures and environmental measure to contain the virus and to self-isolate avoiding to expose vulnerable people whenever a possible contact with positive patients is suspected.

(e) *Interventions in educational and childcare settings*: the role of the school in transmitting the disease is still under debate, because most of the school was closed in the first phase of the pandemic worldwide and because it is still unclear how children can carry and spread the virus. More data are thus needed to properly build health policies that consider the need to respect the children's rights, which include the right of education and the right to socialize with other children, and the need to protect the older part of the population. The same considerations apply to the two following measures. The efficacy and the cost-effectiveness of these measures are still under debate [24–33].

(f) *Proactive school and day-care closures*.

(g) *Reactive school and day-care closures*.

(h) *Adoption of containment measures in the workplace*: similarly to the measures needed to contain potential outbreaks in the schools, the adoption of actions aimed to reduce the spreading of the virus among people that work in a same location is a key factor in reducing the entity of the epidemic. People spend a considerable number of consecutives hours in the same workplace, interacting with other people. These interactions vary in time, space, and type of contact depending on the job. Whereas in some jobs people are likely to get in touch during their working shift with a limited number of individuals that belong to fixed teams (as a team working in a factory with no habitual contact with external clients), other workers interact sometimes very closely, with diffrent people everyday (as in an outpatient department in a hospital, or in a customer care centre). The same workplace can impact on the risk of transmission, ranging from very low in outdoor jobs where workers have

limited interaction among each other (as independent farm workers) to very high for indoor jobs where the spaces are limited and where a great number of people coming from different areas and backgrounds come together for a considerable amount of time (as healthcare workers, drivers and transport workers, or sales workers [34–37]).

(i) *Measures related to people gatherings and mass gatherings* [38–40]: it refers to the limitation of gathering of people in public events, where social distancing cannot be guaranteed. As long as the higher the number of people concentrated in a same place, the higher the chance that at least one person is carrying the virus and can potentially infect other people, different actions may be needed according to the type of event considered. Moreover, in events where a very high number of people come together (as in a premiere league football match or in an international convention open to thousands of visitors), the chance that a positive subject can infect more people increases because of the number of interactions that he or she can have with other people. In these occasions, in addition, people come often from different areas and therefore can carry the virus if infected to other clusters of people living also far from where the event takes place. This consequently leads to the onset of new outbreaks. The same type of event can increase the risk of SARS-CoV-2 infection (indoor vs. outdoor gathering) as well as the clusters of people that attend the same event or that come together for the occasion (e.g. people that normally do not have contact in their everyday life like people attending a meeting in a national or international conference; pilgrims coming from different parts of the globe to participate to a religious event or to visit a sacral place; people coming from different towns to celebrate a wedding; people from a same neighborhood attending a religious service; or colleagues that normally work together every day having a dinner party in a restaurant). Although gatherings are a known and major source of infections, the opportunity to close events and meetings has to be carefully considered taking into account the consequences of these cancellations on the different sectors of the society [39, 41].

Movement Restrictions

Social distancing can be augmented with the adoption of specific measures aimed to reduce the circulation of people. These measures can be implemented locally or at national or international level. Travel restriction means that people are confined to a specific area in order to reduce the spreading of the virus, statistically limiting the number of contacts that a positive subject (especially an asymptomatic one or a symptomatic patient that is unaware to have the infection) can have. The second relevant consequence of movement and travel restriction is that an outbreak can be limited to a single place, reducing the involvement of other locations that may be unaffected by the epidemic or that are already dealing with cases coming only from their area.

Some possible measures include the following:

(a) Local curfews and bans to limit the circulation in a single town or region in specific time and places.
(b) Total movement restriction in a single affected area, with access and exit limitations for people not normally living there.
(c) Movement restriction at local, regional, or national level for specific activities and high-risk categories of people (both people with increased risk of carrying the virus and people at higher risk to develop a severe form of COVID-19) with sliding scale of intervention according to the epidemiological scenario and category or risk-group people belong to.
(d) Partial or total movement restriction in a macro area within a single country or national closure and ban for any not essential movement (measure known as *lockdown*).
(e) Partial or total movement restriction at international level that may include specific bans related to type of travel and to the means of transport considered.

Each one of the previous actions can be unilaterally taken by single countries or may involve decisions taken by more countries

or cluster of countries (as in the European Union [42] where there are already norms regulating the movement of goods and people among the member states), regulating the specific interactions and limitations that can affect the way the epidemic moves from a country to another [43, 44].

In addition, filters at any entry point can be in place to early detect potential sources of infection (as isolation of positive or symptomatic subjects arriving at or departing from an airport) or to minimize the risk of exposure coming from potentially positive people (mandatory or voluntary quarantine of people coming from high-risk areas or that are known to have had a contact with positive people or people exposed to the virus in the previous days or hours).

However, the social and economic consequences of travel limitations and movement restrictions can be enormous and can potentially impact every sector of the society [45]. In terms of global health, this is a major issue, as long as a pandemic is a primary international health concern, but at the same time any intervention aimed to target people's movement is bound to bounce back affecting eventually the same level of health and well-being of the world population [46, 47]. To reduce the burden of those restrictions, different form of *laissez-passer* can be implemented, like the adoption of a digital pass that can assess the non-infectivity of an individual. The effectiveness of this solutions is at the moment only theoretical, as long as there are yet not enough data nor evidences able to evaluate it.

The analysis of the chains of transmission [42, 43, 48–50] at local and international level, also with automatic or semiautomatic systems (e.g., use of data coming from mobile devices [51] analyzed with machine learning techniques and artificial intelligence; see also Chap. 17), is crucial to detect how and why the virus moves from a place to another, in order to detect the more cost-effective ways to reduce the circulation of the disease, limiting at the same time the effects of such restrictions to the global economy and to the society.

Conclusions

COVID-19 is changing the way the world has worked in the latest decades, affecting the peculiar and feeble balance that has keep things running globally. As a new disease emerges, we can count only on a previous knowledge to reduce the impact on the society and on the healthcare systems, but often what we know do not fit the actual scenario, and the measures taken may result very costly and completely ineffective. Because we do not know how to deal with a disease, we tend to apply and adapt models that works with similar conditions. However, the results can be disheartening.

Two major problems may affect the response to a pandemic from a new microorganism: the lack of working pharmaceutical measures and vaccines that can cure or prevent the disease, and the lack of knowledge related to the short-, medium-, and long-term effects of the disease on single patients and on the population.

Non-pharmacological measures are thus needed to contrast the spreading of the infection, as most of these interventions have been proven useful in the past.

However, because the real impact of a new disease is not known, and the efficacy and cost-effectiveness of any measure cannot be calculated *a priori*, some of these measures can be inadequate or may lead to an insufficient response or to an overreaction.

Because there are many sectors of the society that can be affected both by the disease and by the measures taken to contrast it, it is crucial to take every decision carefully, prioritizing the interventions and pursuing only the best interest for the people. During a devastating event, like the COVID-19 pandemic, there should be no space for actions aimed to promote the profit of single people or parties in spite of the public interest.

Moreover, any action should be monitored and data scrupulously gathered to better assess the quality and entity of each intervention and the possible synergies of these same measures, so as to find the best options reducing at the same time the social, psychological, ethical, cultural, and economic burden.

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14

Principles of Management in COVID-19 in Vulnerable Communities

Paola Gaddi, Leonardo Mammana, Valeria Gentilini, and Lucia Branchini

Introduction

According to *Oxford Dictionary*, vulnerability is "the quality or state of being exposed to the possibility of being attacked or harmed, either physically or emotionally." Therefore, vulnerable groups are those that are exposed to the possibility of being easily hurt or attacked. According to this definition, two are the key aspects defining vulnerability: the attacker and what makes an individual or a group exposed to the possibility of being attack.

In the current COVID-19 pandemic, the attacker is known, namely, the SARS-CoV-2 virus, whereas what increase "the state of being exposed" is not so easily definable, because too many

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different factors are involved: some are well-known and easy to determine as the age or the presence of other morbidities (medical vulnerability); some other features are much more difficult to establish both in qualitative and quantitative terms and refer to the social status of every single subject (social vulnerability).

What is clear is that, during COVID-19 pandemic, vulnerable groups are not only elderly people or those with other acute or chronic medical conditions but also people belonging to different socioeconomic background and groups that are likely struggling to cope financially, mentally, or physically with the outbreak and its consequences.

For the purpose of this chapter, we considered vulnerable groups those populations living in great economic instability or experiencing social marginalization: refugees, migrants, and homeless.

In everyday life, these populations already share both physical and social vulnerability; the SARS-CoV-2 epidemic stresses those issues even more, increasing the insecurity and exposure to harm by the same measure needed to protect people from the virus and that affects their living and working conditions. People belonging to these cadres of vulnerable populations often live and work in conditions where physical distancing is not possible or where the recommended hygiene measures cannot be granted because of their poor conditions and economic disadvantages. In addition, the access for these populations to the healthcare system, that is already limited in normal circumstances, is even more restricted. Those two factors can easily increase the risk of infection undermining at the same time the rapid diagnosis and consequently the isolation of positive cases, with undesirable consequences for both the health of the single and of the community. Therefore, considering how COVID-19 affects the population as a whole and avoiding the discrimination of the vulnerable ones, the protection of socially disadvantaged groups is imperative. Thus, health prevention plans must be inclusive considering also the health needs of specific groups as migrants, refugees, asylum seekers, and homeless people.

In this chapter, we present some of the main issues experienced while dealing with vulnerable people and communities during the

COVID-19 health crisis, as well as some of the possible solutions and future scenarios aimed at the development of tailored healthcare programs.

Migration and Health

According to the International Organization for Migration (IOM), there were around 272 million international migrants in the world in 2019, which represent 3.5% of the global population. Global job market and wealth inequalities have been playing a central role in the migratory processes, reflecting the strict connection between migration and the globalized world. At the end of 2017, migrant workers represented 65% of the global stock of international migrants, most of which may tend to gravitate toward high-income countries. Work, family, and study seem to be the main reasons that are pushing people to migrate internationally, but, at the same time, wars, conflicts, persecution, and natural disasters forced around 70 million of people to leave their homeland, causing the highest number of forced migrants and refugees since World War II.

Nevertheless, the relevance of migration phenomena is evident as part of our time, and evidence proves that migrants and refugees' health conditions are usually worse than the host communities.

It has been shown that the burden of diseases presented by the immigrant population is mainly represented by noncommunicable diseases (NCDs), such as diabetes and cardiovascular problems. Also, mental health issues and neoplasms are quite frequent. Communicable diseases (CDs), such as tuberculosis, HIV, HCV, and HBV infections, are still present, but it has been reported that the risk for a migrant to get infected during the journey or in the hosted country (or to reactivate a latent infection after the arrival) is higher than to carry the infection from the country of origin in the host country. On the other side, the health profile of asylum seekers that have reached Europe during the last migratory phenomena shows a higher prevalence of mental health issues and of physical consequences of torture and trauma, reflecting the cru-

elty of the migration path that most of them have passed through. Similar conditions have been shown in other areas of the world referring to different migration paths, showing that the migration process may have a deeper and complex link with health. According to the definition of the WHO of 1948, health is a "a state of complete physical, social and mental well-being, and not merely the absence of disease or infirmity." In other words, how it has been shown in several studies, the health status and the onset of diseases in the population are closely related to individual, cultural, and socioeconomic factors, which may determine a different exposure to risk factors and the acquisition of unhealthy behaviors.

Migration seems to act as an important determinant of health, which may influence all the factors that are implicated into the processes of health and sickness. First, life conditions and accessibility to healthcare in the country of origin and during the journey are the main determinants of the burden of diseases presented at the arrival in the hosting countries. Regarding this, violence and trauma exposition during the journey are responsible for the burden of mental health issues and vulnerability conditions, especially when the migration path is particularly hard and dangerous. This is the case of many asylum seekers that have reached Europe in the last years, facing conditions of journey particularly dangerous and unsafe due the unstable political condition of Libya and due to the presence of criminal groups involved in human traffic. People coming from sub-Saharan Africa and Middle East that want to reach Europe through the Mediterranean Sea are raped, illegally head in detention centers, killed, or tortured to obtain ransom from the family of the same migrants. Also crossing the Mediterranean Sea is particularly dangerous, and as of 2021 more than 30,000 people have lost their life due to frequent sinking and to the border policy of the European Union, which have counteracted progressively the action of NGOs involved in search and rescue operations.

Even if life conditions during the journey may influence migrants' health conditions, evidence shows that the health conditions at the arrival in Europe are usually good, but they seem to get worse during the years. It has been highlighted that the

prevalence of NCDs in migrants in Europe increases in relation with the long stay of immigrants in the hosted country, reaching rates similar or also higher than the host communities, but with worse outcome and prognosis. This is known as the healthy-exhausted migrant effect, caused by the negative effect on migrants' health of socioeconomic factors, such as disadvantaged housing and working conditions and the lack of access to care, which progressively erode the healthier capital of migrants, exposing individuals to the acquisition of risk factors and unhealthy behaviors that are related with the onset and the progressions of most of the common NCDs.

Migrants may also face lack of access to care, due the presence of formal and informal barriers that together with the disadvantaged condition contribute to the progressive negative effect on health conditions. First, the access to care depends on the legal status, which determines the degree of care that is accessible for foreign citizens. Also in countries with public health systems and universal health coverage, access to care for irregular migrants is reduced just to emergency care, or it needs fee payment that usually people cannot pay. Moreover, the continuous change on migration policy (typology of visa, duration, inclusion criteria) and the economic crisis strengthen these barriers, influencing the policy on access to care and causing discontinuity on status.

It is well known that migrants, especially in high-income countries and with a recent experience of immigration, may face linguistic and cultural barriers in access to healthcare services. Differences in linguistic and cultural meanings of sickness, disease, and illness between health professionals and migrants may cause diagnostic mistakes and inappropriate care, influencing the capacity of the health services to address and to respond to the migrant health needs, especially when health professionals are not skilled enough toward cultural diversity and social vulnerability. Furthermore, migrants and asylum seekers can experience difficulties in access to care, due to the lack of knowledge on how to navigate through the health system or due the fear of authorities, denunciation, or deportation. Also xenophobia, racism, and discrimination can directly reduce the access to health services, especially when laws, policy, and protocols on access to care for

migrants are not well known by the health professionals and health practices depend on the political orientation of health professionals.

Homelessness and Health

Homelessness is an extreme expression of social exclusion, and its connection with serious health implications is well known.

The European Federation of National Organizations Working with the Homeless (FEANTSA) identifies four different subgroups of homelessness:

1. Person living without any kind of shelter (rooflessness)
2. People having temporary sleeping place in shelter or institution, but not a proper and fix accommodation
3. People living in insecure housing (insecure tenancies, threat of eviction, violence, etc.)
4. People living in inadequate housing (overcrowding caravans on illegal campsites, etc.)

Without regard to the typology of homelessness, this population experiences poorer outcomes associated with shorter life expectancy and higher morbidity than general populations. Homeless people are in fact at higher risk of suffering from a wide range of health problems, including chronic conditions and their complications (raging from Type 2 Diabetes Mellitus, COPD, heart conditions, malnutrition, etc.), infectious diseases (tuberculosis, HIV, hepatitis, etc.), mental health issues, and substance misuse.

The Institute of Medicine Committee on Health Care for Homeless People identifies three different types of interaction between homelessness and health:

1. The health issue precedes and causally contributes to homelessness.

   For example, an illness that might cause the loss of employment and consequently the homelessness itself, initiating a vicious cycle between lack of job and worsening of the health conditions.

2. The health issues are a direct consequence of homelessness.
   Living on streets, but also in crowded homeless shelters, is extremely stressful and increases exposure to not only communicable diseases (e.g., TB, hepatitis, etc.) but also abuse/violence, exposure to weather changes, malnutrition, mental health issues, and so on.
3. The health issues are worsened and complicated by homelessness.
   The poor living condition implied with homelessness can worsen an already present medical condition. Moreover, homeless, especially when presenting mental health issues, often show poor adherence to treatment or lack of comprehension of symptoms resulting in late seek for care, as well as late diagnosis.

Homeless face significant range of difficulties in accessing the health system when needed. These are the most significant causes:

1. Financial problems (related to the costs of the consultation, exam, or test)
2. Practical concerns (e.g., transportation to and from the Clinic/Hospital)
3. Perceived stigma
4. Previous negative experiences with healthcare institutions

All the above conditions are exacerbated by mental health issues since this condition can reduce people's ability to carry out essential aspects of daily life: one over all self-care (as reduce compliance to doctor appointments or poor adherence to treatment given, etc.). Furthermore, mental health patients might neglect taking the proper precautions against disease (i.e., exposing themself to infectious diseases), resulting in poorer clinical outcomes.

Vulnerability, Health Inequalities, and COVID-19

According to the WHO,[1] at the end of September 2020, more than 30,000,000 of people have been diagnosed with SARS-CoV-2 infection with around 1,000,000 deaths secondary to COVID-19.

[1] https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200928-weekly-epi-update.pdf?sfvrsn=9e354665_6

Nevertheless, while COVID-19 pandemic has been declared a serious global health issue and cases and deaths are still spreading worldwide, numerous evidence suggest that the pandemic is having a greater impact on lower socioeconomic groups and minorities.

In some studies, it has been shown that the infection rate has been three to four times higher in some socioeconomically disadvantaged residential areas compared to the other regional average. Moreover, evidence from the USA has highlighted how African Americans, Latino individuals, and Native Americans have experienced a disproportionate burden of COVID-19-related infections and deaths. Similarly in the UK, Black, Asian, and minority ethnic people are more likely to die from COVID-19 than White populations, confirming that during public health emergencies, members of racial and ethnic minority groups have higher rates of both illness and death.

In Italy, one of the first countries that had to face the arrival of the unexpected pandemic, homeless people were at risk of higher rates of infections and mortalities, a situation proven in many other countries, such as the UK and USA. Also asylum seekers and migrants in high-income countries, especially people who are undocumented, for many reasons, are in a greater risk than the hosting population to get infected and develop severe diseases.

Even if from the beginning of the global pandemic much attention has been given to individual risk factors and clinical conditions that predispose to higher rates of infection and worse consequences, it had becoming evident that COVID-19 is affecting disproportionately vulnerable groups of population all around the world, and the relevance of social determinants of health (SDOH) on COVID-19 pandemic needs to be emphasized in the international debate.

Social determinants of health and health conditions of vulnerable groups are strictly related but seem to be necessary to better understand how and why the global pandemic of COVID-19 is influencing the SDOH and acting on vulnerable groups. Evidences show that the link between vulnerability, SDOH, and the worse

effect on health of COVID-19 pandemic could be summarized in two main points: the increased exposure to the virus that vulnerable groups are having and the predisposition to worse health outcomes. Moreover, what we know about vulnerability is that this condition may change during the time, especially during a serious pandemic that is influencing all aspects of daily life. Also who is not considered a vulnerable person may become it during a pandemic depending on the policy response and how social and health consequences are managed. This is why policy makers should consider the risk of deepening health inequalities, and vulnerable groups must be identified and included in all the action and the interventions.

Inequalities and Increased Risk of Infection

According to the WHO, the actions that communities have to follow in order to reduce the contagion and the spreading of the infection are washing hands, wearing mask, and social distancing. Moreover, during the epidemic, many countries have experienced a total lockdown, reducing contacts and people movement. However, evidence suggests that, for many reasons, these strategies were difficult to follow for some groups of the population, especially for vulnerable groups, and this can explain the higher risk of infection founded in some groups.

At first, physical and social distancing and protecting elderly populations may be difficult when people experience crowded living conditions, such as densely populated areas in urban environments and multigenerational households. Migrants and ethnic and minority groups are within the most disadvantaged groups in high-income countries and usually live in poor conditions that makes self-isolation more difficult, limiting the possibility to protect older generations and vulnerable individuals. Obviously, homeless people, who are living on the streets, in emergency accommodations, or in temporary shelters, are more exposed to the risk of getting infected, due the impossibility to self-isolate and to maintain social

distancing as well as the lack of access to clean water and to adequate hygiene standards.

Moreover, it has been reported that people with lower socioeconomic status, including migrant and ethnic groups, are less able to work from home and more exposed to physical proximity to other people during work activities. This is the case of low-income jobs such as social care, transportation, cleaning, and hospitality or in other words "the essential work." Moreover, these precarious employments are usually based on daily income and related to lack of social insurance, which can both influence the possibility to stay at home during sickness or a lockdown. Similarly, it has been reported that the lack of adequate personal protective equipment, or instructions on how to use them properly, may further increase the exposure risk.

Refugees and asylum seekers in informal settlements as well as millions of people living in low-middle-income countries are also facing a serious and higher risk to get infected, due to the lack of access to clean water and sanitation and the crowdedness of living conditions that limited the possibility to practice social distancing, self-isolation, and protection of elderly and frail, such people with immune suppression HIV or TB. Moreover, overcrowded places and low access to care can make early detection of cases difficult and more in general impact on the control of sudden outbreaks.

This could also be the case of refugees and asylum seekers hosted at the border of the European "fortress." In southern countries, such as Italy and Greece, hundreds of thousands of asylum seekers reside in reception centers and camps, most of which are overcrowded and suffering lack of basic services and access to good quality of care. Moreover, nevertheless, due to the lack of evidence of increasing number of cases in asylum seekers, in Greece, the government decided to prolong lockdown of all the camps, while Italy had strengthened the control at the sea borders, imposed quarantine inside the ships, and reduced the regional distribution after the arrival, concentrating asylum seekers in centers in the southern part of the country.

Inequalities and Increased Risk of Severe COVID-19

Studies highlighted that social vulnerability is associated with higher COVID-19 case fatality. Mortality rate is inequitably distributed among vulnerable populations, such as older adults, people living in densely populated areas, people with lower socioeconomic status, migrants, and minorities. For example, studies from the USA and UK, as discussed above, showed a higher mortality secondary to COVID-19 among African Americans and Latinos compared with White residents. Even if at the beginning of the pandemic, researchers and scientists were focused on studing a possible link between ethnicity or genetic predisposition and COVID-19, the evidences suggestes that is more likely that the comorbid NCD conditions already affecting vulnerable groups (cardiovascular diseases, lung diseases, diabetes, and cancer), are the main reason influencing the worse decorse of the disease in these populations. At the end, the effective result is an NCD-COVID-19 copandemic, underpinned by poverty and structural inequity. Similarly, in LMIC, the risk for severe COVID-19 is posed by the coexistence of higher rates of malnutrition, NCDs, and infectious diseases such as HIV/AIDS and tuberculosis which are all related with immunosuppression.

Also, law access to care seems to be responsible for part of the higher rate on severe COVID-19 on vulnerable groups. For example in China, at the beginning of the pandemic, out-of-pocket expenditure posed a substantial financial barriers for people with severe symptoms. In the USA, the odds to receive a test in case of positive symptoms are lower for African Americans than White people. Other studies reveal that people with poor access to healthcare, especially migrants and ethnic groups with socioeconomic disadvantage, had worse outcomes due to delay or barrier in getting tested with the consequence of access to services in an advantage stage of the disease. Financial and administrative barriers are noted as the only factors that can negatively influence access to healthcare during a pandemic. Minorities and migrant populations may also face language and cultural barriers limiting their access to accurate information on prevention and mitigation.

Similarly, fear of contagion or of deportation can decrease the source of medical care, also in the presence of symptoms related with COVID-19 or with other diseases, especially for undocumented migrants, producing a potential worsening of COVID-19 or other diseases.

Access to healthcare for refugees and asylum seekers is already particularly challenging, but it could become worse during the pandemic, influencing the effectiveness of the control measures. Especially in humanitarian contexts where conflict, political instability, and resource limitations weaken the capacity of health systems to detect and respond effectively to outbreaks, the indirect effects (medical supply chains, health facility closures, and shortages of healthcare workers) may cause more deaths and morbidity than the COVID-19 disease, due the interruption of the continuity of care for the many chronic conditions that are already affecting these groups of populations. Moreover, indirect effects of the pandemic, especially lockdown and the border closures, may determine restrictions on people movement and legal status concerns, reducing individuals' ability or willingness to access healthcare.

Differential Consequences of COVID-19

As a global issue, the COVID-19 pandemic poses the risk for serious and worrying social and economic consequences. First, the lockdown policy, adopted almost in each country hit by the virus, is having a profound economic impact on lower socioeconomic groups especially for undocumented immigrants, many of whom work in the informal economy and in precarious employment conditions. In these groups of population, where the financial margins are already minimal and people may have no resources to sustain a period of lost income, the number of unemployment is strongly increasing overall, posing a serious risk of social and economic exclusion for millions of people. Moreover, economical sustain policies that are being used by several countries to balance the economic impact of lockdown do not always include immigrants or homeless people.

It is now evident that in socioeconomically fragile settings, the lockdown policies without social support are exacerbating social and health inequalities reinforcing the vicious cycle between poverty and ill health.

Moreover, the global economic crisis poses the risk for the return of austerity with cuts on welfare policy as it has been after the 2008 global financial crisis, where access to healthcare became more difficult, especially for undocumented immigrants and asylum seekers. Similarly, austerity politics are in general related with less financing to the health system that affect all the aspects of equity and quality of care, especially for the most vulnerable groups that are already experiencing the inverse care law.

The impact of COVID-19 pandemic on social determinants of health poses the risk for a general worsening of health conditions of vulnerable groups, but evidence suggests that this may be particularly true for mental health issues. The link between unemployment and health is already known, and it has been shown to increase also after the financial crisis of 2008.

The negative impact of unemployment on health is well known and includes poor mental health, increased alcohol and substance use, and family violence.

In addition to the increased medical problems, these communities are experiencing, and there is also an increase in the percentage of the population that suffers with severe and persistent mental illness. COVID-19 has impacted this population disproportionately with regard to their medical and psychiatric issues which put them at risk for psychiatric distress. Separating and isolating oneself from their loved ones can exacerbate feelings in many mental health populations including anxiety, depression, and post-traumatic stress disorder (PTSD). Paranoid ideation and other psychotic symptoms can increase for people who suffer with schizophrenia, and cases of first break have been reported with COVID-19 weaving itself into the delusional and paranoid thinking. Moreover, many patients here suffer from underlying mental health issues with concomitant substance abuse. Both tobacco and alcohol have been known to worsen flu symptoms, so there is a working assumption that this would be true for SARS-CoV-2 as well. Substance abuse with opioids that can cause respiratory depression is also assumed to lead to worse

outcomes, even for those patients who otherwise might have had a mild disease outcome.

International Recommendations and Strategies

It established that all men and women (regular or irregular migrants, homeless, etc.) have to be ensured the protection of the human right to health and advocated for the integration and not discriminatory access to health services and the equal access to information and the affordable testing and healthcare needs to be guaranteed at any level and in any condition.

In response to COVID-19 outbreak, the importance to guarantee inclusion of these population in any planning is even more important not only to achieve vulnerable population's health protection but also because measurements to successfully control an epidemic have to include all population, especially the most vulnerable to be successful.

Since the beginning of the outbreak, many national and international institutions have been trying to highlight the key dimensions that are important to be addressed in order to control COVID-19 outbreak in settings where vulnerable populations live. The starting common ground is that including migrants' health means taking in account all health-related risk and vulnerabilities related to them (described in the previous paragraphs). Among those, the WHO has dedicated lots of attention to the specific measures to apply to vulnerable population when dealing with a disease outbreak [1]. These recommendations mainly focus on the following:

- The adoption of specific strategies and action plan in achieving public health preparedness and ensuring an effective response, aligned with legal responsibilities and commencements related to the international health regulation.
- The issues of communication and the need to overcome barriers in information, as many migrants, refugees, homeless, and

marginalized communities can experience barriers in receiving information.
- Avoiding any stigmatization and discrimination of this population. In this regard, it must be stressed that evidence has proven that in general refugees and migrants show a very low risk of transmitting communicable diseases to host populations but that they experience potentially greater risks themselves due to their social determinants of health.

Other organizations have set recommendations for the management of COVID-19 outbreak in vulnerable settings. Table 14.1 resumes the main recommendations made since March 2020 up to date, remembering that SARS-CoV-2 is a new pathogen and that updates and changes are regular.

The resulting recommendations can be summarized as per the following paragraphs.

Coordination and Planning

The need of preparedness and response plans to anticipate and coordinately manage COVID-19 outbreak at a national level is key to properly succeed in reducing malignant effects within the whole population. Such a plan, as said before, has to include everyone, especially the more vulnerable. Among the foremost considerations about how to coordinate and properly plan in this setting, most of the authors agreed on the following three:

- Know and review legal framework and requirements to provide health services to refugees, migrants, and homeless.
- Enhance capacity to address the determinants of health of these populations.
- Strengthen partnerships with main stakeholders involved: refugee/migrant/homeless communities.

Table 14.1 Main recommendations published by major international health organizations

Organization name and description	Guidance and recommendations Publications available from the individual agencies' websites
World Health Organization (WHO) www.who.int	"Interim guidance for refugee and migrant health in relation to COVID-19 in the WHO European Region," 25th of March 2020
WHO as a specialized agency of the United Nations is responsible for international public health. Its main objective is "the attainment by all peoples of the highest possible level of health" (WHO Constitution)	"Preparedness, prevention, and control of coronavirus disease (COVID-19) for refugees and migrants in non-camp settings: interim guidance," 17th of April 2020 "Actions for consideration in the care and protection of vulnerable population groups for COVID-19," 19th of May 2020
European Centre for Disease Prevention and Control (ECDC) http://www.ecdc.europa.eu ECDC is an EU agency aimed at strengthening Europe's defenses against infectious diseases. The core functions are surveillance, epidemic intelligence, response, scientific advice, microbiology, preparedness, public health training, international relations, and health communication	"Guidance on infection prevention and control of COVID-19 in migrant and refugee reception and detention centres in the EU/EEA and the UK," 15th of June 2020 "Guidance on the provision of support for medically and socially vulnerable populations in EU/EEA countries and the United Kingdom during the COVID-19 pandemic," 3rd of July 2020

(continued)

Table 14.1 (continued)

Organization name and description	Guidance and recommendations Publications available from the individual agencies' websites
European Public Health Association (EUPHA) https://eupha.org EUPHA is an umbrella organization for public health associations and institutes in Europe, with 79 members from 47 countries. It is an international, multidisciplinary, scientific organization that encourages a multidisciplinary approach to public health	"Statement EUPHA migrant and ethnic minority section on COVID-19. Call for action" EUPHA, 24th of March 2020
Centres for Disease Control and Prevention (CDC) www.cdc.gov The CDC is a national public health institution in the USA. Its main goal is to protect public health and safety through the control and prevention of disease, injury, and disability in the USA	"Interim Guidance for Homeless Service Providers to Plan and Respond to Coronavirus Disease 2019 (COVID-19)," CDC, 5th of August 2020
National Institute for the Promotion of the Health of Migrant Populations and for the Fighting of Poverty Diseases (NIHMP) www.inmp.it The INMP is an Italian public health institution dedicated to the study and resolution of the problems of assistance in the socio-health field related to migrant populations and poverty, as well as a national center for cultural mediation in the health field	"Interim operating procedures for the management of facilities with persons who are highly vulnerable and at high risk of health and social care exclusion during the COVID-19 epidemic," 4th of August 2020

Infection Prevention and Control

The prevention of human-to-human transmission among refugee, migrant and homeless, and staff working within the structure needs to be a priority. Possible actions to undertake to reduce the transmissions are as follows:

- *Training staff about COVID-19*. Training about infection prevention and control measures to be taken in these settings and management of suspect/positive case is fundamental.
- *Equipment*. Have the needed equipment and devices ready to be used (mask, gloves, gel sanitizer, soaps, etc.).
- *Entry screening*. Priror to a new entry within the structure is important to plan and arrange a screening for SARS-CoV-2.

Surveillance, Case Investigation, and Management

A proper and in-advance planned protocol has to be in place in order to ensure an early detection and an optimal management of suspect or confirmed cases. To achieve this goal, the most important factors are the following:

- Having a clear connection and an established channel of communication between migrant center or homeless shelters and local public health
- Arranging and planning in advance points of entry screening and quarantine safeguards, in case of necessity
- Owning a clear protocol in case of positive cases that includes how to communicate to the person, how to communicate with other hosts of the structures, where and how to quarantine the person, and how to maintain safety for workers and hosts

Risk Communication and Community Engagement

To provide understandable information about refugees, migrants, and homeless in the appropriate languages and culturally oriented, using the suitable communication technologies is key to

empower them. Eventually, always keep in mind that it is important to ensure that fear of registration for some groups of migrants and refugees will not prevent them from seeking healthcare, which could pose a direct threat to the individual and the community.

Particular attention should also be paid to avoiding any stigmatization and discrimination of this population. In this regard, it must be stressed that evidence has proven that in general, refugees and migrants show a very low risk of transmitting communicable diseases to host populations but that they experience potentially greater risks themselves due to their social determinants of health.

Occupational Health and Safety Measures

The development, reinforcement, and implementation of occupational health and safety measures are also very important. In this context, it is important to ensure that refugee, migrants, and homeless share the same level of health and safety protection at work as all other workers.

Further Recommendations

In addition to the above recommendations, some more considerations need to be done about migrants' mental health, women's health, and unaccompanied minor and children's health.

Mental Health Response

Mental health is one of the main and underdressed issues of migrant, refugees, and homeless healthcare. The migratory process poses several challenges concerning mental health; each phase can present risk factors that threaten mental health. The most frequently reported conditions are PTSD, mood disorder, and depression. PTSD, mood disorder, and depression are also the most frequently reported conditions among international migrants, mainly for refugees and recently arrived asylum seekers. However, the prevalence of mental health disorders in these populations

shows considerable variation depending on the population studied and the methodology of assessment. For example, the reported prevalence of depression in the refugee and migrant population varied from 5% to 44%, compared with a prevalence of 8–12% in the general population.

The isolation produced with the preventive measures related to COVID-19 exacerbated some of the mental health issues:

- Be aware that migrant, homeless, and refugees are more at risk of developing mental health issues.
- Some facilities provide mental health services including full-service on-site services, evaluation of community clients, and referral to off-site providers. Have plans in place for patients who regularly receive mental health services.
- If hosts must be isolated, consider alternative arrangements to continue mental health treatment such as video conferencing for continuity of regular services.

Women's Health

One of the main health issues for female refugees, migrant, and homeless is worse perinatal outcomes. The COVID-19 prevention measures included, for some countries, the shrink of most none-mergency health community services, and in many cases this included the suspension or cancelation of some pregnancy appointment (such as the case of the UK where some trust adopted the strategy of doing the booking appointment over the phone and women did not see a health professional until 25 weeks of pregnancy). For women with limited access to health resources and information, this can reflect in a consistent disadvantage.

Another issue related to women's health and COVID-19 consists in family planning, which knowledge varies widely among refugees and migrants, but in general there can be a lack of awareness of available support available. During the emergency phases of the COVID-19 pandemic, many countries has suspended or shortened the service, leaving women without choice and with lack of support.

Domestic and sexual violence can occur for refugees and migrants in transit setting and in countries of destination. The

lockdown and social isolation have been reported as posing women more at risk of domestic violence and left them with lack of support to emergency rescue services. However, it is important to underline that this has been and it is an issue for women worldwide, not only for vulnerable, migrant, or homeless women.

Unaccompanied Minors and Children's Health

Migration was also found to be a risk factor for children's mental condition, and unaccompanied minors experience higher rates of depression and symptoms of PTSD compared with other refugees and migrant groups. Some of the needed measures applied by governments, to prevent the spread of the SARS-CoV-2, are school and park closures, social distancing, and home isolation that posed several questions for children in general; in migrant children and unaccompanied minors, this aspect is increased exponentially considering other factors such as housing condition, supporting career, integration, and social and relational networking.

Final Recommendations

The COVID-19 pandemic represents an international dilemma, especially when it comes to groups of people that are already little involved in the healthcare systems or that have considerable limited access to the same. For the first time in modern history, the world had to deal with a global health crisis and with the effect of a progressive globalization.

Because most of the people belonging to the vulnerable groups are the expression of those unresolved issues that represent the main part of what global health is, government and nongovernment organization and local and international healthcare institutions must take action. Thus, any contingency and emergency plan aimed to face a pandemic or a major health crisis must include workable strategy to protect these categories of people and to improve their chance to access to care.

However, there are no ready and no one-size-fits-all solutions to address this problem, as long as any context and any scenario have its peculiarities; it also means that people coming from different backgrounds may have different needs. And those needs are fluid as they change over the time and according to local and international conditions.

For this reason, any action must be tailored on the specific condition, setting, situation, and category of people considered. Therefore, any country and any local area should have a readiness plan available that should be regularly updated according to the evolution of the local and international scenario, to the composition and evolution of the vulnerable people's population and the particular needs of these communities.

A Pilot Strategy for the Management of Vulnerable People During COVID-19 Pandemic: The Bologna's Task Force

Italy has been the first Western country hit by a major outbreak of COVID-19 and the first country in the world to experience a mass-scale epidemic in terms of number of positive cases for SARS-CoV-2, of people affected by COVID-19 and relative number of hospitalizations, and of deaths secondary to this novel disease, with the northern part of Italy as the center of the health crisis.

To our acknowledgment, this is the first time that a similar event took place in a single area in recent history.

The consequences were that no one could possibly be prepared to deal with this emergency especially when it comes to the more vulnerable ones that already were outside of the normal access to healthcare.

On the other hand, the Emilia-Romagna (ER) region that is close to the most hit area of the first Italian wave of COVID-19 had time—however tiny—to create a workable model to organize the resources and provide a response plan, especially for the vulnerable community.

The response in Bologna, the most populous city in ER, to the need of this particular population during the COVID-19 epidemic is then probably one of the first example in the world, and the analysis of what has been done during the first phases of the outbreak can better help to understand the challenges and the problems related with this issue.

Background

In the city of Bologna at the onset of the first cases of COVID-19 in a homeless shelter, an interinstitutional working group, made by professional part of different departments of the local health office and the social services of municipality, was formed; the group started to meet regularly in the middle of lockdown via an online platform. The aim of the group, called "Vulnerable Task Force," is to debate, reason together, and produce practical guidelines for the professionals working with the most vulnerable population in the city (homeless and asylum seekers living in reception centers) about COVID-19 prevention and management and appropriate care of positive cases (e.g., avoiding improper use of emergency department).

The Task Force was made up of representatives of the Department of Primary Health Care, the Bologna Health District, the Department of Public Health, the Department of Mental Health and Pathological Addictions of the Local Health Authority of Bologna, and representatives of the social services of municipality operating with homeless people and asylum seekers.

Although integration between health and social services since years has been reported in the National and Regional plans of Prevention, till now, it is still difficult to achieve it in a "macro" level for different reasons starting from the structures of the Social and Health Services to the professional organization of the medical work. In this case, it is interesting to note as in this micro setting that the necessity correlated to COVID-19 promoted different services to operate together starting from the most vulnerable individuals, in line with the international recommendations for this population. By the way, in Italy, general official

recommendations for prevention and management of COVID-19 in the structures where homeless people and asylum seekers live were published some months after the formation of the Task Force. Beyond the guidelines that appear necessarily generic, the role of the Task Force was to reason about the possibility of the local contest, the needs of the vulnerable population, and the needs of the professionals working in the Services and to decline those needs into operative information and creation of paths for COVID-19 positive cases in the structures and shelters.

Actions

The main actions taken by the Task Force were the creation of paths where homeless and asylum seekers could be tested for COVID-19—both as prevention and contact tracing activity—and paths where the cases that tested positive to COVID-19 could conduct the isolation period safely and be monitored by sanitary personnel. Others were the creation of training (in-person and online) about the COVID-19 topic both for the work personnel and the vulnerable people living in the structures and facilitating informative support, medical and psychological, for people tested positive to COVID-19 in quarantine.

The Task Force could also rely on a good vantage point: the cases that are possible to observe from the Task's point of view were emblematic in showing that vulnerability, specifically vulnerability in health, is not equally distributed and that the cases show that COVID-19 does not affect equally the population. Furthermore, facing the virus in the most vulnerable contests means facing upstream the local policy and questioning some decisions in matters of social exclusion.

For example, most of the cases that the Task Force had to afford surged in the months of May and June, the period just after the national lockdown and where there were very few cases in the city. The places of contagion of SARS-CoV-2 in this period concern risk of essential works—healthcare and social operators in communities for elderly people or workers in the logistical complex—often with very precarious types of labor contracts and lacking training in occupational risk prevention.

Aside from the working condition, another SDOH that struck this population were the overcrowded housing conditions: frequently for one person showing symptoms for COVID-19, there were various housemates positive to COVID-19 making physical distancing and sheltering-in-place challenging for some and impossible for others.

One cluster in the city concerned an isolated area (Via del Lazzaretto) where the municipality concentrated various structures for marginalized people with a total of four homeless shelters, two refugee seeker accommodation centers, and one shower center for homeless people. In the month of June 2020, various cases happened among the habitants of the area because of their housing condition and the impossibility for them to conduct an appropriate lockdown due to the overcrowding of their habitations; most of all, this situation enlightens very clearly all the combination of the SDOH of the marginalized people and the inevitable consequences for the diffusion of the infectious diseases when a policy of ghettoization of the most vulnerable is pursued. More in general, this outbreak, like the outbreak in the communities for elderly people, implies rethinking the way we organize society and collective equipment.

Cultural Aspect

Economic position and racial inequality are also associated with levels of trust in social institutions, including the healthcare system. Racial and ethnic minority communities, in particular, have both historical and contemporary experiences of discrimination, leading to distrust. Members of these communities may be more likely to be wary about the public health information they receive, less willing to adopt recommended safety measures, and potentially more susceptible to "fake news." This suggests the need for more targeted public health information and for partnerships between public health authorities and trusted organizations that are internal to these communities.

Why culture? And why invest time and effort on things apparently unconnected with health and infectious disease? Because

infectious viruses are about social networks and cultural norms, as much as about microbes. As science tells us, viruses are inert, unable to attack us. We transmit viral data through our social networks and cultural pathways. We give viral information to each other by how we live and what we do. Otherwise viruses just sit inert, sometimes for thousands of years. So understanding cultural contexts is just as important as sequencing genomes in tackling viral outbreaks.

Accounting for the cultural contexts of health and well-being is a primary health determinant—why the systematic neglect of culture in health and healthcare is the single biggest barrier to the advancement of the highest standard of health worldwide. That is because culture is, in fact, the key to addressing health equity, especially when providers and target populations operate under different shared understandings about what matters most biologically and socially.

To understand what is happening in real time with real people, we need, as did David Mafigiri, to assess vulnerability before a disaster; like his own research team in Uganda, we need an extant interest in the disadvantaged. Ongoing empathy is critical. Without that, you have no access to what you should have known and now cannot. Your belated concern rings hollow in the face of that failure, which makes you liable to blame others. Indeed, if organized humanitarian actions take into account only COVID-19, due to the little knowing of what is really happening on the ground among those most vulnerable (as access barriers, difficoluties to use on line services, ect.), the approches likely proposed risk to have poor efficacy in conteing the pandemic and risk to fail in improving health care status for those populations.

Vulnerability emerges variably, at different times and places. This means that, while already vulnerable populations become even more under stress, new vulnerabilities emerge that often outstrip old ones. Service industry employees without health benefits and depending on daily income become more vulnerable–especially where they have to go back to work–than those elderly who can stay at home and wait it out. High-income physicians without adequate protective gear are as vulnerable as those with chronic preexisting conditions. Places we previously thought of as havens

are anything but: in Europe and the USA, the most vulnerable are in "care" institutions: nursing homes, shared housing, and prisons.

We failed these vulnerable groups because their illness experiences are socially driven.

Strength and Weakness

Some of the strengths of this experience are as follows:

- Creation of relationships between local health office's and the social services of municipality's professionals and the operators working with homeless shelter and refugee seeker accommodation centers;
- Good coordination between operators of the health and social services both in facing COVID-19 positive cases in the structure and in helping operators and hosts' problems;
- Shortening of the distance between the operators of the third sector and the local health and social services.

On the other hand, this experience showed also some weaknesses and constraints:

- There is not enough time to create and enforce trust with the communities;
- Some of the messages delivered for health education and prevention of the COVID-19 and to create awareness on the current medical crisis may not be received or accepted by individuals or communities;
- Some of the receivers of the information delivered during health education programs and campaigns do not accept such recommendations as they are perceived as an expression of an elitist power or consider such guidelines as inappropriate or tailored on the needs of the wealthier ones;
- Subjects that are positive for SARS-CoV-2 infection, but do not present symptoms, do not perceive the virus as a risk or do not believe in the same existence of COVID-19.

Final Considerations and Recommendations

In this global disruption of the COVID-19 pandemic, faced by all the world, the theme of vulnerability appears central. COVID-19 seriously stresses every health system around the globe, but it needs to be acknowledged that it does not affect the population equally, so vulnerable groups need to be included in policy making. This inclusion has to be considered earlier than any kind health emergency, such as the case of COVID-19, as the outbreak only exacerbated issues that were already present for vulnerable groups (such as marginalization, difficult access to care, impact of NCDs, etc.), highlighting the lack of preexisting and well-functioning policies. The lack of proper strategies aimed to tackle those issues can impact negatively on the health outcome of both vulnerable groups and the general population.

Moreover, it is also important to stress that "vulnerability emerges variably, at different times and places". This means that we have to consider not only those populations that are already vulnerable, but even the new emerging socially driven vulnerabilities (e.g., those that are secondary to precarious and unsafe working conditions or shared housing, etc.).

There is a strong need for global and public health policies that are inclusive for every member of the society. Healthcare providers must reorganize themselves strengthening the territories and community services, creating a network able to pursue fair and supportive public social health policies.

These policies must include adequate staffing. Health- and social-worker personnels working with vulnerable groups are often working under very stressful conditions (from moderate to extremely stressed in 74% of cases, according to Curling and Simmons [2]), exposing them easily to burnout. Humanitarian staff often experience exhaustion, depersonalization, and reduced sense of accomplishment, already in regular situations [3, 4]. The stress added by the COVID-19 emergency and the lack of staff exacerbated the practical, organizational, and emotional workload already on the professional shoulders.

Conclusion

COVID-19 seriously stressed every health systems around the globe, highlighting with no pity flaws of current health- and non-health-related existing policies especially in some context, like marginalized populations, where the lack of a preexisting and well-functioning policy had a negative impact on the health outcome of both vulnerable group and general population.

However, the COVID-19 pandemic can also be an occasion to review and improve policies for this population.

A simple and universal response to a major epidemic in vulnerable community does not exist, and it requires planning and considerations according to the specific context takin into account:

- The specificity of vulnerable groups present on the territory.
- In the environment and the society, the integration process should take place.
- The characteristics of the local and national health system.
- The laws and regulation of the territory should be considered.

International and national guidelines are needed in order to guide practice following an evidence-based approach. However, this top-down model should also consider a sight scaling up from the local to national to international planning. Adding a "bottom-up" approach that considers the specificity and the unicity of the individuals and of the local realities can give voice to this fraction of unseen population, having a positive impact on public health.

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15

An Innovative System to Understand the Development of Epidemics Using GIS Spatial Analysis and Based on AI and Big Data

Giovanni Rinaldi and Fabio Capello

The advent of the COVID-19 pandemic (C19) has put a strain on the tightness of the epidemiological forecasting algorithms. These predictive models are traditionally based on SIR (Susceptible, Infected, Removed) [1] and its updates. However, they did not provide reliable answers, especially in the first delicate phase, in which governments must take rapid decisions that are deemed to affect deeply the development and the outcome of the outbreak. This inadequacy derives not only from the model itself; it is also and undoubtedly generated by the lack of correct and timely data. Moreover, on the onset of a new pandemic, the disease is not known or it is only partially known. The first problem is the attitude of predicting it *a priori*, assuming the trend starting from a known mathematical curve. This approach is flawed, because it

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is impossible to provide a truthful forecast at the beginning of the epidemics (or at the onset of a new wave of contagions), when, however, it is necessary to act promptly. Though as expected, as the epidemic progresses and the situation becomes homogeneous, mathematical models of pure interpolation and also SIR give more and more correct results. But during an epidemic, producing precise diffusion forecasts, including information on the structure of the wave front and its speed, is of paramount importance to organize an effective containment response.

Failure to produce reliable previsions is secondary to three major issues: model, data, and methodology.

Which Model for Which Use?

Lately, an overwhelming number of models have been proposed to predict the spread of C19. We can broadly classify those according to two main typologies:

(a) *Forecast models*: they are inspired by traditional epidemiology models associated to the introduction of mathematical functions. However, the results produced are not corrected. Specifically, the forecast of the peaks turns out to be wrong.
(b) A posteriori *models*: they show how the virus has spread; but they passively present a picture showing what has happened so far that is not useful for decision-makers that have to program future responses.

Traditional forecast models (such as contagion dispersion forecast) are mainly focused on the 1927 SIR-like models and its subsequent developments and improvements. In the aftermath, they are useful instruments to analyze the "global" dimension of the epidemics in term of deaths, infected and recovered, and how many resources could be necessary "globally" in the future if the pandemics will occur again in the same terms. Yet, they are not as effective during the course of the epidemic.

The model is based on parameters that describe infectivity and recovered, not dependent on time, and on spatial and medical

homogeneity: the behavior of the infection in one area is identical to the behavior of the infection in any other area. The resolution of the differential equations tied to this system (susceptible→infected→removed) generates the R_0 parameter that allows to identify the peak of the infection at time T_0. In this case the provision of the attenuation curve after the peak is defined, even in more complicated models.

The focus of the model is based on the R_0, which is grounded on infectivity and recovery parameters, and in the homogeneity assumption. Once again, the parameters play a fundamental role because the correctness of the model depends on their precision and accuracy. Above all, the parameter that defines the rate of infectivity depends on many factors, and above all it must be changed over time because it is affected by the actions that are being taken in the meantime. For example, the parameter changes if at a certain point all the infectable subjects are confined in their homes (as in a curfew or in a lockdown), if it turns out that a previous infection guarantees no immunity to recovered patients, and so on. Either the parameters are perfectly known in the homogeneous area, or the model does not work. In fact, in the models presented, the variability of R_0 is very high. This high variability does not allow government, health authorities, and health policymakers to take immediate solutions, especially in the initial stages. During the days of the epidemic, R_0 was constantly updated, dependent on the previous data, until it tended (naturally after time) to the correct result. This does not allow to act timely; even if in retrospect, it could give a correct view of the progress of the epidemic and maybe of the effectiveness of the measures taken in the past. This demonstrates the epidemiological validity and correspondence with an a posteriori model, but it not useful in the crucial phase when decisions need to be taken. We know that the reality is different from the one described by the SIR model. Epidemic evolves in different way in different areas [2]: for example, Lombardia region, New York area, and Madrid have similar features; and these are different from North Europe areas for work characteristics, intensity of contacts, and mitigation measures taken at different times. In a same country, differences are very high: this is the case, for example, of north and the south of Italy.

In addition, we speculated that air pollution and climate features may have a role in the spreading of the diseases, although it is yet to be proven.

The second approach tried during the first months of the C19 epidemics was the mathematical interpolation. As the data was produced over the days and when the homogeneity was achieved due to the actions taken by governments, the mathematical interpolation of real data allowed the real description of the epidemics curve. It does not consider any medical assumption, but only mathematical interpolation of data. Obviously, it is possible only when a regime of clear homogeneity is achieved and when a constant series of correct data is available over the time. These models have provided excellent results [3–5]. Nevertheless, these data can be made available only when it is too late and cannot be provided when they would be more useful, namely, at the beginning of the outbreak, when the most crucial decisions need to be made.

Therefore, none of the solutions proposed can help decision-makers in the initial critical phase.

Moreover, the parameters used in SIR-like models are statistical parameters that incorporate several considerations: the contact model, droplet spreading secondary to sneeze, contact, cough, and talks; the life of the virus on surfaces; the use of physical barriers like masks or other personal protective devices; the effectiveness of the treatments; the discovery and use of vaccines whose level of effectiveness might vary according to the different vaccines in use, the implementation different immunization strategies, and the response of the population to the vaccination campains; and so on. Most of this information might be available later on, but they influence the parameter R_0 all the same. Thus, when this piece of information is missing, the estimated real-time value of R_0 cannot be accurate, and it probably differs to the real one, although their mean values considered at the end of the epidemic may overlap.

At last we have to consider that SIR-like models have never been used online during epidemics, while the parameters involved in traditional annual flu epidemics are mostly known. Furthermore, there were no global epidemics except the Spanish flu that occurred well before the birth of SIR in 1927. Again, SIR-like

models give excellent results only afterwards, a posteriori, for an epidemiological analysis of deaths, infected, and resources spent.

In addition, for C19 we do not have a reliable fatality rate because we do not know a reliable count of how many people have had the disease. If the demand of intensive care unit (ICU) beds exceed the supply (as in some parts of the world), likely people who would have survived with the use of mechanical ventilation or other intensive measures are doomed to die. This depends on local resources and not on the danger of the virus itself: if no treatment is offered to a critical patient, a negative outcome has to be expected.

To know the actual infection rate, you also have to figure out how the virus is moving from one person to another. But we have experimented that transmission is extremely variable: it depends on social behaviors, local environmental details, and political decision, just to name a few. Besides, it is not going to be the same from one country to another; it is going to change over time; and it depends on what actions we take to fight the virus.

We can translate this assumption to a well-studied disease: has malaria a higher incidence in cold dry areas? Or in places where there is a lot of standing water? At present [6] in Africa, in hot and dry areas, the rate of disease is undoubtedly low: does it depend on the climate or on the failure to register disease?

Because of this, modeling potential outcomes means trying out a lot of different transmission scenarios, and these scenarios are not exact, but they are more like a range of approximations. A lot of variables enter in these estimates and each of those is, itself, variable.

The only thing we can control is the rate of contact, which however is not uniform; it differs from person to person depending on factors like their living situation and job, and it changes based on public health intervention and the actual rate of implementation of the same in different areas. Moreover, there are differences in human bodies, in people's behavior, and in their health state. Comorbidity, for instance, can affect the spreading and the outcome of people affected by C19. Cardiovascular diseases, diabetes, or smoking habits might be risk factors for the infection and the rise of complication from the virus. In addition, we do not know how long each single person can spread the virus to other people, when during the disease's progression he or she stays

infectious, if reinfection or chronicity is possible, or if and how a previous infection can guarantee future immunity. Moreover, the impact of the surge of outbreaks of new variants of the virus is still unknown, as the esteem of infectivity and letality of those can be established only *a posteriori* as well. Besides, the evaluation of the diffusion of each new strain of the virus depend on the same factors we mentioned for the spreading of the original virus. In addition, to assess properly the epidemiological meaning of the rise of a new variant, we must assess how it move in the population considering wheter it can infect those that have been already immunized (secondary to a previsous infection or to vaccination), and how it impact on the morbidity and moratlity of the population as a whole and on those that should be cosidered already immune to the disease (again, secondary to previous infection or to vaccination). The complexity of this scenario depends also on the way the new variants move in the populations as the spreading of the virus might follow a parallel pathway that start from foci that affect cluster of people that might have been potentially unaffected by the concomitant spreading of the original virus. It results in the production of simultaneus waves of contagion that impact of the total number of infected people (a number that do not discern the wave the different positive patients belong to), and therefore on the quality of the data and on the efficacy epidemiological model used.

In the traditional SIR models, all of these parameters are used to estimate R_0 [7].

We can make assumptions and build scenarios accordingly.

But that is not all. We are not dealing with a system with infinite means. Yet, health relies on resources and consequently on politics that depends on society, culture, and industrial and social development. In democratic countries, politics should be the representation of the people's will administered by people democratically elected. However, democracy in not a universal condition and resource management, especially when it comes to healthcare, is secondary also to a vision of the society that changes from country to country. Western countries, for instance, with top-rated health providers can deliver care and produce knowledge through research in very different ways, ranging to completely free and

public health system to private hospitals directly or indirectly charging patients for any health service provided.

These aspects reflect also on how research is ran in different realities and for which purposes (vis., public interests versus private commercial or noncommercial exploiting of the research's findings).

There are scientific facts everyone agreed on as the water boils at 100°C or the Planck constant (6.62×10^{-34} Js); however, the use of a simulation model depends on the philosophy behind it. All simulation models are correct if they respect mathematical correctness, but some of them work better than others depending on the aims you want to reach and the philosophy behind the models.

One of the goals of a predictive model and of public interest also for people not directly involved in research or in health politics is how and when epidemics will end? In SIR and SIR-like models, an epidemic ends when a sufficiently high fraction of the population acquires immunity. Nonetheless, if you do not know the biological parameters of the infection—as in this case of SARS-CoV-2—because you are at the beginning of the epidemic, the SIR cannot provide reliable indications. Without public actions, specific treatments, or vaccines, the only way to acquire immunity is to become infected and recover. Desolately, this process involves the death or the disability of a number of people (and we still do not know yet how big the number might be) who never recover from the infection. This assertion then influences the actions required to manage the spreading of the infection. What is indeed the acceptable number, if there is any? Who are the people that the world can consider expendable? And what is the optimal way to reach that fraction?

This is not a clinical problem (research for cure and for a vaccine), but a political problem. The SIR-like models define what grade of immunity it is possible to achieve according the political choice in the absence of vaccines; obviously, it is optimal for policymakers to avoid recurrent epidemics; but since economical activities (work and consumption) require contacts and progress of the epidemic, the optimal policy in the SIR-like models is to restrict or inhibit economic activity. Of course with this approach

the population never reaches the critical level of immunity to avoid a recurrence of the epidemic.

"The optimal policy in this world is to build up the fraction of the population that is immune, curtailing consumption when externalities are large, that is when the number of infected people is high. Such a policy involves gradually ramping up containment measures as infections rise and slowly relaxing them as new infections wane and the population approaches the critical immunity level" [8]. This is no longer an epidemiological model problem, but exclusively a political choice. Going on in this considerations is [8] "To analyze this scenario, we consider a version of our model in which the mortality rate is an increasing function of the number of people infected. We find that the competitive equilibrium involves a much larger recession, as people internalize the higher mortality rates. People cut back more aggressively on consumption and work to reduce the probability of being infected." Applying economic factors into SIR-like models [8] refines the model improving the policy features. Each model could be correct depending on the political choices: achieve the largest fraction of immunity in consideration of the local economy, achieve the largest fraction of immunity in consideration of the accommodation capacity of healthcare facilities, and achieve a low fraction of immunity while keeping economic activities as active as possible. This is the work of SIR-like models. The philosophy behind the models implies a choice of field in the resolution of the epidemic. Providing that a primary infection gives permanent or long-term immunity and that patients recovered from COVID-19 does not have major long-term consequences; for the school that considers SIR as the only acceptable model, the resolution of the crisis lies in the immunity that can be achieved (aimed to end the pandemic or to reduce the number and scale of epidemic waves). It is necessary to see how much this may be acceptable. So the R_0 parameter assumes an important meaning about the spread of the epidemic depending on the economic choices to be made (this is reflected by some questionable political choices made by some heads of state in some Western countries, for instance), but it does not provide information on clinic. There is in fact no neutral model. There may be a model that depends on the data collected or what data researchers and

statistics decide to collect, or on what is simply available, can give directions to decision-makers. These artificial made-for-purpose models are eventually transformed into political decision implementing tailored political solutions that depend also on the political view of the decision-makers and on the different contexts. Therefore, behind all this, there is a particular vision of the world: there are models that *a posteriori* can define the variables that came into play in the pandemic; there are other models that interpolate data and try to reconstruct the missing information in the attempt to follow step by step the evolution of the disease.

So how major international health institution such as the WHO can collect data from all over the world if the complexity of the system we live in produces such a high variability in the type of information available and when these information can profoundly be affected by political choices and by the models used?

Active surveillance is a possible alternative, aimed to stop the virus spreading on the territory at first, with hospitals as second-line resources to fight the disease and the consequences of the infection. We want to make a contribution to this philosophy.

The goal of this project then is totally different. This is not a properly said model but rather a complex set of clinical assumptions, mathematical methods, data collection, information analysis, and knowledge acquired through learning processes on the field. It does not want to provide data *a posteriori*; it wants to follow the epidemics from its onset in order to offer valuable information and sets of hypothesis to governments so that effective models for the prevention and the management of the pandemic can be implemented.

Clinical Data Available

Data availability is always the key. Without data, our models are mere speculations. In the era of *communication*, the *culture of the data* risk passes in second order.

A crucial point is the data availability. There is a lot of variability even between regions of a same nation. The apparent lethality rate depends largely on the test policies of the individual areas in fact; if a territory of a single country carries out few tests, subject-

ing only symptomatic or serious people to swab, it is reasonable to expect that for each swab made, many positive cases will emerge [9]. Certainly data provided by many countries and how data is collected from local or international institutions are incomplete and in some cases deceitful. To resolve this problem, some researchers have proposed adjustment to official data [10]; however, we believe that also these adjustments are artificial and any case based on official data produced by countries who have not shown confidence. On the other hand, the many discrepancies shown in the data provided by different countries are not scientifically explainable, and therefore the correction does not seem correct at all. In addition, there have been so far shared consensus on the definitions of the different variable of the disease, as what is infection, what should be considered a mild or severe case, and when COVID-19 should be considered cause of death (this definition profoundly impacts on the number of declared deaths for COVID-19 and therefore on the mortality rate in different countries).

From this point of view, the method to classify the infected is crucial; it depends on the recognition of cases made with tampons or other recognized methods: the greater the number of swabs, the greater the knowledge of the real cases. There is no doubt that data coming from nations that have made few swabs cannot be merged in the statistics with those coming from countries that have performed many more tests. Furthermore, how are people at home with low fever and few symptoms or asymptomatic or paucisymptomatic (not always known) considered? Is clinical diagnosis of COVID-19 acceptable to define a case, or does a confirming test always needed to make diagnosis? Do the statistcs consider the number of patient with SARS-CoV-2 infection and the ones with overt COVID-19?

In addition, the number of swabs alone and the percentage of positive of the total of test done do not offer too much information if we do not consider why, where, and for which purposes the tests have been performed. We have to know, among other things:

1. The spacing distribution of the test offered to the population and the single percentage of positives in the different clusters of people tested

2. The aim of the tests performed such as:
   (a) Screening of an asymptomatic population
   (b) Screening of a people with a low, medium, and high risk of exposure to the virus
   (c) Screening of people that are at high risk to develop the disease (but may be more confined in restricted areas if infected) versus screening of people—such as the youngsters—that even if infected are less likely to develop the symptoms or the disease but more likely to spread the infection because asymptomatic
   (d) Screening of people coming from or going to area with a high incidence of COVID-19
   (e) Screening of healthy or unhealthy people in routine testing activities performed by healthcare facilities before the performing of a medical or surgical procedure
   (f) Routine screening of healthcare workers
   (g) Testing of symptomatic or asymptomatic people secondary to activities of contact tracing
   (h) Testing of symptomatic patients that have been referred to a general practitioner or to a specialist or that are asked to perform the test because they belong to a class of key workers
   (i) Testing of symptomatic or asymptomatic subjects belonging to a cluster of highly exposed people (such as persons living in a community like a residency for elderly people or a jail)
   (j) Testing of symptomatic people that actively seek for medical attention in emergency settings
   (k) Testing of people already admitted to a healthcare facility that may have been exposed to the virus during their stay in the hospital

To make an easy to understand example, if we test people to detect the blood alcohol content we would expect a high percentage of positive tests if the test involved people attening a pub and a prevalence likely close to zero if we test school children. Moreover, as we have seen, the number of deaths attributed to the COVID-19 varies, because the comorbidities that may have contributed to the

death of the patients are registered in different ways in different systems.

Then if the number of infected is not really known, the ratio of infected/population is not correct; consequently, the number of deaths attributable to COVID-19 and the mortality and morbidity ratio are simply not comparable among different health systems, and at worst they could also be completely wrong. Likewise, in patients with chronic conditions, the cause of death has been in some cases (sometimes in a same hospital) attributed to COVID-19 even when death was secondary to the existing disease and SARS-CoV-2 infection was only an incidental finding that might have not play any role in the disease, or vice versa the chronic condition was declared the cause of death even if COVID-19 actively leads to the death of the patient.

Which model could work with this data variability? How helpful a model can be when it plays by ear, making adjustments as necessary, changing the parameters day-by-day?

We think a new data structure based on the nature of clinical information. Generally each health application (e.g., enterprise resource planning in health context, electronic health records applications) is based on traditional E-R schema in which entities represent logical actions during the clinical workflow. This method joins data in clinical pathway making the extraction and exchange of the exact information we need to share difficult. To overcome this problem, we propose a new information model. In the model proposed, the description and classification of real medical phenomena is designed through the explanation of two levels: the information models able to design minimal unit of information and the semantics of the domain context—the attributes that provide knowledge to the data item. These two levels are connected for providing meaning to the information, but the items belonging to the two domains are composed so to model the complex multifaceted aspects of the clinical environments.

Obviously ontologies of the reality represent the third aspect we have kept in mind. They provide medical understanding and assure that knowledge can be made available in a sharing act, because there is the certainty that it is understood by stakeholders.

Data have attributes and features that specialize them and make them understandable in different situations and contexts, including the possibility of correlation among them and extraction of accidental knowledge. Data is composed and connected together, and the connection has medical meaning through ontologies.

The main goal is to atomize (i.e., unbundle them rather than storing hardwired relationships in the database schema) the fundamental units of data, allowing to change context around them as the landscape around the patient evolves (e.g., changes of diagnosis) while still retaining the ability to trace back the epistemic inquiry from which it originated, like a glass-ball in a sandbox. The various suitable linkages of these items with the semantic medical knowledge provide, thus, the opportunity to configure virtually infinite pieces of medical knowledge. The single clinical data item or a set of items grouped in clusters are linked to different attributes that can provide knowledge and specialization of information to these data item or clusters. We propose to make clinical data in atomic state and associate attributes in order to give meaning to the data. The possibility of extracting information from the relationships is possibly an open research area. In this way the same data can acquire meaning for clinicians, researchers, and patient if considered according the attributes. And at last, this is easily shared and understood. This aim must face the present medical record systems conceived in "individual" form in which, aiming to resolve partial requirements, data are contained in silos that cannot communicate with the others, unless in complex ways, introducing different software layers. In these applications, data are hardwired in the application, in the software workflows; or the meaning of data is connected to the database schema making it in the reality difficult to treat, consume, and analyze the data under the different perspectives that it contains. For these reasons, a sort of separation between information models and domain content models is proposed, fostering the definition of minimal unit of information. In these models, specification and context information must be associated allowing the composition of data items in clusters, mining hidden meaning through the correlation among different data (data coming from the use of

different protocols, data coming from different clinical scenarios, data coming from different health systems, and so on).

This different data organization suggests that medical data must be treated as if they belong to layers in order to allow comprehensive views, allowing the extraction of information on the layers of interest, and consenting moreover the analysis of the correlation between information among the layers.

This allows to create a longitudinal record with the following features: comprehensive record which collects each information related to the patient health; pervasive, distributed, multilayered, and individual centered record, able to manage different types of information, including -omics.

Organization and Management

The correctness of information collection is a necessary condition but it is not sufficient. In these days, we have witnessed discrepancy of data provided by different countries without any scientific evidence to support them; it depends on the registration procedures, accurate knowledge of the clinical case, and almost certainly, unfortunately, the will of some governments not to declare everything. Without trust, the international mechanism of sharing data simply does not work.

Of course, when the same future of our species may be at stake, this is at least irresponsible and in some cases criminal. However, we have to be realistic, and although some errors may be inevitable, awareness of what a proper and accurate data collection is must be awarded, and countries providing reliable information are rated accordingly.

If this system will be adopted, in fact, data must be correct, careful, available, and on time.

We claimed again that we do not want to provide data *a posteriori*; we want to follow the epidemics from onset in order to provide to governments a set of hypothesis to be implemented; this implies that the information obtained daily must make it clear how to act to limit the pandemic, how to ensure adequate care and access to facilities, and how to act in order not to completely break down the economic situation.

So the organizational information that the system must provide involve the level of management behind.

Obviously the management level depends on the good organization and, according to this system, depends on the availability, correctness, and veracity of information. The lack of confidentiality and trust in information generates incorrect models and requires correction. The problem of information correction will be fundamental in the study of possible alternatives. Thus, we want to approach the problem on the one hand by building a series of data corrected through layers of information systems to be applied to HER and on the other by gaining knowledge through learning machine techniques from field data.

Learning, Listening to, Following

What we know for sure is that we do not know. Some scientists claim to know *a priori* how a pandemic goes, but this is more witchcraft or illusionism than science, and this approach is bound to lead us to failure. But we want to know. So we have to learn.

The first action to do is "to learn." We need to know how virus spread; how physical contact, talking, coughing, and sneezing are likely to transmit the infection; as well as how long the virus survives outside the body and how. This allows us to achieve a more efficacy parameter of contact. We can achieve this collecting data and using machine learning in order to learn from data collected on the field.

We do not know but we need to know.

The Mechanism of Diffusion and the Dangerous Behaviors

Human contact alone is not very descriptive of the phenomenon. It would be useful to know how it happens and the concomitant behaviors. We need to understand what happens during coughing, sneezing, and talking; how the microbial load can produce infection in other contacts; and if the onset and gravity of the disease depend on the viral load or on the timing of the contact.

In addition, we must know if some behaviors or contexts are more dangerous than others. It follows that different behaviors and contexts can have different contagion models, so different workers are more exposed than others and can spread the disease more easily [11].

For example, during the phase of containment, people continue to get sick, especially healthcare personnel and also workers who have contacts with other people during the job.

In addition, the use of personal protective equipment (PPE) and the implementation of containment measures (e.g., use of facial masks, in-deep ambient cleaning, social distancing, hand hygiene, and so on) can deeply affect the spreading of the virus (see also Chap. 13). Masks (see also Chap. 6) are a paradigmatic from this point of view [12, 13]; at present, different solutions and typologies are available, but it is important to know what is the grade of protection that a specific mask can guarantee: generally the virus is smaller than the mashes of the masks available on the market. On the other hand, reducing the mashes alone is not a solution as such a fabric would cause breathing problems. Besides, the filter provided by facial masks does not depend only on the mechanical filtering provided by the mesh but also on several factors that vary according to the materials used. Solution based on nanofibers with oriented filaments, for instance, allows the normal breathing, but we have also to consider the hypothetical dovetail of the virus into the mesh. A high efficacy could be achieved replacing constantly the masks, but especially for a high-tech device, it would result in a high expenditure for the users and the society, if no methods for washing and reuse are found. So, also the effectiveness of the mask has to be a variable of the model.

Talking about the spread of the virus on the inanimate surfaces and the loss of viral load over the time, we must know how this happen and if this could be considered a possible way of contagion. From this depends also what measures we need to put in place to reduce the risk of spreading. Some articles published on the scientific journals foresee a possible cause [14]. And again, although there is still not a definitive answer to the question whether SARS-CoV-2 is an airborne organism, some research speculate that pollution may be a carrier [15–18]. If this will be

confirmed, the spread model should take into account also the climate changes due to wind and rain and grossly the air quality indexes.

The lack of knowledge and the difficulty to achieve answers in quick times (especially during epidemics) require us to find new method to get proper and prompt solutions. The use of machine learning techniques will allow us to learn from the reality, being able to test solutions and provide different scenarios.

Machine learning will help to understand how the virus can spread—day-by-day—and how the protection devices can protect people during their work or their daily activities, considering also if pollution and climate can contribute to the spreading of the disease. This is not only an aid to complete the forecast model but also to refine the diffusion model.

"Data feeds AI; AI makes sense of data." Said O'Reily at AI conference.[1]

Dynamic, Revealed Context

Applications increasingly need databases that adapt to complexity and to the myriad of dynamics and to the unpredictability of real-world data. Effective applications use the richness of all available data to reveal context and causality in real time, following at the same time a shared definition and classification of cases and of causes of death.

Security and Data Privacy

As regulations continue to evolve, individuals and governments are more conscious than ever about how and where consumer and people data are used. Developers need to build applications that meet these needs securely and rapidly.

Intelligence and Learning

Operational applications are increasingly components of complex systems that incorporate machine learning and artificial intelligence (AI). For actionable AI, applications need to bridge data science across operational systems and leverage context in real time.

[1] https://www.oreilly.com/conferences/strata-data-ai.html

Tell Me What's Going On

The ability to build an unfamiliar event model depends on the ability to listen. Applying known forms, models, and mathematical functions to complex systems whose mechanism is not known does not lead to acceptable solutions.

The knowledge of the territory is fundamental. But what means do we have to get to know it?

The first tool is the surveillance, but compared to what? Who is the enemy? We do not know it. Thus, surveillance is fundamental. At the moment, we have to leave aside the testimonies of Chinese researchers, unfortunately not published in scientific journals, which allegedly demonstrate the presence of SARS-CoV-2 well before the Chinese government's declaration; also in a democratic world, surveillance did not work. In Italy some researchers reported the presence of abnormal pneumonia since December 2019 [19]. Surveillance is linked to data availability. We suggest that the machine learning system must know immediately when abnormal facts are manifested on a territory. This must be not a voluntary act but an information triggered by default from information systems and Electronic Health Records (EHR). This could be possible if EHR and health information system are built separating the raw data from the collection method and linking it as an item to its meaning.

But which facts are abnormal? We may not know them; for this reason, big data techniques help to extract inconsistencies and anomalies from different data sources. This must happen continuously.

During the epidemics, we need to know how it spreads from people on the territory. An app with symptom descriptor could be useful, but we do not forget that during epidemics, stakeholders are in tension, so these apps refer further direct contacts to healthcare professionals overwhelming a system already in crisis and potentially and paradoxically producing harmful results due to lack of time needed to process all this information. Not to mention that the institutions promptly activated toll-free numbers for these types of contacts. Nonetheless, these might be very useful information that would get lost following a traditional approach. We need to feed our learning machine with relevant data like: the

entity and the pevalence of the symptoms, the course of the disease, if people are quarantined at home—alone or with their familiars—, the number and the occurrence of past contacts. These data can be furthermore organized in cluster considering: general information, daily information, symptoms evolution and final outcome, and so on. The more data could be collected and treated, the more accurate the data analysis could be. The endpoint is the production of a machine learning system able to describe pointy how the pandemics move in a territory and affect it, and how people behavior change as a consequence of that.

The ideal would be that these data are connected to own electronic record, in the part dedicated to user notes, but this, even if proposed several times by us [20], is still science fiction. Let us improvise apps that are able to provide more information and that can do the job as well, although not in an optimal way.

The "Tell me what's happening" model can help the research, but this approach must be considered very carefully in order skip fake news (see also Chap. 16) or to avoid to create alarmism built on wrong assumptions; for this reason, machine learning can clean inconsistent data and search references between information. While it is simple to build a simple app, and we have seen many of them in these days, it is more difficult to create a system of correctness of the information. However, we cannot do that without data coming from the field. If carefully analyzed, these data improve epidemiological models providing visibility of the part of the iceberg that floats below the surface of cases of COVID-19 that are not seeking for medical attention. Moreover, it can track healthcare workers and their exposure and symptoms and support COVID-19 research. But surely these apps cannot be disconnected to a complex system for data analyzing.

Moreover, the geolocalization of the infected will help to track the infected people and the contact with other people.

It could be used for people control in order to push the positives to stay indoors, tracking of positive displacements in order to identify the people with whom they came into contact and isolate them in turn, and making a positive map useful to the population and civil protection.

And at last, it is fundamental to know the clinical course and treatments in order to evaluate the health procedures and drugs

used. Also in this case the variability from country to country is different [21]. The correctness of information collected about the EHR also in this case is essential: to evaluate the efficacy of pharmacological treatments and of the medical procedures in place allows to program immediately the necessary health services. The model proposed by Fergusson [22] or Eichenbaum [8] tried in some way to respond to these needs: how long to delay the wave of infections so to not overload the hospital facilities? Or how many resources are available at every single moment? We want to underline that this organizational model depends on the resources available on the territory. We have to build a model in which it is possible to evaluate and therefore provide the necessary medical resources and estimate the equilibrium between needs and resources before the system collapses on itself. This information, like the others, must also be timely and modeled according to the specific forecasts and should be reevaluated daily.

Follow Me!

If virus does not spread through the air, it spread through the men. But in any case, the displacement must be considered. Let us see the second case. It is pleonastic to say that times have changed. Considering the human life as it was in the early years of the past century is not correct. We are now living in a world where work patterns have changed, the meeting places have increased and enlarged, and the average of daily kilometers to reach the workplace—that is often located in other towns or regions or the places of fun and also often out of town—has significantly increased. This depends on the speed of transport and communication lines.

This is all the contrary of what can be considered "homogeneous": so the virus does not spread homogenously. And models that consider the spread homogeneously fail, especially in the first crucial phase of the epidemic or at least until the conditions of homogeneity are restored that is toward the end of the epidemic.

We have to follow the virus on the territory. The line trajectory of the virus-man complex (namely, the one carrying the disease and that can potentially infect others, and that moves in time and space) meets specific geographical areas in which are present a

given number of susceptible people (during a journey, during entertainment time, during work time, and so on) and in which the virus can spread in different ways. The same virus can evolve and can move in time and space accordingly.

The analysis of the intersection of points, lines, and areas in which the virus-man complex intersects susceptible people is the work of spatial analysis.

And this reconnects to the knowing of anomalies (the previous assumption). Once anomalies are recognized, these must be followed. How to recognize outbreaks is the work of surveillance (see previous topic), how to follow the spread is the task of spatial analysis, and how to understand the contagion depend on contact models that vary from situation to situation: they are different in fact depending on how people travel (e.g., bus, train, airplane), on how people work (e.g., supermarkets, hospitals, public offices, industries), or on how they spend their entertainment or free time (e.g., bar, supermarkets and malls, football match, concerts).

Therefore, it is very important to follow the infected, understanding how they cross areas of possible susceptibility, knowing the potential number of susceptibly, modeling the contact according the different models.

About data regarding the surveillance (EHR or other data source) and their homogeneity, we have already seen, in the previous paragraphs, the data that feed the different contact models (machine learning and big data). There are a lot of data indeed—mainly collected by public organizations—about the people, their displacement, the places of work, entertainment, and so on located on the territory through GIS, allowing spatial analysis.

Yes, data, once again data. These belonged to open data category, but have they been even really open?

But Stay Away!

We have so far introduced the concept of contagion model. We have seen how crucial this concept is and how such a model is different for different opportunities and finalities. If we consider people commuting for work, for instance, we can observe that during the journey, there are different possible contacts depend-

ing on how people travel: in a bus probably the contact is short but intense, in a train and airplane locally intense, and so on. Airplanes on the other hand filter the air inside the cabin with high-efficiency filters able to stop most of the particulate matter and possibly the virus, with an impressive rate of air exchange that is normally not achieved in other means of travel. Therefore, in such a confined environment, the disease may spread less efficiently than in other more open spaces. During entertainment time the most appropriate model depend on the activity chosen: for example in a football match, a model connected to convolution model can be appropriated, whereas in a walk in the mall a drunkards walk with randomness rules describes the possible interactions; In the same way, other models, like Monte Carlo, should be chosen according to the setting analyzed and to the specific need.

Of course, these models depend on the knowledge of the infectivity of the virus. And about this, we know very little. So the way (as previously said) is the collection of data in a machine learning system in order to understand and model the infectivity, considering the different ways of contact. These models, which during the time we hope will become more precise, will allow to run different simulation models to represent the reality.

Moreover, infectivity is not a fix variable, as it can be influenced by other measures or by the evolution of the virus on the one hand, and on the ability to fight it on the other. Consequently the models have to evolve too. Some of the factor that can influence the spreading of the virus in the population for instance are the type of PPE used (i. e. FPP3 or FPP2 masks versus plain fabric face masks; proper duff on-duff off procedures, and so on), social distancing, introduction of an effective vaccine, and so on. So the simulations during the epidemics run different models from those of the beginning.

Surely the models produce scenarios. If we had the certainly of the correctness of biological model of contagion, or the exact spread model, the work will be eased; but new epidemics generally are not known in all their aspects, so we have to learn, listen, follow, and collect data and produce simulation scenarios.

Proposal

For the purpose of our suggestion, we do not propose a model running on a server. We propose instead a complex set of data collection and homogenization, machine learning algorithms and solutions, big data analyst, biological models of spread and defense, mathematical methods describing contacts in different modalities, and spatial analysis contribution that produce different simulation scenarios in order to accompany the decisions of the stakeholders day-by-day.

Data Model and Information Collection

Data model is complex. We need clinical information that are simple regarding only the epidemics and associated clinical data. EHR normally used are unable to provide useful information quickly, so it should consider the implementation of a layer above the medical records. The concept is that information, subdivided in atomic data, must be separated by the collection organizational workflow; each data assumes meaning from the specialization of information connected to the data, more readable and universally exchangeable.

Accredited users (health-related professionals) are prompted to a GUI guiding their evaluation of suspect and ascertained cases, assisting them by design in rating the uncertainty of key records/data. The tool would then prompt and assist in the collection of the first neighbors and contacts/trajectories of each suspect/ascertained case (cross-referencing to GIS) in order to single out geographical and social clusters. Uncertainty qualification will allow to produce analyses of various scenarios with inherited reliability scores, to estimate real-world diffusion speed and infectivity, inferring affordances and most likely contagion channels, by applying methods from causal inference and machine learning, most notably chain graphs, information geometric causal inference, and causal generative neural networks.

We need also territorial data, that is, data about people leaving opportunities and facilities, located on the territory. These include data about transports, stores, supermarkets, malls, and so on; industries and working places; schools; bars, restaurants, and entertainment venues like cinemas, stadiums, gyms, and so on. As well as being localized and georeferenced, capacity and number of accesses must be recorded. Whereas it is probably that cartographic or statistical offices of the regions could have georeferenced data, presence data could be missing. Simulation runs and statistical data could supply.

We need biological and clinical data in order to know how virus acts, develops, and lives and how long it lasts in the human body with or without cures. This requires to know comorbidities, cure time, clinical and pharmacological techniques, the use and effectiveness of remote monitoring systems, the diffusion ways and their differences (sneezing, coughing, talking), the average life on inanimate subjects, dependence on climatic agents, possibility of life in the air, and so on and also sanitization methods, size and structures of the masks and personal protections, etc.

And at last, we need data from the users such as clinical notes collected in specialized apps and displacement data also collected into social networks. In addition, we may use the accreditation for patients to report their own subjective experiences and disease evolution, and traced spontaneous contributions from people are plausible add-ons. These information will be treated according the privacy rules.

Co-Constructing the System

The technical detail of the system is beyond the purpuses of this chapter. The complexity of the system invites to gather information in different areas requiring skills in data science, algorithms and modeling, medicine, biology, statistics, and territorial science [23]. We think that different minds can learn from each other through the construction of own models that integrate with each other.

The data model layer is responsible for the collection and homogenization of data. Different types of data will have different flow and management. Moreover the layer feeds machine learning algorithm, while a Big Data analyst will be used to refine the models that will become able to assess different aspect of the epidemic like the spread of the virus, or the contact tracing in different real life scenarios (traveling, working, in the free time, etc.).

The Analytic Layers

As we described above, when we have usable data, we need to feed the different layers for the analysis.

The layer for the contact diffusion depends on the data about the mechanism of contagion, as described above.

The contagion mechanism has four aspects:

(a) The biological mechanism: virus dangerousness (symptomatic, asymptomatic, paucisymptomatic, etc.), dynamic of spread (sneeze, cough, talk, contact, persistence on inanimate surfaces, etc.), comorbidities associated, incubation time, illness, and healing
(b) The dynamic transmission: by travelling (by train, by bus, by airplane, etc.), by working (in different places with different modalities including hospitals or facilities for elderly, etc.), into entertainment places (bars, restaurants, malls, supermarkets, gyms, cinemas, stadiums, etc.), and at home
(c) The efficacy of PPE and containment measures: masks, clothing, distancing, local cleaning, and so on
(d) To these information, we need to integrate the real tracking of the infected, when available; applying the previous aspects, we are able to know the entity of the spread geolocated on the territory, understanding which areas and structures could be contaminated.

These aspects, taking data from the learning machine in order to always understand better some mechanism from real data, feed

and complement each other, producing a set of scenarios. Each of them uses a proper model appropriate to the availability of data. Spatial analysis is included in this layer in order to intersect the data geolocalized on the territory [24].

Networks assist in simulating transmission of infection due to social contacts. Individuals can have heterogeneous characteristics. So networks can contain various nodes and edges between nodes. The edges or connections can be one-directional or unidirectional and characterized by a weight depending on infection rate, and this is related to the ways to contact (sneeze, cough, talk, contact, etc.), the PPE (masks, glasses, gloves, etc.), and other diffusion parameters. The choice depends on the available data, the type of problem, and the form of the results. Because of random interactions between individuals, spatial models are required for the simulation of contacts during the free time activities; contact network models are appropriate if hosts have few contacts, for example, during the work. Each single model runs on a specific territorial area composed by susceptible people which are considered diffusion ways, barriers, contact ways, intensity, and time spent in contact: the area describes the susceptible population during the activities (work, entertainment, transport, etc.), the interaction depends on intensity (during the football match, e.g., the contact duration and proximity are high), and infected people can infect using different ways (cough, sneeze, talk, contact). Models like convolution, or cellular automata [25] can describe the complex and spatially distributed systems in which the infected individuals act. In the model one host can occupy one grid site. Interactions with other hosts happen only within the local neighborhood. Recursively, people in the complex and spatially distributed systems became infected and subsequently can infect people according to a time distribution in which incubation time and contact time will be taken into consideration.

The Output Layer

If the spread of the disease depends on climate, we could associate a model in which daily climate data complete the analysis. If

the virus is conveyed by air, climate, and pollutants [16–18], the wind and the forecast of dispersion could be calculated and geo-localized intersecting the displacements of the air masses with the anthropic elements of the territory: just as the models of dispersion of pollutants [26].

At last, the layer 3 provides a number of scenarios that must be figured out on the territory [24].

The results are provided in the form of different stackable layers in order to go on details keeping the complexity (see Fig. 15.1).

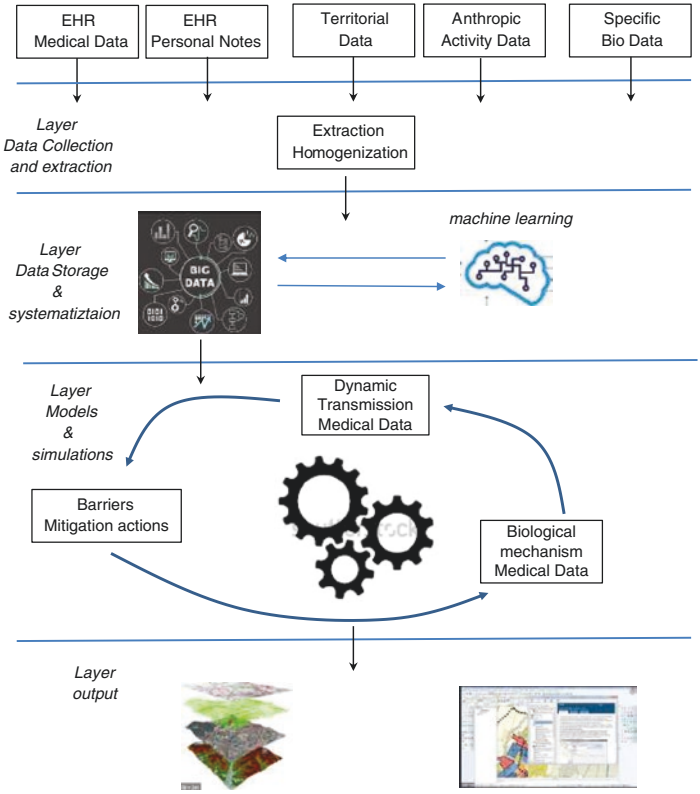

Fig. 15.1 Different layers of complexity the prediction model should be based upon

Conclusion

Forecasts are difficult. We cannot rely on a simple model, but we must take all aspects into consideration. Models based on old assumptions do not work today. On the contrary, purely mathematical models can be effective only if homogeneity is assured and there is the availability of a consistent set of data on which the data interpolation operates [27].

The choice of a single model depends on the philosophical assumptions beyond the model, and it involves a certain vision of the reality: how to act and when to act. So all the models could be right in itself! How many approximation we want to get. In the case of a novel disease, what degree of immunity we want to achieve before a vaccine becomes available? When will vaccine be ready and are we sure we want to use it then? How long can the ICUs resist? SIR-like models respond to these considerations; they do not consider biological parameters or different models of diffusions; the parameter that collects all information is the R_0 that is the level of contamination; all is inside this parameters. It is no coincidence that Boris Johnson's initial declarations were supported by two scenarios prepared by the SIR, providing two possibilities for achieving immunity based on the resources available, without other biological, clinical, social, and economic considerations [22]. Those assumptions have proved themselves wrong. However, they could be considered, although cynical, politically sound: the choice on how to deal with a new disease depends on when we want to achieve the high grade of immunity considering the hopsital and ICU bed availability in order to not clog them, and on how many people are we ready to sacrifice trying to find a balance between the need to provide a high quality healthcare, the use of the available resource, the necessity to preserve the economic interests of a nation.

We do not want to propose a model but a complex system that uses different disciplines to create different scenarios for the stakeholder in order that they can take decisions since the beginning of the pandemic, being able to modify in progress the forecast through different scenarios, through the modification of the assumptions and data from the field, using new and mod-

ern paradigms and considering the profound change in living and working conditions compared to the first years of the past century.

We are also aware about the "data pollution" of these years, whereas while innumerable data sets are produced, they very often belong to silos and are unusable and cannot be shared; so it does not allow to use a correct set of information: that is a paradox! But we are extremely convinced that different techniques—such as machine learning and big data analytics—can help us to put order in this jam of information. This could be the major obstacle, not the abandoning old models.

So, at last, if the Lombardy alert [19] (not adequately considered by central agencies) had been within a more complete and comprehensive project, the surveillance would be scattered according the anomalies recognized; alerted researchers could follow the infected people (also without knowing COVID-19); and understanding the trajectories of the virus-man complex and knowing the areas of intersection, the situation could be analyzed, limited, and known immediately.

And at last we finish with two considerations:

Analyzing data, even if we are aware that they are not completely corrected and in some cases missing, we can estimate the dangerousness of the virus.

In the estimation of mortality index, the death number referred to the infected (e.g., in Italy and on some regions, the five most infected)was 15% in early 2020 [27].

Considering that the Italian Ministry of Health has suggested to not perform autopsy, we expect that the number proposed was higher than the real. We assume these data are more interesting compared to data on the infection number; in fact, it depends on the number of swab performed; accordingly [27], for the region selected, the ratio referring to the population was 6.98%. A very low percentage, so we expect that more people are not counted as SARS-CoV-2 infected, so we would have expected a higher number, considering the infected and not known who got infected but treated at home in a milder form. In the reality, we know that the number of infected cured at hospital were the one with a more severe form of the disease, but little is known about mild

infections, treated at home, or about non-symptomatic or pauci-symptomatic people. In this case, the number of swabs done is the useful number to estimate the level of infectivity. So, considering errors and missing and omitted data, we can consider COVID-19 very infective (the number of infected people is higher than the one announced), but the danger (estimated as the number of death over the number of people in the five regions considered) is 0.6% [27].

If we consider the number of deaths over the number of infected, at the time it was 15.78%; but if the number of infected is underestimated, the index drops further, as we have seen later on when mass testing become available. We take a cue to claim that pandemic is not so dangerous when compared to other, but not to be underestimated, and we have to consider this pandemic as a warning. The next time could be more dangerous and we have a moral imperative to be prepared. For this reason, we propose this system because since the first day of the next pandemic we have to be ready to act. We cannot afford to face another pandemic with such a poor level of preparedness and readiness. This warns us but suggests also that the war against pandemic has to be fight in the territory rather than in the hospitals (also considering that many infections have developed within the healthcare centers as suggested by the fact among other clues that many healthcare professionals have been infected); thus, the knowledge of the territory is of primary importance and it starts with the initial surveillance. Therefore, we must implement tools for the knowledge and the monitoring of the territory.

The hospital-centric organization has failed in fighting pandemics.

This first consideration opens the way for the second one. Our proposal is an attempt and it must be falsified and corrected. We have started with the consideration (for all to see) that models proposed so far did not work. We are convinced that models must be used to provide stakeholders information on how to take decision immediately from time zero, that is, the onset of the epidemic. This lack of information led us to build this attempt, but we are opened to modify and fine-tune the model respecting the initial considerations.

In the name of open science, we propose an open discussion without prejudices.

We noted a paralyzing fear worldwide that has not allowed the immediate choice for a lockdown when it was maybe most appropriate, as right after the onset and the choice of how, where, and when to implement it; in our opinion, this has depended not primarily due to the lack of data (those are available) but to the lack of open models based on the desire to learn from the reality facing a new and unknown virus.

This pandemic caught us unprepared and the next time we have to be ready. Otherwise, there may not be a next time at all.

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Principles of Risk Communication and Health Crisis Outreach Management during the COVID-19 Pandemic

Fabio Capello

Risk communication is a key issue when it comes to the management of major health crisis or disasters [1]. The basic principle of risk communication is to provide the general public with true and reliable information that could help people to understand what is going on, to understand why some measures are required, and to understand what actions should be individually or socially taken on behalf of the singles and of the population as a whole. It implies that no actor involved in the process of information production and delivery should take advantages from the spreading of the news. Moreover, the higher aim of the public service should be always pursued, so that a correct message could be delivered in the most appropriate way.

COVID-19 presented the most challenging scenario, as the enemy to fight was completely unknown, as well as its real strength and its weapons against us. However, the response was inadequate and potentially harmful, revealing how weak the level of preparedness was and how selfish has been the responses by government, mass media, experts, and ordinary people [2–6].

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Background: The COVID-19 Onset and the Communication Management of the Crisis

The onset of the 2020's SARS-CoV-2 pandemic has represented a major challenge for, among the others, governments, health systems, and research institutions [6]. The lack of information, due to the fact that scientists, clinicians, and decision-makers had to deal with a completely new disease, revealed how fragile the modern medicine is, despite the enormous amount of medical discoveries and inventions of the last decades. With no available procedures in place to address the new epidemic, each country found its on way to fight the virus [7].

Surprisingly, however, because of the previous hints that a novel virus pandemic was on its way, major international institutions and local agencies did not produce any effective strategies based on preparedness and readiness' plans [8].

Different health systems, based on completely different models, produced reactions that relayed on action plans built for unsuitable scenarios, failing to create a coordinate response. The same data and knowledge sharing failed with no consensus in place on how to consider and classify cases, contacts, severity of the disease, or deaths secondary to COVID-19. Thus, data were and still are unreliable, with the quality of the information gathered so poor that no solid epidemiological models could be produced. Besides, the same model in use are in most cases outdated and not fit for the purpose (see also Chap. 15).

The abrupt explosion of the health crisis conversely affected institutions and the general public at the same time. The lack and the need of knowledge translate in confounding messages that did not travelled following the usual pathways. In many cases, news reports broadcasted via mass- and social-media preceded the publication of a finding or of a scientific hypothesis on medical journals [9].

In addition, because knowledge was crucial as there were no written guidelines to treat a completely new and unknown disease, and any piece of information was vital, many articles skipped the usual peer-review processes, with unconfirmed data published as commentaries or letters to the editor [10, 11]. Even when methodologically

correct, this spread of raw data bounced on the news with no filter, offering confounding pictures to an already confounded audience.

Furthermore, too many voices rose from self-declared political and scientific experts, offering unsolicited or inappropriate information, based mainly on personal beliefs rather than on scientific findings. In such a scenario, the post of a researcher equaled the one of a politician, and the one of a frontline medical doctor rivaled to the one of a passive spectator with no specific knowledge on viral, public health, or medical matters [12].

The lack of a coordinated top-to-bottom communication plan, needed to present in a proper way what was happening and what were the implications of the pandemic, together with what measures were needed and why to confine the virus, produced different reactions in the population, from panic to complete unawareness of the risk, that accordingly generated inappropriate and risky behaviors that ultimately facilitate the spreading of the disease [13].

This is probably everybody's fault. International health organizations and institutions failed to deliver a guidance for a proper risk communication strategy. National authorities and health systems worldwide ignored the problem and allowed the spreading of untrustworthy information via the media neglecting the communication aspect of the problem. Newspaper and major broadcasters failed to report the news following a risk communication approach, giving voices to self-declared experts that as matter of fact have no evidences to support their declarations. Politicians gave statements that minimized the risk [14] or offered alleged but dangerous medical solutions [15]. Researchers and scientists relied on outdated or oversimplified models that were unable to offer proper solutions but that were presented to the scientific audience and to the general public as accurate or reliable. The academic world failed to gather and process in a coordinated and organized fashion the incredible amount of data produced during the first phases of the pandemics.

Meanwhile, all this constant production of unreliable information was diligently reported in the news, with the voice of scared people with no scientific background that matched the one of professionals that however had no specific knowledge of the disease—no one did as a matter of fact—or direct involvement in the research that

challenged the voices of those that had an active role in fighting the disease in their offices, in the labs, or in the hospitals.

COVID-19, then, exposed the unworking model the whole medical world has been built upon in the last decades and the lack of operational strategies of preparedness, readiness, health education and risk communication.

The Response to the COVID-19 Crisis

SARS-CoV-2 is a new, previously undetected virus, whose effect on the human body and the way the infection spread and travels across the populations were completely unknown at the time of its unset. Some of this information are still unclear. Everything about the disease, thus, was unknown. Even if it is logical and practical to rely on previous knowledge and on functioning models to address a new infection, we must agree on the fact that many of the approaches employed, because designed for different clinical and epidemiological scenarios, could be inappropriate and potentially dangerous, producing hypothetically more damages than benefits if proper feedback strategies aimed to correct and remodel the measures taken are not in place.

Starting from this standpoint, no one could and can offer solutions or advices both to decision-makers and to the general public that can be sold for sure [16]. The same prediction model used to define the effect of taking or non-taking a specific action may not be suitable for a new scenario, and everyone must be aware of that (see Chap. 15).

Nevertheless, we have to concede that some principles can fit the actual scenarios and that therefore some general measures, normally used to contain the spreading of an infection, should be effective.

The first countries that had to face an overwhelming number of cases, namely, China and Italy, produced similar solutions that, however criticized at the moment by some authors, has been reproduced in most countries although following schemes tailored to the specific setting.

Because it is difficult to assess properly the cost-effectiveness of the measures taken, we probably cannot determine if the strate-

gies used were the most appropriated ones, but we can speculate that given the knowledge of the disease and the implications secondary to the implementation of specific actions, those were the best options governments could choose at the time.

However, with no risk communication plan in place, people struggled to accept those measures given the consequences on their social and economic lives, whereas a proper communication strategy is likely to produce proactive behaviors aimed to reduce the spreading of the disease [17].

Besides, conflicting messages came from authoritative sources undermining the same efficacy of the actions taken.

As a result, the compliance at the beginning was scarce, with people ignoring the public health indications and in some cases the rules imposed by the law. On the contrary, the voices of people with no specific knowledge on the problem spread in the media, prompting sometimes harmful behaviours or establishing wrong beliefs and prejudices, that science communicators have been almost unable to refute.

Mass Media and Public Service Response to COVID- 19

The role of mass media has dramatically changed over the last century. The advent of the Internet is only the last frame of a longer motion picture, in which different scenarios can be portrayed. The awareness that people must be involved in the scientific discussion is not novel [18]. However outdated, the idea of scientific divulgation as a top-to-bottom education is still present and, in some cases, useful.

In a world were scientific discoveries and their technological implementations can deeply affect the lives of everybody, everyone has the right to participate to the public discussion.

On the other hand, complex scientific ideas cannot be transferred to the general audience as they are, but have to be translated in a simpler form easier to understand. In this process, however, most of the implications can be lost in that same translation. Conversely, some of the consequences of the adoption of models that come from complicated scientific concepts—which can affect

the lives of many—cannot be fully understood by academics that consider only the theoretical side of an application.

In this process, mass media can be a source of reliable information that in a univocal way can reach a great number of people in real time, without the interferences that can come from an open forum or discussion where all the speakers are considered on the same level, even when they come from very different backgrounds.

Television, radio, or newspaper can thus present in the proper way that vital information that can help people to adopt effective measures to address a crisis. The advantages are mainly the reliability of the source of the news, as the more the media are known to the public, the more the content is considered reliable; the more they made use of professional means and workers that can treat the information translating it into a language that is compressible for the general population, the more the possibility to reach an enormous number of people promptly and in the same time. On the other hand, if the information is not accurate, and facts are not properly checked, people can be misinformed, and because—as we have seen—major broadcasters are generally considered reliable, the level of misinformation is higher [13] and bigger than the one produced on social media by user-generated contents.

Two major bias can however weaken this model: the need for a scoop that can improve the visibility and consequently the revenue of the media, and the use of sources—however authoritative—that have no specific knowledge on what is going on, or that do not have specific training in science and risk communication. In fact, even when the content of the message is accurate in scientific terms, the way it is delivered can create misinformation in the general audience. Besides, in this form of communication, there is no specific target the message can be tailored to. This represents a major limitation. Broadcasting a one-size-fits-all message can create different effects depending on which portion of the population media refer to: a more accurate information might be understood only by a portion of the population, which may be represented by people that already have knowledge on the matter. The more media simplify the message, the more the subject can be understood by a larger number of people. However, following

this approach, most of the original content may be lost. Media should be able to find a right balance producing at the same time useful advices and reliable in-depth analysis, always keeping in mind that in a novel infection, a lot is unknown and predictions are often futile. Yet, this represent a specific field of communication, and it needs of professionals specially and specifically trained in health education, science communication and risk communication. In addition, in case of a maxi-emergency, mass media must strictly follow the indications that should come from the risk communication teams of the local and international crisis management units. These teams must be made by professional equally trained in those specific fields of communication, whilst decisions on what and how to communicate scientific and medical facts must be coheren whit wathever measures have been taken to cotain the pandemic and must be part of a holistic strategy.

Social Media: Inconveniences and Lost Opportunities

Social media are known for being a potential source of unreliable and misleading information. This is because of the very low entry threshold that allows everyone, even without specific professional competences or a proper education in journalism and science communication, to publish contents that can potentially reach billions of people. Without the filter that professional journalism imposes in retrieving the news, checking facts and sources, and editing the material, and without the regulatory consequences that came with the spreading of false news, the quality of the published contents is at least controversial [19]. Besides, the flow of information published and the number of user-generated contents produced creates an overwhelming wave of information [17], known as *infodemic*, that induces the audience to surf over the messages, skipping any point considered redundant or simply too long to read [20]. In the case of the COVID-19 pandemic, that produced only an approximative and often misleading picture of the reality that together with the other source of misinformation had led to inappropriate or dangerous behaviors.

On the other hand, an oversimplified model and the easiness of use, together with the directness of the communication that comes from a peer, help the message to reach also that audience that is normally ignored by the conventional broadcasting systems. In addition, a significant part of the population, as the teenagers or the young adults, nowadays do not access anymore the traditional media and prefer the social as a first source of information. Moreover, information seeking behavior can be common in people with a higher education that often rely on what they found on the Internet through their personal searches, while social media remain a source of information also for healthcare workers [21, 22].

During the onset of the COVID-19, social media have been used by professionals and non-health professional users to discuss the early stages of the epidemic, the characteristics of the virus, or the worldwide implications of the new disease.

Many professionals skipped those forums conventionally used to foster scientific discussions and provided their often unsolicited insight offering comment, indications, and solutions that were based more on personal believes rather than scientific evidences. At the same time, people with a nonmedical background expressed their comments trying to level their argumentations to the one of the experts.

As a result, the target of those messages, the standard users, received information and afterward reposted information with or without personal addictions that had nothing to do with the reality.

Even those professionals that produced reliable contents ran the risk to deliver confounding or improper messages that created prejudices or false convictions in the people, weakening the efficacy of public health interventions based on evidence-based principles.

Because of the lack of a coordinated risk communication plan, aimed to productively involve also big Internet companies, social media failed to offer an alternative solution, able to properly reach people that normally do not have access for a number of reasons to the mainstream information. Moreover, social media can make possible the stratification of the audience, so that the same message can be delivered in different ways, tailoring the communication to specific persons or cadres of people.

Again, these potentialities have not been used or boosted, and vice versa. Most of the posts published on COVID-19 are user-generated contents, with no scientific basis, or, even when accurate, impossible to distinguish from unreliable informative materials.

Of course, social media cannot be completely regulated and its contents censured, because that would mean a suppression of some of the fundamental human rights. Yet, because of this unprecedented health crisis that has dramatic and unpredictable repercussions in all the aspect of the human life, social media should become a means to deliver reliable information that should stand to the same principle of public service as the conventional media.

However, as every user should be responsible of the contents posted on the social media, in a proper campaign of risk communication, health and institutional authorities should inform with the proper means people on the risk of spreading untrustworthy or unverified information or creating unwillingly prejudices that can become extremely difficult to address afterward. Therefore, people should become aware that any post—even when the message is correct and even when the action is based on goodwill—if not properly delivered can prompt people to adopt improper, risky, and potentially dangerous behaviors.

Besides, international health institutions and government should exploit the potentialities of social media and the ability to address specific target with tailored and reliable messages, providing accurate information aimed to prompt correct behaviors to specific clusters of people. In particular, the youngsters are keener to use this new communication approaches, rather than the more conventional ones. Young people, in addition, willingly accept information that come from their peers or the one delivered by well-known testimonials so that a customized communication strategy should be made available to reach also those ones that normally do not read the news in the papers or do not hear them from television.

This may be crucial, especially when it comes to the design of a preparedness model, when the perception of the risk is much lower than in the acute and exponential phase of an epidemic.

Yet, it is not possible to merely translate the contents produced for the mass media and broadcast them via the social media. On the contrary, experts in communication via the Internet and the news media

should be asked to join the team and to provide valuable information for the production of an effective campaign for prevention.

Risk communication is indeed a risky matter. Nowadays, it is extremely difficult to control the spread of information even and especially when the source is within a national or international health institution. Because of the onset of this new communication era we are living in, every comment made in public can potentially reach every corner of the world in matter of seconds. The definition of public in fact is different from the past: it can refer to the general audience, which can be reached through the mass media, or to a restricted circle of people, which can be reached privately via the common communication apps and devices. The target however is potentially the same, as a comment delivered to a private chat can become viral afterwards and virtually spread worldwide.

This is particularly important when the messages come from professionals with a specific authoritativeness on the matter or that have a role in a major national or international health institution.

International Health Institutions and Communication Strategies: Lessons Learned

A pandemic is an event that like few other issues is of public and general interest, as it can affect potentially everyone on the planet. Thus, decision, actions, and behaviors taken in a specific location can have effect on millions of people somewhere else in the world.

For this reason, the effort in terms of preparedness, readiness, and response to a pandemic should go beyond the physical and political borders and need of cooperation among the nations and the different institutions involved in the response to the crisis.

Communication therefore should be coordinated and effective to produce effective and cost-effetive actions aimed to reduce the spread of the virus and to contain the effect of the disease in those people already infected.

However, no risk communication strategy may be of any use, if a prompt and ready response is not available and if the international institutions fail to deliver the right messages, through the right way, to the right people.

During the 2020 COVID-19 pandemic, people received a number of often contradictory messages from different institutional sources. Major international health institutions failed to provide a guidance and governance, so that no risk communication plan was in place [23]. That produced no coordinated actions, while several authoritative sources (private researchers, medical doctors and healthcare workers, heads of health institutions, politicians, nation leaders) delivered—mostly good willingly—unreliable information, based on personal ideas or political reasons.

The communication strategies failed to provide some of the key issues:

(a) This was a novel disease that scientists and health policy makers did not know anything about. People should be made aware that any idea of the disease was based mainly on speculations based on models and knowledge that might not fit the actual scenario.
(b) What were the implications of a new unknown disease spreading around the world, and what possible scenarios people would be likely to face in the short, medium, and long term?
(c) What measures were needed to prevent—to the best of the knowledge of the time—the spreading of the disease, and what action people were asked to take and based on what principles, making clear that any suggestion might be changed according to the new findings?
(d) What measures were needed and were likely to be taken and why, and what would possibly be the scenarios if such measures would not be taken promptly or according to a given timescale?
(e) Necessity to create a tailored communication strategy to address specific target (e.g., research institution, healthcare providers, media, politicians and decision-makers, general public).

On the contrary, some information has been delivered without a second thought with no foresight on the consequences of a poorly delivered message. In particular:

(a) Messages that gave contradictory information on the nature of the new disease delivered from authoritative sources.
(b) Panicky messages that presented worse case scenarios, with no other guidance offered to help decision-makers and the general public to prepare for what measures were needed to contain the epidemic.
(c) Epidemiological data and forecast broadcasted with no explanation on their meaning and on the limitations of the same data.
(d) Messages coming from authoritative sources that minimized the problem, with no data or scientific background to support those statements and that resulted in unhealthy behaviors in the general population.
(e) Publication of guidance and recommendations by authoritative health institutions or politic offices that have no or limited scientific background and that were likely to be reported by the media and that could potentially produce ineffective measures delivered by local health authorities or unhealthy behaviors in the general population.
(f) Messages suggesting not useful and potentially dangerous solutions that contradicted the state of the art on the management of COVID-19, coming from scientific and nonscientific, although authoritative, sources.
(g) Messages provided from experts that had no specific role in the management of the epidemics or of the clinical governance of the same.
(h) Messages provided from experts that had a specific role in the management of the epidemics or of its clinical governance that had only limited access to general information, using the limited scenario they operated in to discuss the whole complexity of the pandemic.
(i) Messages provided by scientists with no specific expertise on the matters they referred to (i. e., virologists that presented public health issues, immunologists that talked about epidemiology, physicians that discussed health policy models).
(j) Head of health institutions or with a specific role that eagerly appeared on the media providing unreliable or unconfirmed information, based on personal ideas rather than scientific evidences.

(k) Health professionals and head of institutions or politicians with or without an active role in the management of the crisis that bypassed any possible risk communication plan using social media to deliver their personal ideas that were mostly not supported by scientific evidences.
(l) Panicky messages by angry, scared, or tired health professionals directly involved in the management of the crisis and shared mainly on social media, and sometimes republished by mass media, that portrayed only a partial and subjective picture of the whole scenario.
(m) Dangerous or wrong behaviors or nonverbal communication shown by health professionals, mostly unintentionally, and widely broadcasted through the media.

These awkward approaches to risk communications although apparently harmless can have a deep impact on people, creating prejudices or wrong impressions that are very difficult to address later and that produce consequences. In addition, every messages on the nature of the disease, or on the pharmacological and non-pharmacological measures used to fight the epidemic, can affect the risk perception of the audience, incepting harmful behavioural patterns both for the individual and for the community. What happened in terms of prompting self-harming, unhealthy, and irrational actions in the population, with the delay in general face mask use, the endorsment of potentially dangerous medications, or the alleged side effects of some anti-covid19 vaccines should be considered paradigmatic.

Once a prejudice is established in the general opition, in fact, any attempt to deliver health educational messages, or information aimed to elicit behaviors useful to fight the spreading of the disease or reduce the effect of the infection on individuals or on a community, might contradict what facts people consider already proven or what knowledge has been already taken for granted.

The key message is that any communication aimed to produce results during any emergency and particularly during a pandemic, where everyone is potentially exposed to a danger and everyone can contribute to increase the risk, must be coordinated.

The idea that whoever delivers a message is responsible for the contents and the effect that it produces should also be part of the

communication campaign, especially when there is a guidance available and professionals deliberately decide to ignore it. In addition, experts and authoritative people showing even unintentionally wrong behaviors to the public produce a message able to trigger the same behavior in the population and often contradict whatever message the professional is trying to deliver (i. e., give an interview to national television explaining what measures are in place or reduce the spreading of the virus while not wearing a face mask or wearing it in the wrong way). On the contrary, no one should be to blame if a top-to-bottom communication strategy is not in place and if there is no preparedness plan available to face potential emergencies.

Thus, international health institution must produce a risk communication model that takes into account the criticalities shown by this pandemic and that must be made available in case of future infective worldwide crisis.

Communication Bias that Can Produce Inappropriate Behaviors in the Population

The main role of risk communication is to inform people that a risk exists so that adequate measures can be taken by individuals and communities to reduce its exposure or effects; thus, communication has to deal, among others, with two main aspects: the awareness and the perception of the risk [24]. Risk perception is subjective, as well as what a risk is, whether it is acceptable or not and whether the measures and the change in behaviors needed to reduce such a risk are acceptable or not [25–27]. This perception depends on several factors among which cognitive, emotional, social, and cultural ones, and on differences between individuals and different countries [28]; even when facts are correctly exposed with transparency and from trustworthy sources, the reception of the information is not univocal and varies among people. The same perception of the likelihood of an event or danger to occur and its severity depend on several factors [29] that are not univocal and that change according to the people's personal and social background. In addition, people that are exposed to a potential danger react differently according to the stage of the crisis, to how media present the facts, to the level of panic generated by the evolution or

escalation of the crisis (often presented according as a worst case scenario), or to the spatial distribution of the events (and therefore the likelihood that a hazard can touch the community people's live in, as well as their acquaintances or their relatives).

For these reasons, it is important to understand how people perceive the risk, using any means available, to understand how people react and understand the risk and its implications, and what issues they are more sensible to, monitoring at the same time how the information is delivered around the world [28, 30–34], so that the communication campaign aimed to present such a risk to the population could be effective. This is crucial to prompt an adequate response and the adoption of behaviors able to contain the spreading of the infection [35]. Moreover, the communication strategy should fit the actual epidemiological scenario and be consistent with the objectives of a preparedness plan [36].

Table 16.1 reports some of the common mistakes made by professional and nonprofessional communicators, that should be addressed in the design of a risk communication strategy.

Principle of Risk Communication in a Pandemic

A pandemic refers to an infective disease that can spread all over the world. However, as society evolves and globalization occurs, the idea of what a pandemic is changes accordingly. We can thereof define a pandemic as the spreading of an infectious disease characterizes by the following features: wide geographic extension, disease movement, high attack rates and explosiveness, minimal population immunity, novelty, infectiousness, contagiousness, and severity [37]. Thus, a pandemic is a grave event able to deeply affect people's lives worldwide.

According to this basic concept, a pandemic represents an event that is of general interest, that involves people from around the world despite their role or their social and economic status, and that can affect the lives of people and of nations if proper measures are not taken. In this sense, a pandemic has to be considered an emergency that needs prompt action and has to be taken as hazard for human health with potential effects on all the aspects of the human societies.

Table 16.1 Common mistakes and communication bias that could affect the quality of risk communication. Those fallacies are known to reduce the effectiveness of the communication strategy in place or to triggering dangerous behaviors in the population

Action	Main features	Main consequences
Delivering the **right message** in the **wrong way**	The contents of the message are accurate and facts correctly checked	Although the facts are correctly presented and the contents are accurate, the message generates a wrong impression or perception of the reality
	Facts are presented by professional communicators or broadcasters or via social media as user-generated content	Part of the information can be missed or the focus of the information diverted to less relevant matters
	The message covers only part of the whole information or the way the message is delivered that produces a false or ambiguous perception or can be understood only by a part of the audience or vice versa misunderstood by part of the audience	People focus only to those facts that appear relevant to them, ignoring anything else
	Communication bias can be present, unwillingly or willingly distorting the content of the message; facts are intentionally or unintentionally presented in an ambiguous way; some aspects are particularly stressed, while others are partly or totally neglected; elements that may not be relevant are highlighted diverting the focus of the message on aspects that are not relevant	The focus of the message is moved from relevant facts to irrelevant facts

Table 16.1 (continued)

Action	Main features	Main consequences
	The information presented may not be relevant but might prevent the delivery of messages effective in creating awareness or in prompting adequate behaviors	The message creates a prejudice that spread rapidly in the population, preventing the diffusion of more accurate messages
	The information presented may not be relevant but may create panic or otherwise can be too reassuring	The message is not capable to prompt behaviors able to reduce the spreading of the virus and the effect of the infection, or vice versa, allowing or promoting behaviors that are irrelevant in terms of infection and disease control or that are potentially dangerous
	The information provided may refer to a specific context or scenario but are presented as a general condition	The message became popular, and people adapt the contents to situations that do not match the one it refers to
	The information provided may refer to a generic condition but are used to present a specific situation that does not match the same reality	Some behaviors may become accepted by the population even if they are not useful or dangerous, while others that are effective or innocuous are improperly stigmatized

(continued)

Table 16.1 (continued)

Action	Main features	Main consequences
	Some of the terminology used can be ambiguous or inappropriate	The interpretation of data presented can appear distorted, even when data are correct and accurate, so that the reading does not match the reality or the evolution of the crisis, creating a false or distorted picture. This can promote the adoption of useless behaviors, distract people from the real problems, restrain people to adopt useful behaviors, or push people to dangerous habits or behaviors
	Data are presented with no interpretation or with a wrong interpretation even when they describe complex situations that can be understood only by professionals	The panicky content of the message is not balanced with useful information, so that a proper preparedness plan can be delivered to the population
	The message may provide panicky information or can scare the population avoiding to give useful information	Projections create false hopes or panicky pictures of the reality, reducing the efficacy of a more proactive communication
	Unrealistic predictions and projections are presented starting from accurate data	Messages with redundant information or too technical or presenting a large number of facts are ignored by the general audience that prefers clearer and shorter messages even when inaccurate
	Too much information is delivered at the same time, so that the key messages are missed	Poorly presented statistics, even when accurate, are ignored because of data conflict with whatever knowledge a person or a group of people already have

Table 16.1 (continued)

Action	Main features	Main consequences
	Professionals use technical terms that may not be understood by the general public	When the consequences of reported data are likely to produce measures that conflict to people's interests, people prefer to ignore the information, even when clearly accurate, because the measures introduced by decision-makers are not acceptable in their opinion or are considered more disrupting, dangerous, or damaging than the virus itself
	Data are presented to individuals or groups of people that have prejudices that conflict with the information covered by the message, without addressing in an effective way and at the same time such prejudices	
	Information on measures needed to reduce or prevent the spreading or the effect of the virus even when correct are reported without addressing the risk/benefit assessment and what are the consequences if such measures are not implemented	
	Authorities or experts may perceive the risk differently from the general audience they refer to; thus, the message delivered does not take this aspect into account	

(continued)

Table 16.1 (continued)

Action	Main features	Main consequences
Delivering the **wrong message** in the **"right" way**	The content of the message is incorrect, the facts not checked, or the data inaccurate or completely wrong	Facts are presented in an effective way, so that the message is rapidly accepted and spread among the population, promoting wrong behaviors or making ineffective any other attempts to present the problem correctly
	Facts are mainly user-generated contents published on social media or willingly delivered by public figures, institutions, or professional broadcasters for specific purposes as distorting the reality for political reasons	The more authoritative is the source, the more difficult it is to deliver a correct information that contradict the content of the first message
	The message appears accurate and the contents consistent with the reality even if the data do not match the truth or facts have not been checked or present only a very limited context that cannot be representative of the whole or of other situations	Malicious messages can be delivered to the populations by those that want to take advantage to the situation
	The message can spread easily especially if the source is an institution or a relevant or authoritative broadcaster, becoming a fact widely acknowledged by the general audience	Messages with a right content delivered to the population in a not so effective way are less convincing than these other messages, proposed in a good way even if wrong, creating confusion or pushing people to refuse the right information favoring the wrong one

Table 16.1 (continued)

Action	Main features	Main consequences
	Nonverbal communication willingly or most often unwillingly promotes wrong or dangerous behaviors even when verbal communication is sending the right message	Facts reported only partially, or facts based more on personal beliefs and that are not supported by evidences, show a misleading scenario, pushing people to adopt wrong behaviors or to ignore those messages that may reduce the spreading and the effects of the virus
	People delivering the message cherry-picked the information, presenting only part of the facts and deliberately or unwillingly hiding relevant information that may change the whole sense of the same message	
	Some contents are generated by authoritative professionals who deliver—In good or bad faith—Information based more on their beliefs rather than on scientific evidences or proven facts	
Delivering the **wrong message** in the **wrong way**	A message whose contents are incorrect is presented in via social media or other mass broadcasting systems, reaching a great number of people	Facts are inaccurate and may be not so convincing in the way they are presented, but because they ring a bell, people are particularly sensible to, given the context and the general scenario

(continued)

Table 16.1 (continued)

Action	Main features	Main consequences
	The message, although not produced by authoritative sources or not so effective from a communicative standpoint, spread easily and often virally through the population, so that almost everyone is aware of such a message	Because the message can reach a great number of people, even if not so effective, a considerable part of the population considers it actual
	Messages are repeated over and over again, so that they become common knowledge even if the contents of such messages are wrong	People reinforces their beliefs even when they are wrong or when those do not correspond to the actual facts, because any part of the information that conflicts with what people know or think to know is ignored. The repetition of a same massage especially when it comes from different sources create an "urban legend" that becomes a given fact, even when it is based on conjectures or do not have any fundament
	A wrong information is shared among a group of people and accepted, so that individuals belonging to such a group avoid to consider alternative options	Information presented by very authoritative people—As world class experts, famous artists or sport idols, politicians, or well-known people in general—Can be considered actual or reliable by a wide part of the population just because of the source, even when the message is clearly untrustworthy

Table 16.1 (continued)

Action	Main features	Main consequences
	Only information that are consistent with what people believe are searched and presented, even when it is clear that the message contains only part of the truth	Information found on the internet or shared via social media or virally via messaging apps are considered actual by a number of people just because they are on the internet. Those same people often share such information to other people creating chain messages. People receiving the information in such a way are keen to believe the content of the message, even when clearly inaccurate or deceptive, because they personally know the sender or because they share a common background
	A clearly wrong message is presented in a clearly unreliable way but by very authoritative people	
	Unchecked facts may be reported by people with clearly no knowledge of the issue	
	Messages can be presented or perceived as too panicky or too reassuring, because the information and the way the information are presented are flawed	

Table 16.2 Main objectives of a risk communication campaign designed to prevent the event of a pandemic. The scheme follows the model applicable also to other context of public interest [2], with a special focus on the worldwide implications of the diffusive nature of an infectious disease

Individuals	Societies
Protect an individual and people related to a single subject	Protect one or more interconnected societies
Prevent exposition	Prevent or reduce the exposition to a cluster of people or to a society
Prevent damages of an exposition Prevent the spreading from individual to individual	Prevent the spreading of the disease when cases are already present in a society
Reduce the effects and the damages of an exposition	Reduce the effect and the damages on public health and social and economic level in a population exposed to the risk
Increase the awareness of individuals and prompt correct behaviors to reduce the spreading and the exposure to the disease	Increase the awareness of a society and prompt social measures aimed to reduce the spreading of the disease and to safeguard specific and general interests of a society

Risk communication has a central role in the response to any emergency that can impact human health [38], allowing a knowledge transfer among professionals involved in the management of a crisis and between professionals and institutions and the general population. The main role of risk communication is to inform that a risk exists creating awareness and pushing people and institutions to take action in a proper and sustainable way. The endpoint is to foster the adoptions of measures and behaviors able to contain or limit the risk, balancing the need to protect individuals and societies and the national and international interests [39] (see Table 16.2).

Risk communication generally refers to a specific risk that may be limited in the time and space or that can potentially occur over the time and in different settings. This requires a level of preparedness of the institution and the population because people should be ready to understand the problem so to take proper measures to achieve an effective result. Because risks are based on probabilities and represent a forecast of pos-

sible outcomes (secondary to an event, an exposure, or a specific situation), people may not willingly accept actions that may limit their behaviors when a danger is still potential and not clearly present.

When it comes to infectious diseases, however, there may not be a clear definition of boundaries that limit the possible event to a specific time or place where it can happen. In addition, any novel virus that emerges can potentially produce a pandemic, whose outcomes are not predictable.

This produces two main issues:

1. People may not be receptive as the danger is considered remote and any action promoted to reduce the risk futile, redundant, dangerous or inacceptable.
2. The information provided are incomplete and vague, and they are likely to change over the time.

That same information can be perceived as contradictory by the general audience if the communication strategy does not address properly the lack of reliable data. This uncertainty however is inevitable because any emerging disease is mostly unknown at the beginning, and most of information provided are based on observations on similar event or pathologies in the best case or on mere speculations most of the time.

Moreover, even in an evolving picture, people may consider someone else's problem an epidemic that is happening far from their homes, even if the likelihood that the virus can reach them is high in epidemiological terms.

For this reason, the four principles of risk communications should always be taken into account, namely, *openness*, *transparency*, *independence*, and *responsiveness/timeliness*.

Following these recommendations, the communication strategy used to prepare people, present the risk, and promote the adoption of proper behavior in the population must be coordinated and must actively involve all the actors involved in the management of the crisis, including the media that have the ethic and deontological duty to inform people for public health purposes rather than commercial ones (following a principle of public service and major public interest).

The information provided should be able to create awareness aimed to promote actions in the singles and in the populations that are consistent with what measures are needed to reduce the risk of exposure and to contain the spreading of the virus. The message should be easy to understand and multilayered so that people coming from different cultural backgrounds or that perceive the risk differently [28, 33, 40] can receive an effective communication able to promote measures and behaviors that can reduce the spreading and the effects of the virus. The same measures introduced to contain a hazard must be clearly explained as well as the principles of cost-effectiveness and of risk-benefit ratio, avoiding to stress those issues that can distort the risk perception of the population, eliciting paradoxical behaviours (preferring a high risk solution to avoid another solution that has potentially no risk but that is wrongly perceived as unsafe).

In addition, the intervention must be coordinated at international level: single nations should have in place communication teams and rules to produce information that can ratify the indication provided by major international health organizations. Those same organizations should have in place a feedback model to modulate the contents and the aims of the messages published or broadcasted according to: the population response to the information and to the crisis; the gathering of new information on the disease coming from research; the geopolitics of the epidemic; and the evolution of the general scenario.

Finally, although the emergency requires mainly a top-to-bottom communication approach, the discussion should remain open, with those in charge of the risk communication strategy ready to listen to any reasonable request that come from the bottom. This is crucial to define a working model and to verify that the messages delivered are effective and that have been translated in actions able to reduce the exposure to the virus and contain the infection.

Conclusions

A good risk communication strategy is essential any time people are exposed to a danger. This is not only because a population has the right to know what is going on in a clear and

transparent way but also because information provided in the wrong way or not provided at all can trigger harmful behaviors and can frustrate any effort made to implement those measures needed to face the crisis.

On the contrary, when information is accurate and delivered correctly and in a transparent way, addressing any issue and any aspect involved in the story, people are keener to accept whatever measure is needed to protect themselves and those they care to.

This also means that the message must be produced and broadcasted in an understandable fashion and tailored on the different targets it refers to.

The implementation of a coordinated communication strategy has to be promoted by communication professionals with a specific expertise in risk communication and with the interaction of professionals belonging to different areas of expertise (e.g., virologists, biologists, infectious disease specialists, public health specialists, health policy makers, sociologists, psychologists, economists, statisticians, mathematicians and prediction models' specialists, disaster management specialists, journalists, experts in people and goods movement and migration, bioengineers, researchers). These professionals should be involved in task forces whose aim is not to find a solution to the pandemics but to create a communication plans where all the information provided are reliable, where the facts have been checked and are tailored to the different audiences the messages are aimed to, from the decision-maker to the general public. The task forces had to be coordinated by an expert in science communication and in institutional science communication, able to help the different experts to transfer their knowledge to other professionals that do not share the same background. The task forces should provide a guidance that any professional should follow when addressing the general public or specific groups or clusters of people.

It is however paramount that the general welfare is preserved and that the interests of those that aim to exploit the pandemic for their own sake are put aside, because during an event able to disrupt people's lives for generations, no one should be allowed to follow personal profits or returns.

Press and mass media have also to be cooperative, making any possible effort to deliver messages that can promote healthy

behaviors and lead people to take any measure needed to control the spreading of the disease, using their knowhow and their means to produce effective communications, coherent with any risk communication strategy in place. Any communication bias should be addressed avoiding to broadcast any news or information, no matter how sounding and tempting it may be, that could lead to wrong and dangerous behaviors or that could interfere or make ineffective the efforts made by health authorities worldwide.

Finally, anyone should become aware that we live in a time where communication can spread from one place of the world to its opposite in matter of seconds and that once the information is out there, little can be done to call it back. Therefore, any one should pay attention, with a special mention to health professionals, in disclosing, producing, publishing, sharing, and spreading information, even when moved by good intention, as the effects of a bad communication can be as devastating as the pandemic itself.

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17 Lessons Learned and Future Perspectives

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Scenario

It is September 2020. The pandemic turned into an endemic in the entire world.

Nobel Laureate J. Lederberg, referring to struggle against microbes, wrote "It's our wits versus their genes"*;* our intelligences have been used so well that now we are losing the battle and we are even in danger of losing the war.

This last hypothesis (the worst-case scenario) must be considered and feared, as written in the manuals of Disaster Medicine and Management of Mass Critical Events. The optimism and hope placed on vaccines that we do not yet have must not let our guard down.

So far, no fundamental lessons have been learned because the reactions of various governments and research institutes have

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been chaotic and inconclusive. The world has not been able to plan a common research strategy, and if there is any progress, it is due to individual groups of experts and researchers.

The battle among the species is not only fought between viruses and humans: today we are witnessing a somehow Darwinian selection also in the fields of studies and research. There is an incoherent amount of unnecessary research among which it is hoped that something useful can emerge before the virus has won the war or otherwise done incalculable damage by subverting the organizational and social structure of the whole world. We should better use our intelligence, not just to understand the enemy but also to invest research resources consistently and rationally.

Indeed, the only lesson we can learn derives from the almost *total absence* of *scientific lessons to be learned*. And this is: the community of health researchers should adhere to a worldwide alliance, exactly following the example of what is done by nuclear physicists around the world, after the atomic and World War II, who created CERN by sharing research strategies. This unifying policy has paid off and made huge strides. If this will happen, the "COVID Bomb," which to date has made four times more casualties than the nukes of Hiroshima and Nagasaki, would produce a truly useful result for the mankind.

Know the Enemy

1. About viruses, we lack a lot of basic information about the dynamics of selection growth and survivorship of their various types, their outbreaks in the context of evolution, and their relationships with guests. The research to clarify these points is crucial but cannot be planned in a few months (particularly in emergency situations).
2. We see, however, that regarding SARS-CoV-2, we still did not produce even the *minimum* research to acquire a *simple* knowledge or know-how, for example, the viral load (VL), the resistance of the virus in various environments, its ability to infect, and other similar information useful to physicians.

Some authors have recently pointed out "the potential risk from environmental contamination in managing COVID-19" and the consequent need for truly effective tools, like the personal protective equipment (PPE) [1]. In a first study highlights the presence of infecting viruses on surfaces touched by COVID-19 patients and recommends a prompt disinfection [2]. This study, however, was carried out only on a few environmental specimens. Environmental research studies of the virus in general are few, and the results often do not directly correlate with clinical parameters, even when there were "natural laboratories" suitable for this type of study (e.g., the confined environments of ships). Something more reliable results have been obtained in particular cases, for example, the *Diamond Princess* cruise ship, the subject of dozens of publications [3], from which quite useful indications have been retrieved.

The lack of information about the persistence of SARS-CoV-2 in the environment has led to uncertainty and also to the failure in taking the appropriate measures for its containment [4]. The same authors note that there is not enough literature on the subject and that "scientific strategies are moving toward therapy and diagnosis, rather than knowing the characteristics of the virus."

3. The initial studies of Kampf [5] and van Doremalen [6] remain fundamental, but they have not found sufficient confirmation studies and have not been translated with sufficient attention and strictness into operating indications.
4. We still have very little information on the VL also in the course of severe acute respiratory syndrome [7]; it has been suggested that the reduction of VL is also a crucial issue in intrafamily transmission at home [8] and should be better controlled. Methodological difficulties (and the absence of studies to overcome them) make it very difficult to define both the amount of viruses emitted and infecting according to the different localizations of the virus, the stages of the disease, sensitivity or resistance to contagion by the host, and other variables.

Some 50 articles have been published on the SARS-CoV-2 VL, but it is difficult to deduce practical information. Some studies correlate VL with the serodiagnostic pattern and suggest that it may have prognostic value [9], while others try to define its relationship between VL and mortality or severity of the disease [10, 11].

5. A study that examined the virus concentration in aerosol samples and on environmental surfaces, in a hospital intensive care setting, would demonstrate that a "strict implementation of virus countermeasures" can be effective to control the risk of hospital cross infections [7]. The results of this kind of studies are strongly influenced by the environment in which they are carried out, as well as by the specific type of prophylaxis or protective measures adopted (e.g., as a specific PPE, what type of disinfection, in which date, how, how much, so on), and therefore these results are more difficult to transfer to different situations.
6. These technical data need to be better and more thoroughly studied. It is not conceivable that for a few months, it was explained to the whole world that the most effective protection measure (and the first in all lists) was to "wash hands with soap and water," only to discover that the virus resists for 5 min (a very long time) to soap [12]. Fortunately, today most messages suggest washing with alcohol-based gels or other disinfectants.
7. Finally, very few investigations have been planned also to "see" and study in vivo and in vitro viruses, and mostly they imply traditional methods of analysis, which are not always suitable for applied and basic clinical research. The virus remains an unknown, despite some triumphalism of molecular geneticists.

Know the Human Host and His Reaction Toward the Virus

1. Many studies have been oriented to the description of the clinical picture, with an obvious selection bias toward lung symptoms, which probably affected the outcomes of some clinical

research and which, in the territory, caused a high number of extra deaths for other causes (cardiovascular, in particular) initially underreported. The lesson learned in this case is obvious: "you live and learn" but it is not a boast to proclaim it.

A certain insistence on the symptoms and evolution in the lungs, associated with the obligation to make the diagnosis of certainty with Rt-PCR (considered—and in some cases imposed—as a *unique* diagnostic tool), has in fact facilitated this huge initial bias, also because Rt-PCR and qPCR performed on swabs of the high airways obviously confirmed "only" cases of airway infection with the presence of viral RNA in mucous or salivary fluids, so it lets classify COVID-19 as respiratory disease. As mentioned, this was a huge methodological error, highlighted and stigmatized by many clinicians but not received by public health experts and regulatory authorities who, especially in the first phase of the pandemic, have target research and resources on only one direction.

The symptoms are highly nonspecific as ever and have very low sensitivity and specificity. The WHO and many other national institutions propose diagnostic flowcharts based on symptoms (cough, breathlessness, etc.) and the presence of fever or the combination of fever and cough [13]. It can be understood that the use of symptom tables is a necessary step, but patient empowerment and guidance for healthcare professionals and regulatory authorities *cannot be based solely, or primarily, on this strategy*, even if associated with viral RNA research.

An important lesson was provided by the Cochrane Collaboration, which concludes that the individual signs and symptoms "appear to have very poor diagnostic properties" [14]. In fact, according to the available data, neither the presence nor the absence of symptoms is accurate enough to possess a diagnostic value. Moreover, the potentially most useful symptoms (anosmia and ageusia) are the least studied and not included in many diagnostic flow charts.

On the other hand, symptoms do not even have a prognostic value, except for dyspnea, the appearance and intensity of which correlate with the admission in intensive care unit [15],

as—we think—any physician would have hypothesized without the need for specific research.

2. Some authors, however, suggested to use a wider spectrum of criteria, integrating clinical, laboratory, and instrumental parameters together; for example, to facilitate diagnosis, a study proposes to consider fever and shortness of breath or dyspnea, associated with laboratory tests (WBC, AST, Cr, PCT, LDH, Hs-cTnI, and D-dimer) [16]
Paradoxically, in this and other similar papers, the main diagnostic integration is missing, that is, the one with the serological data. Conversely, patients should be thoroughly studied with all the parameters that directly or indirectly can express the individual defensive capability.

Some groups of clinicians have strongly suggested to always use this strategy (which in medicine is simply called differential diagnosis) and to think according to the gold standards of clinical methodology and starting from the inception point [17].

In fact, although the serological response to SARS-CoV-2 is very peculiar and with a certain degree of variability, both between individuals and over time [18], identifying specific antivirus antibodies undoubtedly remains the main diagnostic weapon for clinicians facing differential diagnostic problems. Several groups of researchers who have studied VL also recommend that analyses should always be completed with serological tests [9, 19].

In this case, there is another lesson to be learned, and that has a cost in terms of a not small intellectual sacrifice: in fact, we have stupidly conceived an alternative use between serological tests and direct genetic tests (qPCR). Indeed, these are two complementary analyses to be carried out together, always with the assessment of the specialist and the physician and not by virtue of some generic guidelines. Authoritative research institutions and public authorities require for serologic tests that are very highly sensitive and specific, even in the absence of a reference gold standard. Also when using qPCR, one has to hypothesize the possibility (albeit remote) to get some false positives. Above all, it must be stressed that in some settings, qPCR sensitivity resulted to be less than 50%; several studies

have tried to improve it, for example, by using the technique of multiple assays [20, 21].

In short, the epidemiological perspective (how virus spreads among the population and when and how it mutates) has been confused with that of individual diagnostic, which has quite different purposes and is a responsibility of the physician, not of the public health authority.

3. This is one of the main causes of underestimation of the actual spread of the virus and has reduced the ability to identify patients with extrapulmonary viral disease. In the emerging phase, this absurd and unjustified attitude of some regulatory authorities, together with the uncertainties of the WHO, has reduced the ability of health systems or individual doctors to diagnose other diseases in situations in which COVID-19 was not present or was just a lesser comorbidity.
A paper published in the *BMJ* [22] carried out a systematic review and meta-analysis of the sensitivity and specificity of diagnostic tests, and despite the entirely encouraging results of many studies that declare high sensitivity and specificity (especially when the immune response had time to express itself), the conclusions of the authors are negative and in the comment they write "current evidence does not support the continued use of existing point-of-care tests." The authors perhaps foresaw to get a "perfect" diagnostic test, which can be used alone for diagnosis and do not consider what the consequences—in the real clinical practice—of not having this test available, even if sensitivity or specificity is not optimal.

In Iceland, a very extensive and in-depth survey of the immune response SARS-CoV-2 was carried out, showing that 44% of the infected would not have been diagnosed with qPRC alone, and allowed to better calculate, for Icelandic population, the risk of death [23]. In addition, the authors show that the antibody title tends to remain high for at least 4 months and that a low or absent immune response in a population may suggest a greater probability of reinfection [23]. In other words, and unlike the "regulatory" vision—such as semi-bureaucratic and only guidelines-oriented—proposed in the BMJ [22], the authors of this study consider people with negative serological testing not as false negatives tout court but as more exposed

subjects and therefore to be studied and with possible different prognosis. A recent *NEJM* editorial "The Power of Antibody-Based Surveillance" [24] commenting on Stefansson's Iceland study underlines the importance of monitoring the ongoing immune response of epidemics such as that of COVID-19.

The low sensitivity of qPRC has not discouraged regulatory authorities from their willingness to adopt it as a first (and often unique) reference (the underlining philosophy is that never mind if someone is not diagnosed, but on those diagnosed we want to be sure), while a physician will never accept such a vision in the diagnostic phase, and any test that can help individual diagnosis is especially useful if quick and cheap.

The lesson to be learned is as follows: there are no diseases (no one has ever seen a disease walking down the street) but there are only sick individuals; therefore, using on every patient a "unique scheme" to diagnose a disease is a serious and logical mistake and is contrary to every rule of clinical methodology, as Sackett himself taught. *Caveat*.

Avoid Contagion

Vaccines

The vaccine research has absorbed a significant part of economic and time resources; the discussion about vaccines has also been used as a political weapon by governments and as a "promise of hope" for the people. Vaccine research and development represent the hope of all of us, beyond the misuses that can be made by the media, governments, or other stakeholders.

However, it must be considered that at the beginning of a pandemic of a novel disease: (a) it is not appropriate to focus on weapons that are not yet available; (b) even when vaccines will be available, there will be strategic issues (vaccinate "the world"? All the elderly? The wealthy elderly in some countries? And so on…); (c) and the aspects of cost and real feasibility will not be of little consequence. These and other elements of reflection allow us to say, *right now*, that there will be treats and difficulties much greater than those found in other vaccination campaigns.

From a technical point of view, on a very wide literature panel (a few hundred works published in the last year), it has been observed that a few months after the beginning of the pandemic, some preliminary research has led to fairly optimistic results (we cite some as an example without taking a position on the best vaccination strategy) [25–28], and therefore, to date, we can *only* continue to hope. Then, a series of research issues arose on possible reactions after a given time and on the different course in response to vaccines and on late complications of COVID-19, especially in the lungs. As the vaccination campaign is still ongoing worldwide at the time of the pubblication of this book, and as long as a number of vaccines (second generation mRNA-based vaccines, DNA vaccines, adjuvanted or recombinat subunit or protein vaccines, and so on), we do not have an answer to these questions yet.

Do Not Come into Contact with the Virus

Isolation Strategies Are the Safest and, Even, the Most Difficult Measure to Implement

What we have learned is summarized in a recent systematic review and meta-analysis regarding the isolation measures [29]. Its conclusions, credible and hopefully reproducible in different scenarios, are that social distance has a usefulness but that the "1 meter" as standard measure for all situations is not optimal; however, virus transmission was significantly reduced if physical distance was at least 1 m with respect to a distance less than 1 m, calculating an adjusted odds ratio equal to 0.18, with a 95% CI ranging from 0.09 to 0.38, with a −10.2% of infection/transmission risk reduction (95% CI from −11.5% to −7.5%) [29].

The efficiency of a measure such as social distance also depends on the VL and many other factors (presence or absence of barriers, type of ventilation, and behavior of interlocutor: does he/she cough? Sneeze? Speak? Sing?).

The complete isolation at home of the entire population has been adopted in a few countries and has determined very serious economic consequences and side effects and probably contributed to the increase in mortality for undiagnosed COVID-19 and other diseases. Anyhow, this measure has proven to limit the spread of

the virus. We do not go into an in-depth analysis here: we just hope that outcomes of previous lockdown experiences will be thoroughly analyzed to evaluate if and how to use this practice of seclusion again and how much longer. Maybe, it would be possible to define a maximum lockdown index, based on the previously accumulated knowledge.

A specific aspect of the lookdown strategies is the school closures; some recent modeling studies of COVID-19 predict that school closures alone would avoid only 2–4% of deaths that is much less than other social distancing interventions [30]. This result, to be confirmed for the epidemiological aspects, opens an overly complex legal and ethical debate. The topic is of paramount importance, but it is difficult to create experimental settings to understand which can be the best solution. Hence it will be necessary to collect comparable measures and to adjust them by geographical and social variables.

Quarantine has also been shown to be an effective measure [31, 32]. The figures refer mainly to the 14-day quarantine; in recent years, there have been proposals for shortening yet not justified by scientific data but understandable from the point of view of work organization.

We found that the incubation period and lag between the onset of symptoms and first clinical visit for COVID-19 are longer than other respiratory viral infections including Middle East respiratory syndrome and severe acute respiratory syndrome; however, the current policy of 14 days of mandatory quarantine for everyone potentially exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might be too conservative. Longer quarantine periods might be more justified for extreme cases [31].

Individual insulation can be achieved with masks, as long as they can filter a significant proportion of the infectious material. It should also be considered that, given the resistance characteristics of SARS-CoV-2, the virus capable of infecting it can be transmitted:

(a) From particles like the virus or just wider and then with size ≥0.1 μm.
(b) From aerosols or pollutants of very variable sizes, anyway with an order of a μm.
(c) From very large and flashiest droplets (5 μm up to 50 μm).
(d) To the emission of submillimeter or millimetric droplets of potentially infecting organic material (saliva, mucus, etc.)

In our opinion, it is a very serious mistake to focus only on the points *c* and *d* and even worse if one does it to justify the use of totally inefficient or do-it-yourself PPE.

It is evident that for the different environmental conditions and different degrees of risk exposure, very different protection tools are needed, and any DIY mask (home "do-it-yourself mask") can not only prove useless but can even worsen the risk of exposure by making the person and his neighbors feel protected while in fact they are not or are not sufficiently.

The basic distinction between FFP2 and FFP3 or N95 (NK95) and N98/99 based on outdated regulatory definitions, borne tens of years ago for other purposes, does not allow to define exactly the criteria of selection and choice of PPE for individual categories at risk, although the general principle that masks filter more is better suited to more exposed people, shareable only if that principle is translated into precise choices.

The next pictogram (Fig. 17.1) gives a precise description of the texture of several commercial masks used for the COVID-19 and, together, shows how different the filtering capabilities of the individual masks can be, even when they all belong to the same class (surgical face mask, in the example).

The literature confirms this view: in fact the masks were in general protective and useful [33], but results depend on the type of mask. For example, it has been shown that the use of face masks is associated to a strong reduction of odds of infection (adjusted OR = 0.15; 95% CI from 0.07 to 0.34) with a −14.3%

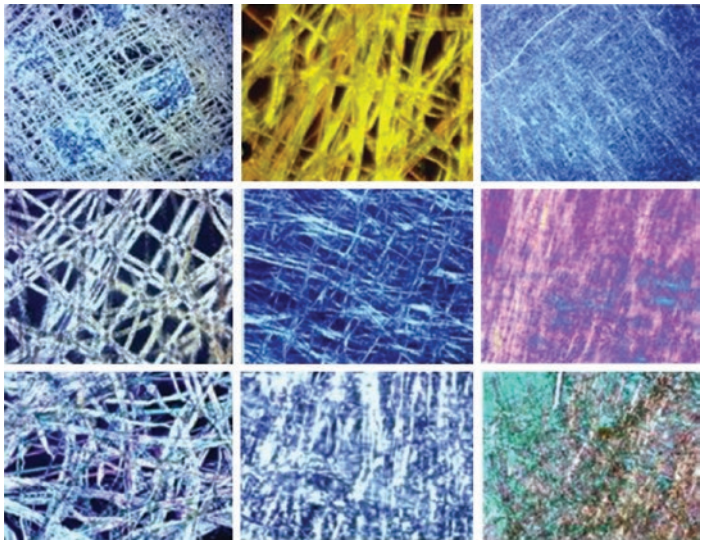

Fig. 17.1 The pictogram, which has only didactic and pedagogical value, illustrates the external structural layers (left) and the internal filtering layers of some surgical masks commonly used. The microscope techniques (polarized light, dark field, and others) serve to highlight the fine structure of fiber woven. At 100–200 linear magnifications, the indicated particles of type (a) and (b) (see above) would be practically invisible. In some cases of **DIY** masks, intermediate (theoretically "filtering") strata were found virtually identical to those shown on the left and in the central figure at the top of the pictogram. Similar results have been obtained from many nonsurgical masks manufactured with spunbond and meltblown techniques, sometimes used indifferently for anti-COVID-19 masks, baby diapers, and diapers for incontinent elderly. **This is not the optimal answer of science and business to a problem such as that of the most serious pandemic affecting the world**

reduction of infection or transmission risk (95% CI from −15.9 to −10.7), with a still more marked result if one uses N95 or similar respirators, with respect to standard surgical masks [29]. Other studies have produced different results [34], possibly influenced by the choice of specific devices; there are too many heterogeneities between the masks on the market today, and there are very significant quantitative differences within the category of face masks, both N/NK 95 and FFP2, which may vary in number and type of filter layers, for breathability and other relevant characteristics.

Inappropriate mask are inefficient and may also induce some side effects: a rich literature, not always perfect for research methodology [35–45], reports a series of problems related to face masks, going from their marketing management and their inappropriate wearing up to *mask diplomacy*. In particular, side effects are bound to the use of PPEs which are totally insufficient or incorrect or without sufficient instructions for use.

Some decrees in favor of the do-it-yourself masks in some countries greatly exacerbated this situation.

Of particular use at this time would be to develop a line of specific antiviral masks, tailored for the different targets with respect to the pandemic, as shown in Table 17.1.

Among the options to be considered is also variolation [46], which can have a justification where the reduction of the LV obtainable with face masks can still facilitate a more efficient response by adaptive immunity [47]. It is clear that if this last condition is much worse than the optimal one of not being infected, that—although true—could never be entrusted to chance, that is to say, the use of "lighter" face masks more permeable to viruses.

These aspects must be subject to a very careful analysis, which must take into account the problem of exposure to low repeat doses. There are also ethical/legal, civil, and criminal implications for the use of improper PPE or the improper use of PPE. The matter is actually very sensitive but very relevant, considering that the PPE is one of the most effective resources available so far.

Avoid the Onset of the Disease if you Have Come into Contact

An interesting, very few investigated perspective is emerging on the possibility of reducing the impact of the disease through proper nutrition and lifestyle, acting on multiple levels, susceptibility to the disease, strengthening the resistance mechanisms, as well as reducing the consequences of the infection once it has occurred [48, 49].

Possible protective interactions between proper nutrition, immune response, and defense against COVID-19 are various and

Table 17.1 Different masks can provide different solutions, according to the specific needs of the wearer and of the community he or she belongs to

What we expect	Expected result	What happens if it does not work	What we need to study	Side effects
To prevent infected people from spreading the virus	Avoid secondary infections caused by infected people	Secondary infection increase. Pandemic gets worse	Designing a mask capable of reducing the viral load virtually to zero	The patient cannot breath properly. The mask becomes virus repository
To prevent healthy carriers from spreading the virus	Halt uncontrolled infections spread in order to protect unaware people.	Uncontrolled spreading mechanic	Designing different masks for different uses. Developing alternative materials and methods of production.	The patient doesn't use the correct mask situation. The patient doesn't wear the mask properly. Difficulties in identifying and monitoring healthy carriers.
Protect people exposed to high viral load or constantly expose to viral load	Regulate healtcare and healtcare-related workers' activities	Spread among exposed workers. Difficulties in carrying out activities, emergency.	Studying the different effects of different levels of exposure Have a better understanding of links between viral load and time/ exposure.	Prolonged use of deviced or masks, lower protection efficiency, higher infection rate.

Table 17.1 (continued)

What we expect	Expected result	What happens if it does not work	What we need to study	Side effects
Randomly lowering viral load levels	Unpredictable, modest, random	Worsening of the pandemic, false sense of security, increased exposure.	Making mask-related regulation more stringent.	Using unfit masks leads to increased exposure to risk. Civil and legal implications.
Knowingly lowering viral load levels	Reducing R0	Loss of control of the pandemic	Different types of mask for different situations and stages of the pandemic.	Risk related to improper use of mask.
Activating variolation-like defence mechanisms	Reducing severity of the infection	Static or worsening pandemic situation	This field requires very strong attention. Uncertain results expected.	Uncertain field.
Giving people a sense of safety	Psychological impact	Individual and social (severe) side effects possible.	Giving information about technical specifications, correct use and the pros and cons of the device.	Reduced risk perception, exposure to risk possibly increased.
For all the above categories: protecting also against pollution and other pathogens.	Limiting exposure to atmospheric pollution.	Higher risk for people's health.	Studying possible common mask uses, especially those suited for specific substances.	Risk related to prolonged use of devices.

range from possible direct immunomodulating actions to interactions with the microbiota up to the action of the diet on other risk factors aggravating COVID-19 and many others [48–51].

A fairly recent systematic review provides encouraging conclusions that balanced nutrition can be useful in both prevention and management of COVID-19 infection [52].

Among the most accreditable and ongoing hypotheses is to use anti-inflammatory diets and to enhance the individual anti-inflammatory response through activation of the pathway of the anti-inflammatory prostanoids of the n-3 series derived from the common precursor that is the α-1-linolenic acid [53].

Telemedicine

Telemedicine is undoubtedly[1] one of the most powerful tools available today. It could be the key in the struggle against SARS-CoV-2. In the specific case of this COVID-19 pandemic, the prefix "tele" takes on particular value because it recalls the possibility of carrying out health services in a distance and remote regime, but actually telemedicine and eHealth refer to a much more complex reality that embraces and includes not only technological aspects related to information and communication technologies (as in the definition shown in the note). More information can be drawn from the sites mentioned in the note or from some[2] reflections in literature [54] and from the numerous sites of international scientific societies.

A few months ago, at the beginning of the pandemic, eHealth had been identified as the main resource to fight the virus, from all points of view—prevention, early diagnosis, treatment, and therapeutic follow-up—to avoid infection between medical and nursing staff but also for epidemiological purposes and for the control of infections.

[1]The terms *telemedicine* and *eHealth* indicate any application of ICT to meet the needs of the patient, health staff, citizens, and governments (as reported first in the joint statement of the EU Health Ministers).

[2]http://www.ehealth.study, www.sitelemed.it

Revealing the title "Virtually perfect? Telemedicine for Covid-19"published in the New England Journal of Medicine [55] a few months ago. Many subsequent publications have highlighted its role and usefulness [56–58], while it is still difficult to apply telemedicine programs or interventions related to patient preparedness, empowerment, and age [59]. Moreover, several studies address and solve the problems of the real applicability of telemedicine and the empowerment of recipients, as demonstrated, for example, by some Italian projects, which are dealing with the management of diabetes and other territorial chronic diseases [60, 61], which have been integrated also with remote control systems for COVID-19 patients.

In the course of this pandemic, telemedicine was adopted late and without effective national and supranational direction, despite the wishes and invitations published in the literature [62–64]. On the other hand, recently the role of specific apps (e.g., Immuni in Italy or the Corona-Warn-App in Germany) has been emphasized, the real utility of which will be tested with experiments *in corpore vili* (that of the entire population…) without being able to set up an integrated system for the control of infections and for the management of the needs of the sick people. The lesson to be learned is obvious: first one builds the architecture of the system and then the single pieces. The emergency cannot justify excessive experiments or even the adoption of systems that, once disseminated and adopted by millions of citizens, make it difficult to change the perception of the population, the creation of different new systems at a higher organizational levels, and whatever else. Again, a higher supranational coordination and the search for more efficient solutions, publishing the results and then proposing them to the population, would have been a more advisable path.

The strategic choice to use transportable resources (mobile, etc.) and/or relocation control systems (smart home, smart city, etc.), together with localization (GPS) and without too many limitations regarding the traceability of the person and his movements, could lead in the future to technologies of very high efficiency and utility. However, there are ethical, legal, database control, and many other issues. Finally, there is a lack of sufficient data to assess their effectiveness and efficiency, and there are

problems of technical, psychological, and social nature, as well as the possibility of possible side effects, unknowable so far. It is staggering to think that with all the potential of eHealth and telemedicine, in some European countries, public opinion and that of the government are almost fully oriented toward a single app which was produced by very valuable and accredited private groups but has been introduced far from any of supranational and long-term public health scientific programming.

Conclusions and Future Scenarios

There are uncertainties and doubts about how the research has been conducted so far. Some authors [65] point out that given the uncertainty about methodological quality, the mostly small sample size, and the trial duration, it would be impossible to gather reliable and high-quality clinical evidence regarding the possible future options of treatment of COVID-19-infected subjects. Thus, the next clinical trial protocols will need a higher design quality involving more sophisticated statistical methods and involving the most promising drugs.

Very clear messages have been sent out by many scientists regarding the ability to manage both the research and the intervention phases. Let's cite one as an example: "Despite an armamentarium of Government officials, researchers […] this novel coronavirus viral pneumonia continues to spread at an alarming rate infecting multitudes and claiming hundreds of lives" [64].

While at the highest levels of health governance, some experts in epidemiology and public health continue to support adamant and somewhat arrogant positions, the ones who are in contact with the patients and with the people (doctors, nurses, enterprises, and organizations) report hardships and inconsistencies.

This position is neither pessimistic nor critical. Simply, by observing the pandemic progression throughout the world, we

must deduce that what we have done so far was not enough, and also we must admit the hypothesis that some mistakes have been made. Let us analyze them and overcome them: it is an awareness of the real situation from which we must derive the new paradigms to improve the future scenario.

Therefore, the main lesson we can learn depends much more on the analysis of errors and mistakes made so far, than from our actual research acquisitions.

Then the future scenario that we *must* (say, *we have the duty of*) foreshadow is the worst, i.e., the current oscillations and resumption of the "first pan-endemia" (and the first and timid variants of SARS-CoV-2) will sum up: (a) the other viral epidemics (influenza), (b) the inevitable damage resulting from not being able to implement isolation measures (lockdown, etc.) too restrictive, and (c) those of the next waves of the *new* coronaviruses.

It is clear that today, while waiting for the vaccination campaign to be fully and effectively carried on worldwide, we must maximize the performance and effectiveness of the weapons that we already have in our hands and not only focus on the hope of a better future or a scientific discovery that will uplift the world.

This scenario is not unlikely, indeed. The level of combat will rise, and the thing we certainly need to do is to quickly remedy the mistakes made so far.

We entrust the summary of these ideas in Table 17.2, clarifying and drawing with energy the attention of all readers on the idea that, in parallel with the correction of errors shown in the table, basic research free and not bound by practical objectives, together with drug-oriented research, vaccines, diagnostic tools, and so on, will have to go ahead at maximum speed, because it is from them, and in particular from the first, that we expect a response that shows that human intelligence can exceed the virus's ability to mutate and attack us. No more emergency research: the emergency phase is over. Now we must rebuild an integrated system of coordination of research and resources in a rational and reliable way.

Table 17.2 Summary of recommendations provided and of the goals that are required to meet in order to defeat the pandemic

Goal	Weapon	Expected result	Availability	Innovative Research feasibility	Effectiveness (^)	Max potential impact	Actual Research Commitment	Desirable Future Scenarios
Kill the virus in the environmet	Chemical and physical methods	Lower contagiousness	Yes	High	Intermediate			Promote research activities, involve businesses
Kill the virus in the host	Vaccines	Contain the epidemic	No	Already underway	Not known, probably high			Go ahead
Rise host resistance	Nutrition, Lifestyle...	Contain the epidemic	Possible	High	Not known, perhaps low			Promote research activities, involve businesses
Save lifes and cure the disease	Drugs	Save lifes and cure the disease	Yes	High	Very heterogenous results			Go ahead
Disease Diagnosis	Lab test	Contain the epidemic	Yes	Already underway	High (under used)			Reducing the diatribe between qPCR and serological tests. Differentiate virus monitoring from different diagnosis
Lower contagiousness	Lockdown	Contain the epidemic	Yes/No	Easy	High			Analyze data from all countries to define utility and economic side effects of the different forms and lenght of lockdown
Lower contagiousness	Social distancing	Contain the epidemic	Yes	Easy	Intermediate			As above
Lower contagiousness	Mask and other PPE	Contain the epidemic	Yes	Easy	High			Improve mask efficiency and define specific PPE for different situations
Multiple goals	eHealth	Contain the epidemic, Improve the cure, Save lifes...	Poor	High and Easy	High			It promotes the support and dissemination of clinical research through eHealth tools

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Conclusions

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The COVID-19 pandemic is reshaping the idea of global health and, broadly, dramatically changing the same way we perceive the world. Yet this was not an unexpected event, but a stage of a process that started when humankind began to take over the planet. In the natural history of our species, the war against human and microorganisms has passed through tragic and sometimes dreadful times. Entire populations had almost been wiped out by germs in the past: with no available cures and with a medicine based more on superstition than facts, human beings had no weapons to fight their battles. Yet, people always outwitted the microbes finding strategies and solutions in an attempt of surviving.

Nonetheless, only sporadically we have been able to learn from our mistakes, so that every time the danger was over, the

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danger level was set back to a lower threshold, and we continued to live our lives confident that history was not going to repeat itself. However, we had been wrong in the past, and we have proven us wrong again this time.

This is how good we are.

Fortunately, our ability to adapt to new situations helped us so far to overcome every attack we received from the microworld that surrounds us and that somehow is also part of ourselves. This is probably why no epidemic so far managed to cause our extinction.

But planet Earth is changing. The same environment we live in has been deeply modified by human actions, and the exponential growth of human activities and interactions is exposing our soft spots to these invisible enemies around us.

In such a scenario, nature is offering a valuable lecture that this time we should be able to understand and retain.

The COVID-19 pandemic revealed three major flaws in the management of international crisis:

- Lack of *preparedness*: although new emerging diseases are a major issue nowadays, because of the dynamics that we have portrayed in this book, international political and healthcare institutions appeared unaware of the problem and unable to present workable plans for the outreach, able to trigger proactive behaviors in the population to prevent the spreading of the disease in the first place. The whole risk communication process, then, suffered from the inability to explain what was happening, what was known and what was unknown, and why some measures—at the best of the available knowledge—were needed. This creates a gap between the public and the decision-makers that prevent the population to adopt the necessary precautions. This same gap was widened by those that for various reasons, scattered untrustworthy or inaccurate information via different media.
- Lack or *readiness*: the COVID-19 pandemic clearly showed that no plan for readiness was in place worldwide, in spite of the onset of other outbreaks of serious infective diseases that

took place in the second decade of the second millennium. The basic containment strategies, that have proven ineffective even for more aggressive diseases, were completely inadequate to deal with a so sly infection as the one from SARS-CoV-2 is. However, that was not unpredictable. A trace, test, treat model is clearly powerless when it comes to a completely new disease, when the epidemiology and way of transmission of the infection are completely unknown; when the same kits for testing are unavailable, because they are insufficient, because the interpretation of the results is doubtful, or simply because there such tests have not been created yet; and when there are no effective treatment options available and the ones in use can worsen the clinical picture or uses so many resources that can lead the entire healthcare system to collapse. A contingency plan then had to be there, able to create an effective response both at local and at international level, with emergency plans in place in single hospital and emergency departments and with action plans for public health available at different levels and ready to be implemented so to react to the crisis with no hesitations.

– Lack of *cooperation*: this is probably the greatest failure that came from this pandemic. For the first time in modern history since World War II, the world experienced a global crisis where everyone—in spite of his or her background, origin, and social status—was potentially directly or indirectly affected. A worldwide cooperation with every sector offering its skills to solve the puzzle was to be expected. However, that was not the case. We have seen head of states and politicians using this pandemic to pursue personal interests; major international institutions giving away cheap advices, being unable to propose a more coordinated action able to involve research and political organizations in a joint effort to find solutions; scientists running solo marathons to try to get to the cure first when they were not busy pursuing television cameras or newspaper headlines; and common people unable to follow the most basic hygiene rules, even when those were the same that everyone should follow also when there are no pandemics in sight. That

was no good. A more cooperative approach, thus, was desirable, possibly with international agreements already available, able to coordinate the action of the researchers and to facilitate the process of decision-making and ultimately the implementations of cost-effective measures.

Nonetheless, most institutions and healthcare facilities had done a great job, using whatever piece of information they could get to produce practicable models for the containment, detection, and management of the disease. Praise has to be made to the countless people and organizations that gave so many hours of their lives to try to understand and fight the disease and that in few months have built an incredible amount of knowledge and strategies starting from scratches: frontline clinicians, independent researchers and research organizations, and policy-makers and decision-makers belonging to government and nongovernment institutions that have spent their sleepless nights in trying to find the key to the problem and therefore its solution.

In our work, we have tried to depict the basic clinical features and challenges that this virus is posing to the medical world. We have tried also to offer some useful advice and to propose workable solutions. The main goal of our work, however, was to underline those limitations that prevented the academic, clinical, scientific, and political world to give an answer to a foreseeable problem. At the same time, we offered an overview of some possible future scenarios in an attempt to describe those possibilities and opportunities that this crisis could eventually produce.

Yet, this implies that medicine and research have to evolve, shunning oversimplified models and procedures that cannot apply to the complexity of the biological world.

This is paramount.

The more the medical knowledge and the technology applied to medicine grow, the more we have to address complexity. Paradoxically, it also means going back to the origins, when clinicians were asked to use their wit to solve complicated problems using merely their theoretical knowledge, their senses, and their wisdom. Simultaneously, the new prospects coming from the ris-

ing integrated medical technologies should be constantly considered and such possibilities exploited at their best.

Machine learning and artificial intelligence should be used to improve the efficiency of those automatic models that do not need the constant supervisions of a human mind, lightening the burden to those that are fighting the battle against the virus, optimizing time and resources, and reducing the flaws in the process. In addition, medicine cannot be bound to physical spaces and places anymore, especially when an international crisis undermines the same access to healthcare and increases the chances of making medical mistakes or augmenting the disparities in the population or neglecting patients affected by pathologies other than COVID-19. From this point of view, telemedicine and eHealth can help.

Clinicians, researchers, health policy-makers, and healthcare institutions can exploit data coming from the use of these technologies to improve the quality of care, to evaluate the effectiveness of the measures adopted and consequently recalibrate the response, to use resources at the best, and to produce workable models able to predict the evolutions of a medical crisis, facing at the same time all its implications.

We have to consider COVID-19 as a warning. Next time in fact could be the last: global health cannot be merely an academic issue, based on considerations produced by those on the right—or from a different perspective, wrong—side of the barricade. It cannot be based on "lessons learned" as well. We, as scientists, have the ethical, moral, and deontological duty to give to every medical issue the same weight, in order to promote the wellness of every human being in spite of any background.

Moreover, what may appear negligible today might be our worst nightmare tomorrow.

For these reasons, we have to be prepared, with contingency and emergency plans in place and with collective agreements aimed to promote the cooperation and the collaboration between healthcare and research institutions and political organizations.

Finally, people worldwide have to be actively involved and encouraged to embrace their own destiny in their arms. This is not only part of a patient-centered philosophy in healthcare but rather is the awareness that no one can be left behind in global health.

But not only: health in fact is for everyone and cannot be used to follow personal interests or to gain profit on the back of the less fortunate.

But the other side of the story is that everyone is responsible because the same destiny of the humankind is at stake today. And that also means that in this endless process, everyone has to do his or her part.

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