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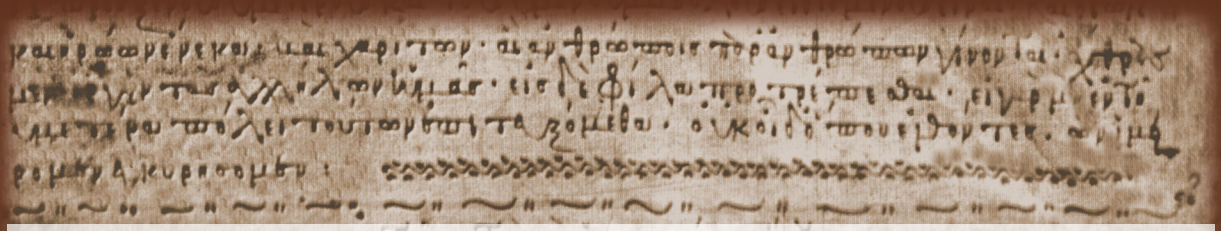
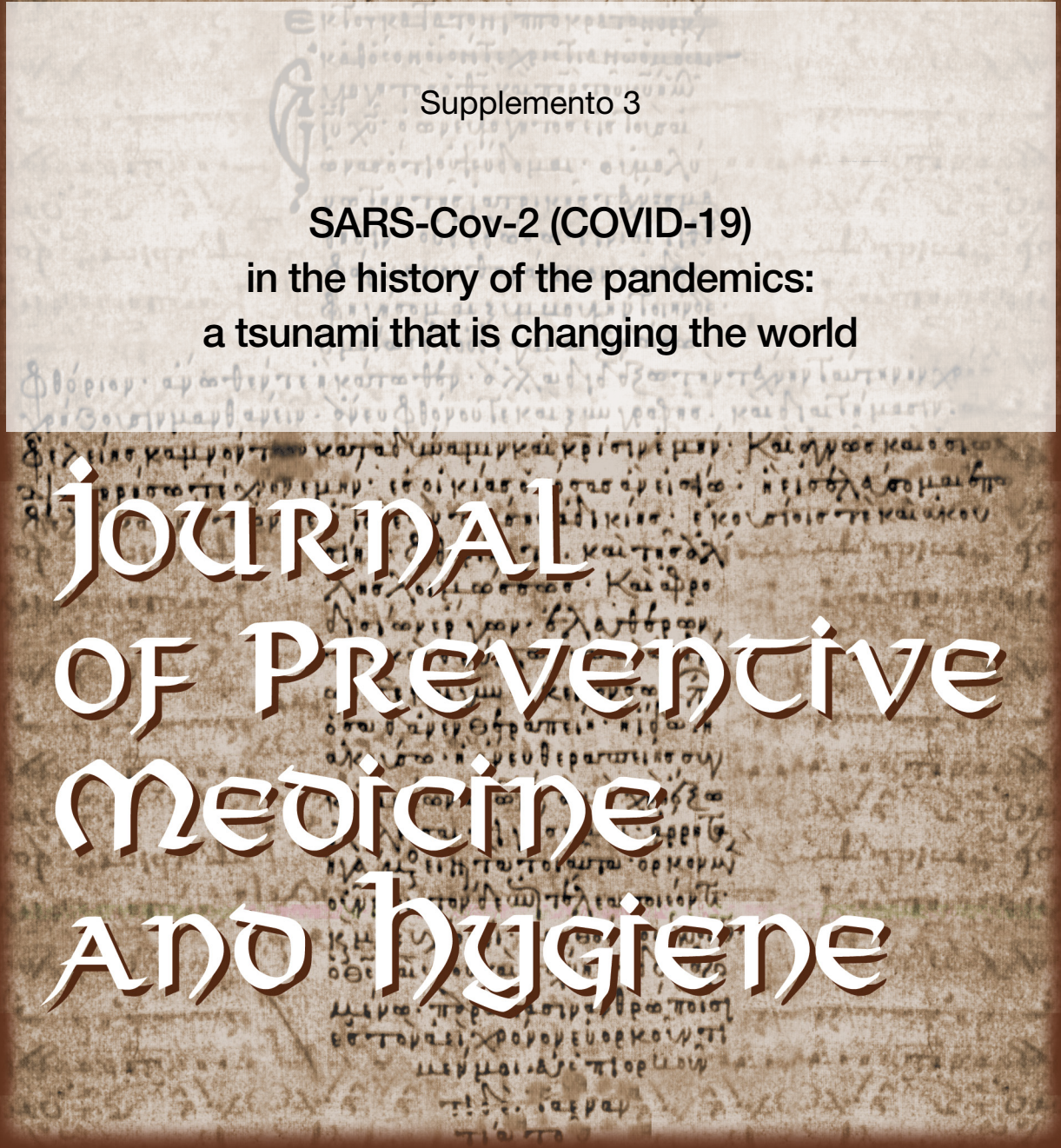


Supplemento 3

SARS-Cov-2 (COVID-19) in the history of the pandemics: a tsunami that is changing the world



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SARS-CoV-2 (COVID-19) in the history of the pandemics: a tsunami that is changing the world

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EDITORIAL

SARS-CoV-2 (COVID-19) and the teaching of Carlo Urbani in Vietnam: a lesson from history almost 20 years after SARS

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Keywords

SARS • Vietnam outbreak • Infectious diseases • Carlo Urbani • Covid-19 • Early detection • Prevention • History of infectious diseases

Summary

Carlo Urbani was an infectious diseases expert for Health Organization (WHO), who in 2003, first identified Severe Acute Respiratory Syndrome (SARS) as a new and highly contagious disease. In February, 2003, an American businessman with an unknown lung disease was admitted to a hospital in Vietnam. Doctor Urbani immediately understood that it was a new virus and right after he alerted the WHO and the Vietnamese government; he involved also foreign doctors in the investigation of this case. He advised the authorities to immediately implement quarantine measures and thanks to his quick and unyielding response, the spread of the virus could be stopped quickly, many patients were identified and early isolated. His early warning to the World Health Organization triggered a swift and global response credited with saving numerous lives. He shortly afterwards himself became infected and died. The shut down of Vietnam's first outbreak was really a very important step for the whole world community and the Urbani's quick actions were crucial because ensured an early detection of SARS and an effective response from international community.

Background

Carlo Urbani (1956-2003) was an Italian microbiologist and infectious disease expert for World Health Organization (WHO) in Hanoi (Vietnam) who first identified in 2003 Severe Acute Respiratory Syndrome (SARS) as a new and highly contagious viral disease.
He was born on October 19, 1956 in Castelplanio, near Ancona (Italy); even as a young man, he volunteered for different organizations that looked after the less privileged both in Italy and in developing countries.
In 1981 he completed his medical studies and specialized in infectious diseases and tropical medicine at the University of Messina; at the beginning he worked as a doctor in Castelplanio, at the Institute for Infectious Diseases in Ancona and in the Macerata Hospital. He became a consultant to the WHO and joined "Doctors Without Borders" (Médecin Sans Frontières-MSF) for whom he went to Cambodia working on control of Schistosoma mekongi. He became also head of the Italian section of *Doctors Without Borders* just the year the organization was awarded the famous Swedish Nobel Peace Prize. After Cambodia, he was transferred to Vietnam, where he worked at the Hanoi hospital (Fig. 1).

A worldwide outbreak of "severe acute respiratory syndrome" (SARS)

On February 28th 2003, he first examined a Chinese-American businessman admitted, two days before, to *Hanoi's Vietnam France Hospital* for a suspected avian flu infection. The patient suffered from pneumonia, difficulty breathing, fever, dry cough, and also many healthcare workers at the hospital had analogous symptoms few days later [1].
Doctor Urbani quickly recognised that the disease was probably new and highly contagious on between March

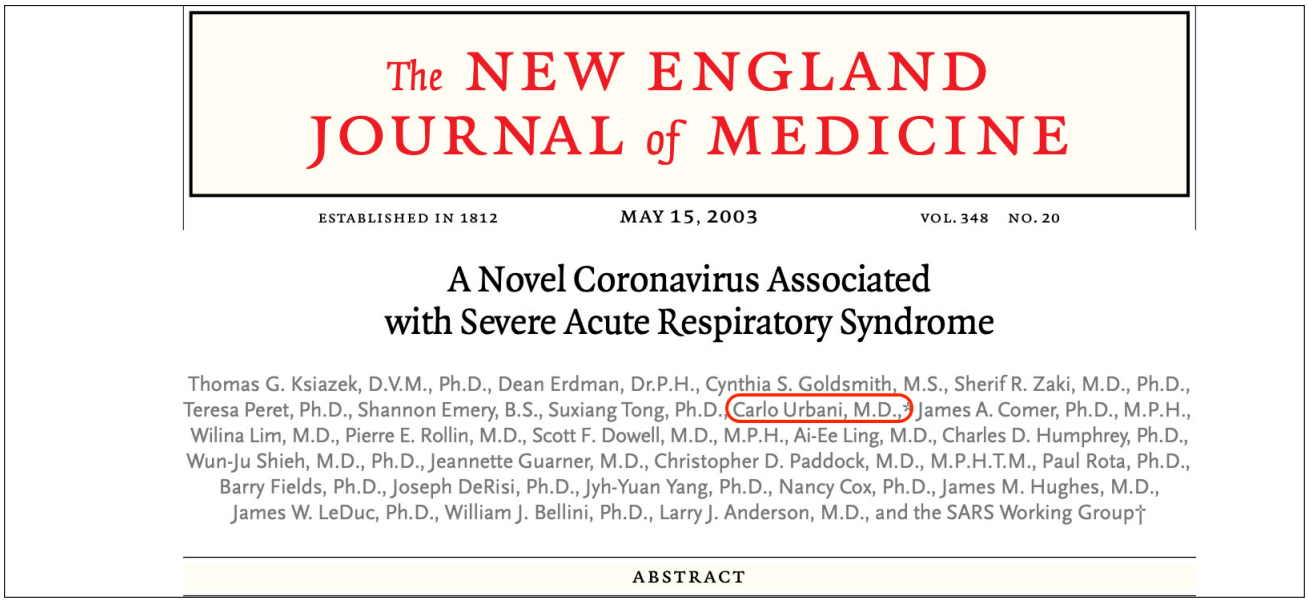
Fig. 1. Archive of the Carlo Urbani' s family. (permission to reproduce the photo to Prof. Mariano Martini).

3rd and 4th he began implementing infection control procedures like high filtration-masks, double gowning and other protective clothing, which were not routine in impoverished Vietnam; then he alerted public health authorities.
All infected patients were isolated and the hospital was closed to the public with security guards outside and infection control measures were instituted at other hospitals.
On March 7th Urbani alerted WHO headquarters in Geneva, and then convinced the officials at the Vietnamese Health Ministry of the need to begin isolating patients and screening travellers, despite the possible damage to its economy.
Over the following days, WHO experts, a task force from *Centers for Disease Control* and *Prevention* (CDC) and specialists in epidemiology from all over the world, went to Hanoi to help contain and study the outbreak.
The syndrome was designated "Severe Acute Respiratory Syndrome" (SARS) [2-6] (Fig. 2).
Clinical specimens from patients meeting the case definition of SARS were sent to the Centers for Disease Control and Prevention (CDC) by collaborators in Vietnam, Singapore, Thailand, Hong Kong, Canada, Taiwan and the United States as part of the etiological investigation [7].
On March 15th, the WHO declared the disease identified by Carlo Urbani to be a "world health threat" [8].
Carlo Urbani realized he had been infected with the SARS few days before, on 11 March during a flight from Hanoi to Bangkok (Thailand) where he went to talk at a conference on the subject of childhood parasitic infections; he started feeling feverish on the plane and a colleague who waiting for him at the airport called an ambulance so Carlo Urbani was admitted to Bangkok Hospital.
He had immediately recognized that the SARS virus had infected him and he continued to study as much as possible until the end so that science could learn more about this disease.
He contracted SARS while treating infected patients in Hanoi; he was one of about 80 people, including many healthcare workers, who were infected by the businessman. At the end of the outbreak, 774 deaths worldwide were attributed to SARS [9].
Carlo Urbani died on March 29th, after 18 days of intensive care. During some moments of consciousness he asked for his lung tissue to be donated for scientific research.
The shut down of Vietnam's first outbreak was really a very important step for the whole world community and the Urbani's quick actions were crucial because ensured an early detection of SARS and an effective response from international community. WHO never had reacted so quickly to an outbreak.
The syndrome was intitled "severe acute respiratory syndrome" (SARS) in March 2003, and worldwide efforts to recognize the cause of this illness and prevent its spread were introduced immediately. Many cases could be linked through chains of transmission to health care workers from Guangdong Province, China, who visited Hong Kong, where he was hospitalized with SARS and died [7].

The pivotal role of Carlo Urbani

Surveillance is a very important tool for identifying infectious diseases causing serious public health problems [10] and preventive measures to reduce the risk of infections have a fundamental role [11].
Quarantine works when introduced early alongside other prevention measures are the fundamental pillars for reduce the number of people infected and the number of death [12].
The quarantine is most effective, and cost less, when it was started earlier [13].
Carlo Urbani really played a key role in containing the spread of SARS infection: he was the one who very

Fig. 2. N Engl J Med. 2003 May 15;348(20):1953-66. doi: 10.1056/NEJMoa030781. Epub 2003 Apr 10.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A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome

Thomas G. Ksiazek, D.V.M., Ph.D., Dean Erdman, Dr.P.H., Cynthia S. Goldsmith, M.S., Sherif R. Zaki, M.D., Ph.D., Teresa Peret, Ph.D., Shannon Emery, B.S., Suxiang Tong, Ph.D., Carlo Urbani, M.D., James A. Comer, Ph.D., M.P.H., Wilina Lim, M.D., Pierre E. Rollin, M.D., Scott F. Dowell, M.D., M.P.H., Ai-Ee Ling, M.D., Charles D. Humphrey, Ph.D., Wun-Ju Shieh, M.D., Ph.D., Jeannette Guarner, M.D., Christopher D. Paddock, M.D., M.P.H.T.M., Paul Rota, Ph.D., Barry Fields, Ph.D., Joseph DeRisi, Ph.D., Jyh-Yuan Yang, Ph.D., Nancy Cox, Ph.D., James M. Hughes, M.D., James W. LeDuc, Ph.D., William J. Bellini, Ph.D., Larry J. Anderson, M.D., and the SARS Working Group†

ABSTRACT

quickly saw that the disease was something very strange; because of his early detection of the disease, global surveillance was intensified and many new cases have been identified and isolated before further infections.
As said the UN Secretary-General Kofi Annan (April 8th 2003) "*Dr. Carlo Urbani dedicated his life to helping protect and save the lives of others.*
It was characteristic of his vigilance, professionalism and expertise that he was instrumental in ensuring an early response by the international community to Severe Acute Respiratory Syndrome. Had it not been for his recognition that the outbreak of the virus was something out of the ordinary, many more would have fallen victim to SARS". It was the cruellest of ironies that he lost his own life to SARS while seeking to safeguard others from the disease. Dr. Urbani leaves an inspiring legacy in the United Nations family and the global public health community. For his contribution on the front lines of the fight against disease, he will be remembered as a hero -in the best and truest sense of the world" [14].
Today, with SARS-CoV-2 (Covid-19), after about twenty years, what did we learn from Urbani's teaching?

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Conflict of interest statement

The author declare no conflict of interest.

Authors' contributions

MM conceived the study, drafted the manuscript, revised the manuscript and performed a search of the literature. MM read and approved the latest version of the manuscript.

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Review

Evaluation and review of preventive measures applied during COVID-19 pandemic: strategies adopted by European countries

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Keywords

COVID-19 pandemic • SARS-CoV-2 • Preventive measures • Strategies • Europe

Summary

The COVID-19 pandemic has greatly jeopardized the European continent and the spread of SARS-COV-2 has led European countries to implement a series of preventive interventions aimed at decreasing the incidence rate of the disease, in consideration of the lack of specific therapies and of a vaccine. Each European country has behaved in different ways and timing accordingly to the epidemiological trend and to different political strategies. The main purpose of preventive measures is to lower the incidence rate of the disease, avoiding the collapse of health systems and limiting the total number of severe cases and deaths. All these targets should fit with needs that go beyond scientific evidence such as economic interests, decisions of neighboring countries and specific socio-political factors for each country. The objective of this research is to clarify which preventive measures have been recommended and applied in different European countries.

Background: COVID-19 in Europe

The pandemic in Europe

The COVID-19 pandemic has caused an unprecedented threat to Europe, given that many member states have experienced a sustained spread of the virus for several months [1]. The lack of a specific therapy and of a vaccine has forced all affected countries to implement various non-pharmacological measures in order to counter the spread of the infection [2]. As of October 9th, 2020 there were 3,874,181 cases in the area that includes the European Union (EU), the European Economic Area (EEA) and the United Kingdom, while in the world the total number reaches 36,583,084 cases. Fortunately, in the aforementioned area as a whole, a progressive downward trend in the incidence of the disease has been observed during the summer, even though sustained community transmission was still present in many member states [3]. Eight of the European countries that registered most cases of COVID-19 as of October 5th, 2020 are: the United Kingdom, Spain, Italy, Germany, France, Sweden, Belgium and the Netherlands [4]. This research aims to evaluate the different preventive measures implemented by these eight countries.

Key points on the ways of transmission of the SARS-CoV-2 virus

The modes of transmission of the SARS-CoV-2 virus are mainly two: through the respiratory tract with production of droplets and transmission by contact, which can be direct or indirect [5]. Contagion by respiratory tract occurs through the emission by the infected subject of droplets of saliva with a ≥ 5 μm diameter; these droplets can spread through normal daily gestures such as talking, sneezing and coughing [6]. This way of transmission implies that droplets can spread for short distances (about one meter) and directly reach susceptible subjects (direct contagion) through close person to person contact involving buccal/nasal mucosae or conjunctiva [7].

To date, it cannot be excluded that viral transmission may also be possible by air, especially in specific situations of particular interest for the hospital/healthcare environment, such as the formation of aerosols during intubation, tracheotomy and forced ventilation. Another situation of potential risk for air-transmitted infection could be identified in closed and very crowded environments in relation to droplets and to air recirculation due to air conditioning systems [8]. Transmission via the fecal-oral route remains doubtful [7, 9]. Given that the virus is able to survive for a variable time (from few hours to several days) on objects and surfaces (Fig. 1), indirect contagion is possible if the people who come into contact with the aforementioned fomites do not apply proper hand hygiene and/or disinfection procedures [10].

Disinfection methods and types of biocides

The products currently used for disinfection of surfaces contaminated by the SARS-CoV-2 virus are those previously used for other coronaviruses, accordingly to a supposed similar survival time on surfaces and the lack of specific studies on this new virus [7]. The

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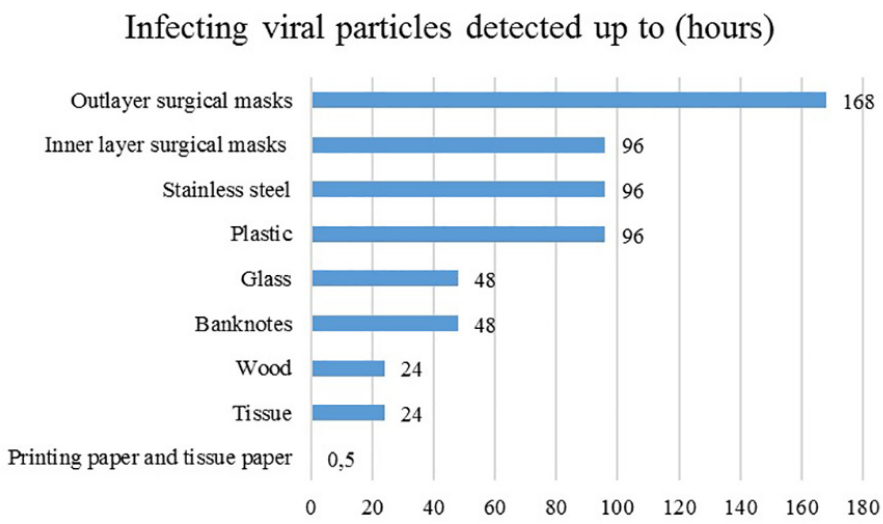
Fig. 1. Survival time of SARS-CoV-2 on different surface. Modified from [10].



main disinfectants recommended at international and European level are the following: ethanol (ethyl alcohol), quaternary ammonium salts, hydrogen peroxide and sodium hypochlorite, to be used accordingly to the technical data sheet of the different products [10].

Description of preventive measures

General/collective measures

Collective preventive measures aim to limit the transmission of the virus by reducing social contacts. One of the main recommendations taken into consideration in Europe was social distancing which consists of minimizing interpersonal physical contact/distance to reduce the possibility of transmission and new infections.

In support of this rule, during the acute phases of the pandemic, communications and recommendations were issued to stay at home (#stayathome message) and to go out only if strictly necessary. Depending on the epidemiological findings in progress, the creation of "red zones" was arranged at national level as a measure of total isolation of inhabited centres affected by disease outbreaks and during the acute phases of the pandemic a "lock-down" was imposed to the entire population (Fig. 2). In addition to the aforementioned social distancing, the governing bodies of the individual European states have gradually introduced a series of collective measures such as the closure of schools, universities and educational centres, as well as of workplaces and businesses such as coffee shops, restaurants, factories, shops and sports centres. The possibility of remote working through smart working, where possible, was also implemented and encouraged. In many countries, restrictions have been imposed on visits to residences for the elderly and the frail subjects and to prisons. Besides, in order to avoid gatherings of people, the cancellation of events open to the public was ordered, including religious and socio-cultural events such as theatre performances, movie theatres, concerts, sporting events such as football matches, outdoor and indoor sports competitions [11].

Individual measures

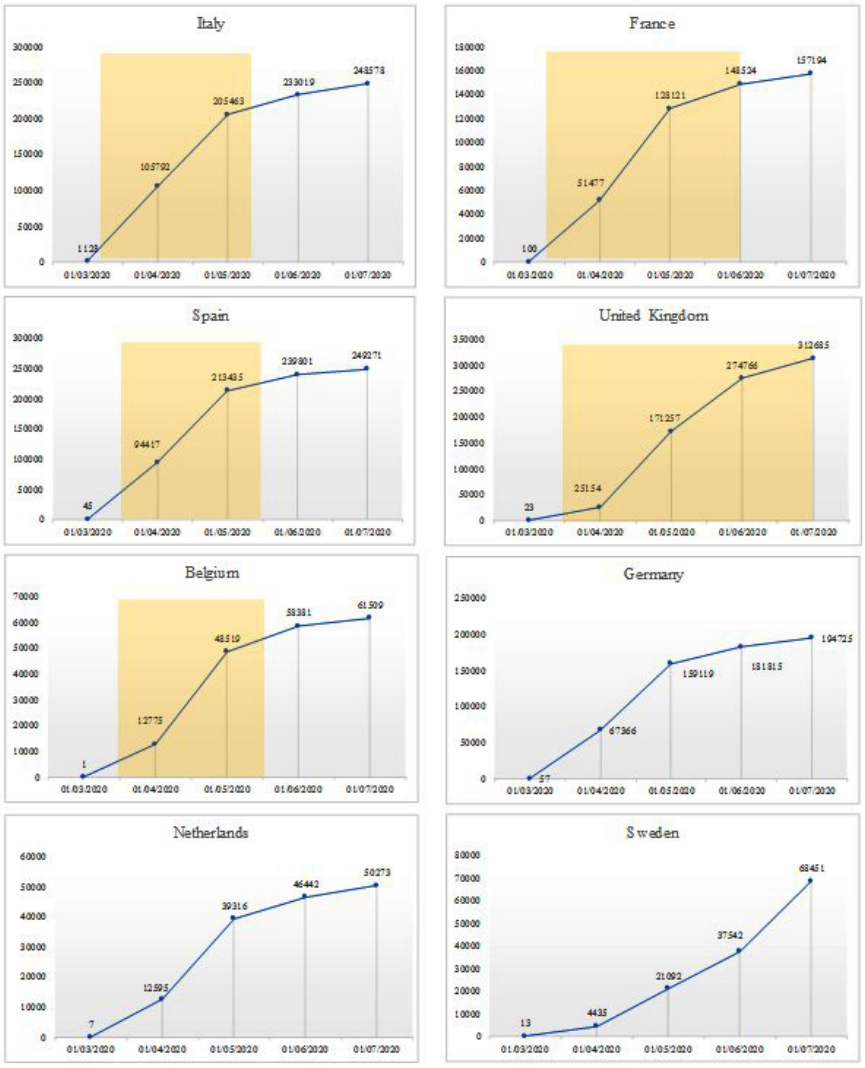
Individual measures have been considered essential for the prevention of direct and indirect SARS-CoV-2 infection. According to the provisions by the World Health Organization (WHO) and the European Centre for Disease Control (ECDC), adequate hand hygiene is defined as the basic point of preventive measures. Frequent hand washing with soap and water or thorough disinfection with alcohol-based gel is recommended. Another precautionary measure adopted by European countries is to adequately cover nose and mouth with disposable tissues or to use the bend of the elbow in case of sneezing and coughing in order to limit hands contamination [12].

Another non-pharmacological personal protective device is represented by face masks which are classified on the basis of the level of protection they provide. They range from masks produced with household tissues to surgical facial devices. Filter masks are also available, which protect users from viral particles, for use in healthcare settings during medical procedures that produce aerosols. Other personal protective equipment such as gloves, disposable gowns and face/eye protections should be used by healthcare professionals or those dealing with positive cases. The masks must be frequently changed to maintain their effectiveness and the combination with other preventive measures such as hand washing together with their proper use can increase its protective effectiveness [11].

Environmental measures

Environmental measures aim to combat indirect contagion. The SARS-CoV-2 virus is more stable in

Fig. 2. Total number of confirmed cases and "stay-at-home" orders in Italy, France, Spain, United Kingdom, Belgium, Germany, Netherlands and Sweden; March 1st - 1 July 1st 2020. The coloured area represents the period of national enforced lockdown. Modified from [31, 36-40].



the environment than other enveloped viruses and it is therefore advisable to implement additional preventive measures aimed at reducing the risk of infection such as: limiting exposure to the virus, correct hands hygiene, correct use of personal protective equipment and disinfection of surfaces and environments [13].

Proper management of indoor environment is one of the tools to limit the spread of COVID-19. The exchange of the air in the closed environment (home, offices, shops etc.) reduces the concentration of pollutants and the risk of exposure of those who stay indoors; it is recommended to open the windows for a few minutes several times per day rather than once for a long time. In case of impossibility of natural ventilation, it is advisable to carry out proper periodic maintenance of the air conditioners by regularly cleaning the air filters. The cleaning of the surfaces with detergents and disinfectants must be carried out following the instructions given by the manufacturers, remembering that the incorrect use or dilution of a product can reduce the effectiveness of cleaning. Noteworthy, the effectiveness of disinfectants (e.g. ethyl alcohol, sodium hypochlorite etc.) is linked to the need to preventively remove dust and dirt. All products must be properly used, always wearing gloves. For daily house cleaning, particular attention must be paid to the most frequently touched surfaces (e.g. doors, door handles, windows, tables, light switches, toilets, etc.). When materials or furnishings cannot be washed (e.g. rugs, carpets and mattresses), use steam appliances for cleaning is advisable [14]. With regard to indoor environments in the health and social care and hospital sectors, in addition to the aforementioned regulations, a modification of the methods and timing of aeration and cleaning of the premises is necessary; personnel should be equipped with personal protective devices and adequately trained [5].

Based on current knowledge, there is no international evidence that justifies the use of disinfectants outdoors,

while the possibility of using normal detergents or water for ordinary street cleaning is confirmed, provided that the production of dust and aerosols is avoided. The use of disinfectants such as that based on sodium hypochlorite is not of proven usefulness and is currently not recommended due to an increased risk of environmental pollution [7].

Timing and execution of preventive measures in Europe

Contact-tracing and isolation

A crucial point in the management of the pandemic has been the isolation of not only the subjects who tested positive but also of suspected and/or asymptomatic cases and close contacts. The isolation and quarantine measures adopted in various European countries were in many respects overlapping with an average duration of 14 days, which roughly coincides with the duration of the disease incubation [15]. Sweden stands out from other states in that it has always maintained isolation as a voluntary and in no case mandatory measure, in order to stimulate a responsible behavior of the population [16]. In order to decrease the spread of the infection, as suggested by the main international bodies, all the considered countries have advised the population, from the beginning of the pandemic, to self-isolate in case of onset of suspicious symptoms such as fever > 37.5°C, cough, difficulty in breathing, sore throat and cold [12]. The isolation measure applies to symptomatic positive subjects who do not require hospitalization, to asymptomatic positive cases, to suspected cases and to close contacts of COVID-19 positive subjects. This measure consists in keeping the individual at home, so as to avoid contact with other people. During home isolation, subjects must not have physical contact with family members and roommates; when possible, it is recommended to avoid common areas, to eat and sleep separately and to use different bathrooms [17]. When it is not possible to guarantee a correct home isolation regimen, secondary facilities have been set up. It should be noted that the criteria for the definition of the "suspected case" have changed over the course of pandemic, in particular with regard to the epidemiological criteria [18].

European states have tried to cope with the COVID-19 emergency by adopting a common guideline, enhancing health personnel in numerical and qualitative terms, developing open-source digital capabilities and implementing contact tracing. In Germany, for example, the Ministry of Health funded the training of medical students to support health authorities in contact tracing, managing documentation and data entry.

As for contact tracing, the general trend has been to invest in technology, while at the same time guaranteeing the anonymity of data and preferring Bluetooth technology over geo-localization. In almost all the considered countries, the first opensource applications were developed such as "Corona Warn" in Germany, "Immuni" in Italy, "StopCovid" in France and "NHS COVID19" in the United Kingdom. "Radar Covid" in Spain and "Corona Melder" in the Netherlands are still in development. The goals of these apps are to inform users as quickly as possible about exposure to a possible case of COVID-19 and to identify infected people before they present symptoms, preventing potential secondary transmission [19].

The use of these applications also makes it possible to lighten and facilitate the workload resulting from epidemiological investigations for healthcare professionals.

It should be noted that the federal state of Schleswig-Holstein in Germany has created a monitoring system entrusted to general practitioners (GPs); GPs have been entrusted with the care of infected patients isolated at home while the public health offices manage contacts and organization of isolation. From 20 April 2020, the Public Health Office in Berlin's central "Mitte" district started using the SORMAS software app ("Outbreak Response Analysis and Management System") for contact tracing activities.

As regards the acquisition of national data in Belgium, a daily report on the number of COVID-19 patients was planned to be published with data collected and transmitted by private facilities, hospitals, residential care centres and medical doctors to the Belgian Department of Public Health. In France, a database was created to collect on a national scale positive cases (SIDEP system) and related contacts (CONTACT COVID system). In Italy, a national observatory coordinated by the Italian National Health Agency (Istituto Superiore di Sanità) has been established collecting all data from the regions and from the Agency's laboratory on a daily basis. In Germany, the daily report of cases on the national territory can be consulted on the website of the Robert Koch Institute. The Netherlands and Spain publish reports on the website of the Ministry of Health, while in the United Kingdom data are published on the website of the National Statistics Office. Finally, in Sweden, the National Board of Health and Welfare follows and publishes the statistics relating to COVID-19 on a dedicated web page.

The Italian government, in addition to the management of positive cases in the general population, has also had to face and implement preventive measures to avoid the spread of COVID-19 among migrants hosted by immigration centres. To this end, special places have been identified (ground centres or specially equipped ships) to test incoming subjects. In addition, the Sicily region has set up a medical task force in the province of Syracuse to provide basic health services during the pandemic. Another difficult area to manage was that of the prison system. In Italy, where overcrowding is very often present in prisons, suspected cases have been placed in preventive isolation, in order to avoid the emergence of epidemic outbreaks. The same precaution was taken by the British Office which also arranged for the release of 300 inmates considered to be at high risk [16].

Planning and reorganization of the hospital and territorial health services

Examined European states have changed the organizational plans of hospitals and local services trying to adapt their functioning accordingly to the various phases of the pandemic. To date, the situation is constantly evolving depending on the number of COVID-19 cases present in each country.

Europe had to face three important issues in the first phase of the pandemic: the containment of infections, the ability to perform high numbers of swabs per day for the diagnosis of COVID-19 cases, the organization of treatment for COVID-19 cases and at the same time the concomitant temporary suspension of treatment for non-urgent or temporarily non-curable diseases.

As can be seen in Table I, all the examined countries have increased their ability to carry out and process nasopharyngeal swabs compared to the initial stages of the pandemic in order to be able to identify as many cases as possible to limit and stem the spread of the SARS-CoV-2.

One of the prevailing actions that has been taken by each country during the acute phase has been to postpone non-urgent care, both at hospital and community levels. All the examined countries have activated hospital emergency plans by increasing the capability of semi-intensive and intensive care beds, cancelling scheduled non-urgent surgeries and specifically postponing interventions that could potentially decrease the availability of resuscitation places.

The reorganization of intensive care places varied in different countries. Since the beginning of March, in Belgium a national plan for the notification of saturation of intensive care places has been activated, in order to allow for transfers between hospitals; in France was activated the "White Plan" with the reorganization of the healthcare offer of hospitals and the creation of new intensive care places. In Germany, an online register has been set up with mandatory updating by hospitals indicating free places in intensive care and the estimated maximum occupancy in the 24 hours following publication. Besides, on 11 May 2020, the Corona Treatment Center Jaffestrasse was opened for the exclusive treatment of COVID-19 patients. In Italy, the Minister of Health published a circular requesting all regions to increase intensive care places by 50% and to increase by 100% the number of pulmonary and infectious disease hospitalization places adequately equipped with semi-intensive care devices. In regions with highest incidence rates, such as Lombardy, COVID-19 hospitals have been established to treat only infected patients. The Italian national response has been fragmented in the different regions, with different local organizations. Table II shows the cumulative incidence, intensive care units (ICU) capacity and maximum daily ICU occupancy in every Italian region related to the first months of the pandemic [20]. Figure 3 shows how ICU occupancy has changed during the early period of pandemic in the evaluated European nations. ICU capacity data was not available as well as occupancy data from Spain [21]. In Spain, field hospitals have been set up, most of them in Madrid, to treat less serious cases. At the end of April, Sweden doubled the availability of intensive care places by adopting an interregional coordination plan. The Swedish Armed Forces have also been involved by setting up 30 intensive care places in field hospitals in Stockholm and in general no hospitals have been designated exclusively for COVID-19 patients. At the end of January, the NHS in the UK said it would make at least 30,000 ICU and 100,000 acute care beds available nationwide. COVID-19 was declared a "high consequence infectious disease" and the care of the sick was initially entrusted to five adequately equipped national hospitals. As the number of cases increased, all the hospitals available in the UK were used and available operating theaters were transformed into ICUs to increase the availability of beds [16].

As regards the territorial management of the acute phase, several countries have activated a telephone triage system for general practitioners and various national lines

Tab. I. Number of nasopharyngeal swabs performed by each country from week 10 of 2020 to week 29 of 2020. Modified from [42].

Nations	Week number of the year 2020			
	Week 10-14 (N)	Week 15-19 (N)	Week 20-24 (N)	Week 25-29 (N)
Belgium	96.963	510.361	456.034	432.619
France	363.858	679.521	1.064.100	1.469.235
Germany	1.370.655	1.806.652	1.852.338	2.406.653
Italy	671.004	1.874.451	1.715.994	1.617.331
Netherlands	92.261	175.417	218.631	368.431
Spain	NA	589.689 *	1.436.527	1.011.926
Sweden	53.739	120.945	205.831	372.130
United Kingdom	NA	1.393.248	3.699.076	3.250.062

* Data available from week 18. NA: data not available; Week 10: 2020 March 2 - 2020 March 8; Week 29: 2020 July 13 - 2020 July 19.

Tab. II. COVID-19 cumulative incidence for 100,000 inhabitants, ICU beds for 100,000 inhabitants, maximum daily ICU occupancy for 100,000 inhabitants (Italy; period March, 1 - July 16, 2020). Modified from [20].

Region (Italy)	Cumulative incidence	ICU capacity	Max daily ICU occupancy
Abruzzo	252	8.24	5.75
Basilicata	71.2	8.59	3.33
Bolzano (Aut. Prov.)	504	7.53	12.2
Calabria	62.4	7.18	1.17
Campania	82.1	8.67	3.10
Emilia-Romagna	653	10.1	8.43
Friuli-Venezia Giulia	274	10.4	5.01
Lazio	142	9.44	3.44
Liguria	642	11.9	11.4
Lombardy	951	8.98	13.8
Marche	443	7.02	11.0
Molise	144	6.12	2.90
Piedmont	718	7.29	10.3
Apulia	112	7.53	3.91
Sardinia	83.8	7.44	1.88
Sicily	69.8	8.13	1.58
Tuscany	277	11.9	7.94
Trento (Aut. Prov.)	831	5.91	15.0
Umbria	163	7.87	5.40
Aosta Valley	943	7.88	21.3
Veneto	397	10.1	7.25

dedicated to COVID-19 for information for citizens. In the case of telephone triage, in Belgium doctors were asked to go to the suspected positive/infected patient's home with the appropriate personal protective equipment (PPE). In the Netherlands, outpatient visits were allowed only by appointment. These visits were planned at specific times only for COVID-19 suspected patients, and telematic visits were recommended if possible. In the UK, the Royal College of General Practice offered free telemedicine lectures to general practitioners and recommended visits only in case of need. In some regions of Italy, general practitioners, after adequate telephone triage, were able to activate the special continuity of care unit (USCA). Doctors and nurses belonging to these units went at home to test and provide care to patients not requiring hospitalization. In France, some territorial outpatient services have been created, managed by municipalities on a local basis, with private doctors and nurses to support the national health service. In Sweden some general medicine units have been organized. These units went at home of patients with flu symptoms to test their positivity to COVID-19; however, the responsibility for territorial management has been fragmented following the division of the country into different municipalities. In Germany, special indications for outpatient care have been established by the "Federal Joint Committee" to limit physical contact between patients and healthcare professionals and doctors have been offered the possibility of making paid tele-consultations. Spanish primary care centres have cancelled non-urgent appointments and implemented online drug prescription for patients with chronic conditions.

The automatic renewal of drug prescriptions, especially for the chronically ill patients, has been implemented in several countries such as Italy, Germany and Spain in order to avoid crowding of people waiting in general medicine clinics. In some cases, such as in Germany, pharmacists have been allowed to modify, partially and if strictly necessary, medical prescriptions, and to dispense equivalent drugs in case of emergency. In England, the at home use of abortion drugs was allowed starting from March 30th 2020; this measure was extended to Scotland and Wales subsequently.

The compliance to the vaccination schedule, especially in children, has been heavily affected by the pandemic as well. In Europe, the suspension of the vaccination offer has not been officially declared, but some countries, such as the United Kingdom, report the possible failure to comply with the planned vaccination cycles which could increase the risk of epidemic outbreaks of vaccine-preventable infectious diseases. Belgium, in this regard, has indicated paediatric vaccinations in the age group under 15 months and new-born screening as essential and not to be delayed.

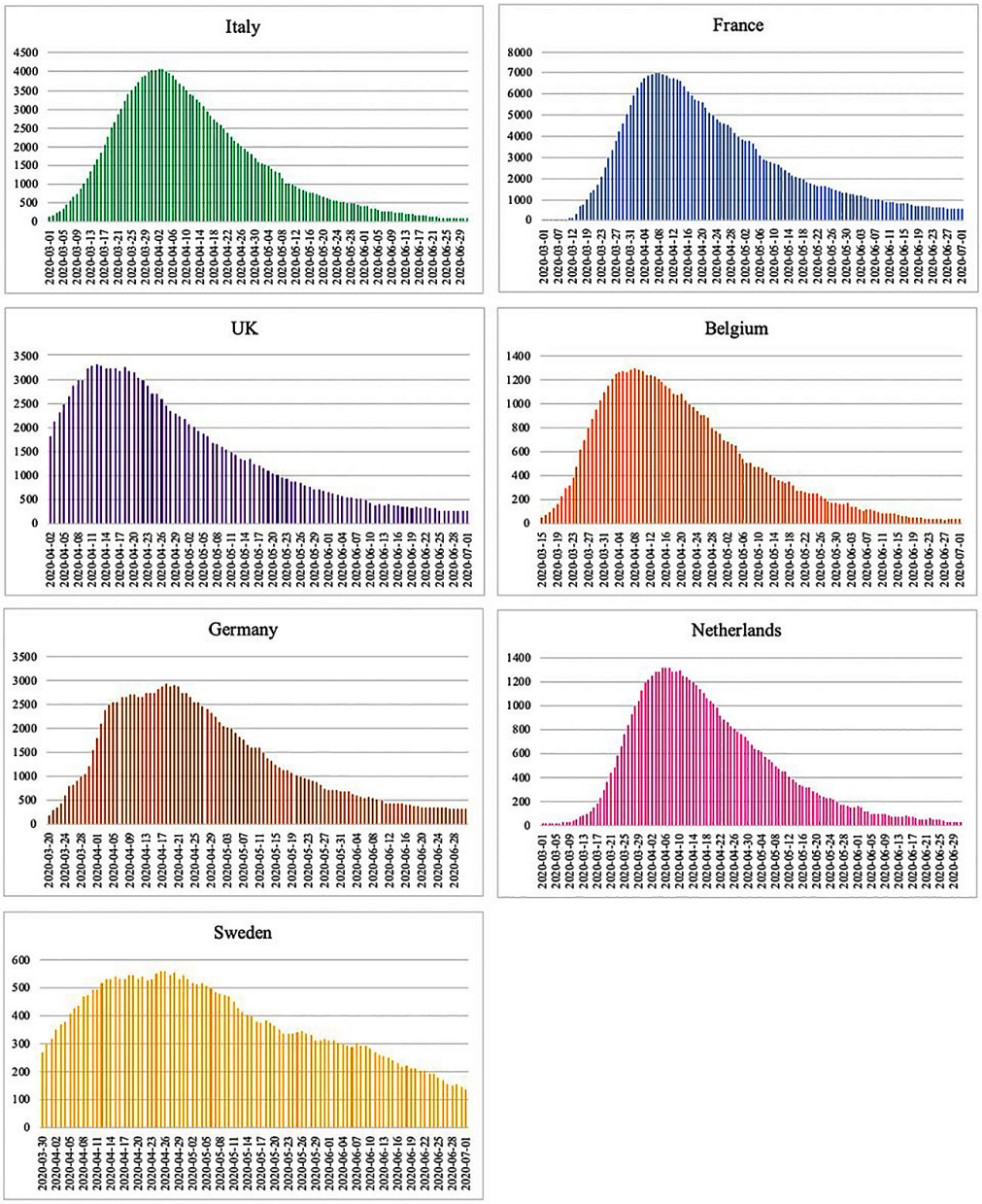
Mental care was completely transformed during the COVID-19 epidemic: psychological support services, mainly by telephone, have been implemented in several countries such as the Netherlands, France and Belgium. Many specialists in the sector have pointed out that the maintenance of mental health and support for chronic psychiatric patients has been underestimated; in France it has been considered in the guidelines since the end of March 2020.

The evidence that most deaths were recorded in residences for frail and elderly patients has placed the focus on the adequate management of these facilities, which were initially not considered to be at the same risk as hospitals. In many countries, access to these facilities has been forbidden for visitors to avoid contagion from the outside; group activities and the use of common areas have also been limited. In Belgium, it is estimated that about half of COVID-19 deaths have occurred in nursing homes; on April 15th, 2020, the Inter-ministerial Public Health Conference approved a project to support hospitals for elderly to increase manpower and materials if needed. In Sweden, the National Board of Health and Welfare has published some guidelines to support the care sector for the elderly and a fund has been set up to finance the same. In Belgium, many residential institutions for the elderly have suffered from the lack of supply of personal protective equipment and in Italy the Italian National Health Agency has published a guide for the prevention and control of COVID-19, specifying the organizational and structural requirements to limit the risk of infections [16].

Health communication

During these months, most of the government bodies have used the various means of communication, such as TV, radio channels and direct streaming on the web

Fig. 3. Daily ICU occupancy, March, 1, 2020 - July, 1, 2020. Data from Spain relatively to this period was not available; data from Germany, Sweden, Belgium and UK are available later than March, 1 [21].



to inform, through press conferences, their citizens on the progress of the pandemic and on the progressively adopted measures (Tab. III).

Interviews and debates with public health experts were often held to inform the population about the epidemiology and severity of the infection. The use of commercials and social media has played an equally important role in promoting public health campaigns, reaching, especially in the second case, also adolescents and young adults.

In this context, the so-called "influencers" with the launch of the well-known hashtag #stayathome contributed in an important way to spreading the message. In general, from January until now, there has been a progressive increase in information and official communications in line with the spreading of the epidemic.

Already starting from the end of January, all major European countries have progressively equipped themselves in communicating, through conventional channels, information on proper hand sanitation, respiratory etiquette and maintaining physical distancing when coughing or sneezing. In the following months, the broadcasting of television and radio commercials on the subject was intensified, with the dissemination of these also online, for example on platforms such as YouTube.

The use of the internet was also useful to support citizens with regard to the management of offspring, provide advices for the correct way to do the grocery

Tab. III. Health communication strategies during the pandemic. Modified from [27].

Health communication strategies	
Often used	Sometimes or rarely used
• Daily conferences and briefings by government and/or public health agencies • Public health campaigns on traditional media (TV and radio) and social media • Information on COVID-19 webpages of existing official websites	• Dedicated COVID-19 website • COVID-19 telephone hotline for questions • Posters, billboards, leaflets in public spaces • Text messages via SMS or emails • Leaflets and letters via post • Chatbots for standard COVID-19 questions

shopping and keep physically active. In addition to this, in countries such as France, especially following a drastic drop in healthcare supply in the first month of the lock-down, the use of these forms of communication was also useful in highlighting the need to provide continuity of care and to support for those suffering from chronic diseases.

Almost all European governing bodies have used similar methods of communicating information on the progress of the pandemic and on the measures progressively adopted. In Germany, official information on the epidemic was communicated regularly through daily bulletins organized by the Robert Koch Institute (RKI), the government's leading scientific institution on infectious diseases. In Italy data were communicated through the official sites of the Ministry of Health, the Italian National Health Agency and Civil Protection; the government also provided daily bulletins on the epidemiological situation through live streams in which the head of civil protection and the director of the Italian National Health Agency were available to answer technical-scientific questions.

The Italian Ministry of Health, through the COVID-19 website, provided information about the disease and related symptoms, epidemiology, methods of prevention and treatment. In the UK, information was communicated through official government sites, social media and mass media (such as the BBC broadcaster). Since mid-March, daily conferences have also been held by the Prime Minister, flanked by other important political figures and experts in the scientific sector. A dedicated COVID-19 section on the British government website was immediately made accessible to the public. The Spanish government has released news on the progression of the epidemic and the implemented policies through daily press conferences. While the Minister of Health took over all the responsibilities relating to the management of the epidemic, it was in fact the head of the Coordination Centre for Health Alerts and Emergencies who provided most of the daily information. From March 14th 2020, at the start of the lock-down, all the ministries involved in this operation (health, economy, defence, domestic affairs) have been responsible for communicating any type of update on the adopted measures. Noteworthy, a consultation channel on WhatsApp, called Hispabot-COVID-19, has been launched; an artificial intelligence was designed with the aim of responding to citizens' doubts about the COVID-19 disease. In the Netherlands, from a communicative point of view, the management of the pandemic was comparable to that of many other countries, except for masks, the use of which has not been promoted, except for health workers and for suspected or confirmed cases needing access to treatment. Besides, a series of webinars organized by patient associations was launched in order to inform about the risk related to a specific disease and the prevention measures to be implemented.

The controversy over the use of masks turned on again in May with the reduction of restrictive measures, especially with regard to their use in places where keeping the distance is difficult, such as public transport. Supporters argue that these certainly make a contribution, albeit minimal, to containing the spread of the virus while the opponents argue that the use of masks gives a false sense of security. Studies published to date on the effectiveness of using the mask outdoors do not clarify this controversy [22-26].

In France, the government has often taken different positions on the usefulness of using masks; most recently, the one according to which masks should be reserved for healthcare professionals and subjects at risk such as frail patients, seems to be related to the difficulty in finding masks for the entire population.

Although the different governments have been committed to disseminate correct information regarding the epidemic, the progressive increase in the circulation of information even on unconventional channels has led to its fragmentation and often inconsistency, creating confusion among citizens. A problem of significant importance that has arisen is that of the spread of "fake news". The Italian Intelligence Company (SOCINT) has warned the government of how numerous news concerning the origin of the virus and the alleged existence of a SARS-CoV-2 vaccine deliberately not made available to the population were gaining ground on the net. It is estimated that in other European countries such as Germany, Spain, France and the UK the total number of people involved in spreading disinformation on different web platforms has reached about half a million [16].

One of the limitations shown by the various governments is that they have not adequately implemented information channels for ethnic minorities [27]. Sweden is an exception: via the public health website it has provided citizens with information on COVID-19 in 25 different languages. The Swedish government has also tried to get the message across to people for whom the language barrier is a serious problem (e.g. those living in poor socio-economic conditions and those who have recently moved to Sweden) through the dissemination of printed information leaflets in several languages. Since January, Belgium has launched a website specifically created to provide information on the pandemic, available in the

three national languages (Dutch, French and German) and in English. In addition, leaflets were also created and made available in other languages such as Arabic, Spanish, Italian, Polish, Romanian and Turkish [16].

Collective and individual preventive measures

Since the beginning of the pandemic, physical distancing has been the essential tool to limit the spread of SARS-CoV-2. In all the examined states, this measure was one of the first to be adopted and is still in force.

The physical distancing has in fact allowed the partial and progressive resumption of various activities. Shops, restaurants, coffee shops, gyms, churches, museums and other places frequented by a large number of people have had to review their activities and organization in order to respect interpersonal distancing and to avoid a rapid increase in the number of infections.

According to the WHO, the distance to be maintained between individuals is at least 1 meter [28]. Not all the examined states have complied with this minimum distance; Belgium, Germany, the Netherlands and Spain have in fact defined 1.5 meters as the minimum distance to keep from other people. In Italy, the distance is increased from 1 to 2 meters during intense physical activity. In England the distance to be maintained is 1.5 meters, but from July 5th 2020, if this is not feasible, the distance of 1 meter can be maintained. In Scotland and Wales, however, the distance to be maintained is 2 meters [16].

The difficulty in maintaining social distancing lies in the fact that it is often very difficult to calculate, without suitable tools, at what distance one places oneself from other people. In order to facilitate the maintenance of distance from other individuals, various solutions can be used, especially in closed places or in places where crowding is possible. Some of these include: the use of adequate signs to define the correct distance, restricted access and the use of face masks. In addition, for entry into the shops, two states (Belgium and Italy) have given precise indications, with reference to how many people can enter the place depending on the width of the same [16].

At the beginning of the pandemic, the use of face masks was recommended only to people with suspected symptoms of COVID-19 and to groups of workers at risk for contagion. With the progress of knowledge about SARS-CoV-2 and the role of asymptomatic infected subjects in the spread of infection, many states have decided to make the use of masks mandatory or recommended in different situations (Fig. 4). In the UK, face masks have been used as a recommended but not mandatory temporary measure until the end of July; in Spain, Italy, the Netherlands, France, Belgium and Germany it is a mandatory measure adopted especially during the transition phase. In particular, Italy, France and Spain have made it mandatory in any situation in which interpersonal distance cannot be maintained. Belgium has made it mandatory in means of transport and in the workplace, if the minimum distance cannot be respected, and from June 8th 2020, given the reopening of coffee shops and restaurants, it is also mandatory for waiters. It remains strongly recommended in public spaces when the inter-personal safety distance cannot be respected. For the Netherlands, where the use of the mask is seen as a measure of dubious utility, it remains mandatory to wear it on public transport. It should be noted that in this country the general population is not advised to use surgical masks as they must be preserved for use by health professionals while the use of community masks is instead encouraged. Finally, for Germany, the mask must be worn in public transport and in shops, but this obligation is not uniform throughout the national territory [16, 29].

It is important to keep in mind, as WHO continues to remind, that the use of face masks can be a great help in containing the spread of SARS-CoV-2 especially when it is difficult or cannot be kept the safe distance, but it is not the most important preventive measure. In fact, the use of masks can lead to a false sense of safety that tends to make subjects to forget all other preventive measures. It is essential to try to keep as high as possible the awareness of the population that preventive measures work best when applied together because they have a synergistic effect [30].

If in public places it is potentially easier to check compliance with safety measures, the problem remains for gatherings in private places. Belgium, France, Germany, Scotland and Wales have in fact defined the number of people/families who can get together privately already this summer [15].

Physical distancing plays an even more important role in the reopening of schools and workplaces. While for workers who can take advantage of smart working this is always the preferable choice, in realities like schools and educational centres, remote work becomes an increasingly difficult tool to manage [16]. In May and June, all the examined states that had closed schools (Belgium, Germany, Italy, Netherlands, Spain and United Kingdom) [31] progressively reopened kindergartens, educational centres, nursery schools, primary and secondary schools, even if in different ways and timing. School attendance has not been compulsory for Belgium, the Netherlands and Spain until the end of August; in these countries the reopening of these services had had the main objective of relieving parents from managing their children, especially for those who carry out essential jobs and who cannot take advantage of smart working. In Spain, in fact, children/teenagers who needed learning support activities, who had to take exams or whose parents did not have the opportunity to use teleworking, were admitted to educational services. In France, attendance at kindergarten, primary and secondary school returned to be mandatory from June 22nd 2020 and it is mandatory for teachers and high school students to wear a mask. In Germany, however, the decision to reopen schools is left to the individual federal states. In Italy, summer education centres and kindergartens have reopened, while mandatory schools have restarted their activity in September 2020. In

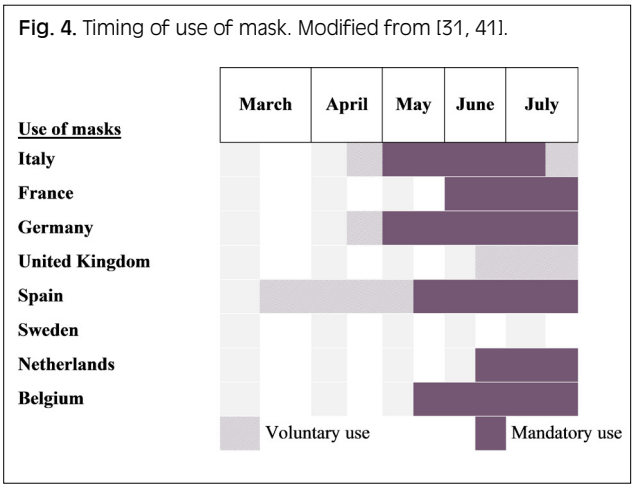


Fig. 4. Timing of use of mask. Modified from [31, 41].

Sweden, from 15 June 2020, upper secondary school students can return to school, while school services have never been suspended for < 16 years-old students. In the UK, the recovery of primary schools started in September even though the initial goal was to reopen in June. Although in this country all the schools were closed on March 23rd 2020, a service for the children of essential workers, for children/young people with disabilities and for socially vulnerable ones was still active [16].

As regards the management of the progressive slowdown of restrictive measures, France, Spain and Italy have defined the epidemiological risk of the various regions and, for this reason, slowdown has been different in the different areas of each country [32].

Germany, on the other hand, left the decisions to individual federal states. In any case, all states mainly made their decisions by evaluating not only the national and regional epidemiological trend, but also taking into account the capability of their health system (particularly intensive care units) and hospitals in order to avoid the saturation of the system and to allow to have sufficient resources to manage a new possible increase in cases [16].

All states, except Sweden, Germany and the Netherlands, have adopted the restrictive measures that characterized the enforced lock-down in March, while the gradual slowdown began in May. From this point of view, there is a relative uniformity in the application of the measures and their subsequent withdrawal (Fig. 2) [16, 31].

Another crucial point is the management of restrictive measures applied to trips. From mid-March until June 15th, 2020, the countries of the European Union and the Schengen area, except Ireland, agreed to coordinate by applying restrictions on non-essential trips, as recommended by the European Commission [33]. All the states have then drawn up their own, continuously updated, list of the countries for which particular restrictions are applied. In addition, Italy, the United Kingdom, Belgium, Spain, Germany and France have requested, upon entry into the country, a period of quarantine in different ways (each country makes it mandatory or recommended for different states). Sweden, on the other hand, has never applied this measure by asking incoming travelers to self-isolate if potentially at risk [34].

Conclusions

Dealing with and managing a pandemic like the one we are experiencing has created considerable difficulties for governments. In all the considered states, various task forces have been created to make the management of the crisis and the state of emergency more targeted. The two most affected areas were obviously the health system and the socio-economic one. Essential and necessary measures adopted during the lock-down have led to a decrease in infections during the most critical phase of the pandemic, but at the same time they have created social and economic hardship due to the closure of non-essential economic activities and the imposition of permanence at home. Managing these difficult situations has been a global challenge and, in some countries more than others, has further aggravated already ongoing economic crisis [16].

We believe that the correct and timely application of preventive measures to limit the infection from SARS-CoV-2 are the most effective tool to limit the new epidemic peak which is further aggravating the already highly compromised European situation, both from a social and economic point of view. The methods and timing of application of the aforementioned measures at European level have been assessed individually by the states and with substantial different approaches. To date, sharing objectives and strategies seems absolutely relevant in order to face the impact of COVID-19 throughout Europe.

Fortunately, a first step in this direction was taken when planning the vaccination campaign against COVID-19. The Health Ministers of Belgium, France, Germany, Italy, Luxembourg, the Netherlands, Spain and Switzerland in their declaration of December 15th 2020 are committed to greater sharing especially in view of the phase that will follow the administration of anti-COVID-19 vaccines [35]. This is certainly a strong signal that anticipates a continuous and ever greater sharing of preventive strategies aimed at containing the pandemic. Having a single strategy, obviously to be adapted to the epidemiological context of each country, can also be helpful in facilitating the understanding and sharing of the measures by individual citizens. In this case, it is not a question of renouncing national individuality but of sharing common objectives so that all Europe can cope with the pandemic.

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Authors' contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

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Review

COVID-19 vaccines: evidence, challenges and the future

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Summary

Through an unprecedented research and development process, in early 2021, just one year after the COVID-19 pandemic started devastating the world, there are several vaccines commercially available or in advances phase of testing, each with its own characteristics and challenges. For the first time in the history of vaccination, a global immunization program has started at a time of intense pandemic activity characterized by high virus transmission, facilitating selection of variants potentially able to escape the vaccine-induced antibody response. The reality is that one cannot rely on a single vaccine when dealing with a pandemic emergency: the urgent need of billions of doses clashes with the production capacity of the pharmaceutical industry. There is therefore no ideal vaccine, but there are many good vaccines to be used immediately. The current international debate about COVID-19 vaccines is today the hottest topic in global health whether it relates to technical and scientific issues or to the ethical aspects of access to vaccinations for all. This article aims at reviewing the status of vaccines that are used, or about to be used, in immunization campaigns worldwide.

Introduction

In recent decades, major outbreaks of emerging infectious diseases have become a serious and recurrent problem. According to a study published in Nature, about 40 new pathogens have been identified since the beginning of the new millennium, many of them from animal reservoirs [1]. In fact, most of these new infections are zoonoses, since they may originate in animals, at least in their initial emergence. Among all microorganisms, the ones that best fulfill the role of an emerging pathogen are viruses. In general, the risk of contracting a new virus of animal origin depends on the frequency of contact between humans and the animal species that is infected (the natural host). Measles and smallpox probably passed from livestock to humans with the introduction of farming over 10,000 years ago. In recent years, new viruses have emerged with increasing frequency from the animal context and have become a major global health threat: avian flu, Hendra, Nipah, SARS-CoV, MERS-CoV, Ebola, Zika, Chikungunya are just a few examples [2, 3].

The frequent emergence of zoonoses and their penetration into humans depend on many factors. Economic interests are leading to deforestation and therefore destruction of natural habitats with, as a consequence, greater contact among wild animals, domestic animals and humans. The trade of bushmeat in urban markets, once limited to rural areas, represents another factor that could carry new pathogens to humans. Climate change has also a significant role in facilitating the progressive movement of vectors towards previously un-infested areas. Furthermore, with the multiplicity of aspects of globalization and with the abolition of previous barriers, humans, animals and goods can move over long distances and reach different continents in a few hours. Hence, the conclusion that "a health threat anywhere is a health threat everywhere". Coping with the spread of new infectious diseases therefore requires a worldwide coordinated effort, that is at the same time in the realm of a health response as well as of political and economic nature.

The current international debate about COVID-19 vaccines is today the hottest topic in global health whether it relates to technical and scientific issues or to the ethical aspects of access to vaccinations for all. Through an unprecedented research and development process, in early 2021, just one year after the COVID-19 pandemic started devastating the world, there are several vaccines commercially available or in advances phase of testing, each with its own characteristics and challenges. This article aims at reviewing the status of vaccines that are used, or about to be used, in immunization campaigns worldwide.

An unprecedented research and implementation effort

The remarkable phenomenon one has witnessed in the past several months is that, after the approval of the first vaccines from Pfizer-BioNTech, Moderna and

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AstraZeneca, other pharmaceutical companies have continued their research efforts, and stringent regulatory authorities have not shied away from the preparatory work to approve new vaccines. This is per se something exceptional, as is the recent announcement that two competitor pharmaceutical companies have agreed to cooperate in the production of a vaccine that one of the two has developed [4]. In fact, it would be imprudent to rely on one vaccine only to cope with a major health emergency such as this pandemic that requires a simultaneous response worldwide. The need of billions of doses to be made readily available clashes with the pharmaceutical industry production capacity, and this has prompted an unprecedented intensive response by industry and governments. Indeed, one has little options: several vaccines must be developed, and all those authorized must be rapidly put into use through effective and strategic campaigns in every country. At the moment, clinical trials are being conducted worldwide on over 80 vaccines, half of which have reached the final phase of experimentation, and at least 180 experimental products are currently in preclinical phase of trials and animal testing has started [5]. Nine vaccines were already authorized in some countries for emergency use based on preliminary evidence of their safety and efficacy, and eight of them (Pfizer/BioNTech, Moderna, AstraZeneca, Cansino, Sinovac, Sinopharm Wuhan, Gamaleya, Vector Institute) were approved by regulatory agencies in some other countries after review of the final trial results [6].

The progress carried in the biotechnology field over the past few years has provided an important boost in the development of vaccines produced through the use of less complex and less expensive methods such as genetic engineering techniques. These techniques allow to obtain in a short time massive amounts of vaccines compared to traditional techniques which were based on the isolation followed by the attenuation or inactivation, and finally the purification of the pathogen. Regardless of the technology used in their development, all vaccines approved or still under study were developed to stimulate in the vaccinated individuals an immune response targeting the blockage of the SARS-CoV-2's Spike protein which has a key role in the viral entry into human cells.

EMA and FDA approved vaccines

The European Medicines Agency (EMA) is the agency of the European Union (EU) responsible for the evaluation and supervision of medicinal products. As of the end of May 2021, the EMA had approved four COVID-19 vaccines: two of them are mRNA vaccines and two are viral vector vaccines. The other major stringent regulatory authority is the US Food and Drug Administration (FDA) that had approved, as of the end of May 2021, three vaccines: two are the same mRNA-based vaccines approved by EMA, while one is a viral vector vaccine. Table I shows the main characteristics of the EMA and FDA approved vaccines as of the end of May 2021.

mRNA-based vaccines approved by both EMA and FDA

Pfizer/BioNTech (BNT162) and Moderna (mRNA-1273) vaccines were approved by EMA in December 2020 and January 2021 respectively, and by FDA, which issued emergency use authorizations in December 2020 and extended them in May 2021 to include adolescents between 12 and 15 years of age [7].

They are both composed of molecules of messenger ribonucleic acid (mRNA) which contains the instructions for the synthesis of the Spike protein in the cells of the vaccinated subject. Both vaccines were demonstrated to be safe in clinical trials. They require two administrations (at 21 or 28 days from the first administration, with a maximum delay between two doses of 42 days). The Pfizer/BioNTech vaccine phase 3 trial [8] involved 43,998 subjects between 12 and 85 years of age who received both doses, whereas Moderna phase 3 trial [9] included 30,000 participants older than 18 years (3,000 teenagers between 12 and

Tab. I. Characteristics of the four COVID-19 vaccines approved by stringent regulatory authorities and available in Europe as of the end of March 2021.

Vaccine	Type	Efficacy	Indications	Administration	Effect on transmission	Activity against variants	Side effects	Cold chain	Price in EU (€)
Pfizer-BioNTech COMINARTY	mRNA	95%	> 16 Also elderly Pregnancy	2nd dose 21-28d	Unknown	Unclear	Fever, local reaction, allergy	-70°C (2-8°C x 5d)	12.00
Moderna-mRNA 1273 (NIAID)	mRNA	92%	> 18 Also elderly Pregnancy	2nd dose 28d and up to 42d	Unknown	Probable	Fever, local reaction, allergy	-20°C (6 months)	15.30
Oxford-AstraZeneca AZD1222	ChAdOx1	63%	> 18 Also > 65 Pregnancy	2nd dose 8-12w (longer interval increases efficacy)	Unknown	Possible slight reduction of effectiveness on B1.1.1.7	Fever, local reaction, allergy	2-8°C	1.80
Johnson & Johnson Ad26.COV2.S	Ad26	85%	>18	Single dose	Unknown	Unknown	Fatigue, headache, myalgia, fever		7.30

18 years were also included) receiving the two doses. The most common reported side effects related to BNT162 were fatigue (3.8%), headache (2%), together with severe allergic reactions (2/10,000 vaccinated subjects in United Kingdom). Fatigue (9.7%), muscle and joint pain (8.9% and 5.2%), headache and injection site erythema were described for mRNA-1273 vaccine. The efficacy estimated in these trials was 95% (95% CI: 91-98%) for the Pfizer/BioNTech vaccine, with 170 infections reported at 4 weeks from the 2nd administration. For the Moderna vaccine the estimated efficacy was 94% (95% CI: 90-97%) with 196 infections reported at 2 weeks from the 2nd administration. In addition, the Moderna mRNA-1273 vaccine had an efficacy of 86% (95% CI: 61-95%) among patients over 55 years old [10], compared to 95% (95% CI: 67-100%) of the Pfizer/BioNTech product. The major drawback of these two mRNA-based vaccines is the storage requirement at -70°C (or 2-8°C for 5 days) for the Pfizer/BioNTech vaccine and at -20°C (for 6 months) for the Moderna vaccine.

Because of their safety and high efficacy, these two mRNA-based vaccines are now recommended in persons older than 16 years, in particular in high-risk individuals that are more vulnerable to severe forms of COVID-19. At the end of May 2021, EMA and AIFA approved the use of the vaccine from Pfizer/BioNTech in adolescents from 12 to 15 years [11].

Viral vector vaccines approved by EMA and FDA

AstraZeneca/Vaxzevria's vaccine, ChAdOx1 nCoV-19, is the viral vector-based vaccine approved by EMA and filed for FDA approval. It uses a modified version of a chimpanzee's adenovirus which is not able to replicate but can provide the instructions for the Spike protein synthesis. Once the protein is produced, it can stimulate a specific immune response of both cellular and humoral nature. Compared to mRNA-based vaccines, this vaccine has a better stability which does not require excessively cold temperatures for storage and transportation (between -8 and +2°C). The phase 3 trial on the vaccine involved more than 24,000 subjects aged over 18 years from UK, Brazil and South Africa.

It requires 2 administrations. The efficacy in subjects who received two standard doses was 66.7% (95% CI: 57.4-74.0%) and 81 infectious cases were described among vaccinated individuals 2 weeks after the 2nd administration. However, the efficacy was 76% after a single standard dose (from day 22 to day 90). Most participants in the UK received the booster dose more than 12 weeks from the first administration, and the vaccine efficacy was higher in this population (81.3%) compared with those who received the second administration earlier [12]. The primary analysis of a trial conducted on over thirty thousand patients in the US showed an overall efficacy of 76% (95% CI: 68-82%) after the 2nd dose and an efficacy of 85% (95% CI: 58-95%) in adults older than 65 [13].

Its safety and efficacy in older age groups was assessed on a phase 2/3 trial carried out in the UK involving 240 adults older than 70 years. Local and systemic reactions were less frequent in older age groups, with similar humoral and cellular immune responses compared to younger populations [14]. Earlier on, doubts on safety arose due to two cases of transverse myelitis being described following vaccination (at 10 and 14 days from the 2nd administration). Both cases were later reported to be unlikely related to the vaccine. However, later the use of the vaccine was associated with some deaths in different European countries that were attributed to thromboembolic events. These were mainly reported within 14 days from the first dose in individuals younger than 60 years and with a greater frequency in females. This phenomenon has been attributed to a response similar to the one occurring in heparin-induced thrombocytopenia. These adverse events prompted some EU countries (e.g., Austria, Bulgaria, Denmark, Estonia, Germany, Iceland, Italy Latvia, Lithuania, Luxembourg, Norway and Romania) to suspend the administration of the vaccine as a precautionary measure pending further investigations. The EMA's safety committee (PRAC), after reviewing the available information, on 18 March 2021 suggested that "the vaccine's benefits continue to outweigh the risks of side effects", adding that the vaccine is not associated with an increased risk of thromboembolic events nor that specific batches were related to those events. WHO confirmed the recommendations of the EMA stating that the "benefits of the AstraZeneca vaccine outweigh its risks" and therefore recommended that vaccination campaigns continue [15]. However, in April 2021, as further episodes of thromboembolic events (in particular cerebral sinus vein thrombosis: 169 identified cases; and splanchnic vein thrombosis: 53 cases) were described, the European PRAC committee advised that very rare cases of thromboembolism associated to thrombocytopenia should be included as possible side effects of Vaxzevria vaccine [16].

As of May 2021, EMA and WHO still recommend the administration of the vaccine with a careful monitoring of vaccinated individuals, and a preferential use in individuals older than 60 years has been adopted in different countries.

The Johnson & Johnson vaccine, recently approved by the US FDA and by EMA [17], is a viral vector-based vaccine, which uses type 26 human adenovirus administered intramuscularly to adults ≥ 18 years of age. It requires a single administration and its storage temperature does not represent a problem as it can be kept stable for 3 months at +2/+8°C and for 2 years at -20°C. This vaccine was tested in over 43,000 subjects of different age groups (including 34% over age 60) and at different latitudes, from the USA to Latin America and South Africa. It was especially evaluated in patients with comorbidities such as obesity, diabetes, cancers, HIV, obtaining results reaching 100% efficacy in preventing hospitalization or death, and 85% against severe forms of COVID-19 [18]. Furthermore, this vaccine was tested in South Africa when the South African variant was already in circulation. The mean efficacy in moderate to severe forms was 65%, meaning that it has

partial efficacy against the variant. The most common adverse events reported in the trial were injection site reactions, headache, fatigue, myalgia, nausea and fever [19]. Similar to the case of Vaxzevria, some cases of thrombosis with thrombocytopenia were described in patients who received Janssen's vaccine. For this reason, at the end of April 2021, EMA listed these events as a very rare side effect of the vaccine, still recommending, however, its usage [20].

Of relevance, Johnson and Johnson is planning to start testing in children between 2 months and 18 years in different international centers. Based on all these considerations, the US-based company filed phase 3 trial data for a single administration of its anti-COVID-19 vaccine and the US FDA authorized it for use in emergency situations on February 27th, 2021.

Remarkably, a very recent agreement between Johnson & Johnson and its competitor pharmaceutical giant Merck & Co, brokered by the White House, could lead to a faster production of the vaccine in the US. According to this agreement, Merck & Co will be co-manufacturing the Johnson & Johnson vaccine thus allowing production of enough doses sufficient to cover the entire adult population of the United States by the end of May [4]. The EU authorized at the beginning of March the emergency use of the vaccine and already established an agreement for the purchase of 200 million doses together with an option for another 200 million doses.

Vaccines being considered for approval

Sputnik V

The delays in the delivery by Pfizer and the safety concerns arisen by the AstraZeneca vaccine are now prompting the EMA to explore approval of the Russian Sputnik V vaccine which may result in purchasing by the EU Member States. The Sputnik V vaccine was so named from the first Soviet space satellite, Sputnik-1, which was launched in 1957. This event resulted in a new boost to space research all over the world creating the so-called "Sputnik moment" shared by the global community. This viral vector vaccine employs two human adenoviruses (rAd26 and rAd5) which transfer the SARS-CoV-2 Spike protein gene into human cells. Human adenoviruses are considered among the easiest viruses to engineer and therefore became very popular vectors. Sputnik V utilizes these two distinct adenovirus vectors dispensed separately in two administrations at 21 days distance from one another and induces a strong and specific antibody response against SARS-CoV-2. This strategy is conceived to prevent development of immunity against the first adenovirus injected (rAd26) which could impair response to the booster dose if the same virus were used as vector. This vaccine has now been registered in more than 25 countries. The clinical study post Sputnik V registration carried out in Russia involved more than 31,000 volunteers (study population between 18 and 60 years) while phase 3 clinical trials were conducted in United Arab Emirates, India, Venezuela and Belarus. Initially, doubts arose regarding the efficacy of the vaccine lacking assessment by an independent stringent regulatory agency. These doubts however were successfully addressed by a large study finally published in February 2021 [21]. This study showed an efficacy of 91.6% (95% CI: 85.6-95.2%) based on the analysis of data from almost 20.000 volunteers (18-87 years) who received both a first and second administration either of the vaccine or of a placebo.

Starting at 21 days after the first dose of vaccine (the day of dose 2), 16 (0.1%) of 14,964 participants in the vaccine group and 62 (1.3%) of 4,902 in the placebo group developed COVID-19; vaccine efficacy was therefore estimated to be 91.6% (95% CI: 85.6-95.2). Of note, the vaccine efficacy was 91.8% (95% CI: 67.1-98.3) in participants older than 60 years. The study also showed the safety of Sputnik V, the most common adverse events being flu-like illness and local reactions, observed, respectively, in 156 and 56 participants in the vaccine group. The freeze-dried form of the vaccine can be stored at temperatures between +2 and +8°C, which is a strong point in favour of this product since it allows for an easier distribution around the world including in areas which are difficult to reach or when the cold chain cannot be guaranteed. In Moscow, Russia, the vaccine is administered in drugstores and even in some supermarkets.

Novavax

The Novavax NVX-CoV2373 vaccine is a protein-based vaccine composed of SARS-CoV-2 Spike recombinant proteins. It contains an "adjuvant" (saponins), which contributes to strengthen the immune response to the vaccine. Two administrations are planned to be dispensed at 21 days distance from each other. The vaccine target is set to adults between 18 and 84 years of age. Novavax vaccine can be stored between 2 and 8°C and is shipped in a ready-to-use liquid formulation. The company announced an efficacy of 89.3% (95% CI: 75.2-95.4%) following a phase 3 trial conducted in Great Britain (15,000 volunteers, 27% of which were over 65), in a moment in which the UK variant was emerging and circulating widely. Sixty-two COVID-19 cases were described in the trial, 6 of which were among the vaccinated subjects. Of these infections, half were caused by the UK variant, allowing to estimate an efficacy of the vaccine against the Wuhan strain of 95.6% and against the British variant B.1.1.7 of 85.6% [22]. A smaller phase 2b clinical trial conducted in South Africa (4,400 volunteers, 6% of which were HIV-positive) could raise doubts regarding its efficacy on variants. In that context, an antibody-resistant variant was found in a high percentage of infected persons (90%), lowering the overall efficacy of the vaccine to 60% (95% CI: 19.9-80.1%) and to 49% (95% CI: 6.1-72.8%) among HIV-positive volunteers. A phase 3 trial is currently being carried out in the United States and Mexico (30,000 volunteers) to evaluate the efficacy,

safety and immunogenicity of this vaccine in different populations [23]. The vaccine is under rolling review since February 3rd, 2021 [24] and the European Commission is currently negotiating a pre-purchase contract with the company. The rolling review is a regulatory tool that EMA uses to speed up the evaluation of a drug during emergencies, this involves the EMA's human medicines committee (CHMP), which reviews data coming from ongoing studies as soon as they become available.

Valneva

Another vaccine in advanced phase of development is that of Valneva, a French-Austrian company. This vaccine uses inactivated viruses incapable of infecting and multiplying. The virus, despite being killed, maintains all its antigenic properties beyond the Spike protein. This characteristic makes it potentially more immunogenic. Valneva started its phase 1 and 2 trials in December 2020 on patients between 18 and 55 years of age [25].
Once studies are completed, both the Novavax and the Valneva vaccine manufacturers are likely to sign agreements with the EU for the provision of large quantities of vaccines. The negotiations between the EU and Valneva are on an advanced stage for a supply of up to 60 million doses of VLA2001 [26]. The EU is also close to reach a final agreement with Novavax for 100 million doses together with another optional 100 million doses [27].

ReiThera

The ReiThera vaccine, developed by the Italian company from the Pomezia's technopole together with the Spallanzani Hospital of Rome and the University of Padova, uses a technology that is very similar to that of AstraZeneca and that takes advantage of a primate's adenovirus (from gorilla) modified so as to express the Spike protein. It recently obtained the green light by AIFA at the end of phase 1 showing safety and immunogenicity, and the testing is now proceeding with phase 2 of trial in different Italian centers [28]. Healthy adults will be included, followed by those over 65 and those affected by chronic conditions [29]. The objective is to rapidly obtain the required registration from both the Italian and EU medicine authorities and swiftly proceed with the large-scale utilization of the vaccine. The Italian Government is financing phase 2 and 3 of the trial which should be completed in June 2021. An effort was requested to the Italian Regional Governments to help finance an early production of the vaccine, trusting in the favorable outcome of the trial, in order to have the first doses readily available as soon as the vaccine is authorized thus shortening the time required to reach full production capacity.

CureVac

Early in February 2021, EMA started a rolling review of CureVac's CVnCoV, a mRNA vaccine, based on preliminary results from laboratory and clinical studies [30]. The results of the rolling review will provide evidence for a possible marketing authorization. Phase 1 study results showed a good tolerability together with a strong antibody and T cell response, reaching titers comparable to those of recovered COVID-19 patients. The vaccine should be administered twice, at day 1 and at day 29 and can be stored at suitable conditions (+5°C for at least three months and 24h at room temperature before administration) [31]. Additionally, a preclinical study on mouse models showed protection against the "South African" SARS-CoV-2 variant. The HERALD study, a phase 2b/3 study initiated in December 2020 has so far recruited 40,000 participants worldwide and will further characterize the efficacy of the vaccine against SARS-CoV-2 and its variants [32].
Of interest, at the beginning of March 2021, the Swiss company signed an agreement with Novartis for the production of CVnCoV, which should start in the 2nd quarter of 2021, with the production of 50 million doses by the end of the year and further 200 million doses in 2022 [32].

Sinovac

At the beginning of May, EMA announced the starting of another rolling review, evaluating the efficacy and safety of the Chinese company Sinovac Life Sciences Co. (Life'On) vaccine, Vero Cell Inactivated [33]. The vaccine was first authorized in China in February 2021 and has since then been authorized by more than 30 countries in adults older than 18 years, with 260 million doses which have been already distributed worldwide [34].
Vero Cell is an inactivated viral vaccine containing inactivated SARS-CoV-2 as antigen, together with an adjuvant. The vaccination schedule consists in two administrations, at 14-28 days distance, and the vaccine can be stored at 2-8°C. Phase 3 studies are taking place in different countries (China, Brazil, Indonesia, Turkey, Chile). As of end of May 2021, the most common adverse events which were described are pain at the injection site, headache, fever and myalgia. In China, where more than 35 million doses have been administered, 49 serious adverse events were reported. These include demyelination, cerebral hemorrhage, Henoch-Schönlein purpura, anaphylaxis and laryngeal edema. Overall, the vaccine showed an efficacy of 67% (95% CI: 65-69%) in preventing the infection and of 85% (95% CI: 83-87%) in preventing hospital admissions [34].

Is there an ideal COVID-19 vaccine?

With several COVID-19 vaccines now available and in an advance phase of the development pipeline, country authorities would be tempted to try and rank them to make a rational decision on which would better fit the needs of a certain country and that therefore should be adopted. However, the reality is that one cannot rely on a single vaccine when dealing with a pandemic emergency: the urgent need of billions of doses clashes with the production capacity of the pharmaceutical industry. There is no alternative therefore to the adoption

of all authorized vaccines and their urgent delivery to people through well-thought strategic campaigns. The development and validation of those still in trial phase is essential, as this is one important way to reduce the circulation of the virus and the potential emergence of new variants. The situation is extremely delicate: for the first time in the history of vaccination, a global immunization programme has started at a time of intense pandemic activity characterized by high virus transmission. This is a very favorable situation for the virus, facilitating selection of variants potentially able to escape the vaccine-induced antibody response. There is therefore no ideal vaccine, but there are many good vaccines to be used immediately. In other words, we do not have the 'luxury' of selecting one ideal product since to vaccinate billions in a very short time requires urgent adoption of all vaccines that are authorized.

Current vaccination campaign in Italy

The anti-COVID vaccination campaign in Italy began in late December 2020 and has been structured in 4 phases by the government. The strategy has been subsequently updated in early February 2021 after the approval of the AstraZeneca vaccine, which was shown to be suitable for the target population of phase 3 (school and university staff; armed police forces; prisons; community places) [35]. More than 84 million doses should be administered (2 doses per vaccinated person) to achieve the goal of vaccinating 80% (conventionally established to guarantee herd immunity) of the Italian population by September 2021 [36]. As of 31 May 2021, 34,900,000 doses had been administered and 12,000,000 people had been fully vaccinated (of those, 630,000 were vaccinated with a monodose vaccine), representing 20.38% of the total population [37]. The initial slow coverage has been attributed mainly to delays in supply and distribution of vaccines by pharmaceutical companies, compounded with poor planning and organization of vaccination services in some regions. However, at the current pace and with the current average rate of daily vaccinations, it would take almost 4 additional months to cover 70% of the population. Therefore, the government's target would be reached by end of September 2021 (with a delay of one month with respect to deadline of end of August 2021 set by the government) [38]. This situation could be complicated by the consideration that 70% vaccination coverage may no longer be sufficient to interrupt virus transmission given the new and more transmissible variants already circulating and progressively replacing the original strain of SARS-CoV-2 against which vaccines were produced.

Limitations of current vaccines

While an unprecedented research effort has in one year resulted in the development of numerous vaccine candidates and the introduction of large-scale campaigns of a few of them, there are important and critical limitations that may prevent a successful containment effort of the COVID-19 pandemic: the emergence of variants and the uncertainties around the duration of protection. These factors add to the widespread adverse feelings in some segments of the population that oppose vaccination practices due to ignorance and misinformation.

The appearance of virus variants is an expected event and is part of nature's variability. The identification of variants is possible by applying advanced gene sequencing techniques capable of detecting mutations in the viral genome. These mutations occur more frequently in RNA viruses, including the influenza Orthomyxoviruses, Hepatitis C virus and HIV, especially when they find a way to replicate and widely spread in the population. Neutralizing antibodies are usually induced by infection or vaccination, so that a strong neutralizing antibody response is built up to suppress virus replication. A weak response does little to suppress replication, but neutralizing antibodies that have intermediate potency are thought to cause the virus to evolve and create ways to escape the constraint on its ability to replicate.

Therefore, the occurrence of SARS-CoV-2 mutations capable of producing variants able to replace original wild strains if they become more transmissible, was predictable. Among the SARS-CoV-2 genes that most frequently mutate there is the one encoding for the Spike protein. This protein is a key to transmission as it is involved in binding with the ACE human cell receptors and is also the target of neutralizing antibodies produced as part of the natural response or the vaccine. Data published by WHO on over 10,000 SARS-CoV-2 genomes from 68 countries sequenced to date indicate the appearance of almost 6,000 mutated strains. Not unexpectedly, only a few of those became well established in the population by showing a relevant epidemiological advantage. Hence, the denomination of "variant" [39]. The "English", "South African", "Brazilian" and "Indian" variants are among them. It is known today that all four variants are characterized by a higher transmissibility and the vaccine seems to be protective against the English one, while there are less certainties for the South African, Brazilian and Indian ones. Table II shows the significant variants identified so far.

The most recent identified variant, the Indian one, has 13 mutations, including two notable ones in the Spike protein that the virus uses to bind and infect cells. One of the mutations, E484Q, is similar to that found in the variants identified in South Africa and Brazil (E484K). The other, known as L452R, may boost viral transmission. The two mutations are in important parts of the structure of the Spike protein that is linked to the interaction of the virus with the host.

Scientists are also looking into a third mutation, P681R, which might help the virus replicate more quickly [40].

In laboratory-based studies, the South African variant was found to be partially resistant to neutralizing antibodies induced by 2 doses of the Pfizer mRNA

Tab. II. The main characteristics of the principal variants identified as of the end of March 2021.

Lineage and variant name	Location of first detection	Date of first detection	Mutations	Spread [63]	Clinical significance	Vaccine efficacy
B.1	China	02/2020	D614G (spike protein gene)	Global	More infectious, overgrew wild type strain globally	Pfizer: 95% Moderna: 95% AstraZeneca: 82% Johnson & Johnson: 85-100% Novavax: 95% Sputnik V: 91%
B1.1.7 (VOC 202012/01 or 501Y.V1)	UK	03/2020	P681H (may increase the production of Spike proteins) N501H (not likely to be involved in vaccine resistance) H69-V70 Y144/45 (may help evade antibodies)	Variant reported by 94 countries, sequenced in 102 countries	More infectious, causes more severe infections	AstraZeneca: 74% Novavax: 85%
Cluster 5 ΔFVI-spike	Denmark	09/2020	Y453F 69-70deltaHV	Extinct as the Danish minks' population was culled	Spread from minks to humans, causing an infection not more severe than the B.1 lineage. Causes weaker antibody response	Not known, but mutation may be related to a reduced vaccine response.
B1.351 (501Y.V2)	South Africa	10/2020	N501Y (similar to N501H mutation) K417N E484K (may help evade antibodies)	Variant reported by 48 countries, sequenced in 58 countries	More infectious and more resistant to neutralization	Novavax: 60% Johnson & Johnson: 65%
P.1 (501Y.V3)	Brazil, Japan	12/2020	N501Y K417T E484K	Variant reported and sequenced by 26 countries	More infectious, more severe infections. Escapes neutralization by circulating antibodies	AstraZeneca: preliminary data shows efficacy (results not published)
B.1.427, B.1.429 (CAL.20C)	USA	06/2020	L452R (increases transmissibility)	B.1.427 reported by 14 countries B.1.429 reported by 15 countries	Not yet shown to be more infectious, neither to be related to a more severe infection	Not known
B.1.617	India	10/2020	E484Q (may help evade antibodies) L452R P681R (increases infectivity)	Variant reported by 30 countries	More infectious and reported to be more resistant to neutralization	Bharat's Biotech: preliminary results show efficacy [64]

vaccine, the Moderna mRNA vaccine, and the Novavax protein vaccine [41, 42]. Moreover, single-dose Pfizer vaccine serum antibodies were shown to be completely ineffective in neutralizing this particular variant. At present, most scientists active in this area are reasonably optimistic that the efficacy of the mRNA vaccines will

not be substantially compromised by the South African and Brazilian variants, but there is a clear need for a definitive, national testing program to determine the properties of virus variants. Neutralizing antibodies induced by the AstraZeneca adenovirus vaccine had very low activity against the South African variant and the vaccine was ineffective at protecting against this strain [43].

Two doses of the Pfizer, Moderna, and Novavax vaccines are widely thought to be required for maximal efficacy, given that neutralizing antibodies can be detected after the first vaccine dose, but their titers are strongly boosted by the second one. Accordingly, the vaccines are less effective during the interdose period than after the second dose administration. Increased efficacy is not the only advantage of administering the second dose. In fact, when people are infected after the first dose but before the second dose, the virus can replicate in the setting of a suboptimal level of neutralizing antibodies, a situation in which resistant variants may emerge [44].

Another issue with significant implications involves what happens when a mRNA vaccine is given to a person who has recovered from COVID-19. Recent studies seemed to demonstrate that a single mRNA vaccine dose rapidly boosts neutralizing antibody titers to very high levels. Moreover, antibody responses against South African and Brazilian variants seems to be reduced in patients who had been infected with the Wuhan strain or United Kingdom variant but a single dose of Pfizer/BioNTech vaccine seems to increase neutralizing activity against them [45].

Considering the number of people in the world who have had COVID-19 and the possibility to only administer one dose to those who recovered from COVID-19, there is a potential to save a huge number of vaccine doses. A related issue is that the mRNA vaccines appear to trigger stronger adverse effects (headaches and mild fever) in people who have previously been infected with COVID-19. One potential solution to the adverse effect problem might be the administration of the Novavax protein vaccine. This vaccine seems to boost antibody levels in previously infected patients, particularly in younger individuals and to elicit fewer adverse effects than the mRNA vaccines with a similar efficacy. However, data from carefully designed clinical trials are needed to address these issues and inform the best decisions [46].

In conclusion, the more the virus changes and additional variants emerge and spread in the population, the more it will be necessary to adapt the vaccine formulations to obtain adequate protection for the population. However, anti-SARS-CoV-2 vaccines are able to elicit SARS-CoV-2-specific CD4+ and CD8+ T cell responses [47] which do not seem to be impaired in the response to the variants [48].

Therefore, a major concern is that of the durability and duration of current vaccines which on the basis of the various clinical trials has been estimated to be in the range of 10-12 months. Continuous monitoring of circulating viral strains is therefore essential to assess the impact of variants on the efficacy of vaccines, besides the performance of diagnostic tests. Only through quick adaptation of diagnostic methods and vaccine composition can one hope to keep the pace with the rapid evolving of SARS-CoV-2. Modern technology should be able to cope with this natural phenomenon [49]. Initiatives such as that recently proposed by the European Commission and consisting in a bio-defense preparedness plan against COVID-19 variants called "HERA Incubator", are necessary. This emergency program will tackle the short to medium-term threat and simultaneously prepare for the future. It will serve as the vanguard for the European Health Emergency Preparedness and Response Authority (HERA). HERA would provide a structural system to enable the EU to anticipate and tackle better future pandemics. In particular, work with researchers, biotechnology companies, manufacturers and public authorities has been planned to rapidly detect and analyze new variants, provide incentives to develop new and adapted vaccines, speed up the approval process and ensure scaling up of manufacturing capacities [50].

What's the future of COVID-19?

The current COVID-19 pandemic has undoubtedly raised awareness of the impact infectious diseases may have on health, economy and society as a whole. The valuable lessons to learn from this situation can be summed up in three words: speed, preparedness and public health response. First, speed has characterized not only the spread of the pandemic but also the deployment of all the efforts to counter it as well expressed by the rapid development of several diagnostic tests and vaccines which were authorized for use in less than a year. Secondly, preparedness is the key when fighting epidemics. To successfully organize a response and control effort while the epidemic is ongoing is a difficult task. Health systems and services need to be in place before an epidemic outbreak occurs. Preparedness is an essential requirement of the International Health Regulations (IHR) and signatory countries should implement a proper monitoring system based on the State Party self-assessment annual reporting tool and on joint external evaluations as recommended by WHO [51, 52]. Thirdly, the considerable impact of COVID-19 on society and the economy has abruptly brought the concept of an adequate public health response to the top of priorities of the contemporary highly inter-connected world: surveillance of new infections, rapid detection of epidemics, and ability to interrupt the transmission chain of the virus through pharmaceutical and non-pharmaceutical tools are crucial interventions to be implement at local, national and global level.

Vaccines have an established role in preventing pandemics and in curbing the spread of a disease like COVID-19. However, ensuring worldwide access to COVID-19 vaccines remains a major concern. Authorizing the use of a product in a country does not automatically translate into wide access to all and especially the poorest and

most marginalized [53]. The price needs to be affordable and effective health systems must be in place to guarantee access at-scale. Crucially important are negotiations with industry that are crucial to facilitate access for the poorest countries. An initiative named COVAX has been established through an agreement among the Coalition for Epidemic Preparedness Innovations (CEPI), the GAVI Vaccine Alliance and WHO, jointly with the delivery partner UNICEF, with the aim to "accelerate the development and manufacture of COVID-19 vaccines, and guarantee fair and equitable access for every country in the world" [54]. However, it has been previously reported that entities representing only 16% of the worldwide population secured 70% of the doses of vaccines available [54]. More recently, at the end of May 2021, high- and upper-middle income countries that include 50% of the worldwide population had administered 85% of all vaccines available, while low-income countries, mostly in Africa, could access less than 1% of vaccines available worldwide [55]. COVAX has tried to address the inequity by shipping 76 million vaccines to 126 participants [56], in what is considered "the largest vaccine roll-out in history" [57]. While this is progress, it is far from sufficient to address the needs of the poorest countries. In the month of January 2021, WHO issued a call open to anybody in any country, including public health and political authorities as well as pharmaceutical companies, to build a global sense of solidarity and ensure that as soon as possible vaccination for the highest-risk people, especially the elderly and health workers, becomes possible everywhere [58].

Lately, several activist organizations have voiced their frustrations about the lack of access to vaccines in the poorest countries and issued calls to stakeholders to urgently find a solution. MSF, for instance, has applauded "the US government's bold decision to support the waiving of intellectual property on COVID-19 vaccines during this time of unprecedented global need" [59]. Likewise, the International Federation of the Red Cross has requested an acceleration, under the World Trade Organization (WTO) umbrella, of negotiations related to intellectual property and other barriers to a rapid scaling up of vaccine production all over the world [60]. A political debate has thus ensued. Already in October 2020, India and South Africa proposed a temporary waiver of certain Trade-Related Intellectual Property Rights (TRIPS) Agreement provisions to the WTO. Recently, this call has been backed by most low and middle-income countries as well as by the WHO. Despite the call, high-income countries, including the UK and the European Union where many pharmaceutical companies are located, have blocked negotiations and progress of the initiative. The political debate has thus created a divide between those for whom access to COVID-19 vaccines is a needed humanitarian gesture towards the poorer and those who instead are concerned about the consequences for the pharmaceutical industry that, deprived of the patent benefits, may reduce future involvement in research and development and loose motivation to invest in innovations. The political discussion continued during the Global Health Summit held in Rome on 21 May 2021 in the context of the G20 Italian Presidency. Leaders of the G20 and several international organizations issued a document called "Rome Declaration" where, besides strong support to the prevention and preparedness efforts to be undertaken by all countries, a statement was made to be "working consistently within the TRIPS agreement and the 2001 Doha Declaration on the TRIPS agreement and Public Health; and Promoting the use of tools such as voluntary licencing agreements of intellectual property, voluntary technology and know-how transfers, and patent pooling on mutually-agreed terms" [61]. Hopefully, this development will be the basis for a definitive solution to the issue of access to COVID-19 vaccines for all countries worldwide.

In conclusion, as the WHO declaration spells out, "distributing COVID-19 vaccines quickly and equitably is essential to end this pandemic, restart our economies and begin to tackle the other great challenges of our time, like food insecurity, inequality and the climate crisis" [62].

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The authors declare no conflict of interest.

Authors' contributions

ET wrote the manuscript; CG, MT, CF performed the bibliographic research, revised and updated the manuscript; MCR and AA conceived the design and critically revised the manuscript. All authors have read and approved the latest version of the manuscript.

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Review

Nine ideas to improve the clinical management of HIV infected patients during the COVID-19 pandemic

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Keywords

HIV • COVID-19 • PLHIV • Italy • Antiretroviral therapy

Summary

Globally, in 2019, HIV infection was still responsible for 1.7 million new infections and for 690,000 deaths in the same year. Tailored and new antiretroviral therapy (ART) regimens, individualised follow-up and new technologies to support data-sharing between health-care professional caring for people living with HIV (PLHIV) and to deliver ART to patients are desperately needed to reach the 90-90-90-90 ambitious goals. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, responsible for the Coronavirus-19 (COVID-19) pandemic that spread globally in 2020, posed a huge challenge for PLHIV and HIV physicians worldwide in terms of continuum of care. In this paper we encourage "up-to-date patient-centred HIV medicine" and we give nine ideas to improve HIV management in clinical practice during the COVID-19 pandemic.

Introduction

Globally, in 2019, HIV infection was still responsible for 1.7 million new infections (range: 1.2 million - 2.2 million) and for 690,000 (range: 500,000-970,000) deaths in the same year [1].

In Italy, in 2018, 2,847 new HIV infections were reported and, despite the continuous progress in terms of screening, 661 new cases of AIDS were notified [2]. The median age of new HIV diagnoses is 39 years for males and 38 years for females, with a higher incidence between 25 and 39 years [2]. Antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) have the potential to massively decrease the global burden of HIV new infections; however, no "one size fits all" approach can reach the ambitious goal of HIV eradication [3]. Moreover, in time of health-care system disruption due to the Coronavirus-19 (COVID-19) pandemics, dedicated integrated service for people living with HIV (PLHIV) should be ensured to maintain retention to care and avoid loss to follow-up due to the fear of COVID-19 [4, 5]. Tailored ART, individualised follow-up and new technologies to support data-sharing between health-care professional caring for PLHIV and to deliver ART to patients are desperately needed [6, 7].

Again, from the Italian epidemiological picture, it is clear how aging of new infected patients should be a main concern, effectively addressing multi-morbidity, polypharmacy, co-infections; thus, HIV-care is constantly becoming a sub-specialization of Infectious Diseases that needs continuous updating and that embraces other medical specializations (e.g. Internal Medicine, pharmacology, Geriatric, Public Health) [8].

Aim of this paper, in a view of "up-to-date patient-centred medicine", is to give nine ideas to improve HIV management in clinical practice during the COVID-19 pandemic.

Methods

The text of this nine-point manuscript was ultimately organised in the following major paragraphs: i) HIV-tailored follow-up; ii) integrated HIV outpatient service; iii) HIV online-consultation; iv) ART-delivering; v) ART-monitoring; vi) inter-regional clinical data sharing; vii) pro-active screening; viii) HIV-dedicated wards; ix) HIV-physician training; x) future challenges and conclusion.

Every paragraphs highlights how to implement the subject within the clinical practice.

HIV-tailored follow-up

Thanks to ART, sustained viral suppression (viral load < 50 copies/ml) and prompt immune stability (CD4+ cell count > 500 cell/mm^3) can be achieved, ensuring immunovirological benefits to our patients [9, 10]. However, art became a life-long treatment that requires

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laboratory monitoring, clinical follow-up visits, tailored regimens adjustments according to patient needs, side effects, drug-drug interactions (ddi), comorbidities, co-infections, and availability of drugs, in order to preserve efficacy, safety and, ultimately, adherence to treatment and retention to care [11, 12].
Substantial time and costs for patients and healthcare systems are deployed to standard check-up, while individualised visits and laboratory monitoring should be tailored on patients'profile, enhancing patients' quality of life and decreasing healthcare costs [9].
In the setting of acute infection, late presenter, and in any case in which patients need to start art, prompt antiviral treatment should be initiated.
For instance, in case of virological suppression, immunological recovery, good psychological and clinical condition, no comorbidities, no risk-factors for co-infections, well tolerated art regimens, good adherence to treatment, and no complains by the patient, laboratory monitoring, co-infection screening, and clinical check-up could be delayed every 6-8 months [13]. Vice-versa, if a patient displays risky behaviours for co-infections, immunovirological goals are not met, art regimen is leading to intolerance and/or ddis and/or scarce adherence to treatment, follow-up visits should be anticipated, even monthly, in order to offer counselling, timely screening, and treatment simplification to improve patients' quality of life [14, 15].

Integrated HIV outpatient service

Hiv-outpatients service should be "patients-centered", offering clinical answers to patient both for hiv related issues and non-hiv complications resulting from art, co-infections and/or aging, as well as prep and post-exposure prophylaxis (pep) [16, 17]. Scheduled follow-up visits with the possibility of specialists'consultation other than infectious diseases specialists (namely: pulmonologist, gastroenterologist, cardiologist, gynecologist, gerontologist, immunologist, psycologist, psychiatric, hospital pharmacist, cultural mediator as well as peer-patients meetings) can improve patients retention to care, creating an unique environment to pursue the goal of hiv-care. This integration can be done by a group of hospital in confined area.

HIV-online consultation

When disruption of normal health-care system procedures prevents access to care or when it is not feasible for the patient reaching her/his hiv-dedicated outpatient service, retention to care should be still ensured [18]. Telemedicine, with free online video-call and text-message reminders for appointment and art delivery, could overcome the problem created by interrupted hiv-services, avoiding exposure to pathogens in time of pandemics, offering continuum to care to our patients [19]. However this consultation does not replace the face-to-face visit, but constitutes a new way of relating.

Art delivering

Again, if normal follow-up of PLWH is not possible or risky due to external conditions or patients' inability, technology-supported ART delivery should be considered [20].
In sub-Saharan Africa, drone delivery of HIV test and ART has been found feasible as well as mobile fully-equipped ART clinics; this switching the paradigm from "patients go to ART" to "ART goes to patient" [20]. Strategic placement of electronic pick-up machines, where registered patients can receive tailored treatment refill, coupled with text-message reminders on patients' mobile phone, is another example of how ART delivering could be made more efficiently and safer for patients. Moreover, ART delivering shouldn't be offered monthly, but according to patient's peculiarity (adherence to treatment, effective presence at online tele-consultations), it can be delivered for the following 2-3 months, reducing costs.

Art monitoring

To fulfil the UNAIDS third "90" (viral suppression) ambitious goals, ART monitoring can be enhanced through periodic text reminder for ART administration, portable point-of-care HIV-viral load self-testing with results live-delivered to health care providers, in order to timely decide possible clinical visit, further laboratory test (e.g. resistance testing, CD4+ cell count) and treatment changes [21, 22]. Indeed, treatment-as-prevention (TasP) can be achieved only if our patients are constantly virologically suppressed, highlighting how even the first two "90" of the UNAIDS strategy are linked to effective ART monitoring. ART monitoring includes for the HIV physician to be updated with new antiviral agents in commerce, possible side effects, DDIs, and with national and international guidelines, to promote best patients'care [23].

Inter-regional data sharing

To convey and uniform clinical data, clinical practices, monitoring patients' laboratory exams and treatment' history, discuss challenging cases among HIV physicians, and to share data to perform trial, an online inter-regional platform should be implemented between HIV-referral centres across the nation [24]. The experience of the "Rete Ligure", in the Ligurian Region of Italy (extended to other infectious diseases such as tuberculosis), which enables physicians to track and monitor patients' progress, retention to care, and HIV historical genotype as well as ART history, is an example of how health care providers can deliver a better service to patients and reduce ART related expenditure thanks to an interconnected health care system [25-27].

Pro-active screening

HIV screening, with opt-out strategy, should be part of daily clinical activity in Infectious Diseases wards, pregnant woman, outpatients service for sexually-transmitted infections, patients undergoing immunosuppressive treatment (e.g. oncology, haemato-oncology), and before surgical procedures [28]. Moreover, person at risk should be offered HIV periodically-scheduled screening in dedicated outpatient services or at home with self-testing with immediate linkage to care if resulted positive [28].

However, "pro-active screening" does not involve just HIV-testing in at risk population, but regularly screening viral hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D), tuberculosis, human papilloma virus (HPV), opportunistic infections, sexually transmitted diseases, and, when actively circulating, virus-responsible for pandemic in PLHIV [29, 30]. Active vaccination of vaccine-preventable infections should be promoted.

HIV-dedicated wards

Viruses with pandemic potential are emerging faster causing exponential growth of infected patients, reallocation of health-care resources, disruption of ambulatory services and fear of health-care settings [18, 31]. However, preparedness to avoid to stop or to reduce HIV routine care should be prioritized, as well as the creation of HIV dedicated wards for patients that require hospitalization, with properly trained staff (doctors, pharmacists, nurses and other health care professions), screening for pandemic viruses prior-to-admission and linkage to HIV-outpatient service after discharge.

HIV-physician training

HIV care is evolving quickly and, to provide comprehensive primary health care services to PLHIV, it is necessary for young Infectious Diseases specialists to own a solid background in infectious diseases, internal medicine, and epidemiology. Moreover, HIV-specialists need to be updated on new drugs available, DDIs, comorbidities, PrEP, PEP, and psychological counselling at diagnosis and during follow-up [32]. HIV-related continuing medical education should be encouraged and periodically done to awake and answer to intellectual challenges encountered by HIV physicians in daily practice (e.g. drug interactions between new ART regimens) and to care for the whole person rather than just to achieve viral suppression [33].

Future challenges and conclusion

Currently, online consultation, via email, in the Ligurian Region has been implemented, giving the chance to all patients to consult ID specialists even during lock-down. In the next future, pro-active HIV screening should be encouraged among General Practice doctors, through dedicated courses by ID specialists, in order to implement the path to linkage to care. Moreover, annual inter-regional or national post-graduated course for ID specialist, willing to take care of PLWH, should be promoted. Finally, inter-regional data sharing through dedicated online platform should be implemented.
The over-mentioned goals may represent the first steps to improve HIV management in clinical practice to keep delivering to our patient the best possible care.

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Conflict of interest statement

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Authors' contributions

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Review

Antioxidants and COVID-19

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Keywords

COVID-19 • Oxidative stress • Antioxidants • N-Acetylcysteine • Glutathione

Summary

Oxidative mechanisms are not only involved in chronic degenerative diseases but also in infectious diseases, among which viral respiratory diseases. Antioxidants have the capability to counteract the action of oxidants by scavenging reactive oxygen species (ROS) and by inhibiting oxidant generating enzymes. Overproduction of ROS and deprivation of antioxidant systems play a major role in COVID-19 occurrence, progression, and severity. Interconnected pathways account for the relationships between oxidative damage and inflammation resulting from an interplay between transcription factors having opposite effects. For instance, Nrf2 downregulates inflammation by inhibiting endogenous antioxidant enzymes such as NQO-1 and HO-1. On the other hand, NF-κB upregulates pro-inflammatory cytokines and chemokines, such as IL-1β, IL-6, IL-8, PGE-2, COX-2, TNF-α, MMP-3, and MMP-4. A central protective role against oxidants is played by reduced glutathione (GSH), which is depleted in SARS-CoV-2 infection. N-acetylcysteine (NAC), a precursor of GSH, is of particular interest as an anti-COVID-19 agent. GSH and NAC hamper binding of the S1 subunit of SARS-CoV-2 spike proteins to the angiotensin-converting enzyme 2 (ACE2) receptor. In addition, NAC and its derivatives possess a broad array of antioxidant and antiinflammatory mechanisms that could be exploited for COVID-19 prevention and adjuvant therapy. In particular, as demonstrated in a previous clinical trial evaluating influenza and influenza-like illnesses, the oral administration of NAC may be expected to decrease the risk of developing COVID-19. Furthermore, at the very high doses used worldwide as an antidote against paracetamol intoxication, intravenous NAC is likely to attenuate the pulmonary and systemic symptoms of COVID-19.

Balance between oxidants and antioxidants in human diseases

Oxidative mechanisms play a key role in the pathogenesis of virtually all human diseases, and consequently antioxidants share a broad range of protective effects. It should be made clear that, like the exposure to oxidants just increases the risk of contracting a given disease, generally in association with other pathogenetic determinants, antioxidants alone are not likely to fully prevent a pathological condition but are just expected to contribute to lower its risk and to attenuate the severity of its consequences. Together with deprivation of antioxidant mechanisms, oxidative stress is also involved in the aging process, especially when causing mutations in the mitochondrial DNA.

Free radicals include reactive oxygen species (ROS), such as the superoxide anion (O_2^-) and the hydroxyl radical (•OH), an extremely reactive species, as well as 'non-radical reactive molecules', such as hydrogen peroxide (H_2O_2), and reactive nitrogen species (RNS), such as peroxynitrite ($ONOO^-$). These species cause redox-modulated signaling cascades involving the transcription factors AP-1 (activator protein-1), NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and/or Nrf2 (nuclear factor erythroid 2–related factor 2), which can mediate a variety either of physiological functions or alterations of macromolecules leading to pathological conditions [1]. Free radicals may either be introduced into the body from exogenous sources (for instance, smoking one cigarette produces 10^{16} radicals) [2] or be generated in the body via biochemical reactions, such as the Fenton reaction and the Haber-Weiss reaction. While a controlled production of reactive molecules is essential for normal physiological and cellular functions, their uncontrolled or excessive production can cause 'oxidative/nitrosative stress' [1].

Natural or synthetic antioxidants have the capability to counteract the actions of oxidants either by directly scavenging ROS or by inhibiting oxidant generating enzymes, e.g. xanthine oxidase, or by stimulating ROS metabolizing enzymes, such as catalase, superoxide dismutase, or glutathione peroxidase, or by regulating the aforementioned redox-sensitive transcription factors. Therefore, in principle, agents possessing antioxidant properties can prevent the generation of ROS and hamper their deleterious effects. However, an indiscriminate use of antioxidants should be avoided because under certain conditions and at certain doses some of them may become pro-oxidants [1]. A typical example is provided by ascorbic acid that, at high doses and in the presence of transition metal ions, such as iron and copper, can acquire pro-oxidative properties, in spite of the fact that the interaction between ascorbic acid and iron is of nutritional, physiological, and pharmacological interest [3].

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Involvement of oxidative stress in respiratory viral diseases and protection by antioxidants

Oxidative stress is strongly involved in the pathogenesis not only of chronic degenerative diseases, such as cancer, atherosclerosis, arterial hypertension and other cardiovascular diseases, neurological disorders, dysmetabolic conditions such as diabetes mellitus, rheumatoid arthritis, etc. [4], but also of infectious diseases. Respiratory viral diseases are often associated with cytokine production, inflammation, and other pathophysiological processes resulting from a redox imbalance, disruption of the thiol redox cycle and other redox circuits [5]. Thus, overproduction of ROS and antioxidant mechanisms deprivation are one of the key events that is linked to viral replication and the subsequent virus-associated disease [6].

Respiratory viruses cause infections of the upper or lower respiratory tract that affect every year millions of people. They include influenza viruses (*Orthomyxoviridae* family), human respiratory syncytial viruses (HRSV, *Pneumoviridae* family), human rhinoviruses (HRV, *Picornaviridae* family), human metapneumoviruses (HMPV) and parainfluenza viruses (both belonging to the *Paramyxoviridae* family), adenoviruses (*Adenoviridae* family), and coronaviruses (*Coronaviridae* family). With the exception of adenoviruses, having a DNA genome, all the other respiratory viruses are RNA viruses. Many lines of evidence suggest that marked signs of increased production of ROS accompany all respiratory viral infections, along with disturbance of antioxidant defences [6]. The sources of ROS in airway epithelial cells infected with viruses are mainly NADPH oxidases, dual oxidase, xanthine oxidase, and Nox2 (NADPH oxidase), which is mainly expressed in macrophages. Alterations of ROS-producing and scavenging pathways that are caused by respiratory viral infections are implicated in inflammation, lung epithelial disruption, tissue damage, and cell death resulting in macrophage activation. In addition, oxidative stress triggers an antiviral immune response, whose excess may lead to a cytokine storm and a severe inflammation [5]. Respiratory viral infections have been associated with inhibition of Nrf2 pathways and/or NF-kB signaling activation, leading to inflammation and oxidative damage [7].

The role of oxidative mechanisms is also supported by experimental and clinical findings that show protective effects of antioxidants such as vitamin C, vitamin E, and *N*-acetylcysteine (NAC). NAC is the only agent that has been shown to attenuate the risk of respiratory viral diseases in humans. In particular, a double-blind trial involved 262 subjects of both genders who were enrolled in 20 Italian Centres. These subjects were randomized to receive either placebo or NAC tablets (600 mg) twice daily for 6 months. The results demonstrated that administration of NAC during the cold season can attenuate the incidence and severity of influenza and influenza-like illnesses, as shown by the fact that both local and systemic symptoms were sharply and significantly reduced in the NAC group. Moreover, only 25% of A/H1N1 influenza virus-infected subjects receiving NAC developed a symptomatic form *versus* 79% in the placebo group [8]. In the same study, a time-related shift of anergic condition to normoergic condition was observed in the NAC group thereby showing a beneficial effect of NAC administration on cell-mediated immunity [8].

The protective effects of NAC towards respiratory viral diseases have also been confirmed and explored from a mechanistic point of view in experimental test systems. Influenza A and B viruses and HRSV are responsible for COPD (chronic obstructive pulmonary diseases) by increasing apoptosis and inflammatory events through mechanisms that involve ROS generation and release of mucins from epithelial cells. NAC inhibited the replication of influenza A and B viruses and HRSV and restored the normal functions of alveolar type II A549 cells by modulating MUC5AC overexpression and release and by inhibiting IL-8, IL-6 and TNF- α as well as NF-κB translocation to the nucleus and phosphorylation of MAPK p38 [9]. In addition, NAC inhibited virus replication and expression of pro-inflammatory molecules in the same cells infected with the highly pathogenic H5N1 influenza virus [10]. *In vivo*, NAC attenuated the pulmonary inflammation and oedema and decreased myeloperoxidase activity, neutrophils, macrophages, TNF-α, IL-6, IL-1β and chemokine ligand-10 in the bronchoalveolar lavage fluid of mice inoculated intranasally with A/swine/HeBei/012/2008/H9N2 influenza virus [11]. Interestingly, in the perspective of using NAC for COVID-19 treatment in association with antivirals, NAC exerted protective effects towards influenza viruses when administered in association with either ribavirin [12] or oseltamivir [13].

Oxidative mechanisms in COVID-19 pathogenesis

The clinical patterns in most SARS-CoV-2-infected subjects are similar to those of other respiratory diseases. The forms are often paucisymptomatic or even evolve as an asymptomatic infection. However, approximately 15% of COVID-19 patients suffer from impairment of gas exchange and pneumonia, and 5% undergo acute respiratory distress syndrome (ARDS), the leading cause of death in COVID-19 patients, and can experience septic shock and/or multiple organ failure that require hospitalization in intensive care units (ICU) [14]. ARDS involves a systemic inflammatory response that has been attributed to the release of mediators triggering an attack by the immune system [15]. Like other viruses, SARS-CoV-2 stimulates the massive production of proinflammatory cytokines and chemokines, such as TNFα, IL6, and IL8, referred to as "cytokine storm", which is responsible for lung tissue damage and causes cell death [5]. Although SARS-CoV-2 primarily replicates in the respiratory tract, autopsies demonstrate that this virus can infect cells in multiple

organs, including the lungs, pharynx, heart, liver, brain, and kidneys [16]. Cardiovascular alterations include a plethora of disorders, such as stroke, diffuse thrombosis, acute changes in myocardial demand and supply due to tachycardia, hypotension, hypoxemia resulting in type 2 myocardial infarction, acute coronary syndrome due to acute atherothrombosis, microvascular dysfunction due to diffuse microthrombi or vascular injury, stress-related cardiomyopathy (Takotsubo syndrome), direct viral cardiomyocyte toxicity, and myocarditis [17]. Moreover, some COVID-19 patients exhibit widespread neurological manifestations including acute ischemic stroke, intracerebral haemorrhage, cerebral venous sinus thrombosis and anosmia. COVID-19-associated coagulopathy is increasingly recognized as a result of acute infection and is likely caused by the inflammatory cytokine storm [18].

Similarly to influenza virus infection, infection of experimental animals with coronaviruses has provided evidence for the involvement of the oxidative stress machinery, with enhancement of ROS production and weakening of defence mechanisms [19]. Many lines of evidence suggest that overproduction of ROS and a deprivation of antioxidant system play a major role also in the pathogenesis of SARS-CoV and SARS-CoV-2 infections in humans as well as in the progression and severity of the related diseases [4]. Activated neutrophils and mononuclear phagocytic cells are to a large extent responsible for the massive release of ROS into the lung tissue [20]. In addition, the massive TNF-α release during the cytokine storm could exacerbate ROS production via a positive feedback loop by activating NADPH oxidases [21], and TNF-α induced ROS production could contribute to the extension of COVID-19 effects to distant tissues [2].

The importance of oxidative stress in COVID-19 is also reinforced by the role of ROS production in associated co-morbidities. Many studies highlighted the importance of redox-sensitive pathways as novel cell-based targets for therapies aimed at blocking both viral replication and virus-induced inflammation [23]. As discussed in the next session, the prominent role of oxidative mechanisms in the pathogenesis of COVID-19 is corroborated by the perspective of implementing antioxidative strategies in the prevention and therapy of COVID-19 [24].

Some antioxidants proposed for COVID-19 prevention and treatment

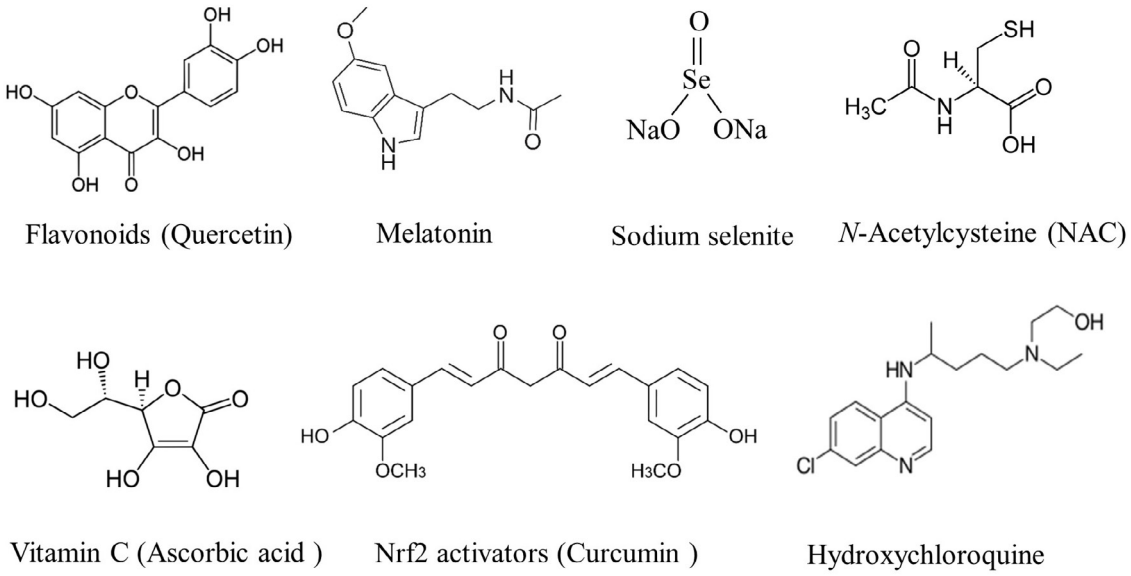
Several agents endowed with antioxidant properties have been assayed or proposed with the goals of lowering the risk of being affected by SARS-CoV-2 infection and/or of being used as an adjunct treatment in case of severe COVID-19 forms [25]. Often, these compounds share multiple mechanisms, which may render them capable of exerting broad-spectrum protective effects. On the other hand, antioxidants working with different mechanisms of action may complement each other thereby enhancing their protective properties in a synergistic fashion. Most antioxidant compounds are molecules from natural sources and especially of dietary origin [26], a poor nutrient status being associated with oxidative stress, inflammation, and impairment of the immune system [27, 28]. Therefore, a balanced diet and supplementation with proper nutrients may play a vital role in prevention, treatment, and management of COVID-19 [29].

The scientific literature in this area of research is evolving very rapidly. Some examples of protective antioxidants are shown in Figure 1. Among phytochemicals, polyphenols have been shown both *in silico* and *in vitro* to interfere with various stages of coronavirus entry into cells and replication [30] and disclose inhibitory activities towards viral components, which may render them potentially suitable to counteract the SARS-CoV-2 infection [31]. For instance, flavonoids, which are a class of polyphenols including quercetin (Fig. 1), baicalin, luteolin, hesperetin, gallocatechin gallate, epigallocatechin gallate (EGCG,), etc., are able to inhibit key proteins involved in the coronavirus infective cycle, such as PL^{pro}, $3CL^{pro}$, and NTPase/helicase [30]. It has also been postulated that quercetin may exert a synergistic antiviral action with vitamin C due to the overlapping antiviral and immunomodulatory properties of these agents and to the capacity of ascorbate to recycle quercetin [32]. In molecular simulations, quercetin has been hypothesized to inhibit the protease $3CL^{pro}$, which is an essential player in the coronavirus replication cycle [33]. It is noteworthy, however, that the U.S. Food and Drug Administration has cautioned against advertisement of unauthorized health claims of quercetin.

In theory, vitamin C (ascorbic acid) may represent a suitable tool against SARS-CoV-2 infection because this vitamin is a reducing agent and antioxidant acting by electron transfer reactions and therefore it reacts with ROS such as $^{\bullet}OH$. However, the appropriateness of its use in COVID-19 is still uncertain [34] also because the use of vitamin C in ARDS or sepsis is still a matter of debate [35]. A multicentre prospective randomised placebo-controlled trial has been recently designed in order to evaluate the effects of high dose intravenous vitamin C in COVID-19 patients hospitalized in ICUs [36].

A promising agent for the treatment of viral diseases, including COVID-19, is melatonin, a potent multifunctional signalling hormone secreted by the pineal gland that acts as an antioxidant with immunomodulatory and anti-inflammatory properties [37]. Melatonin can reduce oxidative stress and efficiently combat the cytokine storm and sepsis. In addition, melatonin is an inhibitor of calmodulin, an essential intracellular component to maintain angiotensin-converting enzyme 2 (ACE-2) on the cell surface [38]. Melatonin has been proposed in subjects with obesity and diabetes, who may undergo severe inflammation and oxidative stress following infection with SARS-CoV-2 infection [39]. It has also hypothesized that children do not suffer from COVID-19 as much as their grandparents because

Fig. 1. Some agents endowed with antioxidant properties that have been shown or suspected to play a role in COVID-19 prevention and/or adjuvant therapy. The quercetin formula is shown as an example of flavonoids and curcumin is shown as an example of Nrf2 activators.



they have lower levels of melatonin, which is lost with age [40]. A clinical trial with an injectable formulation of melatonin for intravenous perfusion in ICU patients suffering from COVID-19 has been designed [41].

Drugs that are being tested for the treatment of COVID-19 may also possess antioxidant properties. For instance, hydroxychloroquine, an old medication for malaria that is also used to treat autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus, shares a number of protective effects, also including antioxidant mechanisms [42]. Note however that, on the contrary, the same drug has also been reported to have oxidative properties due to a decrease of GSH levels [43].

A Chinese medicinal formula consisting of 21 herbs (QFPDT) has been recommended in the 6th and 7th versions of Clinical Practice Guideline on COVID-19 in China due to its antioxidant, immunomodulatory and antiviral mechanisms [44].

Nrf2 activators are a broad category of antioxidant agents that could potentially inhibit SARS-CoV-2. In fact, Nrf2 is a transcription factor that regulates the expression of antioxidant cytoprotective enzymes via a promoter sequence known as antioxidant response element (ARE). Regulation of the redox state by Nrf2 results in the modulation of genes involved in immunity and inflammation, also including antiviral mechanisms. Nrf-2 activators include a variety of food-derived compounds that have extensively been investigated for their protective properties, such as curcumin, capsaicin, gingerol, EGCG, genistein, the carotenoid lycopene, resveratrol, caffeic acid phenethyl ester, diallyl sulphide, indole-3-carbinol, and sulphoraphane. Moreover, using primary human pulmonary artery endothelial cells, the synthetic Nrf2 activator PB125® was found to downregulate 36 genes encoding cytokines, such as IL-1-beta, IL-6, TNF-α, the cell adhesion molecules ICAM-1, VCAM-1, and E-selectin, as well as a group of IFN-γ-induced genes, many of which have specifically been identified in the cytokine storm observed in fatal cases of COVID-19 [45].

Among natural Nrf-2 activators, it has been hypothesized that, in the light of its low toxicity and of its antioxidant, anti-inflammatory, and antiviral activity, curcumin may be used as a therapeutic drug for viral pneumonia and ALI (acute lung injury)/ARDS. Curcumin exerts protective effects by regulating the expression of both pro- and anti-inflammatory factors such as IL-6, IL-8, IL-10, and COX-2, by promoting the apoptosis of polymorphonucleate cells, and by scavenging the ROS that exacerbate the inflammatory response [46]. EGCG, the most abundant ingredient in green tea leaves and a well-known antioxidant, has been proposed as a supplementation therapy in COVID-19 patients. Besides some antiviral and anti-sepsis actions, the major EGCG benefits lie in its anti-fibrotic effect and in the ability to downregulate expression and signaling of many inflammatory mediators [47]. Flavonoid supplements, combined with vitamin D3, are expected to activate Nrf2, which may be a potential target to prevent and/or decrease SARS-CoV-2 infection severity, reducing oxidative stress and inflammation, enhancing innate immunity, and downregulating ACE2 receptors [48]. As it will be specifically discussed in more detail below, the thiols GSH and NAC are additional activators of Nrf2 [49].

Selenium (Se) is another important antioxidant whose deficiency is likely to play a role in affecting SARS-CoV-2 virulence and COVID-19 severity. A positive association has been reported between COVID-19 rates

and previously measured population Se status in 17 cities across China [50], and Se deficiency has been associated with an increased mortality risk from COVID-19 [51]. Se is a component of glutathione peroxidase 1 (GPx1), a cytosolic selenoenzyme with known antiviral properties (see below), and the interaction between the GPx1 detoxifying system and the main protease (M^{pro}) of SARS-CoV-2 represents a novel molecular target for COVID-19 [52]. Low Se status is a common finding in conditions considered at risk for severe COVID-19, especially in the elderly, and Se might be beneficial via restoration of the host antioxidant capacity, reduction of apoptosis and endothelial cell damages as well as platelet aggregation [53]. As inferred from an online search for articles published in the period 2010-2020, the direct evidence that the micronutrients zinc, Se, and vitamin D might be involved in the course and outcome of the COVID-19 disease was evaluated to be observational and weak. However, based on experiences from treatments of SARS and other viral infections, it was postulated that nutritive supplements administered at an early stage of the infection would be important in order to enhance the host resistance against RNA viral infections, which might also include severe COVID-19 [54]. Another Se compound of interest is ebselen, an organoselenium compound exhibiting hydroperoxide- and peroxynitrite-reducing activity that behaves as a GPx and peroxiredoxin enzyme mimetic. Ebselen reacts with a multitude of protein thiols, forming a selenosulfide bond, which results in pleiotropic effects of antiviral, antibacterial and anti-inflammatory nature that may potentially be beneficial in COVID-19 [55].

The glutathione (GSH) system

Reduced glutathione (GSH, γ-glutamylcysteinylglycine) provides key protective effects against toxic substances and infectious agents. GSH is available at micromolar concentrations in biological fluids and at millimolar concentrations in cells within the endoplasmic reticulum, mitochondria and nucleus. The thiol redox circuit involves interconversions between GSH and glutathione disulfide (GSSG), which are in an approximately 100:1 ratio inside cells. As shown in Figure 2, GSH is oxidized to GSSG via the enzyme glutathione peroxidase (GPx), whereas GSSG is reduced to GSH via glutathione reductase (GR). The main enzyme involved in GSH synthesis is glutamate cysteine ligase (GCL). Besides being a potent antioxidant, GSH is a nucleophile that can block reactive molecules either *per se* or via glutathione-*S*-transferases (GST)-catalyzed conjugation.

Literature data support the concept that an endogenous deficiency in GSH may underlie the serious manifestations and death due to COVID-19 [56]. A common denominator in all conditions associated with COVID-19 appears to be the impaired redox homeostasis responsible for ROS accumulation. Therefore, GSH levels could be critical in extinguishing the exacerbated inflammation that triggers organ failure in COVID-19 [57]. In addition,

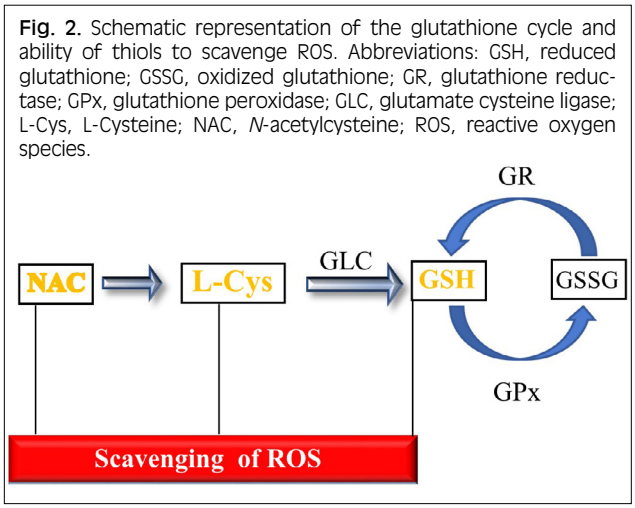


Fig. 2. Schematic representation of the glutathione cycle and ability of thiols to scavenge ROS. Abbreviations: GSH, reduced glutathione; GSSG, oxidized glutathione; GR, glutathione reductase; GPx, glutathione peroxidase; GLC, glutamate cysteine ligase; L-Cys, L-Cysteine; NAC, *N*-acetylcysteine; ROS, reactive oxygen species.

GSH plays a central role in the pathophysiology of most human diseases [58], including those that occur as co-morbidities with COVID-19.

It is noteworthy that GR was found to be significantly increased in the blood serum of COVID-19 patients, especially when admitted to ICUs [59]. This alteration reflects an oxidative stress imbalance, being an attempt to replenish the GSH stores that are depleted by the infection. GPx, the other enzyme of the glutathione circuit, belongs to a family of antioxidant selenoenzymes that functionally link selenium and glutathione, both of them showing correlations with clinical outcomes in COVID-19 [60]. Cytosolic GPx1 has been shown to interact with an inactive C145A mutant of M^{pro}, the main cysteine protease of SARS-CoV-2, but not with catalytically active wild-type M^{pro}. In addition, M^{pro} may be targeting not only GPx1 but also several other selenoproteins as well as GCL, the rate-limiting enzyme for glutathione synthesis [60]. Thus, M^{pro} is a potential drug target, and a screen with over 10,000 compounds identified ebselen as a particularly promising inhibitor of this protease [55].

Liposomal GSH has been proposed as an adjunctive treatment in COVID-19 patients [61]. Moreover, a case report study showed that the repeated use of both oral administration and intravenous injection of GSH was effective in relieving the severe respiratory symptoms of COVID-19, suggesting for the first time the efficacy of this antioxidant therapy for COVID-19 [62].

Inhibition of ACE2 by antioxidant thiols

The S1 subunit of SARS-CoV-2 spike proteins binds to the angiotensin-converting enzyme 2 (ACE2) receptor thereby starting the virus replication cycle in cells. Both the receptor binding domain of the viral spike proteins and ACE2 have several cysteine residues, and the binding affinity is decreased when the disulfide bonds of ACE2 and SARS-CoV-2 spike proteins are reduced to sulfhydryl groups. Therefore, the redox environment of cell surface receptors is regulated by the thiol–disulfide

equilibrium in the extracellular region [63]. ACE2, which is expressed in epithelial, endothelial and myocardial cells as well as in T lymphocytes, macrophages, and hepatocytes [64], is a protease that is involved in the renin/angiotensin system together with the angiotensin-converting enzyme (ACE), which has opposite effects. In fact, while ACE causes vasoconstriction, inflammation, apoptosis and oxidative stress due to the production of ROS through the activation of NADPH oxidase and the generation of peroxynitrite anions, ACE2 causes vasodilatation, angiogenesis, antioxidative and antiapoptotic effects [65].

Both animal studies and clinical studies suggest that treatment with the GSH precursor NAC, which is known to attenuate the tolerance to nitrates, modifies the function of the renin/angiotensin system *in vivo*, an effect that is probably mediated by inhibition of ACE activity [66]. Therefore, by modulating the renin/angiotensin system activity, GSH and its precursor thiols are likely to inhibit entrance of SARS-CoV-2 into cells.

N-Acetyl-L-cysteine (NAC). A promising anti-COVID-19 agent

The thiol NAC easily penetrates cells where it is deacetylated to yield L-cysteine (L-Cys), the only naturally occurring amino acid that carries a thiol-containing side chain (sulfhydryl group). Alternatively, at least in the blood, NAC acts by freeing in the plasma L-Cys that then enters erythrocytes [67]. L-Cys is the rate-limiting substrate for GSH biosynthesis, which is mainly achieved through activation and upregulated production of GCL (Fig. 2) [68]. Therefore, replenishment of depleted GSH stores occurs both by GSH recycling and by *de novo* synthesis of this tripeptide (Fig. 2).

The physiological recycling of GSH is increased but cannot match its high consumption in COVID-19 lung disease. NAC works both *per se* in the extracellular environment and as a substrate and precursor of GSH inside cells. Accordingly, all its intracellular effects are mediated by GSH replenishment. It is known since a long time that rescue of GSH through NAC is a treatment strategy for a broad array of different diseases, all of which have in common a pathogenetically relevant loss of GSH [69]. It may be possible to discriminate whether the effects of NAC are either due to NAC itself or to GSH replenishment by comparatively testing its unnatural D-isomer that is not a precursor of L-Cys and GSH [70].

NAC has been in clinical use since the 1960s as a mucolytic agent, usually at the oral dose of 600 mg, due to its ability to break the disulfide bonds of mucus and to depolymerize mucin. Later on, this drug has been proposed or used for the therapy and/or prevention of a variety of diseases involving GSH depletion and redox status imbalances, such as heart diseases, diabetes, AIDS, neurodegenerative diseases, neuropsychiatric disorders, and several other conditions, which generally are treated with 2 daily oral doses of 600 mg [71-73]. Even higher dose regimens (3 daily oral doses of 600 mg) have been used for several years for the treatment of idiopathic pulmonary fibrosis, whose pathogenesis has been ascribed to oxidative agent-mediated alveolar epithelial cell injury, accompanied by an abnormal fibroblast response [74]. Note that COVID-19 pneumonia may present as an acute exacerbation of idiopathic pulmonary fibrosis [75] and that most of the COVID-19 patients undergo postinflammatory pulmonary fibrosis on the follow-up CT scan when discharged [76]. Moreover, high-dose intravenous NAC exerts protective effects in ARDS [77, 78] that, as previously mentioned, is the leading cause of death in COVID-19 patients. ROS play a key role in the pathogenesis of the acute lung injury, and the alveolar epithelial lining fluid (ELF) of patients with ARDS is deficient in GSH [79]. Likewise, GSH is depleted in the ELF of patients with sepsis [79], which is another condition associated with COVID-19 [80]. In addition, the intravenous administration of NAC at very high doses (150 mg/kg b.w.) is used to treat inflammatory conditions, such as contrast-induced nephropathy [81], and it is in clinical practice as an antidote against paracetamol (acetaminophen) overdosage. For this reason, NAC is quoted in the WHO Model List of Essential Medicines as an antidote in poisonings, being almost 100% effective against paracetamol intoxication when injected within 8 hours after intake of the drug [81]. Furthermore, intravenous NAC may have a role in the management of acute liver failure (ALF) attributable to administration of remdesivir, a direct-acting nucleoside RNA polymerase inhibitor with activity against the novel SARS-CoV-2 virus used in the treatment of COVID-19 pneumonia [82].

Mechanisms of NAC

NAC works via a broad variety of mechanisms, which could be exploited for COVID-19 prevention and treatment. First of all, as previously reported, thiols can hamper penetration of SARS-CoV-2 into cells. Another important property is their ability to block free radicals and reactive molecules responsible either for acute effects or long-term effects. Nucleophilicity of thiols is related to the property of sulfhydryl groups to react with electrophilic metabolites. An example of reactive intermediate is the paracetamol metabolite *N*-acetyl-p-benzoquinone imine (NAPQI) formed via cytochrome P450 enzymes, which is bound by GSH and excreted in conjugated form. Likewise, NAC and its thiol derivatives have the ability to competitively block electrophilic derivatives of carcinogens that are capable of binding DNA. This may be particularly important in the case of smokers, since there is evidence that smoking is associated with a negative progression and adverse outcomes of COVID-19 [83]. In fact, exposure to cigarette smoke increases ROS levels and causes a depletion of GSH intracellular concentrations [84] by reacting with nonreducible glutathione-aldehyde derivatives [85] thereby accelerating cigarette smoke-

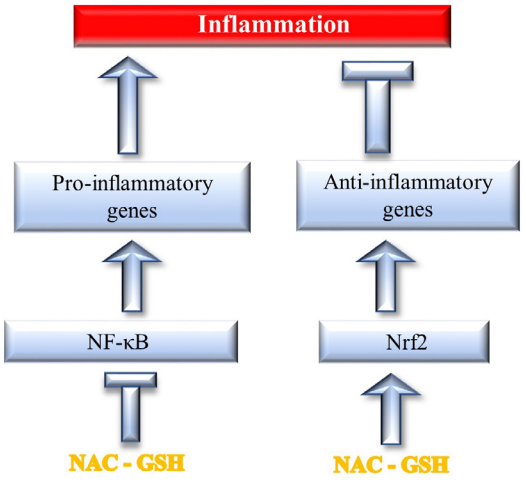


Fig. 3. NAC and GSH trigger two parallel channels that attenuate inflammation either by inhibiting NFκB-dependent pro-inflammatory genes and/or by stimulating Nrf2-dependent anti-inflammatory genes (see Text for details).

induced inflammation and airspace enlargement [86]. NAC has the ability to modulate a large variety of smoking-related end-points, due to many mechanisms and effects demonstrated in experimental test systems. They include NAC nucleophilicity, antioxidant activity, modulation of metabolism, effects in mitochondria, decrease of the biologically effective dose of carcinogens, modulation of DNA repair, inhibition of genotoxicity and cell transformation, modulation of gene expression and signal transduction pathways, regulation of cell survival and apoptosis, antiinflammatory activity, anti-angiogenetic activity, immunological effects, inhibition of progression to malignancy, influence on cell cycle progression, inhibition of preneoplastic and neoplastic lesions, and inhibition of invasion and metastasis [87]. In addition, NAC was shown to modulate several biomarkers in a randomized, double-blind, placebo-controlled, Phase II chemoprevention trial in heavy smokers who received NAC tablets (600 mg) twice daily for 6 months [88].

The key mechanisms shared by NAC, L-Cys and GSH are related to their antioxidant activity, which is mainly due to a potent ability to scavenge ROS (Fig. 2), and especially hypochlorous acid (HOCl) and $^{\bullet}OH$, and additionally hydrogen peroxide [89]. The SH-groups within the NAC molecule can also scavenge several RNS that play a role in the oxidation of lipids, proteins, and DNA [90].

The antioxidant effects are interconnected with antiinflammatory effects, which is crucial for COVID-19 control [49]. First of all, oxidative stress is linked with inflammation via two parallel biochemical channels that are modulated in opposite direction by NAC (Fig. 3). The first one involves inhibition by NAC of the ROS-mediated activation of NF-κB and consequently the hindrance of biochemical pathways upregulating pro-inflammatory genes [71] involved in COVID-19 pathogenesis, such as interleukins (IL-1β, IL-6, IL-8), prostaglandins (PGE-2), cyclooxygenases (COX-2), tumor necrosis factor (TNF-α), matrix metalloproteinases (MMP-3, MMP-4), and intercellular adhesion molecule (ICAM-1). NAC also inhibits NF-κB translocation to the cellular nucleus and phosphorylation of MAPK p38 (p38 mitogen-activated protein kinase) by reducing the intracellular hydrogen peroxide concentration and by restoring the intracellular total thiol contents [91]. On the other hand, NAC further enhances the stimulation of Nrf2 by oxidative stress [92]. Nrf2 downregulates inflammation by favouring the ARE-mediated transcription of phase II enzyme genes. These include endogenous antioxidant enzymes such as heme oxygenase 1 (HO-1), NAD(P)H dehydrogenase [quinone] 1 (NQO-1) and additionally GCL [93]. It is noteworthy that the heme-HO-1 system has been proposed as a target to prevent severe complications following SARS-CoV-2 infection [94].

Besides acting as antioxidants by scavenging ROS, NAC and GSH elicit antioxidant and antiinflammatory effects via other mechanisms that may bear relevance for the control of COVID-19 and associated co-morbidities. For instance, NAC can exert antioxidant activity via p53 mediated apoptosis [95]. In the cardiovascular domain, NAC is well known to interact with nitric oxide by potentiating its vasodilator and antiaggregatory effects [96]. Moreover, NAC inhibits the ROS-producing vascular NAD(P)H oxidases, which bears relevance in the prevention of hypertension and atherosclerosis [97]. NAC has also been proposed with the goal of preserving endothelial function and limiting microthrombosis in severe forms of COVID-19 [98]. Of particular interest in the framework of the COVID-19 clinical picture is inhibition of epidermal growth factor receptor (EGFR), a tyrosine kinase involved in inflammation, which also results in a decreased inactivation of α1-antitrypsin that, together with oxidative stress, plays an important role in the pathogenesis of COPD and its exacerbations [99, 100]. In addition, NAC is a hydrogen sulfide donor, because L-Cys, derived by NAC catabolism, is the substrate for this vasodilator, anti-inflammatory and readily diffusible compound [101], which is a pleiotropic mediator having effects on many elements in the inflammatory cascade and promoting the resolution of inflammation and injury [102].

Conclusions

Oxidative stress represents a major mechanism in the pathogenesis not only of chronic degenerative diseases but also of infectious diseases, also including viral respiratory diseases. Oxidation, inflammation and immune response impairment are strictly interconnected and are key determinants in COVID-19. Various antioxidants have been proposed as anti-SARS-CoV-2 agents. One of the most promising drugs is NAC, a precursor of GSH, both because the redox environment of the ACE2 receptor of SARS-CoV-2 spikes is regulated by the thiol-disulfide balance in the extracellular region

and because replenishment of depleted GSH stores by NAC exerts formidable antioxidant and antiinflammatory effects. These effects are potentially suitable to control the cytokine storm that is characteristic of COVID-19. Due to their pleiotropic mechanisms, both NAC and GSH have been evaluated or are under scrutiny for a variety of end-points in a large number of clinical trials (162 studies for GSH and 714 studies for NAC) [57]. We [49] and several other authors [43, 103-115] have proposed the use of NAC in the prevention and/or the treatment of COVID-19. Due to its low toxicity profiles, the 60 year-experience of clinical use and the fact that NAC is approved by FDA under various formulations and is popular as a health supplement, this drug may be repurposed as an anti-COVID-19 agent.

In particular, two strategies can be envisaged. The first one is the oral administration of NAC, at the dose of 600 mg twice per day, in order to decrease the risk of developing COVID-19 and to attenuate its severity, especially during epidemic periods and in high risk individuals because of age and/or concomitant pathological conditions or because they have been in contact with infected SARS-CoV-2 carriers. Interestingly, having previously demonstrated that this protocol is effective in lowering the incidence and severity of influenza and influenza-like illnesses [8], the hypothesis that NAC administration may confer a broad spectrum protection against different respiratory viral diseases is mechanistically sound. It is also noteworthy that oral NAC (600 mg/twice daily) was safe and effective to prevent and delay ventilator-associated pneumonia, and improved its complete recovery rate in a selected, high-risk ICU population [116]. At the same NAC dose, a cross sectional study evaluating 164 COVID-19 patients in Kolkata (India) found that moderate-severe patients who received NAC along with standard therapy had a variety of benefits from the clinical standpoint [117].

The second perspective, in case of manifest COVID-19 forms, is to use NAC as an adjuvant therapy, possibly in association with other drugs, at the high intravenous doses that are commonly used as an antidote against paracetamol intoxication. It is noteworthy that paracetamol, which is the preferred drug for the symptomatic and domiciliary management of the early stages of COVID-19, may cause GSH depletion, especially in people at higher COVID-19 risk, thereby increasing further the risk of developing severe COVID-19 forms [118]. Accordingly, the preferential use of paracetamol in COVID-19 as a safer alternative to nonsteroidal antiinflammatory drugs (NSAIDs) should be carefully reconsidered [119] and it would be important to further investigate whether NAC supplementation should be adopted, irrespective of COVID-19, in case of prolonged administration of high doses of this antipyretic and analgesic compound [118]. A case of severe COVID-19 infection treated with hydroxychloroquine in a patient deficient in glucose 6-phosphate dehydrogenase (G6PD), which facilitates human coronavirus infection due to GSH depletion, had benefit from the intravenous administration of NAC [43]. On the other hand, a double-blind, randomized, placebo-controlled trial enrolling 135 patients with severe COVID-19 (confirmed or suspected), conducted in São Paulo, Brazil, did not show any benefit from the intravenous injection of 21 g NAC (approximately 300 mg/kg) for 20 hours, at least in terms of need for endotracheal intubation and mechanical ventilation [120].

Several clinical trials evaluating the efficacy and safety of NAC treatment in COVID-19 are now in progress in various countries, including Brazil, China, Iran, Nigeria, Saudi Arabia and USA (http://www.ensaiosclinicos.gov.br/rg/RBR-8969zg/; https://clinicaltrials.gov/; https://doi.org/10.1186/ISRCTN60069084; https://clinicaltrials.gov/show/NCT04279197; http://ethics.research.ac.ir/PortalProposalListEn.php?code=&title=acetylcysteine&name).

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

SDF wrote the manuscript. RB and SLM made literature search and revised the manuscript.

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RESEARCH ARTICLE

Spine surgery after the COVID-19 emergency: an algorithm for management of elective surgical cases

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Keywords

COVID-19 • Spine surgery • Elective surgery • Nosocomial transmission

Summary

Introduction. *During the COVID-19 pandemic emergency, all non-urgent surgical procedures including elective spine surgery were performed. Now many countries have passed over the epidemic peak and the time to organize re-opening of non-essential activities has come. After the emergency phase of the COVID-19 pandemic, the viral outbreak is supposed to reduce but will not reasonably disappear until a vaccine is available. Resuming elective spine surgery while ensuring safety for patients and healthcare workers has become an issue of critical importance. We propose a simple algorithm with the aim to help worldwide spine surgeons in management of elective spine surgery cases after the COVID-19 emergency ensuring safety for patients and healthcare workers.*
Methods. *An expert panel composed by Spine Surgeons, Neurosurgeons, Anesthesiologists and Intensivists with direct experience in COVID-19 management developed an algorithm for management of elective spine surgery based on evidence-based indications. The algorithm has been used for management of hospital admissions of undelayable spine surgery cases during the COVID-19 emergency period. Data regarding COVID-19 nosocomial transmission on patients and healthcare workers have been retrospectively reviewed and reported.*
Results. *Hospital admissions of 159 patients have been managed according to the proposed algorithm. Since the application of the protocol, we have not reported COVID-19 nosocomial transmission in our department.*
Conclusions. *According to our preliminary results, we think that the proposed algorithm may successfully help management of spinal elective surgical patients in the post-COVID-19 emergency era, avoiding unnecessary risks for patients and healthcare workers.*

Introduction

Since the beginning of the Coronavirus-disease-2019 (COVID-19) pandemic, more than 52 million people have been infected and more than 1 million people have died [1].
Due to high inter-human transmissibility, COVID-19 is taking an unprecedented toll on emergency departments and hospitals. With the aim of reducing pressure over the already stressed healthcare system and minimizing risks of nosocomial transmission, during the COVID-19 emergency period all non-urgent surgical procedures that might have been safely delayed without negatively affecting patients' prognosis have been delayed [2, 3].
Spine surgeons frequently manage conditions that cause pain and functional impairment with subsequent reduction of quality of life. Despite the benign nature of these diseases, they present significant impact on social and community life [4], therefore their treatment is of paramount importance. During the COVID-19 pandemic emergency all these non-urgent procedures were performed.
Italy has passed over the first epidemic peak and, the time to organize the performance of all non-urgent surgical procedures has come, even if we are currently experiencing a second epidemic peak [5]. As long as it will be safely possible, it is of paramount importance to provide medical and surgical treatment even to non-urgent patients.
Even after the emergency phases of the COVID-19 pandemic, the viral outbreak is supposed to reduce but will not reasonably disappear until a vaccine is available [6]. The need for reorganization of healthcare systems in order to cope with both suspected COVID-19 and non-COVID-19 patients has become urgent. In present times and in the next future physicians and particularly spine surgeons will face the challenge of performing non-urgent procedures ensuring safety of both patients and healthcare workers (HCW).
Different indications for spine surgery during the COVID-19 pandemic have been so far provided [7-12]. To the best of the authors' knowledge, the issue of resuming non-urgent spine surgery procedures after the COVID-19 emergency phase has not yet been addressed.
We propose a simple algorithm with the aim to help worldwide spine surgeons in management of elective spine surgery cases after the COVID-19 emergency ensuring safety for patients and HCW (Fig. 1).

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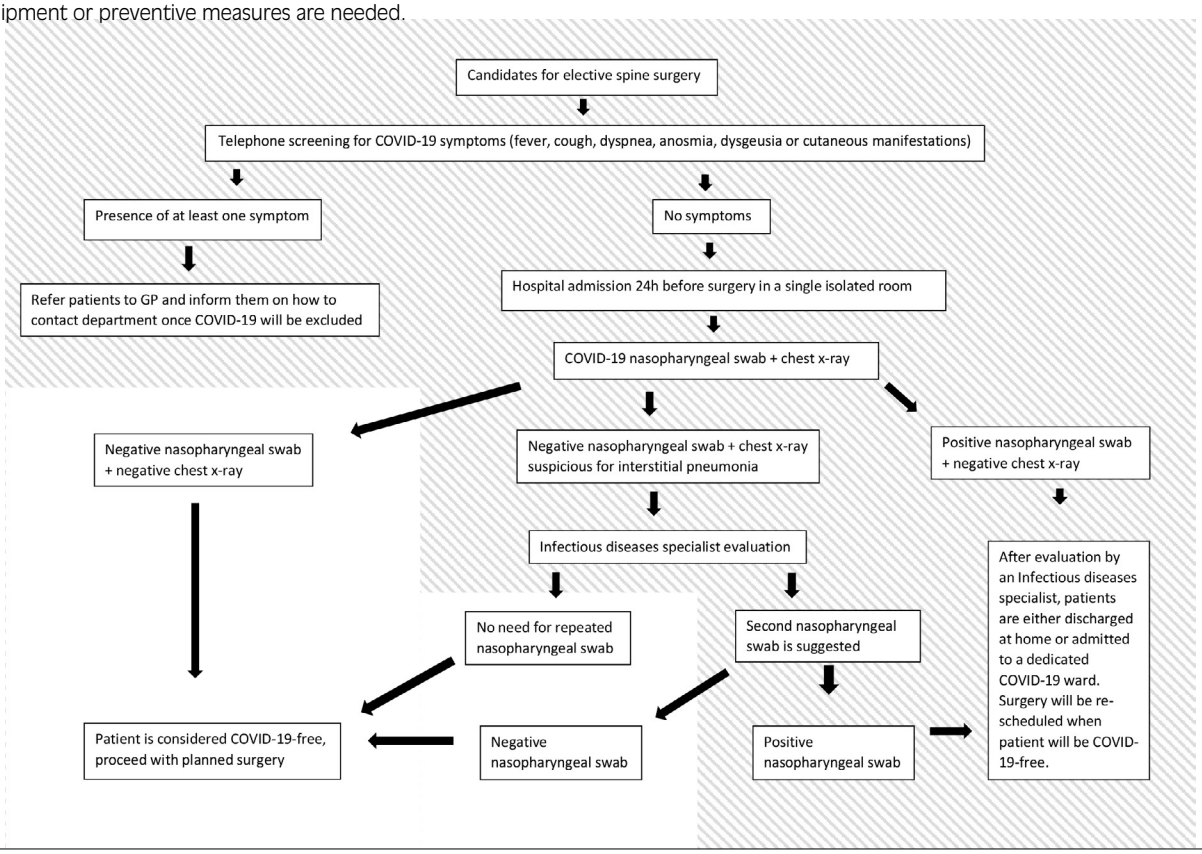
Fig. 1. Algorithm for management of elective spine surgery cases after the COVID-19 lockdown. Grey color indicates steps in which patients are considered suspect for COVID-19, therefore health-care workers should use adequate personal protective equipment and preventive measures should be put in place. White color indicates steps in which patients are considered COVID-19-free and no specific protective equipment or preventive measures are needed.



Methods

An expert panel composed by Spine Surgeons, Neurosurgeons, Infectious Diseases Specialists (IDS), Anesthesiologists and Intensivists with direct experience in COVID-19 management from our institution (Ospedale Policlinico San Martino, IRCCS for Oncology and Neuroscience, Genova, Italy), discussed and reviewed the criteria that should be taken into account in the management of elective spine surgery during the COVID-19 pandemic.

A brief literature review was performed in order to provide evidence-based suggestions. Our review mainly focused on articles in English language published in PubMed from of December 21st 2019 to the October 30th 2020 regarding COVID-19 disease.

The proposed algorithm reflects the current guidelines of our institution and has been used since the COVID-19 lockdown period for management of undelayable spine surgery cases. Data regarding COVID-19 nosocomial transmission in operated patients and HCW have been retrospectively reviewed and reported in an attempt to evaluate safety and feasibility of the algorithm.

Preoperative screening protocol

Before scheduling patients for elective spine surgery several considerations should be made:

- for degenerative spine surgery cases a maximal conservative treatment should be always attempted. Conservative treatment gains even more importance in pandemic times in order to minimize the number of surgical operations [13];
- the availability of COVID-19-free Intensive Care Units (ICU) should be evaluated in order to be prepared to treat possible surgical or anesthesiological complications, without providing additional risks of infection to the patients;
- due to the risks of significant blood loss of many spine surgery procedures, the availability of blood products from the local transfusion center must be preoperatively ascertained as a shortage of blood products is possible during the COVID-19 pandemic [14].

After these considerations, if surgery is still considered safely feasible, patients who definitely need surgical operation will be telephonically screened before hospitalization for evaluation of COVID-19 symptoms (fever, cough, dyspnea, anosmia, dysgeusia or cutaneous manifestations) [15]. In case any symptom is present, surgery will be postponed, patients will be referred to the general practitioner and will be informed on how to contact our department when COVID-19 will be ruled out.

At this point, patients who are considered eligible for surgery are scheduled. Hospital admission will take place

24 hours before surgery. A SARS-Cov-2 nasopharyngeal swab and a chest X-ray will be performed at admission. All patients need to be treated as COVID-19 positive patients until proven otherwise, HCW should therefore use adequate personal protective equipment (PPE [16]. Until negativity for COVID-19 is proven patients should be hospitalized in a single room. Suspect patients cannot be grouped together in order prevent nosocomial transmission in case a positive patient is found. Patients' isolation at admission is crucial for prevention of nosocomial transmission. Considering the elective nature of the procedures, we think that departments that are not able to guarantee patients' isolation at admission should not perform elective spine surgery operations during these delicate times.

If both nasopharyngeal swab and chest X-ray are found to be negative, patients will be considered COVID-19-free. Patients with a negative nasopharyngeal swab and a chest X-ray suspicious for interstitial pneumonia are evaluated by an IDS. After this evaluation, a second nasopharyngeal swab is performed if judged necessary, otherwise the patient is considered COVID-19-free. When the second swab is found to be negative, the patient will be anyway considered negative. COVID-19-positive patients will be evaluated by an IDS as well, but surgery will not be performed and they will be either discharged at home with proper indications or admitted to a dedicated department for COVID-19 patients.

Our algorithm allows performance of elective spine surgery exclusively on COVID-19-free patients. Increased rates of complications and mortality have been reported when surgery is performed on a COVID-19 positive patient during the incubation period[17]China, has spread rapidly worldwide. In the early stage, we encountered a small but meaningful number of patients who were unintentionally scheduled for elective surgeries during the incubation period of COVID-19. We intended to describe their clinical characteristics and outcomes. Methods: We retrospectively analyzed the clinical data of 34 patients underwent elective surgeries during the incubation period of COVID-19 at Renmin Hospital, Zhongnan Hospital, Tongji Hospital and Central Hospital in Wuhan, from January 1 to February 5, 2020. Findings: Of the 34 operative patients, the median age was 55 years (IQR, 43À63. Therefore, considering the non-urgent nature of elective spine surgery, we think that a surgical operation on a patient, either positive or suspected for COVID-19, symptomatic or not, is not justifiable.

Results

Since March 16th 2020 we have used this algorithm for spine surgery procedures. During the national lockdown period (until May 4th 2020) we operated on patients whose treatment could not be delayed; after the end of lockdown, we progressively resumed surgery also for non-urgent cases. Hospital admissions of 159 spine surgery patients were managed according to our algorithm. In 8 cases (5%) the nasopharyngeal COVID-19 swab performed at admission resulted positive; management of these patients according to the proposed algorithm allowed the use of proper preventive measures. Since the application of the protocol, we have not reported COVID-19 nosocomial transmission in our department.

Discussion

Before scheduling surgery during the COVID-19 pandemic, even using the proposed algorithm, spine surgeons should consider some specific ethical issues. Unfortunately, it is not possible to provide universally valid suggestions as these considerations should be done on a national, regional or local basis.

First, spine surgeons should always deal with the availability of human and technical resources in the treating hospital. This should be done before surgery for non-urgent cases in order not to reduce resource-availability for eventual urgent cases. Furthermore, the availability of resources, as ICU beds and staff availability, should be considered in order to be always able to treat eventual complications [18].

We have not included in our algorithm antibody testing for SARS-Cov-2 because these tests currently have an epidemiological value for population screening. For elective surgical patients, who have already been tested with a nasopharyngeal swab, it does not add useful clinical information [19]. Even if these tests don't seem to be useful in elective spine surgery planning, they may however play a role when little or no access to molecular testing is available [20].

Even if our algorithm allows to perform surgery over COVID-19-free patients, the regional COVID-19 pandemic situation should be always considered. In some cases, during a national lockdown, people's movements outside their homes should be prevented, as happened during the first Italian national lockdown [2].

Conclusions

Considering our preliminary results with no reported nosocomial COVID-19 transmissions, we think that our algorithm may successfully help management of spinal elective surgical patients in the COVID-19 era, avoiding unnecessary risks for patients and HCW.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

AB and PF conceived the study, AB and IM drafted the manuscript; MC, MT, PA and PF revised the manuscript. AB and IM reviewed the literature. GZ, PF, PFS and AG critically revised the manuscript. All authors have read and approved the latest version of the manuscript.

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RESEARCH ARTICLE

How to improve TB outpatient service in a TB low-endemic country during SARS-CoV-2 pandemic

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Keywords

Tuberculosis • Outpatient care • Italy • TB-care • Medical ethics

Summary

Despite notable progresses in the recent decades, tuberculosis (TB) continues to remain a public health concern even in Europe. TB prevention and care should be people-centred, improving ambulatory models across countries, in order to expand access to diagnosis and treatment for both TB infection and disease. Even more, during emergencies such as the current pandemic, when seeking of TB care has been replaced by the fear of coronavirus disease 2019 (COVID-19), TB patient's care is fundamental. In this short communication, we document how was possible to implement a TB outpatient service meanwhile a local outbreak of SARS-CoV-2 transmission was ongoing.

Despite notable progress in the recent decades [1, 2], tuberculosis (TB) remains a public health concern in the World Health Organization (WHO) European Region, which includes Italy, currently being the leading cause of death from a single microorganism [3, 5].

The emergence of drug-resistant (DR)-TB in TB low-endemic countries is a consequence of failings in the health care system that does not provide easy access to TB care to those in need, fuelling the TB epidemic and slowing the progress to TB elimination [6, 7].

A milestone of TB prevention and care is a people-centred approach, which implies overall improving ambulatory models across countries, in order to expand access to diagnosis and treatment of both TB infection and disease [6]. In fact, hospitalization of TB patients is needed only for case of severe localizations (e.g. TB meningitis, TB pericarditis) and/or when complications arise because of the treatment (e.g. severe allergies) and/or if the patient has comorbidities that require close monitoring during anti-TB and TB preventive treatment (TPT) [8].

Otherwise, independently from the spectrum of resistance of the *Mycobacterium tuberculosis* (Mtb) strain, all TB continuum of care, from screening and diagnosis to treatment and post-treatment follow-up, should be carried on in specialized outpatient services [8]. Even more during pandemic times, where seeking of TB care has been replaced by the fear of coronavirus disease 2019 (COVID-19) and outpatients services have been hampered by the health emergency status, TB patients care is fundamental [9, 10].

Aim of this paper is to describe how a TB outpatient service was implemented in a referral centre for Infectious and Tropical diseases in Northern Italy when the COVID-19 pandemic was raging in the area.

Following the example of the Regional TB Reference Centre of Lombardy Region, Villa Marelli Institute/ASST Niguarda Ca' Granda (Milan, Italy), which works as an outpatient reference centre for drug-susceptible and DR-TB, serving a population of > 10 million people and managing ~250 patients per year (3% with DR-TB) [7], we created, at the IRCCS Sacro Cuore Don Calabria Hospital (Negrar di Valpolicella, Italy), an integrated outpatient TB service with a multidisciplinary team composed by infectious disease specialists, pulmonologists, pharmacists, microbiologists, radiologists, gastroenterologists, and geriatrics.

Moreover, *on demand* cultural mediators allow to further improve the service, guaranteeing the patient's full understanding of the disease, treatment, scheduled follow-ups visits as well our full understanding of the patient's complaints. In case of other organ involvement (e.g. genitourinary tract) other specialists were called on demand for consultations.

The outpatient TB service was based on the following major pillars against the most common barriers:

1. easy and direct access for patients (reducing barriers to access);
2. rapid molecular diagnosis and drug-resistance profiling (reducing risk of suboptimal treatment or resistance induction and optimizing treatment duration);

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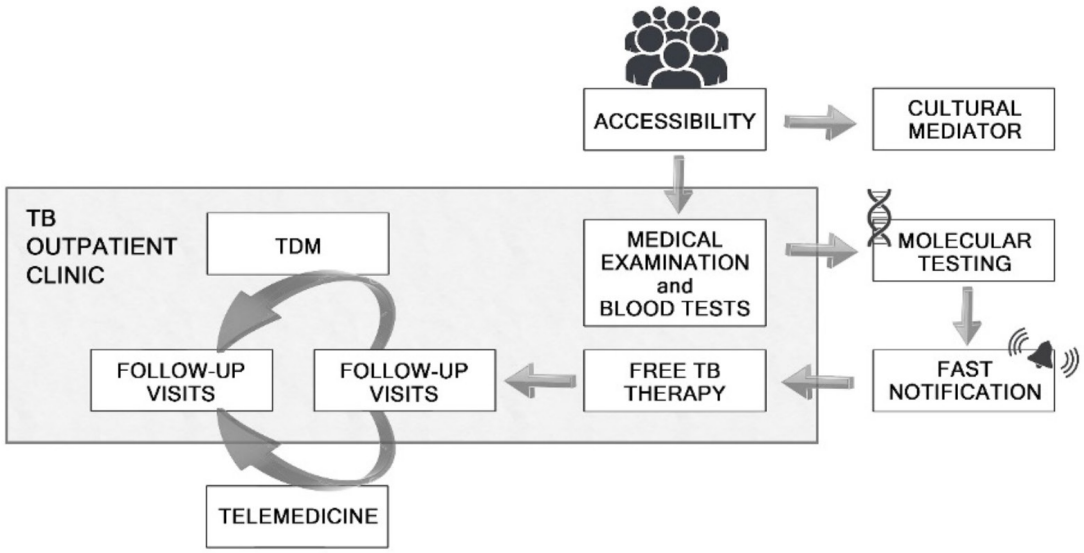
Fig. 1. TB outpatient service workflow at IRCCS Sacro Cuore Don Calabria Hospital.



3. instant notification of molecular and microbiological tests' results to the treating physicians (timely adjustment of treatment);
4. tailored treatment regimens mindful of patients' co-morbidities and at-risk behaviours (like unhealthy diet, comorbidities, drug-drug interactions etc.);
5. direct distribution of anti-TB drugs to the patient (delivered to patients at time of visit, in order to increase adherence to treatment);
6. consultation vie e-mails with patients between follow-ups (essential during COVID-19 lock-down period);
7. scheduled follow-up visits with the possibility of convenient specialists' consultation (to give comprehensive care to patients);
8. therapeutic drug-monitoring of anti-TB drugs (increasing adjustment of treatment and tolerance) [11];
9. track patients' adherence using electronic tools to reduce dropouts (increasing compliance);
10. infectious (e.g. hepatitis B virus, hepatitis C virus, HIV, aspergillosis) and tropical (e.g. schistosomiasis, strongyloidiasis) diseases screening for patients from endemic areas;
11. discussion of difficult-to-treat cases with experts from the Villa Marelli Institute (Fig. 1).

Applying the model to the current context of the COVID-19 ongoing pandemic, we established to screen all patients with rapid antigen test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before entering the hospital and, if the results are either positive or pending, adequate personal protective equipment is worn by both patients and health care workers.

Since the beginning of the outpatient service in July 2020, 30 tuberculosis cases have been diagnosed, 28 (93,3%) and 2 (6,7%), DS and DR-TB, respectively.

Twenty-three were diagnosed pulmonary TB and 7 extra-pulmonary TB. Overall, 6 patients were born in Italy and 24 were foreigners. Just one patient (3.3%) was lost to follow-up.

In conclusion, starting from a people-centred approach, our outpatient service for TB patients care was organized to be nearer and more accessible to the people who need it the most [12].

Overall, it points to a model easily replicable in other low-endemic-high income countries in order to increase patient's adherence to treatment and to answer to patients' necessities [5, 13].

Furthermore, hospitalization can be restricted only to those with severe disease, with reduction of isolation stay and related costs; leaving hospital-bed free for other infective-pathologies such as the current numerous cases of COVID-19 pneumonias [5].

Finally, our contribution represents a step forward in building up extended regional and national networks for TB outpatients. Ensuring quality care, sharing information on diagnosis, management and outcomes, and addressing social and cultural aspects by employing professional mediators may help to increase treatment success, reduce drop out and, ultimately, contribute to the WHO goal of ending global TB epidemic by the year 2035 [14].

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

NR, AA and GB conceived the study; NR, PR, SD, SV, MM drafted the manuscript; NR, PR, LRA, PC, MF, MM, TZ, RT, CC, LC revised the manuscript; NR, PR, SD, SV, PC, MF, MM performed a search of the literature; NR, PR, SD, MM, LC, GB and AA revised critically the manuscript. All authors read and approved the last version of the manuscript.

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RESEARCH ARTICLE

How Iranian people perceived the COVID-19 crisis? Explored findings from a qualitative study: current concerns, ethics and global solidarity

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Keywords

Societal concerns • Stressful • Pandemic • COVID-19 • Coronavirus • Iran • Ethics

Summary

Objectives. *This nation-wide project aimed to investigate the common perceptions and concerns regarding COVID-19 outbreak in Iran.*
Methods. *This qualitative study was conducted in Iran from February to March 2020 via an online open-ended questionnaire. The participants were also selected using convenience and snowball sampling methods. As well, the data collection process continued until data saturation was achieved. Thematic content analysis was utilized to analysis the transcribed texts.*
Results. *The statements retrieved also represented the most challenging psychological stress experienced by the participants. Four themes were accordingly recognized based on the content analysis including stressful conditions, health concerns, social and political concerns, and economic concerns. Throughout the study, a major proportion of the participants commented that psychological disorders such as fear, anxiety, stress, and ennui were their main challenges regarding this pandemic. Furthermore, lack of social responsibility, worries about high-risk and susceptible groups, decreased economic power of the public, financial hardships for low-income groups, shortage of healthcare facilities, and adverse effects of disinfectants were expressed as the main concerns.*
Conclusions. *As a whole, it is evident that people have confronted with several challenges and need help together with effective policies and strategies during and after COVID-19 pandemic to reduce their current concerns. The study findings provided a favorable ground to develop and adopt the required policies in Iran and other countries. It was concluded that creating local, national, and global solidarity in such outbreaks is an inevitable necessity.*

Introduction

On February 20, the first COVID-19 cases were reported in Iran, and then the virus spread rapidly throughout the country, so that over 2.3 million positive cases and approximately 69000 deaths have been reported in this region until April 23, 2021 [1]. Several policies and strategies have been correspondingly adopted to prevent and control the spread of COVID-19 by the government such as social distancing, business closure, restricting domestic and international flights, etc. [2, 3]. Although these measures have had considerable impacts on reducing the incidence rate of COVID-19, a number of problems have arisen [4]. Indeed, job losses and financial concerns have been usually among the first knock-on effects of pandemics [5]. In addition, due to the sharp increase in positive cases, both public servants and medical staff have been subjected to psychological disorders including depression and anxiety [6, 7].
As reported, the negative economic effects of COVID-19 have been significant [8]. For instance, over 6 million people have registered for unemployment insurance in the United States since one month ago [9]. Additionally, the United Nations (UN) has demonstrated the catastrophic impacts of this pandemic on economies of developing countries [8]. Specifically, based on the related literature, nearly 65% of economic activities have been reduced in manufacturing and service sectors in Iran following COVID-19 outbreak [10]. Fall in oil prices is on other challenge for Iran's economy, which will cause a severe government budget deficit [1]. Behind these economic shocks, a major proportion of population has confronted with the deaths of family and friends as well as physical consequences of this pandemic [11]. On the other hand, social lockdown and self-isolation can lead to the occurrence of high-risk behaviors such as alcohol abuse or even increasing incidents of domestic and family violence [12].
Following COVID-19 pandemic, people have faced many concerns, especially Iranian population with a large number of previous socioeconomic and cultural problems [1, 13]. Therefore, comprehensive identification of these concerns can provide a favorable ground in order to develop and adopt effective policies and strategies, interventions, and guideline documents to fight COVID-19 and to alleviate its adverse effects.

For this purpose, this nation-wide project was conducted to investigate common concerns regarding COVID-19 outbreak in Iran.

Methods

The present study was part of a larger survey project conducted at Health Policy Research Center (HPRC), Institute of Health, Shiraz University of Medical Sciences (SUMS), Iran, conducted from February to March 2020. The protocol of this project had been previously confirmed by the Institutional Review Board (IRB) of SUMS.

Participants

The participants were selected using convenience and snowball sampling methods at a national level. To this end, the research team strived to select individuals representing maximum variation in terms of age, gender, employment status, marital status, level of education, and geographic location. As well, the data collection process continued until data saturation was achieved. Although there was no valid evidence, 150 responses with duplicate data were considered to confirm the saturation. Prior to sending the open-ended online questionnaire, a written consent form and an invitation letter including information about research objectives and related ethical principles, were given to the participants via WhatsApp and Telegram as the top social messaging applications used in Iran. Furthermore, additional information was provided by the research team to these individuals if requested.

Data collection

An online questionnaire including open-ended items was utilized to investigate common concerns among Iranian people regarding COVID-19 pandemic. In this questionnaire, the participants were asked to express and write their concerns and experiences. Based on the provided feedback from initial responses, the format of the items was modified for further clarity. After receiving responses, the transcribed texts were simultaneously organized and saved by the first author (a male PhD Health Policy) in the Microsoft Office software to facilitate the analysis process.

Data analysis

The collected data were analyzed using thematic content analysis. Inductive approach was further considered to grasp latent and obvious content. The approach developed by Braun and Clarke consisting of six steps including: (1) familiarizing with collected data, (2) establishing initial codes, (3) identifying primary themes, (4) evaluating emerged themes, (5) labeling identified themes, and (6) reporting results, was used to analysis the collected data [14].

Rigor and trustworthiness

There are a series of techniques to upgrade rigor and trustworthiness of qualitative studies. Credibility (i.e., credible interpretation of data), confirmability (that is, truthfulness of findings), transferability (namely, degree of applications of findings in other contexts), dependability (viz. repeatability and soundness of findings), and authenticity (meaning, faithfulness of authors in describing realities) are thus determined as the main criteria of trustworthiness [15]. According to the approach proposed by Guba and Lincoln, several techniques can be utilized to ensure the suggested criteria including member checking by co-authors (confirmability), considering a large sample size (transferability), peer debriefing and data triangulation (credibility), participation of four authors in data analysis process (dependability), and use of citations from various participants (authenticity) [16]. For this reason, the analysis process was performed in parallel with data collection in this study. Four authors were also involved in this process, reading and re-reading the transcribed texts independently. Then, meaning units were recognized as the initial codes. The established codes were subsequently monitored by two authors, and similar codes were reduced to sub-themes. Finally, the potential relationships among the emerged sub-themes were assessed, and the final themes were established. Discussions and consensus strategies were also used to solve any disagreements among authors during the analysis process. The analysis was performed manually, and if required, the MAXQDA 11 software package (VERBI GmbH Berlin, Germany) was employed. To diminish the potential risk of bias in this qualitative study, critical reflectivity was implemented as one of the various methods suggested for this purpose. To ensure this strategy, authors with different backgrounds and scientific experiences were participated in data analysis process.

The standards for reporting qualitative research (SRQR) [17] and the consolidated criteria for reporting qualitative studies (COREQ) [18] were additionally considered to confirm all parts of this qualitative study.

Ethical approval

The Ethics Review Committee of the SUMS (IR.SUMS.REC.1399.090) approved the study and all individuals gave informed consent form.

Results

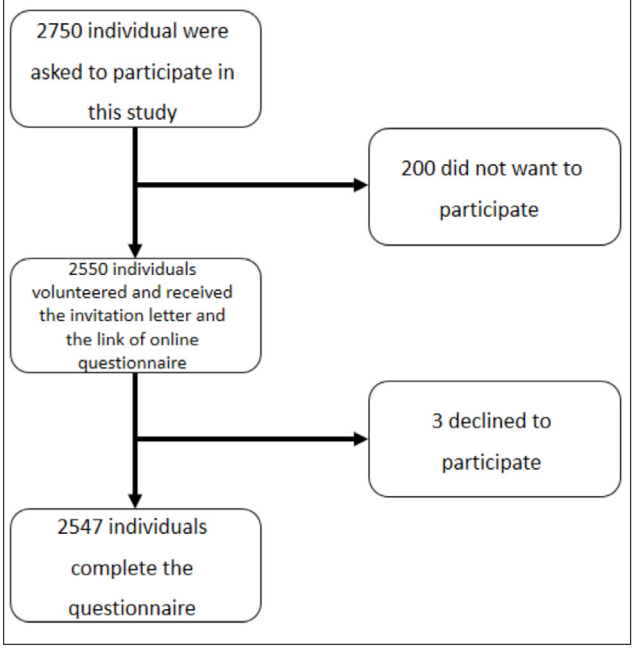
In total, 2,547 individuals agreed to participate and completed the questionnaire (Tab. I). Figure 1 summarizes the recruiting process. The data analysis in this study showed that all the participants were living with chronic stress and anxiety during COVID-19 pandemic. The responses implied a form of individual and social uncertainty about COVID-19. There was also social anxiety and fear because of this pandemic. Concerns about disease transmission, as well as worries about social and economic affairs, were the most pronounced ones by the participants. Four themes were ultimately

Tab. I. Characteristics of participants.

Total sample (n)	**2,547**
Age, mean (SD)	36.38 (10.64)
Male, n (%)	1246 (48.9)
Education level, n (%)	
Under diploma	149 (5.8)
Diploma	311 (12.2)
Associate degree	195 (7.6)
BSc	850 (33.3)
MSc	684 (26.8)
PhD	358 (14.0)
Missing	3 (0.1)
Marital status, n (%)	
Single	799 (31.3)
Married	1,698 (66.6)
Divorced	34 (1.3)
Wife died	16 (0.6)
Missing	4 (0.2)
Employment status, n (%)	
Government employment	760 (29.8)
Non-government employment	365 (14.3)
Self-employment	319 (12.5)
Student	382 (15.0)
Housewife	307 (12.0)
Retired	120 (4.7)
Unemployed (job seeker)	160 (6.3)
Unemployed	15 (0.6)
Day worker	103 (4.0)
Missing	19 (0.7)
Income level, n (%)	
Below the poverty line	592 (23.2)
Poverty line	1,133 (44.4)
Above the poverty line	816 (32.0)
Missing	9 (0.4)

recognized through the content analysis including stressful conditions, health concerns, social and political concerns, and economic concerns. Each theme also had sub-themes containing a number of assigned codes (Tab. II). In what follows, detailed findings accompanied by quotes from the participants' responses translated from Persian have been presented.

Fig. 1. COREQ flowchart of recruiting process.



Stressful Conditions

The retrieved statements revealed stressful conditions filled with fear and social anxiety. In this respect, a major part of the participants commented that psychological disorders such as fear, anxiety, stress, and ennui were their main challenges regarding COVID-19 pandemic. Indeed, they believed that a significant degree of worry, fear, and concern especially among certain groups such as disabled people, older adults, healthcare providers, and patients with underlying health conditions had emerged as the virus was rapidly spreading across the country. For example, some participants stated that:

"I think, these days, a very bad atmosphere has been created. We always feel stressed-out about everything"[0024].

"My wife is exceedingly sensitive and disinfects everything and everywhere so much that, I think, she is hurting her respiratory system"[0146].

Fear of an uncertain future was another sub-theme comprised of several codes such as disruptions in personal programs. Some participants also claimed that this pandemic has interrupted their predefined appointments and plans. Furthermore, uncertainty about the future of their jobs and employment status was expressed by most of the participants. Some individuals, especially students, additionally aired their concerns regarding the future of their academic education. For instance, one of the participants asserted that:

"As a Master's student, I am very confused. Virtual training does not really exist. The due time for starting university courses has not been announced yet. So, we have to wait and kill time!"[0291].

Health concerns

Health and hygiene issues were explained by a majority of the participants. Mysterious and unknown virus, lack of healthcare facilities, and adverse effects of disinfectants were thus identified as the main sub-themes in this category. The participants also reiterated that the virus had caused stress since it was unknown. Furthermore, the rapid spread of the virus had been considered as a potential factor inducing such worries. As a whole, uncertainty about routes of virus transmission, unknowing carriers, long incubation period of the disease, and lack of the same symptoms in patients were among other concerns. In this line, some participants added that:

"The virus is very mysterious. It is not clear how it is transmitted. This has made us feel down"[0065].

"For the reason that some patients do not have symptoms, we are obsessed with everyone"[0401].

A large group of the participants in this project described COVID-19 as a terrible phenomenon. They further noted that they were always afraid of becoming infected due to the rapid transmission of the virus. On the other hand,

Tab. II. Central theme and coding.

Main themes	Sub-themes	Codes
Stressful conditions	Psychological disorders	• Fear • Anxiety • Delighted • Disappointed • Stress • Restlessness • Ennui
	Indefinite future	• Disrupt personal programs • Uncertainty about the future of the job • Uncertainty of academic status • Uncertainty about when the situation will return to normal
	Terrible coronavirus	• Fear of getting infected • Fear of being a virus carrier • Fear of recurrence of disease • Fear of the lasting effects of the disease • Fear of death from corona • Unpleasant way of burying the dead • Getting close relatives and family
Health concerns	Mysterious and unknown virus	• Unknowing the virus • Unknowing the origin of virus • Fast spreading of disease • Uncertainty about transmission routes of virus • Unknowing the carriers • Long incubation period of disease • Lack of the same symptoms in patients • Airborne transmission • The ambiguity of the effect of temperature on the virus
	Lack of health facilities	• Shortage of hospital capacity • Shortage of expert staffs • Shortage of preventive appliances • Shortage of treatment equipment • Shortage of medicine • Lack of vaccine • Hoarding of sanitary goods
	Adverse effects of disinfectants	• Adverse effects of alcohol use • Adverse effects of bleach • Adverse effects of excessive hand washing
	High-risk and susceptible groups	• Infection of pregnant women • Infection of children • Infection of elderly people • Infection of health workforces • Infection of bank workforces
Social and political concerns	Lack of social responsibility	• Lack of understanding of the seriousness of this crisis by the people • Non-compliance with quarantine by the people • Gathering people in stores • Lack of cooperation and participation of people in control programs • People travel • Lack of awareness • Lack of attention to warnings
	Incompetence and negligence of the authorities	• Inconsistency between institutions • Lack of accountability of authorities • The dishonesty of the authorities • Poor performance of authorities • Lack of proper crisis management by government • People's distrust of officials • Political considerations • Don't take the crisis seriously • Lack of transparency by the authorities • Lack of presence of officials in the media
Economic concerns	Financial pressure on the poor	• Day-wage workers • Working children • Badgers
	Expensiveness and inflation	• Essential goods become more expensive • Prevention appliances become more expensive • High-cost of health care services
	Decreased economic power of public	• The financial losses of market people • Closure of most jobs • Loss of income

fear of being a virus carrier was a common concern, which was detected all through the study. Many people were also concerned that they might be carriers of the virus and pass it on to their relatives and other people around them, especially vulnerable groups. As a notable conclusion, some participants pointed out the fear of death from COVID-19 and its unpleasant burials.

"I am always afraid of getting infected. When I come home, I disinfect all my clothes and belongings. But I am still pessimistic about this virus"[0563].

Furthermore, concerns regarding high-risk and susceptible groups were another category emerged from the data. Based on this category, fear of making others around like women, children, elderly people, healthcare providers, and bank employees sick, were repeated in almost all responses.

"My husband is a bank employee. Banks must be open according to the announced protocol in Iran. Given the deaths of several bank employees across the country, I have extreme stress that something bad will happen to him"[0186].

Regardless of these findings, almost all the participants criticized the policies and strategies adopted by the government and other authorities. In fact, they argued that there was an inconsistency between institutions and actors and even no clear responsibilities.

"It is very unreasonable that the Ministry of Health and Medical Education says one thing, the Ministry of Industry declares one thing, and at the end of the night, Mr. President criticizes everyone"[1603].

In addition to shortage of healthcare facilities as a major factor raising concerns regarding this pandemic in Iran, the participants illustrated several other challenges such as inadequate hospital capacity, absence of specialists, unavailability of sanitary and preventive equipment, lack of medications and vaccines, as well as hoarding of sanitary goods throughout the study.

"The hospital located in my hometown does not have enough capacity at all. So, if we get sick, where do they take care of us? "[2221].

Ultimately, many participants mentioned the adverse effects of disinfectants. For instance, most participants reported their concerns regarding the negative impacts of alcohol use on their respiratory systems as well as other organs. In addition, many women expressed concerns about the adverse effects of bleach cleaners, which are widely used for disinfection. Since hand washing had been introduced as one of the initial strategies to prevent the virus transmission, a large group of the participants described a kind of concerns regarding their skin conditions.

"Many of our citizens have lost their lives due to alcohol abuse. We are very concerned about the misuse of disinfectants, especially by children."[0508].

Social and Political Concerns

In this category, a number of challenges and concerns were expressed throughout the present study. The participants suggested lack of social responsibility as one of the main concerns. No understanding of the seriousness of this crisis, non-compliance with quarantine, gathering in stores, travels, and inattention to warnings were among the considerable results.

"Many people do not take the disease seriously, especially at its onset. When you go out, you can see many people there"[0035].

Economic Concerns

The participants mentioned the negative impacts of COVID-19 pandemic in the short and long term. In this respect, some participants said that:

"After this pandemic, quarantine policies have disrupted many of my career plans. Someone like me who has bank debts has to work to make money. If I do not work, I will be in the red."[0065].

Most of the participants believed that the adopted policies in Iran such as social distancing had significant financial hardships for low-income groups. Accordingly, daily-wage workers, street children, and beggars were introduced as the most susceptible groups following this situation.

"I know a lot of people who have a daily income, but now they have no take-home pay"[2106].

The findings from the content analysis indicated an increase in the prices of basic goods across Iran. Many people additionally cited higher inflation rate, fall in oil prices, and devaluation of the national currency as short-term effects of this pandemic, which could cause many other problems. In addition, weak healthcare insurance coverage as one of the main challenges of Iran's healthcare system could confront households with catastrophic expenditures. Therefore, majority of the participants had faced high rate of out-of-pocket pays regarding COVID-19. Besides, information about the rising costs of sanitary and preventive equipment was declared by these individuals several times.

"The high costs of sanitary and preventative equipment such as masks have made everything very difficult. The price of masks has increased by tenfold"[0052].

Decreased economic power of the public was another big concern identified in this study. In this regard, the participants had experienced that a large part of Iran's population had lost their incomes, especially self-employed ones. In addition, COVID-19 pandemic had resulted in business closure and job losses, which could be a source of many other concerns.

"I work in the market. Now that the market is closed, I have no income. I have also lost my financial capital."[0949].

Discussion

Four themes and a broad spectrum of sub-themes and codes were identified in the present study. Accordingly, the findings highlighted common concerns of Iranian people regarding COVID-19 outbreak.

The main findings of this study reflected on widespread psychological concerns following COVID-19 pandemic in Iran. Indeed, this situation was considered as an

unprecedented period for all people, especially for children confronting a massive disruption in their daily living [19, 20]. However, being at home might expose all household members to increased risks. Domestic and family violence has been similarly reported as a common high-risk behavior after home quarantine in parts of the world [21]. For instance, such violence has respectively risen by nearly 25-60% in the United Kingdom and Mexico since government policies have merely focused on controlling the disease progression [22, 23]. In this situation, vulnerable groups such as children and older adults might be more affected [24]. Regarding these abuses, countries like France have developed policies to help the victims. As the movement of the citizens has been restricted, France has been advising female victims to seek help at drugstores using code words [25, 26]. Findings had also indicated the fear of an uncertain future as the negative impact of this pandemic. Based on the evidence, this fear could stop the population from fulfilling their duties very well, and it could even retain many people holding onto situations hurting them [27]. Therefore, decision-makers and policy-makers should develop effective and community-based policies and strategies to reduce individual concerns in these stressful conditions following COVID-19.

In this study, lack of social responsibility was identified as one of the main social concerns. Although public education was being conducted through the Islamic Republic of Iran Broadcasting (IRIB) and the mass media following COVID-19 pandemic, some groups resisting such recommendations. Experts also believed that having a single voice in the society could increase social responsibility [28, 29]. Another part of concerns was in terms of dealing with vulnerable groups such as pregnant women, children, older people, and healthcare providers. The findings additionally showed that a large proportion of the population was worried about the risk of exposure to COVID-19 in these vulnerable groups. Concerns about the infection affecting pregnant women and children also fueled after the confirmation of the birth of a newborn child in China [30]. Nonetheless, the World Health Organization revealed no evidence that pregnant women are at higher risk of severe COVID-19 in a population [8]. In accordance with the literature, verbal and emotional support could significantly reduce such concerns [31].

Moreover, concerns about incompetence and dishonesty of authorities were one other social and political challenge addressed throughout the study. The occurrence of political and social events in recent years, and especially in the last year, in Iran, could be effective in such situations. On the other hand, the weakness of social capital in this country had a long history [32, 33]. Several studies have correspondingly revealed the importance of social capital in pandemic periods [34]. For instance, generalized and institutional trust in healthcare provision was considered as a potential factor influencing the acceptance of health-protective behaviors in Sweden following the 2009 swine flu pandemic (H1N1) [34]. Therefore, using effective solutions to promote the credibility of the government and community-based networks might positively affect prevention and control of COVID-19 pandemic in Iran.

Short- and long-term adverse effects of this pandemic on Iranian economy were among common concerns underscored by the participants. In fact, pandemics are accompanied by considerable economic disruptions although they are rare [35]. Based on the WHO report [36], pandemics such as avian influenza could lead to significant economic losses e.g. the H1N1 and severe acute respiratory syndrome (SARS) pandemics have had significantly negative impacts on national and global economies [37, 38]. Following these trends, a major proportion of society, especially low-income groups, had been confronted with financial hardships, as mentioned in the study. Furthermore, rising inflation and unemployment rates as other impacts of economic recession following the pandemic could result in severe concerns and anxieties across the country [39]. Therefore, developing and adopting economic policies at macro- and micro-level to control the adverse effects of COVID-19 pandemic fairly and immediately is an inevitable necessity. In addition, sanctions have worsened the situation for Iranians facing the virus [1]. There is thus a need for global solidarity in such epidemics and even acting against unfair sanctions.

The special feature of new COVID-19 is that it is unknown and mysterious [2]. The participants pointed out this feature as the origin of a number of concerns. Indeed, lack of clarity about the source of the virus, as well as its modes of transmission, had created tensions and obsessions for society. In addition, following this pandemic as well as a sharp growth in the number of new positive cases, shortage of sanitary and preventive equipment in Iran, as in most affected areas, have raised concerns in the public. Furthermore, COVID-19 similar to other previous pandemics such as SARS has no definite treatment and its incubation period has left people in a state of ambiguity [40]. More importantly, overuse of alcohol and bleach cleaners as disinfectants has resulted in mild respiratory disorders for Iranian people, so that many people expressed concerns about the side effects of these substances on their health status [41]. Therefore, informing the public about the common ways the virus spreads from person to person, how to prevent it, and how to use disinfectants to prevent or at least moderate these concerns can be among effective strategies in this respect.

Conclusions

As a whole, four main themes i.e., stressful conditions, health concerns, social and political concerns, and economic concerns were identified as the common concerns about COVID-19 outbreak in Iran. It is evident that people have confronted with several challenges and need help with regard to effective policies and strategies during and after the pandemic to minimize their current concerns. The study findings also provided a favorable

ground to develop and adopt the required policies in Iran and other countries. In this situation, human beings need some kind of solidarity at local, national, and international levels.

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; UN: United Nations; IRB: Institution Review Board; SUMS: Shiraz University of Medical Sciences; WHO: World Health Organization; SARS: severe acute respiratory syndrome.

Ethics approval

The Ethics committee of the Shiraz University of Medical Sciences (SUMS) has confirmed the study protocol (IR.SUMS.REC.1399.090).

Availability of data and materials

The data collected and analyzed during the study are available from the corresponding author on reasonable request.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

STH, LZ, and KBL conceptualized and designed the study. STH and LZ collected data. AS and SSH involved in analysis process. SSH contributed to the first draft. STH, LZ, MM, MB revised critically the manuscript and performed a search of the literature. All authors contributed to the final draft. The authors read and approved the final manuscript.

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