

World Journal of *Virology*

World J Virol 2022 January 25; 11(1): 1-89



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Editorial Board Member of *World Journal of Virology*, Ming-Ke Wang, MD, PhD, Associate Chief Physician, Deputy Director, Department of Disease Control and Prevention, Naval Medical Center of PLA, Naval Medical University, Shanghai 200052, China. wmke021@163.com

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INDEXING/ABSTRACTING

The WJV is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Hua-Ge Yu; Production Department Director: Xiang Li; Editorial Office Director: Jin-Li Wang.

NAME OF JOURNAL

World Journal of Virology

ISSN

ISSN 2220-3249 (online)

LAUNCH DATE

February 12, 2012

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Mahmoud El-Bendary, En-Qiang Chen

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3249/editorialboard.htm>

PUBLICATION DATE

January 25, 2022

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ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



COVID-19: A pluralistic and integrated approach for efficient management of the pandemic

Nouhoum Bouare, Daouda Kassim Minta, Abdoulaye Dabo, Christiane Gerard

ORCID number: Nouhoum Bouare 0000-0002-8362-6740; Daouda Kassim Minta 0000-0002-0333-5227; Abdoulaye Dabo 0000-0002-7238-3894; Christiane Gerard 0000-0002-9439-1692.

Author contributions: Bouare N contributed to manuscript drafting, reviewing and reading the final version; Minta DK and Dabo A contributed to manuscript reviewing and reading the final version; Gerard C contributed to manuscript drafting, reviewing and reading the final version.

Conflict-of-interest statement: The authors declare no conflict of interest.

Country/Territory of origin: Mali

Specialty type: Virology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an open-access article that was

Nouhoum Bouare, Biomedical Sciences Researcher, National Institute of Public Health, Bamako 1771, Mali

Daouda Kassim Minta, Department of Infectiology, CHU PointG, Bamako 333, Mali

Abdoulaye Dabo, Department Epidemiology & Infectiology Disease, Faculty Medicine & Dentistry, CNRST/Univ Bamako, Bamako 3052, Mali

Christiane Gerard, Formerly Responsible for the Blood Bank, CHU-Liège, University of Liège, Liège 4000, Belgium

Corresponding author: Nouhoum Bouare, DSc, PhD, Research Scientist, Biomedical Sciences Researcher, National Institute of Public Health, Hippodrome Rue Hamilcar Cabral, Bamako 1771, Mali. nouhoumsamakoro@yahoo.fr

Abstract

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which triggered the ongoing pandemic, was first discovered in China in late 2019. SARS-CoV-2 is a respiratory virus responsible for coronavirus disease 2019 (COVID-19) that often manifests as a pneumonic syndrome. In the context of the pandemic, there are mixed views on the data provided by epidemiologists and the information collected by hospital clinicians about their patients. In addition, the literature reports a large proportion of patients free of pneumonia *vs* a small percentage of patients with severe pneumonia among confirmed COVID-19 cases. This raises the issue of the complexity of the work required to control or contain the pandemic. We believe that an integrative and pluralistic approach will help to put the analyses into perspective and reinforce collaboration and creativity in the fight against this major scourge. This paper proposes a comprehensive and integrative approach to COVID-19 research, prevention, control, and treatment to better address the pandemic. Thus, this literature review applies a pluralistic approach to fight the pandemic.

Key Words: SARS-CoV-2; COVID-19; Pandemic; Pluralistic approach; Global approach; Efficient management

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Received: April 21, 2021

Peer-review started: April 21, 2021

First decision: July 27, 2021

Revised: August 10, 2021

Accepted: December 28, 2021

Article in press: December 28, 2022

Published online: January 25, 2022

P-Reviewer: Pereira AA, Şehirli AO

S-Editor: Wang JJ

L-Editor: Webster JR

P-Editor: Wang JJ



Core Tip: Pandemic control requires optimal knowledge of the pathogen, infection routes, mode of transmission, and intervention strategies. The contagiousness of coronavirus disease 2019 (COVID-19) complicates pandemic control or containment because asymptomatic carriers, incubating patients, and recovered patients are all potentially contagious. This literature review proposes and justifies the value of a pluralistic and integrative approach to COVID-19 research, prevention, control and treatment.

Citation: Bouare N, Minta DK, Dabo A, Gerard C. COVID-19: A pluralistic and integrated approach for efficient management of the pandemic. *World J Virol* 2022; 11(1): 20-39

URL: <https://www.wjgnet.com/2220-3249/full/v11/i1/20.htm>

DOI: <https://dx.doi.org/10.5501/wjv.v11.i1.20>

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen of the ongoing pandemic, was first detected in late 2019 in Wuhan, Hubei Province, China. This novel respiratory virus causes the infectious coronavirus disease 2019 (COVID-19), which often manifests as pneumonia[1]. At least two previously identified coronaviruses, responsible for SARS-CoV and Middle East respiratory syndrome coronavirus, respectively, have accelerated the understanding of the epidemiology and pathogenesis of SARS-CoV-2[1-4]. Investigations are ongoing to determine the precise origin of the virus.

To control this global scourge, the scientific community and health professionals must invest in understanding the virus, the infection, its spread, the distribution, and its evolution to develop reliable strategies for prevention and/or response. However, public health professionals and/or infectious diseases specialists are often at the front line in the fight against outbreaks or pandemics. However, the statistics provided by epidemiologists often contrast with the information collected by practicing clinicians regarding their patients[5]. Although data collected from travelers coming from areas with a high incidence of COVID-19 may be useful for estimating the incidence, this risk measure is controversial. While epidemiologists use statistical methods or mathematical models to assess the magnitude of the epidemic in the community (*e.g.*, incidence), clinicians focus on patients based on the number of hospitalizations[5]. According to the literature, 80% of confirmed COVID-19 cases did not have pneumonia, approximately 15% had severe pneumonia, and approximately 6% were admitted to intensive care units (ICUs) for the treatment of respiratory failure, shock, or multiorgan damage[6]. Asymptomatic infected persons and incubating patients (potential sources of virus transmission) or patients who have recovered from COVID-19 without showing a reduced SARS-CoV-2 viral load by a factor of $1/10^6$ (*i.e.*, a 6-log reduction), can pose serious challenges for disease prevention and control[1,7].

This raises the issue of the complexity of pandemic control or containment. We believe that a pluralistic and integrated approach will put into perspective the specificities of each discipline and reinforce collaboration and creativity in the fight against this scourge. This paper proposes a collaborative approach of competencies to capitalize on expertise, an integrated strategy for interventions for the control of epidemic or chronic diseases, and a global patient management plan for disease and/or pandemic control.

METHODS

We analyzed the scientific literature according to six main areas of expertise. We searched the PubMed database to construct a clinical scientific bibliography. The basic search term used for the literature search was "covid+19," followed by one or other thematic terms, including virology, epidemiology, prevention, control, Africa, infection, and treatment. Preference was given to the "review" and "most recent" filters. The most appropriate articles for each thematic term were selected for the analysis and discussion. Table 1 summarizes the reference portals according to the corresponding target groups and disciplines. An additional search focused on the

Table 1 Documentary research by target groups and by specialty disciplines

Target groups	Documentary research links	Documentary search dates and periods	Main fields/remarks
Biologists	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+virology&filter=pubt.review	12/10/2020	Medical biology (virology, molecular biology, clinical biochemistry, hematology, immunology, etc.)
Public health professionals	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+epidemiology&filter=pubt.review	14/10/2020	Public health (epidemiology, community health, etc.)
	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+prevention&filter=pubt.review	12/10/2020	
	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+control&filter=pubt.review	13/10/2020	Communication (transversal)
	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+Africa&filter=pubt.review	12/10/2020	
	https://eu.boell.org/en/2020/08/17/dr-congo-challenge-convincing-people-coronavirus-exists		
Clinicians	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+infection&filter=pubt.clinical+study	12/10/2020	Medicine (infectiology, pneumology, cardiology, internal medicine, etc.)
	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+treatment&filter=pubt.randomized+controlled+trial	13/10/2020	
	https://pubmed.ncbi.nlm.nih.gov/?term=covid+19+vaccination&filter=pubt.review	14/02/2021	
Researchers	https://pubmed.ncbi.nlm.nih.gov/32230900/	January 2021	Research (transversal or universal character of science)
	https://www.ncbi.nlm.nih.gov/research/coronavirus/		
	http://www.health.belgium.be/eportal/disclaimer/		
	https://rega.kuleuven.be/if/corona_covid-19		
	https://covid19.sciensano.be/sites/default/files/Covid19/Covid19_fact_sheet_ENG.pdf		
Decision-makers	N/A		A pluralistic approach to inform and guide health policies

basic term “covid+19,” followed by “vaccination” with “most recent” as the preferred filter. The PubMed literature search (including the additional vaccination search) was performed from October 12, 2020, to February 14, 2021 (Table 1). Figure 1 presents the flow chart of the search for articles and publications.

RESULTS AND DISCUSSION

Biology and virology

SARS-CoV-2 is a member of the coronaviridae family. It is a beta-coronavirus (subgroup B Sarbecovirus) enveloped with a large single-stranded RNA + that can infect animals and humans[8]. In humans, the structural (spike) protein of the viral envelope recognizes angiotensin-converting enzyme 2 (ACE2) as a receptor and preferentially infects pulmonary epithelial cells. The spike protein binding domain binds to ACE2; the host transmembrane protease serine 2 protease then cleaves the protein to expose fusion peptides that fuse the virus to cell membranes[2,9]. ACE2 is expressed in several human tissues, including the lung, small intestine, kidney, heart, thyroid and adipose tissues, which can be infected by SARS-CoV-2 and cause various symptoms[8,10].

The genome of SARS-CoV-2 is 96.2% and 79.5% identical to the sequences of RaTG13 (bat) CoV and SARS-CoV, respectively. Accordingly, bats are considered the natural host and a potential origin of the virus and may have transmitted the virus to humans through an unknown intermediary or directly *via* the aquatic wildlife market in Wuhan[8,11,12]. In the absence of strong evidence of pangolins as an intermediate host, some authors have suggested the need for coronavirus surveillance in these animals in the wild to minimize human exposure[13]. SARS-CoV-2 may also be transmitted by aerosols or vehicles (hands or soiled objects). Depending on the amount of inoculum, the virus can remain viable and infectious for hours in aerosols and days

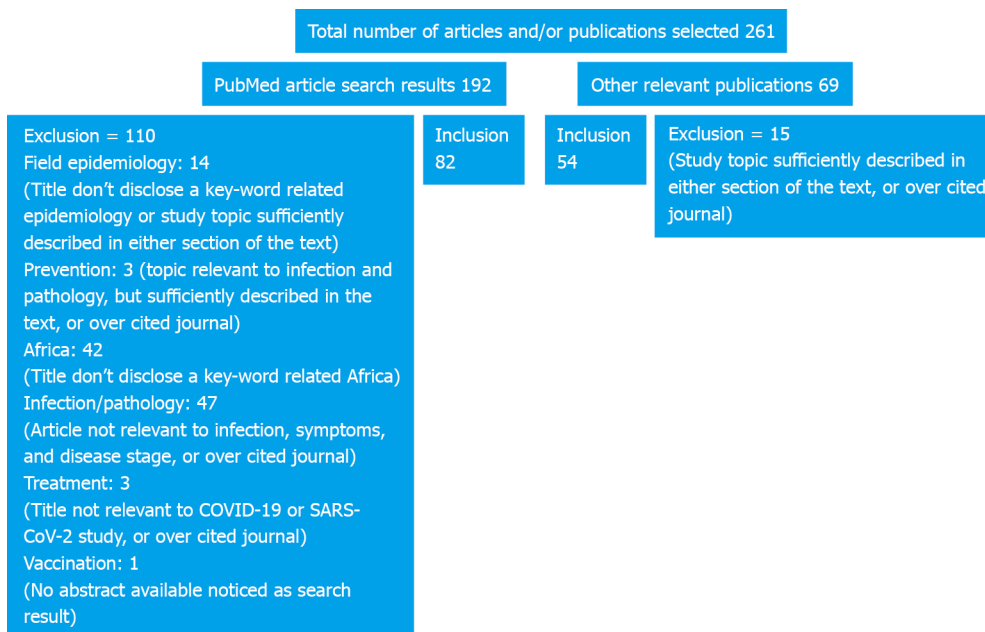


Figure 1 Flow chart of the search for articles and publications. COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

on surfaces[14-16]. Longer SARS-CoV-2 and SARS-CoV-1 viabilities on stainless steel and plastic have been reported. The median half-life of SARS-CoV-2 was 6 h for stainless steel and 7 h for plastic[17]. Hence, universal hygiene precautions such as hand washing with soap and water, wearing masks, and cleaning surfaces have been recommended.

The pre-analytical phase is crucial. The quality of the analysis or results depends on the sample quality. Sputum samples may have viscous consistency due to mucus (purulent or not).

The effective extraction of viral nucleic acid requires the liquefaction of sputum to avoid false-negative results[18]. Moreover, the use of swabs made of non-compliant materials may inactivate the virus particles or inhibit polymerase chain reaction (PCR). For nasopharyngeal or oropharyngeal swabs, swabs (standard or flocked) with a flexible plastic shaft are recommended. Quantitative molecular tests (quantitative reverse transcription-PCR) are used to complement clinical, biological, and radiological investigation tools[19]. Although molecular tests are highly specific for the diagnosis of COVID-19, their sensitivity depends largely on parameters such as the specimen type, time of specimen collection, sampling technique, test quality, and technician qualification[20-23].

Immunoassays measure the levels of antibodies [circulating immunoglobulin M (IgM) and IgG] in patients with COVID-19. However, the usefulness of these tests as an epidemiological tool is questioned in terms of their sensitivity and specificity, since the results may vary depending on the serological window. This window must be neither too early nor too late to produce an interpretable result[24].

One study reported a higher sensitivity for the detection of IgA (about 4-25 d after disease onset), with IgG reportedly better for diagnosis in later stages of the disease [25]. A diagnosis of COVID-19 is suspected in cases in which the symptoms of respiratory infection occur within 14 d (consistent with the incubation time) in an asymptomatic person coming from an epidemic area[26]. The association of SARS-CoV-2 viral load relative to the nasopharyngeal specimen with COVID-19 severity has been reported, in which a higher viral load was associated with a lower lymphocyte count, greater organ damage, and longer time to molecular test negativity[27]. Higher viral loads were detected soon after symptom onset, with higher loads in the nose compared to throat swabs. The same study suggested that the kinetics of SARS-CoV-2 nucleic acid clearance resembled that of influenza and differed from that of SARS-CoV. In addition, the similarity of viral loads in symptomatic and asymptomatic patients suggests that minimally or asymptomatic people may potentially be infectious. Therefore, transmission may occur early during infection. Case detection and isolation may require strategies different from those previously used to control SARS-CoV. The identification of minimally or asymptomatic patients and modest

levels of viral RNA (detectable in the oropharynx) suggest the need for further investigation to determine the transmission dynamics and inform screening practices[28]. Furthermore, the implications of positive (or negative) test results in asymptomatic individuals remain undetermined, as well as the interpretation of these results for immune passports (detection of signals of past infection). The findings seem to contradict much of the popular literature on the use of the test as a tool for COVID-19 management. Although testing is an essential part of disease management, including COVID-19, its inappropriate use may have unintended adverse consequences[29]. Therefore, clinicians must consider other factors when interpreting a patient's test results. The Food and Drug Administration (FDA) issued approval to biotechnology firms to provide COVID-19 tests. One of the major areas of FDA intervention is to increase the availability of tests, treatments, and materials such as ventilators and personal protective equipment (PPE)[30,31]. The World Health Organization (WHO) regularly updates the list of qualified reference laboratories to confirm COVID-19 test results[32].

Epidemiology

To better control the epidemic, scientists are investigating how SARS-CoV-2 is transmitted and spread. Initial data from patients in China provided information on the mode of human-to-human transmission, mainly *via* the respiratory route, most likely through close contact[33,34]. Human-to-human transmission was demonstrated in the first confirmed cases of infection in Wuhan, China[28]. It is generally accepted that the more a person interacts with others and the longer this interaction lasts, the higher the risk of COVID-19 transmission. However, further investigations are needed to understand if and how different animals may be affected by this disease. Researchers at the Friedrich Loeffler Institute in Germany reported that raccoon dogs (*Nyctereutes procyonoides*), an invasive carnivorous animal used for fur, are a potential intermediate host in SARS-CoV-2 transmission. The researchers proposed that the farms where these animals are raised may serve as reservoirs for SARS-CoV-2 and that this risk should be mitigated by effective and continuous surveillance. In their opinion, while it is possible to control the virus on farms, spillover to susceptible wildlife and, in particular, to free-living raccoon dogs would be a major challenge to elimination[35]. Signs of respiratory pathology and increased mortality have also been described in farmed minks (*Neovison mink*) infected with SARS-CoV-2[36,37]. Evidence of animal transmission of SARS-CoV-2 to humans on mink farms was also reported in a phylogenetic study[38]. However, the authors indicated that some farm residents may have been infected within their households and not directly *via* the mink. They added that the survey did not identify common factors that could explain the spread among farms, probably *via* temporary workers not included in the tests. They were concerned that the fur production and trade sector not become a reservoir for the future re-emergence of SARS-CoV-2 in humans.

Globally, incidences ranging from 0.00 to 61.44 per 1000000 persons were reported for COVID-19 at the end of February 2020. Much lower incidences (perhaps due to weaknesses in reporting systems) were recorded in Africa (0.00 for Nigeria and 0.02 for Algeria). In contrast, higher incidences of 55.06 and 61.44 were reported in China and the Republic of Korea, respectively. The numbers of deaths per 1000000 people ranged from 0.00 in Nigeria to 1.97 in China[39]. Africa accounts for less than 1% of the global SARS-CoV-2 mortality[40].

A molecular study reported the early transmission of COVID-19 and a heterogeneous epidemic in South Africa[41]. The study sought to better understand the epidemic heterogeneity of SARS-CoV-2 strains and their introduction during the first month of the epidemic in that country. The early introduction of SARS-CoV-2 into Kwazulu Natal resulted in a localized outbreak in one hospital, which is a likely explanation for the initially high mortality rates in the province. The high rate of COVID-19 transmission in the Western and Eastern Cape highlights the critical need to strengthen local genomic surveillance in South Africa.

All 54 African countries officially reported cases of COVID-19. More than 3000000 people tested positive for COVID-19, with more than 99000 deaths (3.3%). These relatively low levels of mortality may be due to the rapid response in some countries, including South Africa, Uganda and Ethiopia. In addition to the rapid and insightful implementation of stringent response measures, the demographics of the continent (the youthfulness of the sub-Saharan African population) may have conferred some advantage, as a large fraction of deaths caused by COVID-19 occurs in patients over 70 years of age[42,43]. However, the hypothetical effectiveness of containment measures across this continent may be premature. Poor reporting quality, limited communication systems for patients and health professionals, and insufficiency of

surveillance and screening centers across the continent may also contribute to the low reported numbers. The registration rates of all deaths and their causes are incomplete in many African countries because accurate estimates are difficult to obtain, with coverage of registered deaths varying from 5% in Mozambique, 16% in Zambia, 25% in Botswana and Ghana, and 67% in South Africa[44]. In addition, COVID-19 may be confused with other infectious diseases, such as malaria, typhoid, human immunodeficiency virus (HIV)-AIDS, and tuberculosis[45]. These confounding factors can negatively impact the reporting of cases and deaths attributable to COVID-19[42]. Moreover, cultural challenges such as community stigmatization of infected patients, who consequently avoid medical assistance and consult traditional practitioners, further lead to underreporting. Country experience with pandemics and epidemics varies across the African continent, which may influence preparedness (*e.g.*, availability of testing and PPE). West African countries may be better able to respond given their recent experiences with Ebola. Similarly, East African countries have also gained critical epidemic experience from cholera, which has repeatedly affected the region in recent years[46].

The uncertainties regarding the impact of SARS-CoV-2 infection in Africa underscore the need for critical monitoring of the evolution of the pandemic and the factors affecting disease burden. Even in the absence of more effective vaccines and treatments, Africa can lead the fight against this scourge provided that appropriate containment intervention systems are put in place by addressing systematic challenges such as access to water, improved food systems, health education, bed capacity in intensive care hospitals, and increased funding and investment in health care[40].

Infection and pathology

The onset of clinical symptoms seems to favor contagiousness. In some individuals, contagiousness may occur several days before symptom onset. However, contagiousness is more marked in symptomatic persons during coughing. The average incubation period varies from 5 to 6 d, ranging from 2 to 14 d, which justifies the 14-d quarantine period[34]. The initial symptoms (headache, muscle pain and fatigue) are not specific and are followed 2 or 3 d later by fever and respiratory signs.

The clinical manifestations can be severe. Scientists are still seeking to understand COVID-19 severity. Preliminary descriptive studies of databases in China indicated an average time of 1 wk from symptom onset to hospital admission when the disease becomes severe. At this stage, the symptoms include fever, cough, chest pain, and respiratory discomfort. Chest computed tomography (CT) scans almost always show bilateral pneumonia[47]. Since the initial studies, other reported clinical signs include central nervous system involvement (*e.g.*, disorientation, especially in the elderly); sudden loss of taste and/or smell, which occur infrequently but allow confirmation of COVID-19 diagnosis[33,48]. Many patients with COVID-19 present neurological symptoms (including headache, myalgia, and altered consciousness), that are suggestive of the disease.

Some patients with SARS-CoV-2 present with symptoms suggestive of acute stroke, epilepsy, encephalopathy, and demyelinating neuropathies and without cough, fever, or other respiratory problems that could provide clues to the underlying pathology. Diagnosing and administering appropriate treatments to these patients is challenging and requires specialized neurologists, which are sorely lacking in Africa[42].

Real-time Assessment of Community Transmission-1 study data showed that chills, loss of appetite, headache, and muscle pain were the symptoms most strongly associated with infection, along with the four classic symptoms. The presence of one or more symptoms was associated with SARS-CoV-2 infection, with stronger associations with increasing numbers of symptoms. A loss or change of smell was less predictive of COVID-19 infection, while the proportion of people testing positive with a persistent new cough appeared to be increased[49].

The severity of clinical signs requires hospitalization in approximately 20% of patients, while 5% require admission to intensive care. The most severe forms are mainly observed in people who are vulnerable because of their age (over 70 years) or comorbidities (including diabetes and cardiovascular diseases)[47]. Patients with COVID-19 requiring ICU hospitalization are generally frail and have significant comorbidities. The outcomes in this group were generally poor and did not appear to be influenced by ICU admission. Symptoms of COVID-19 infection occurred during hospitalization for a different medical problem in 38% of the patients analyzed[50].

Observational and modeling studies have shown 30% to 60% of infected patients are asymptomatic (absence of clinical manifestations) or “paucisymptomatic” (presence of few symptoms)[47].

Determination of the clinical, laboratory, and radiological characteristics of patients suspected of COVID-19 infection are essential for early isolation, treatment, and contact tracing[51]. A positive COVID-19 test result in patients with hip fractures was associated with a 2.4-fold increase in 30-d mortality risk[52]. During the peak period of the COVID-19 epidemic in New York city, more than half of patients with emergent large vessel occlusion (ELVO) stroke were positive for COVID-19 and were younger, more likely to be male, and less likely to be white. These findings also suggested an increased incidence of ELVO stroke during the peak of the COVID-19 epidemic[53]. One study suggested that conditions (comorbidities, rheumatic diseases) and abnormal laboratory parameters such as C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), and increased serum ferritin levels were significantly associated with mortality, in contrast to a previous use of antirheumatic drugs. The authors suggested that inflammation was closely related to COVID-19 severity. Their key findings were as follows: (1) Most patients recovered from COVID-19 disease; (2) The use of antirheumatic drugs, corticosteroids, and biological agents did not increase the risk of mortality; and (3) Rheumatic disease activity may be associated with mortality[54].

Advanced age, diffuse distribution, and hypoxemia may help clinicians to identify COVID-19 patients with a poor prognosis. Similarly, aggregated social media data may also influence disease prognosis[55]. Higher troponin T levels and lower lymphocyte counts were predictive of disease progression. Early ventilation may be an effective treatment for severe cases[56]. Severe and consistent lymphopenia with significantly reduced lymphocyte subgroups with normal CD4/CD8 ratio has been reported in critically ill patients. In addition, extremely reduced transferrin saturation at ICU admission and a significant increase on days 3 to 6 with constant hyperferritinemia during the ICU stay have been reported[57]. More severe COVID-19 disease was observed in patients who were older, male, African-American, obese, diabetic, and with a higher overall comorbidity burden. Certain comorbidities paradoxically increased the risk in younger patients in most cases. Among inpatients, male sex was the primary determinant of the need for more intensive care. Further investigations are needed to understand the mechanisms underlying these findings[58]. A cohort study of COVID-19-related deaths in Ontario, Canada, reported a concentrated risk of mortality among residents of long-term care (LTC) facilities, which increased over a short time. A study on preventing the spread of COVID-19 between facilities reported the need for the early identification of risk, which necessitates screening and provision of PPE to staff as well as restructuring of LTC staff[59]. Patients with COVID-19 with an increased ST-segment myocardial infarction (STEMI) picture showed a favorable disease course to a high thrombotic burden and poor prognosis[60]. The authors suggested the need to determine the COVID-19 status in all STEMI cases. They also suggested the need for further work to understand the mechanism of increased thrombosis and identify aggressive antithrombotic therapy. An observational study reported the correlation of amino acid and fatty acid metabolism with COVID-19, providing information on the mechanism, potential markers of clinical severity, and potential therapeutic targets[61]. LDH and CRP may influence respiratory function and may be considered predictive of respiratory failure in patients with COVID-19. The authors suggested the usefulness of these biological markers for the early identification of patients requiring closer respiratory monitoring and more aggressive supportive therapies to avoid a poor prognosis[62]. One study observed that ischemic and hemorrhagic strokes complicated the course of COVID-19. In that series, these events occurred mainly in patients with severe pneumonia and multiorgan failure. Liver enzymes and LDH levels were markedly increased in all cases, and the prognosis was poorer[63]. Another study reported that more than half of the infected patients with cancer were susceptible to severe COVID-19. This risk was exacerbated by concurrent anticancer treatment and predicted poor survival despite COVID-19 treatment[64].

A transient twofold increase in the incidence of out-of-hospital cardiac arrest, associated with reduced survival, was observed during the pandemic, in contrast to data observed in a similar period during previous pandemic-free years. The authors proposed that this finding was partly related to COVID-19 but was also likely due to the indirect effects of the pandemic associated with lock-in and rehabilitation of healthcare services. They suggested that these factors should be considered when reviewing mortality data and public health strategies[65]. While the correlation between the prevalence of heterozygous beta-thalassemia and COVID-19 immunity has been reported, further investigations are required to confirm this finding[66].

Prevention, control, and communication

Communication strategies should focus on the routes of transmission (upper airways), modes of contamination (direct contact with respiratory secretions through airborne droplets and indirect contact through hands or soiled objects), and means of prevention. These strategies must be based on reliable and credible information and data. Prejudices and misinformation about the disease are often based on preliminary observations that are sometimes unreliable and speculative. However, this leads to confusion, panic, and anxiety among citizens[67]. This situation has been described as an "infodemic" by the WHO[68]. Clear and simple coherent messages based on the risk of transmission are preferred for good compliance with barrier measures[69]. Strict compliance with individual protective measures, combined with collective measures (containment, discouragement of gatherings), contributes synergistically to breaking the chain of transmission of both SARS-CoV-2 and other respiratory pathogens[70]. Measures such as containment and discouragement of gatherings help to reduce population density and, thus, reduce viral transmission.

Above all, distracting and/or annoying messages, as well as biased and sometimes unjustified measures, should be avoided. Anxiety-provoking messages should be avoided, as they cause panic and stress, emotional factors that weaken the immune system and, thus, expose the body to pathogens. Collective concerns can influence daily behaviors, economics, prevention strategies, and political decision-making of health organizations and medical centers, weakening COVID-19 control strategies, resulting in high morbidity and mental health needs worldwide[71].

The following means of protection and/or prevention are recommended: (1) Hand washing with soap and water; (2) Antiseptics (hydroalcoholic hand rubs); (3) Disinfection of soiled areas and materials using sodium hypochlorite or glutaraldehyde; (4) Wearing protective equipment (bibs, masks, gloves, lab coat, gowns, *etc.*); (5) Prohibition of activities that encourage gatherings to reduce the risk of viral spread; and (6) Home confinement if possible, especially during the outbreak[33,72-74].

However, frequent hand washing involves prolonged exposure to water and other chemical or physical agents, which results in pathophysiological variations. Undesirable dermatological effects such as excessive skin dryness or contact dermatitis (most often irritating and sometimes allergic), can occur, especially in people with a history of atopic dermatitis. These skin conditions are manageable with the application of a moisturizer immediately after hand washing or disinfectant use to prevent hand eczema[75].

It is important to remember certain public health concepts. The public health system (PHS) plays a key role in both patient management and disease prevention or control. In other words, achieving medico-social objectives requires an efficient, proactive PHS that is well adapted to the realities on the ground. Weak PHSs often face two main challenges in the management of an epidemic or a pandemic: The quality and/or the capacity of response and the compliance of people with the measures prescribed to cut the chain of transmission. Therefore, in the context of COVID-19, one study suggested strengthening the response capacity while recommending adequate prevention measures to avoid the risk of a resurgence of the epidemic[76].

The detection of more COVID-19-positive patients in the community along with compliance with adequate quarantine rules will reduce the number of secondary cases. This requires an increased testing capacity[77]. The limited availability of diagnostic tests makes it almost impossible to detect asymptomatic patients and adds to the uncertainty of the potential impact of SARS-CoV-2 infection in Africa, particularly concerning prevention strategies and economic impact[40]. The implementation of a robust prevention system along with compliance with individual or collective barrier measures (*e.g.*, containment, even if it appears more difficult to bear), is the most effective way to respond to the COVID-19 pandemic[78-80]. The WHO contributes to regularly updated guidelines for the home care of patients with COVID-19 with minor symptoms and the management of contacts, as well as operational guidelines for the management of patients in health facilities and communities, the quarantine of individuals in the context of COVID-19, the clinical management of severe acute respiratory infection when COVID-19 is suspected; and laboratory testing of suspected cases of COVID-19[81]. In addition, in the context of microbiological biosafety, the PPE guidelines are regularly updated[82]. In general, these guidelines are intended to provide information on PPE options in relation to safety and effectiveness to ensure better protection of healthcare workers and patients[74].

In addition to national and international guidelines, special attention must be paid to chemical or physical agents. Chemical agents exist in liquid or gaseous form; physical agents are, among others, heat, UV, and gamma rays. While chemical agents are used for antiseptics, disinfection, and/or sterilization, physical agents are generally

used for sterilization[83]. As PPE remains insufficient and decontamination methods are less cost-effective because they are complex, slow, expensive, and particularly unsuitable for low- and middle-income countries where the need is greatest, some researchers are investigating a new PPE decontamination option. They suggested a low-temperature, low-ambient humidity (WASP-D) decontamination method based on the 30-min or shorter half-life of SARS-CoV-2 (and other common pathogens) at temperatures $> 45^{\circ}\text{C}$, combined with the fact that most PPE is designed to be transported and stored safely at temperatures $< 50^{\circ}\text{C}$. They concluded that the decontamination of PPE at 12 h, 46°C , and ambient humidity reduced the SARS-CoV-2 viral load by a factor of 10^{-6} (e.g., $1/10^6$), without adversely affecting PPE materials or performance[84]. A test of three mask models purchased from supermarkets and drugstores showed that surgical masks, normally intended to be discarded after 4 h of use, retained very good filtration capacities after 10 machine washes at 60°C . These masks also remained breathable enough to be worn for several hours without excessive discomfort. Finally, even after several washing cycles, these masks exceed the minimum requirements for fabric masks with an official filtration guarantee[85, 86]. Results in the literature showed that a universal face mask could help to reduce disease severity and strengthen the immunity of the wearer, since high doses of viral inoculum can overwhelm and deregulate the innate immune defenses, aggravating the disease[87]. While there has been apprehension regarding the accumulation of carbon dioxide during prolonged face mask wear, experimental studies have refuted this hypothesis. An observational clinical study reported that wearing face masks neither significantly restricted gas exchange (oxygen flow) nor contributed to carbon dioxide accumulation, even in individuals with pulmonary insufficiency. Nevertheless, prolonged use of face masks can negatively impact breathing, leading to heat stress, drowsiness, breathing difficulties (restricted flow of fresh air), and unusual heart rates. The discomfort experienced with the use of a surgical mask has also been attributed to neurological reactions or associated psychological phenomena such as anxiety, claustrophobia, or affective responses to a perceived difficulty in breathing. In addition, if a face mask is worn for a longer time, the filter becomes wet due to facial sweat and vapor from breathing, promoting particle clogging. Wearers may also experience a false sense of security, encouraging them to spend more time in public places. The other potential side effects of wearing face masks include skin irritation, discomfort from exhaled air entering the eyes, and speech quality and volume during conversations[87].

In addition to the classical measures (barriers or prevention), other factors can optimize COVID-19 prevention or control. Vitamin D is a promising agent for COVID-19 control, as it is involved in various pathophysiological mechanisms that occur during SARS-CoV-2 infection. High-dose vitamin D supplementation, particularly for at-risk groups, is recommended for the maintenance of serum levels between 40 and 60 ng/mL of 25-hydroxy vitamin D needed to prevent or treat COVID-19[88]. Vitamin supplementation or treatment of deficiency may be useful in areas with a high prevalence of hypovitamin D. The role of medicinal plants, including *Allium sativum*, *Camellia sinensis*, *Zingiber officinale*, *Nigella sativa*, *Echinacea spp.*, *Hypericum perforatum*, *Glycyrrhiza glabra*, and *Scutellaria baicalensis*, in enhancing immunity has been reported. Terpenoids show promising effects in inhibiting viral replication, a finding that requires further study. Some alkaloids such as homoharringtonine, lycorine, and emetine have shown potent anti-coronavirus effects. Naturally occurring products such as emodin and baicalin can inhibit protein S production. Other enzymatic targets involved in coronavirus replication, included 3-chymotrypsin-like protease (3CLpro), papain-like protease, helicase, and RNA-dependent RNA polymerase, are inhibited by iguesterin, cryptotanshinone, silvestrol and sotetsuflavone. Consequently, natural products have been introduced as therapeutic agents against COVID-19[89]. A study reported the importance of essential nutrients in the diet for their beneficial effects on immune system function. The intake levels of relevant micronutrients (D, C, B12, and iron) were inversely associated with higher COVID-19 incidence or mortality, especially in subjects genetically predisposed to suboptimal micronutrient levels[90]. The nutrigenetic data obtained from the joint assessment of essential nutrients and the genetic factors that limit their bioavailability can serve as a fundamental tool to help strengthen the immune systems of individuals and prepare populations to fight infectious diseases such as COVID-19[90]. The multiple biological actions of hesperidin and vitamin C suggest that these two major citrus components that modulate systemic immunopathological phases, may be candidates to fight SARS-CoV-2 infections. Experimental studies are needed to corroborate the hypothesis that herbal or plant foods could contribute to COVID-19 prevention[91,92]. The beneficial role of Chinese medicine in the control of respiratory diseases, such as the common cold, has

been reported[93].

The “mandatory *Bacillus Calmette-Guérin* (BCG)” vaccination approach has shown a reducible effect on COVID-19 infection and mortality rates. Two immunological mechanisms; namely, the heterologous effects of adaptive and innate immunity induced by BCG vaccination, could explain host tolerance to COVID-19 infection. However, no direct evidence supports this biological background. Clinical trials related to BCG vaccination against COVID-19 are currently under investigation. In the absence of strong evidence, BCG cannot be recommended for COVID-19 prevention, although this is not an absolute contraindication[94].

Data suggest that people with epilepsy (PWE) have a low risk of being infected with SARS-CoV-2 and have less severe manifestations of COVID-19 due to their epileptic pathology alone[95]. The mechanisms of the activating effect of hyperventilation (HV), which causes deep and rapid breathing during seizures in PWE, are less well known. Although concrete evidence is lacking, if wearing a face mask can stimulate HV, at least to some extent, this practice should not be indiscriminately recommended to all PWE. However, in the absence of any proven COVID-19 treatment or vaccine, prevention is the best available strategy and it is probably not reasonable to suggest avoiding face masks in PWE under any circumstances[95]. Logically, this population does not need to wear a face mask most of the time, as long as there is no close contact with others, especially during intense physical activities. Instead, it is probably more beneficial to wear a face mask with intermittent breaks in crowded areas in safe, low-density areas[95].

Given the COVID-19 pandemic, there is emerging evidence that, compared to the general population, patients with cancer are particularly vulnerable to infection and adverse events, with correspondingly worse outcomes[64,96]. On admission or before initiating systemic therapy or radiotherapy, confirmation of COVID-19 status is recommended in asymptomatic or paucisymptomatic patients, especially those with high-risk features[23].

Regarding transfusion, the American Blood Bank Association and the Centers for Disease Control and Prevention (CDC) have made no specific recommendations regarding SARS-CoV-2[97].

Although no evidence of the transmission of SARS-CoV-2 through blood transfusion has yet been established, the blood supply has been affected by the COVID-19 pandemic[24,34].

The opportunity now exists for schools and academies to collaborate to advance science and potentially improve student outcomes[98].

SARS-CoV-2 has developed mutations in various parts of its nonstructural proteins (NSPs), particularly NSP2, NSP3, protein S, and RNA-dependent RNA polymerase. Because of the critical importance of mutations in SARS-CoV-2 pathogenicity and the development of serodiagnostics, antivirals, and vaccines, continuous molecular surveillance of the virus is recommended[99]. While seasonal changes, coordinated laboratory testing, isolation/quarantine, and school closures may help to control the COVID-19 pandemic, they are unlikely to stop SARS-CoV-2 transmission. Therefore, effective policies complementary to currently available control measures must be adopted to minimize the exponential spread of infection[100].

Achieving global goals, including the control of pandemics such as COVID-19, requires a strong commitment to impactful public policies and international collaborations, including universal vaccinations against COVID-19, with potential combination with both childhood and adult immunization programs and programs for the treatment of malaria, tuberculosis, HIV/AIDS, and neglected tropical diseases[101]. The core unit (public health office) of the Sri Lankan health system has earned the trust of the community because of its deep-rooted operations on the ground. It has expertise and extensive connectivity with the community. Thus, rigid prevention and control measures have been implemented in the geographical areas assigned to these health facilities. The managerial role of this unit should be further explored for future health system reforms[102] and effective strategies should be developed to strengthen the PHS at its core[103].

It is important to note that information may vary depending on the evolution of the epidemic and research findings[23]. In COVID-19, studies are progressing rapidly and knowledge is changing such that we must realize that today's truths may not be tomorrow's and that we must continue to increase our knowledge of this disease.

Treatment

To avoid patient harm, because of possible coinfections, a diagnosis should be made before starting possible anti-infectious probabilistic anti-influenza, oseltamivir, and/or antibiotic treatment[72]. Other drugs and/or vaccine candidates have been suggested

for treatment, although clinical studies are needed to provide solid evidence of their effectiveness[104].

Tocilizumab improved the clinical status of patients with severe COVID-19[105]. Corticosteroid therapy with high-dose methylprednisolone, followed by tocilizumab when necessary, rapidly restored respiratory function, decreased in-hospital mortality, and reduced the need for invasive mechanical ventilation in patients with COVID-19-associated “cytokine storm” syndrome. However, further investigation of these promising results is required[106]. The role of Chinese medicine as an adjunctive treatment for SARS-CoV-2-induced inflammation has also been reported. Yidu-toxicity could address SARS-CoV-2-induced inflammation by blocking pulmonary syndrome by eliminating inflammatory agents[107]. Moreover, Xuebijing injection effectively improved the levels of inflammatory markers and prognosis of patients with severe COVID-19[108].

Other conventional drugs have also been used. Ruxolitinib showed faster improvement in clinical status, significant improvement in heart tomography, faster normalization of lymphopenia, and a favorable side effect profile in patients with severe COVID-19. These results are informative for testing the efficacy of ruxolitinib in a larger population[109]. Colchicine showed a statistically significant improvement in the time to clinical deterioration in patients hospitalized with COVID-19; however, this result should be interpreted with caution because of the low statistical significance of the results[110]. Remdesivir (RDV) did not show a significant clinical outcome in patients with moderate COVID-19 compared to standard therapy[111]. However, this antiviral agent has shown efficacy against the severe form of COVID-19[111]. This drug also showed favorable pharmacokinetic (PK) and safety profiles in healthy volunteers who were administered the drug once daily[112]. These PK and clinical safety data and preliminary clinical data support further investigation of RDV in patients with COVID-19[112].

Drugs such as hydroxychloroquine are thought to be effective owing to their effects on the ACE2 receptors required for viral entry into the cell. While chronic treatment can lead to heart disease with impaired left ventricular function and conduction disorders with bradycardia, short-term treatment can also cause cardiac damage in some patients. It is important to consider parameters such as age, female sex, ionic disorders, renal insufficiency, and the combination of many products, which are risk factors for cardiac damage. Thus, it is prudent to follow recommendations for safe treatment with “chloroquine” to minimize damage and/or adverse reactions[24,113]. In patients with persistent (mild to moderate) COVID-19, the rate of negative conversion of hydroxychloroquine was comparable to that of standard treatment alone [113].

Regarding adverse drug reactions, a hospital-based pharmacovigilance study reported a high prevalence of adverse reactions in patients with COVID-19, a fortiori caused by drugs inducing gastrointestinal and hepatic disorders. The length of hospital stay, number of drugs used, and underlying diseases were risk factors for the occurrence of adverse reactions in patients with COVID-19[114].

Researchers believe that “the” treatment will require a combination of drugs to effectively control emerging diseases, including COVID-19, HIV, and hepatitis C infections[104]. Early triple antiviral therapy has shown superiority over lopinavir-ritonavir to suppress symptoms and shorten the duration of viral clearance and hospitalization in patients with mild to moderate COVID-19. Future investigation of dual antiviral therapies is warranted, with interferon beta-1b as the background regimen [115].

A ligand-protein interaction study in Africa reported that more than half of the 20 major alkaloids and terpenoids interacted favorably with 3CLpro, which controls coronavirus replication, and had higher binding affinities than those to lopinavir-ritonavir. The study identified substances such as 10-hydroxyusambarensine, cryptoquindoline (alkaloids), 6-oxoisoiguesterin, and 22-hydroxyhopan-3-one (terpenoids), which bind to the receptor and 3CLpro catalytic dyad of SARS-CoV-2. These compounds were identified by predictive analysis of the (absorption, distribution, metabolism, and excretion)/tox and Lipinski filters. However, further experimental analysis of these leads is required for the discovery of natural anti-COVID-19 therapeutic agents to combat the pandemic[116].

Immunotherapy *via* the administration of the plasma of people cured of COVID-19 may be a useful treatment method in countries in which this practice is possible[117].

A Jewish business news source reported that 96% of patients administered an innovative drug (EXO-CD24) were cured[118]. Testing of this technology in the first clinical phase in humans showed that 29 out of 30 patients with moderate to severe disease were discharged from the hospital within 3-5 d. EXO-CD24 is an innovative

preparation based on exosomes enriched with the CD24 protein. According to Nadir Arber, one of the leading physicians and researchers on the team that developed the drug, “Even if the vaccines work and no new mutations are produced, SARS-CoV-2 will stay with us”. He adds that a drug was developed within 6 mo from the time the idea was conceived and the technology was developed until it was first tested in humans in the first clinical phase. The Ichilov Medical Center reported that EXO-CD24 uses exosomes - tiny carrier sacs that shuttle between cells - to deliver a protein called CD24 to the lungs and has been the subject of decades of research by Dr. Arber. CD24 is located on the cell surface and plays an important role in regulating the immune system. The protein helps to modulate the immune response and curb the lethal hyperreactivity of the immune system known as a cytokine storm. The administration of EXO-CD24 by direct aspiration into the lungs inhibited immune hyperreactivity resulting from cytokine amplification following SARS-CoV-2 infection[118]. Cytokine storms are a physiological reaction in humans, in which the innate immune system causes uncontrolled and excessive release of pro-inflammatory signaling molecules called cytokines. EXO-CD24 is moving into further testing phases[118].

Vaccination

Vaccination has generated significant interest among people in general, and researchers in particular. People with severe mental illness are at risk of SARS-CoV-2 infection because of the morbidity and mortality associated with COVID-19. Therefore, this population requires early access to safe and effective vaccines. However, further studies are needed to evaluate the efficacy, safety, and interactions of the vaccine with psychotropic drugs, specifically in patients with COVID-19, so that they can be properly informed about the benefits and risks of vaccination[119]. The rapid development of vaccines can have adverse effects, prompting long-term studies and years of post-vaccination treatment. However, for most treatments, the benefits outweigh the risks and many more people - and in most countries - need the vaccine, due to the collapse of economies and the subsequent crippling of livelihoods. With families losing large numbers of relatives to the virus, vaccination may help to restore the quality of life for hundreds of millions, if not billions, of people worldwide. Innovative strategies have improved the efficiency of processes within research models for novel therapies, ultimately accelerating the administration of potential novel treatments to patients [120]. Because the types or incidence of the side effects of COVID-19 vaccines in individuals with Parkinson's disease (PD) do not appear to differ from those observed in the general population, COVID-19 vaccination with approved vaccines can be recommended to patients with PD unless there is a specific contraindication. However, some caution is warranted in the vaccination of very frail and terminally ill elderly patients with PD living in LTC facilities[121].

The Standing Committee on Vaccination (STIKO) vaccination recommendations are recognized as medical standards. The current instructions for the vaccination of immunocompromised patients and the recommendation for COVID-19 vaccination, together with the scientific knowledge and rationale of STIKO, represent a valuable basis for medical action in the field of vaccination against infectious diseases[122]. To date, vaccine-related allergic reactions are rare. Current CDC reports suggest that anaphylactic reactions related to Pfizer-BioNTech mRNA vaccines may occur more frequently than with other vaccines. Therefore, to support large-scale COVID-19 vaccine delivery programs, allergists should offer clinical phenotyping, risk stratification, and clear recommendations based on reliable and credible information[123]. At present, there are insufficient data on COVID-19 co-infections with influenza or how these cases would evolve clinically, although they could place a significant burden on an already stressed healthcare system. Until an effective and proven COVID-19 vaccine is available, high influenza vaccination coverage should be the highest priority[124]. The obese population is vulnerable to COVID-19, requiring special attention during this pandemic to avoid complications. In the absence of COVID-19 vaccination, regular physical activity and a healthy diet are recommended, with special attention paid to mental health. Extended quarantine and prophylactic vitamin D administration should also be considered[125]. A study conducted in Australia reported that successful COVID-19 vaccination requires that the government consider elements in its vaccination policy such as the estimation of herd immunity thresholds, vaccine delivery strategies, vaccination clinic locations, provisions for health personnel and training, and strategies for prioritizing vaccines. Moreover, pharmacists should play a key role in the delivery of mass COVID-19 vaccination programs[126]. For the pediatric population, before a safe and effective COVID-19 vaccine is available, the focus should be on making the best use of already available childhood vaccines. Vulnerable or healthy children must be vaccinated according to

the recommended schedules to protect young patients and avoid future epidemics caused by vaccine-preventable diseases such as measles[127].

Independent groups of experts must be involved in life-saving actions to counter anti-vaccine propaganda and provide scientific information to the general public. If the pandemic is to be controlled to benefit the public interest, academic and medical societies and policymakers must speak the same language. Otherwise, the battle will be lost to those who oppose scientific evidence while offering no solution to the problem[128]. The key to success in promoting vaccine uptake is a strategic program, including local capacity building, to build and maintain trust. A critical factor in implementing such a confidence and demand-building approach is the need to invest in communication, especially related to influencing behaviors and the capacity for community engagement[129].

COVID-19 vaccines are expected to induce high-affinity neutralizing antibodies. They should also polarize the T-cell response towards type 1 immunity and avoid the stimulation of cytokines that induce T-helper 2 immunity. To avoid type 2 inflammatory responses, careful selection of the vector and antigen is mandatory. The addition of toll-like receptor ligands (TLRs) and other type 1 immunity-stimulating molecules could be useful for obtaining sufficient CD4+ T cells for antibody production as well as suppression of undesirable type 2 immunity leading to eosinophilia. However, it is only somewhat possible to predict vaccine efficacy and safety. Due to its urgency, COVID-19 vaccination should receive the highest priority[130].

Research

The COVID-19 outbreak is a striking reminder of the need for constant epidemiological surveillance, prompt diagnosis, and robust research[28]. Mapping of the structure of the SARS-CoV-2 spike protein at the atomic scale has allowed the development of therapies to combat the virus[131]. An international research effort is ongoing to understand the COVID-19 pandemic to answer questions regarding epidemiology, clinical epidemiology, biology, therapy, and vaccination. Researchers are also publishing the results of epidemiological, biological, and clinical trial studies in peer-reviewed journals. Moreover, clinical trials are underway to identify reliable, effective, and safe therapeutics[132-135]. Immunological and epidemiological data on endemic human coronaviruses (HCoV) showed that infection-blocking immunity wanes rapidly but that disease-reducing immunity is long-lived. In other words, anti-infectious immunity that prevents pathogen replication to render the host refractory to reinfection (*i.e.*, immune efficacy in relation to susceptibility), declines rapidly, while disease-reducing immunity due to reinfection and/or transmissibility-reducing immunity or infectiousness, with possible reinfection, lasts for a long time. This may be evidenced by the current severity of SARS-CoV-2 and the benign nature of HCoV, suggesting that once the endemic phase is reached and following primary exposure during childhood, SARS-CoV-2 may not be more virulent than the common cold. A different scenario is foreseeable for an emerging coronavirus capable of causing more severe disease in children. These results support the importance of behavioral compliance during pandemic vaccine use and suggest the need to evaluate scenarios for continued vaccination during the endemic phase[136].

CONCLUSION

The development of a robust prevention and/or response system relies on the capitalization and judicious use of knowledge in fields including epidemiology, infectious diseases, pathophysiology, biology, virology, in addition to scientific research. Hence, local or international collaboration in pluralistic teams may guarantee success. The dissemination of simple, coherent, and reliable messages reassures the population and reinforces compliance with individual or collective barrier measures (*e.g.*, confinement, even if it is difficult to bear). An integrative pluralistic approach coupled with efficient communication may be a more effective way of responding to an outbreak or pandemic, especially that caused by SARS-CoV-2. A pluralistic collaborative approach; in other words, the capitalization and judicious use of knowledge, will help to overcome the pandemic in the short or medium terms. Our results suggest the benefits of a pluralistic approach in managing COVID-19 a fortiori in relation to health and related fields. This work would be even more comprehensive if the search source was larger, the collaborative approach was more detailed, and the pluralistic approach extended to complementary disciplines such as biochemistry (vaccines), statistics, and mathematics, biomedical science and biotechnology, inventions (respirators, ven-

tilation equipment), physical therapy, *etc.*

ACKNOWLEDGEMENTS

We thank Prof. Hubner ROLAND from the Belgian High Committee of Health for his strong and continuing intellectual and technical support for this work. We thank Babri GALLEDOU, the Head of the DNP (National Head Office of Pedagogy), Mamadou BOUARE of the CDL (Center de Langues), and all the staff of the DNP/CDL for their generous support in the English translation of the French version of the manuscript text.

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