COVID-19 PANDEMIC UPDATES AND PERSPECTIVES. NEED FOR AN INTEGRATED AND EQUITABLE APPROACH.

Grigoris T Gerotziafas, Mariella Catalano, Ioannis Theodorou, Patrick van Dreden, Vincent Marechal, Alex C Spyropoulos, Chalres Carter, Nusrat Jabeen, Job Harenberg, Ismail Elalamy, et al.

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Abstract:
One year after the declaration of the COVID-19 pandemic by the World Health Organization (WHO) and despite the implementation of mandatory physical barriers and social distancing, humanity remains challenged by a long-lasting and devastating public health crisis.
Non-pharmacological interventions (NPI) are efficient mitigation strategies. The success of these intense NPI is dependent on the approval and commitment of the population. The launch of a mass vaccination program in many countries in late December 2020 with mRNA vaccines, adenovirus-based vaccines, and inactivated virus vaccines has generated hope for the end of the pandemic.
Current issues: The continuous appearance of new pathogenic viral strains and the ability of vaccines to prevent infection and transmission raise important concerns as we try to achieve community immunity against SARS-CoV-2 and its variants. The need of a second and even third generation of vaccines and the possibility of potentially harmful side-effects of the vaccines (i.e. venous thromboembolism) have already been acknowledged.
Perspectives: There is a critical and urgent need for a balanced and integrated strategy for the management of the COVID-19 outbreaks organized on three axes: (1) Prevention of the SARS-CoV-2 infection, (2) Detection and early diagnosis of patients at risk of disease worsening, and (3) Anticipation of medical care (PDA).
Conclusion: The "PDA strategy" integrated into state policy for the support and expansion of health systems and introduction of digital organization (i.e. telemedicine, artificial intelligence and machine learning technology) is of major importance for the preservation of citizens' health and life world-wide.

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The COVID-19 pandemic and the need for an integrated and equitable approach: An international expert consensus paper

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Abstract

One year after the declaration of the COVID-19 pandemic by the World Health Organization (WHO) and despite the implementation of mandatory physical barriers and social distancing, humanity remains challenged by a long-lasting and devastating public health crisis.

Non-pharmacological interventions (NPI) are efficient mitigation strategies. The success of these NPI is dependent on the approval and commitment of the population. The launch of a mass vaccination program in many countries in late December 2020 with mRNA vaccines, adenovirus-based vaccines, and inactivated virus vaccines has generated hope for the end of the pandemic.

Current issues: The continuous appearance of new pathogenic viral strains and the ability of vaccines to prevent infection and transmission raise important concerns as we try to achieve community immunity against SARS-CoV-2 and its variants. The need of a second and even third generation of vaccines has already been acknowledged by the WHO and governments. .

Perspectives: There is a critical and urgent need for a balanced and integrated strategy for the management of the COVID-19 outbreaks organized on three axes: (1) *P*revention of the SARS-CoV-2 infection, (2) *Detection* and early diagnosis of patients at risk of disease worsening, and (3) *Anticipation* of medical care (PDA).

Conclusion: The “PDA strategy” integrated into state policy for the support and expansion of health systems and introduction of digital organization (i.e. telemedicine, e-Health, artificial intelligence and

machine learning technology) is of major importance for the preservation of citizens' health and life world-wide.

Keywords

COVID-19, SARS-CoV-2, pandemic, thrombosis, healthcare system

Introduction

One year since the declaration of the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) as a pandemic infection by the World Health Organization (WHO), physical barriers and social distancing have been implemented in most countries. Nevertheless, humanity is facing a long-lasting and devastating public health crisis which has already cost more than 3,800,900 lives with at least 176,052,575 cases as of June 12, 2021. In most of the countries worldwide, hospitals and healthcare systems were under an unprecedented pressure during the three epidemic waves. A fourth epidemic wave seems very probable whereas the tolerance of the populations and the resistance of economies at the lockdown policies are reaching their limits.[1]

During the spring of 2020, the world faced the new coronavirus pandemic with limited knowledge of SARS-CoV-2 and the resulting coronavirus disease (COVID-19), without widely available validated diagnostic tools, therapeutic strategies, and prepared health care systems. Therefore, in most countries the mandatory national lockdown was the only strategy to control virus propagation, to save lives, and to protect health systems from the collapse. Since then, non-pharmacological interventions (NPI) - particularly curfews and lockdowns - and vaccinations have been the principal strategies for the management of the epidemic waves. In addition, large scale population testing has been adopted for epidemiological surveillance at regional and national levels.

The molecular evolution of SARS-CoV-2 is another public health threat since transmission rates appear to have increased with some recently identified variant strains with varying pathogenicity and potentially higher resistance to natural and vaccine induced immunity.[2],[3],[4] Management of the forthcoming epidemic waves will become a major issue for public health, the world economy as well as for social adhesion and democracy. Considerable knowledge on the biological characteristics of SARS-CoV-2, the pathophysiology and natural history of COVID-19, and diagnostic tools and therapeutic strategies have been gained and have significantly

improved the clinical outcomes of the patients with severe or critical COVID-19.

This article reviews the limitations of the current policies for the management of the pandemic and proposes an integrated and balanced strategy including the anticipated management of patients with COVID-19.

Limitations of the "Stop and Go" strategy

Non-pharmacological interventions, including simple physical barriers (i.e. masks, hand washing and distancing), radical measures to avoid crowding and to reduce social contact (such as closing of restaurants, bars, commercial shops, curfew), mandatory national lockdowns combined with testing the population by rt-PCR for SARS-CoV-2 and close tracing of contact cases are efficient for the mitigation of the pandemic and decrease of the virus reproduction number (R0).[5],[6]

The "Stop and Go" strategy is a temporary measure mainly intending to reduce the number of new cases per day, to facilitate contact tracing, and to diminish severe COVID-19 requiring hospitalisation.[7,8,9] Individual's compliance with a series of behavioral recommendations provided by the public health authorities play a critical role in the control and prevention of SARS-CoV2 infection. The success of such severe NPI requires the approval and the commitment of the population. Sociocultural, psychosocial, and social cognitive factors are determinants of individual differences in the health preventative behaviors.[10,11]

The available hospital beds and the number of the healthcare workers at the conventional wards and intensive care units (ICU) are major factors which, together with the strength of the epidemic wave, determine the intensity and the duration of the NPI. Nevertheless, they have devastating midterm and long-term effects on socio-economic activity and may restrict human constitutional rights and increase social inequalities.[12,13]

A complementary mitigation strategy relies principally on intensive investment in epidemiological surveillance, contact tracing and isolation of infected cases which is more easily accomplished when the number of new infections per day is limited as recommended by the WHO

accompanied by localized lockdowns.[14, 15] Hence, the management of patients with COVID-19, at least in European countries, remains centralized in hospitals whereas primary health care structures are less implicated and an organized campaign for therapeutic intervention in the community is still limited. [16]

The long-term strategy is actually based on the concept of fast development and accelerated authorization of vaccines. Indeed this is an efficient way to increase the population's immunity against SARS-CoV-2. Moreover, high vaccination rates are associated with lower infection rates at later time points among the unvaccinated citizens.[17] Accordingly, application of wide scale international vaccination programs could lead to the control of the pandemic and to the decrease of R0. Indeed, in EU countries the main plan is to vaccinate 70% of the entire adult population by the summer of 2021.[18] However, sufficient vaccine doses are far from being available leading to serious doubts about the short-term success of vaccination. In addition, vaccination acceptance is highly variable from one country to another and largely depends on the public trust on state policy for the management of the pandemic and the impact of misinformation spreading on large Social Media.[19],[20],[21]

Considerations to improve the feasibility of vaccination programs

There are four categories of vaccines tested in clinical trials: whole virus, protein subunit, viral vector and nucleic acid (RNA and DNA). To date, 185 vaccines are being explored in laboratory experiments and animals and 97 are in phase I-III. Table 1 summarizes the vaccines which have been studied in Phase III trials and the results have been published or communicated in press releases of the companies. Among the 15 vaccines which are currently being offered to the general population 2 are nucleic acid base, 2 are protein based, 4 are viral vector based and 7 are whole virus.[22] Among them, the most widely used vaccines in mass vaccination programs to prevent symptomatic Covid-19 are those encoding the spike protein antigen of SARS-CoV-2 in mRNA-based technology (BNT162b2 - BioNTech/Pfizer and mRNA1273 - Moderna) and adenovirus vector -based

vaccines (Gamaleya, AstraZeneca, CanSino, Johnson&Johnson). In addition, 3 inactivated virus vaccines (Sinovac, Sinopharm, Baharat Biotech) are also used in some countries. The launching of the vaccination program in December 2020 generated hope for the forthcoming end of the pandemic. Nevertheless, real life concerns emerged about the midterm efficacy of the vaccines and developing limitations of the feasibility of a rapid mass vaccination program on a global level whereas some concerns because of very rare thrombotic complications emerged. Several important limitations can be outlined.

1. The phase III trials of the vaccines have variable endpoints such as (i) protecting against the most severe forms of COVID-19, (ii) reducing hospitalization for COVID-19, (iii) preventing infection and/or transmission of SARS-CoV-2. Knowledge of protection against mild COVID-19 disease is also needed. The designs of the randomized clinical trials might overestimate the level of vaccine protection compared to real-world settings.[23]

   The translation of the efficacy of the vaccines and the duration of protective immunity, the protection of the virus spread or even the protection of some groups of citizens which were not included in the studies (i.e., multi-morbid patients, children) need to be specifically tested.[24,25,26]
2. The cost of vaccines (particularly those based on mRNA technology) raises a major obstacle for vaccination of large populations, especially in developing and low income countries.[27] Limitations of production plants and supply chains provoke significant delays and compromise the implementation and the trust of the population to vaccinate. Indeed, mRNA vaccines' stability, storage, and distribution require very low temperature chain logistics which are limited notably in less developed countries. The applicability of the global vaccination program is questioned, particularly in low and middle-income countries, having limited human and financial resources.
3. Wealthy nations representing just 13% of the world’s population have already accounted for 51% of the promised doses of leading COVID-19

vaccines.[28] Until April 2021 Although more than 700 million vaccine doses have been administered globally, richer countries have received more than 87%, and low-income countries just 0.2%.[29] The vaccines are essentially absent in most countries of the sub-Saharan African region, Asia, and South America. Even in developed countries, there are great discrepancies in the vaccination rate ranging from 8% to 98%.[30] Chile is a notable exemption regarding the vaccination rate, of the population (47% of the population is fully vaccinated of June 12). Surprisingly, this did not prevent an intensive third epidemic wave which actually hit the country, underlying that even a high vaccination rate which is lower that the threshold of community immunity is not sufficient to prevent an epidemic wave. These data reveal an important gap between the production capacities of the pharmaceutical companies and consortiums, producers of vaccines, and the need for the rapid mass vaccination of the world population. This gap together with the commercial strategies of some pharmaceutical companies raise serious ethical questions and drawbacks in the application of the vaccination worldwide with significant negative consequences on public health.[31,32]

Vaccines' nationalism, as it has been described by the WHO, compromises the effective control of the pandemic and could increase the risk of the SARS-CoV-2 mutations and appearance of resistant variants of the virus.[33] In addition, the great discrepancies on vaccination rate among countries reveal the geopolitical concurrence at the international level. These figures raise serious concerns regarding the achievement, before the end of 2021, of collective immunity at the threshold of 70%, which has been set by the WHO as a prerequisite for the control of the pandemic.

4. The low vaccination rate has an enormous impact on the national and global economy. According to the World Bank world gross domestic product of the global economy probably shrank by 4.3% in 2020 (i.e. $3.94 trillion).[34] A study commissioned by the International Chamber of Commerce Research Foundation showed that the global economy

stands to lose as much as $9.2 trillion if governments fail to ensure developing economies access to COVID-19 vaccines. As much as half of this amount will fall on advanced economies.[35]

To challenge this issue the COVAX (COVID-19 Vaccines Global Access Facility), which is co-led by GAVI (the Vaccine Alliance), the Coalition for Epidemic Preparedness Innovations, and the WHO aims to guarantee fair and equitable access to every country in the world. In addition, WHO calls to promote technology transfer to low- and middle-income countries with the potential capacity to accelerate global production of COVID-19 vaccines.[36]

5. The fast evolution and transmission of SARS-CoV-2 has generated several particular mutations across geographic regions. The continuous appearance of new SARS-CoV-2 variants and strains with a longer-term potential for immune escape from natural or vaccinal immunity raises important concerns on the threshold of the vaccinated population required to gain collective immunity, and on the efficacy of the vaccines against novel SARS-CoV-2 variants.[16,37,38] The S-protein, which is considered as optimal target for vaccine and drug development, is highly glycosylated and polymorphic and relatively tolerant to the mutation process of viruses. Actually, mutation in the S-protein is a central way for the virus to adapt to its host and gain new functions such as escape to immune response, infectivity, and transfer to new species.[39] Several SARS-CoV-2 “variants of concern” have been described that warranted special scrutiny. These include the United Kingdom (UK) variant (B.1.1.7), South Africa variant (B.1.351), Brazilian variants (P.1 and P.2), California variants (B.1.429/CAL.20C and B.1.427/CAL.20C) and the Indian variant (B.1.617).[40],[41]These variants were designated as “concerning” predominantly due to their reported enhanced person-to-person transmission in some geographic areas, and they have since been detected in several countries worldwide.[42],[43],[44] A novel SARS-CoV-2 variant derived from clade 19B (HMN.19B variant or Henri Mondor variant) has been recently identified and is actually circulating in France.[45] Whether HMN.19B will

be less susceptible to protection by natural, therapeutic, or vaccine-induced immune responses remains to be determined. Some SARS-CoV-2 variants such as the Danish[46] one disappears rapidly whereas others, like the most recent Indian strain represent a real threat due to the high transmission rate. Thus, there is a real challenge for the continuous development of effective vaccines or monoclonal antibodies with broadly protective activities.[47,48,49]

It is not surprising, but rather concerning, that SARS-CoV-2 variants with variable degrees of resistance to some of the vaccines emerged within a short interval from the launching of the vaccination program.[50],[51] The need for a second and even third generation of vaccines, which overcome the resistance of the new variants, has already been acknowledged by the scientific community.[52] The discussion on the design of clinical trials, the procedure for validation and production of new vaccines and even vaccine mixtures has already started.[53] It seems that this will follow the paradigm of flu vaccines where a continuous development of vaccines against new strains is the rule for the future.

A global and extensive vaccine strategy in all the countries is thus mandatory to limit as much as possible the consequences of a boomerang-like pandemic with limited countries vaccinated, but not really protected against emerging variants in the numerous not yet vaccinated countries or communities. The efficacy of that program is based on a rapid and global deployment of a vaccine shield under the WHO hospices.

6. The legal frames of intellectual property limit the major projects for production of COVID-19 vaccines to less than 10 pharmaceutical companies and corporations worldwide and render the vaccines more expensive and still rare. The risk of seeing the emergence of vaccine black markets should not be neglected. Surprisingly, the infrastructure and the production capacity of the pharmaceutical industry in the EU and other countries in Asia, Africa and Latin America remains largely unused. If the actual status quo about intellectual property protection

prevails, human health, social and economic stability of the nations will be definitively linked to the business plans of the pharmaceutical companies. This is at the very least a non- productive liaison.

In that exceptional world situation, a real rupture with the traditional management of individual intellectual property is needed in the service of the general and common interest of humanity. In France, a legal procedure called "*licence d'office*" exists and would allow the country to produce high amounts of patented vaccines in case of a sanitary emergency, as is currently the case.

7. Some rare cases of unusual, severe thrombotic events (i.e. cerebral venous sinus thrombosis or splanchnic vein thrombosis) and moderate to severe thrombocytopenia, strong increase of D-Dimer or disseminated intravascular coagulation (DIC), have been reported in citizens who received the AstraZeneca vaccine[54],[55] and Johnson&Johnson vaccine[56],[57] and have caused a great deal of concern within the population and the medical community. This type of vaccine-induced immune thrombotic thrombocytopenia (VITT), also called thrombosis with thrombocytopenia syndrome (TTS), implies an immunological reaction that mimics heparin induced thrombocytopenia (HIT) or catastrophic antiphospholipid syndrome.[58] The incidence of VITT has been estimated to be approximately 1 per 100,000 doses.[59] High levels of heparin-Platelet-Factor 4 (PF4) antibodies were identified in patients with VITT. These antibodies activate platelets monocytes and polymorphonuclear leukocytes and induce thrombocytopenia and thrombosis with a mechanism similar to that seen in HIT.[55,60] Positive PF4/polyanion enzyme immunoassays can occur after SARS-CoV-2 vaccination with both mRNA- and adenoviral vector-based vaccines, but the majority of these antibodies likely have minor (if any) clinical relevance.[60] Scientific societies and experts on thrombosis stress the value of continuing vaccination programs in order to protect patients against severe COVID-19 and to slow viral circulation, particularly

of the variants. The diagnostic and therapeutic algorithms available today decrease the probability of serious complications or fatal outcomes of VITT.[61],[62] Some rare cases of classical venous thromboembolism (VTE) (have been observed in citizens who received the mRNA based vaccines.[63] Hence, the benefit of vaccination is clearly high. Despite systematic pharmacological thromboprophylaxis in patients hospitalized with COVID-19 at the conventional ward or intensive care unit the incidence of thrombosis ranges from 7-8% to 25–30% respectively.[64],[65],[66], In western countries, the actual mortality rate in patients with COVID-19 admitted in ICU is up to 30% whereas the morbidity of long COVID-19 complications is not negligible.[67],[68] Nevertheless, this situation might negatively affect the psychological adherence of the population at the vaccination program and raise some concerns leading to enhanced pharmacovigilance. Vaccine hesitancy threatens to reverse the progress made in the massive vaccination program.

8. In order to improve the efficacy of the vaccination process, combined vaccination approaches using two types of vaccines instead of one type of vaccine are currently being considered. Such approaches may provide broader spectral protection against COVID-19 variants. Additional benefits may include improved long term safety outcomes in the use of these agents compared to one type of vaccine. A few small clinical trials are currently in progress to demonstrate the effect of combination approaches, however there is a need for pre-clinical trials to understand the mechanisms involved for the control of viral infection along with the efficacy and safety outcomes.[69]

Think globally and act locally

There is an increasing consensus among experts that globally SARS-CoV-2 is likely to remain endemic in the medium term even when many parts of the world reach collective immunity.[70] In addition, the limitations of the “Stop and Go” strategy, the prolonged duration of the pandemic and the

devastating consequences on public health (including the non-COVID-19 related morbidity and mortality), social adherence and the shrank of global economy impose the elaboration of a balanced and integrated strategy for the management of the pandemic. This new strategy includes mitigation measures, collective immunity, and targeted medical interventions for prompt, home-based medical care of patients at high risk for COVID-19 disease worsening aiming the prevention of SARS-CoV-2 infection and the severe morbidity of patients with COVID-19. Furthermore, this strategy is expected to release the pressure on hospitals during the epidemic waves.

Profiles of populations at risk

The majority of the infected population is asymptomatic or develops the mild and moderate non-severe and non-specific form of COVID-19. About 15% of infected patients develop severe COVID-19 that requires hospitalization in a conventional ward and 5% of patients suffer a critical disease and require ICU admission.[71] It is well established that clinical worsening of patients with COVID-19 is induced by the cytokine storm related with exacerbated inflammatory response, blood hypercoagulability and activation of endothelial cells, which start after the 5th day of the disease.[72],[73] Microvascular thrombosis in the lungs and other organs, as well as pulmonary embolism are major causes of morbidity and mortality in patients with severe or critical COVID-19.[74] Thrombosis is a leading cause of mortality in patients with COVID-19. Indeed, the mortality increases by more than two times in patients with COVID-19 who present VTE as compared to those without VTE.[64],[75] Noteworthy, about 38% of patients with COVID-19 who died at home had VTE and in 12% pulmonary embolism was the cause of death showing that the risk of thrombosis is mainly determined by SARS-CoV-2 infection and COVID-19 severity.[76],[77] Meta-analysis including more that 40000 patients with COVID-19 showed that although routine administration of the recommended pharmacological thromboprophylaxis the rate of symptomatic, objectively

documented VTE was 7% in those hospitalized in conventional ward and 28% in those admitted in ICU.[64,75]

Consequently, a rationalized strategy aiming early identification of patients with COVID-19 at high risk of worsening and the prompt offer of medical care, including antithrombotic treatment, is expected to contribute to the improvement of the clinical outcomes and hopefully could decrease hospital congestion. Nevertheless, this method needs to be coupled with prompt quarantine for up to at least 10 days and contact tracing in order to control virus spread. This approach, beyond the evident benefit of public health, could lead to a lessening of the pressure on hospitals.

The profile of patients at risk of severe or critical COVID-19 has been well described. Male gender is associated with the risk of disease worsening. The risk is further amplified by the combined vascular comorbidities present in older people. About 65% of patients with critical COVID-19, hospitalized in the ICU and 40% of patients with severe COVID-19 hospitalized in a conventional hospital ward have pre-existing vascular disease (personal history of arteriopathy or arterial thrombosis, patients with history of ischemic stroke, carotid artery disease, coronary artery disease or acute myocardial infraction, peripheral artery disease, or arterial thrombosis of rare localization, patients with history of DVT, PE, or vein thrombosis of rare localization (i.e. cerebral vein thrombosis, splanchnic vein thrombosis, upper limb thrombosis) or present with cardiovascular risk factors (hypertension, diabetes or obesity). Patients with COVID-19 and dementia, congestive heart failure, atrial fibrillation, or chronic obstructive pulmonary disease (COPD), liver or renal disease or some forms of immunosuppression are at high risk of disease worsening or death. VTE risk assessment models such as the IMPROVE-DD VTE model have undergone extensive external validation in hospitalized COVID-19 patients and have shown good discrimination to identify high risk patients.[78] Cancer patients, particularly those with metastatic solid cancer with COVID-19 show about two-fold higher mortality.[79,80,81,82,83,84] On the other hand, well-controlled blood pressure and glucose levels in

citizens with arterial hypertension or type 2 diabetes mellitus respectively is associated with markedly lower mortality as compared to individuals with poorer control of these parameters during hospitalization for COVID-19.[85] There are many disparities in the risk and outcomes from COVID-19. Old age, men, living in more deprived areas - mostly urban, Black, Asian and Minority Ethnic groups with more inequalities and comorbidities are at higher risk for mortality.[86]

Clinical and biological risk assessment models for COVID-19 disease worsening, though not perfect yet, are continually improving. Furthermore, electronic health (eHealth) technologies and artificial intelligence/machine learning tools will help in early diagnosis, better precision and personalized therapeutic approaches for COVID-19 patients.[88,87],[88]

Introduction of “mobile apps” in the daily life of citizens may improve their education on early recognition of COVID-19 symptoms and facilitate prompt diagnosis of SARS-CoV-2 infection, warrant the connection with the primary healthcare center and the treating physicians for safer and effective follow up of the patients and early identification of those who are at high risk for disease worsening. The e-Health technologies will allow the offer of high quality health care to population, which for financial or geographic reasons, has restricted access to health services.[89],[90] Artificial intelligence/machine learning-based risk assessment models show improved accuracy and clinical performance. The introduction of the appropriate biomarkers of disease worsening, treatment efficacy etc will allow personalized and optimized therapeutic strategies (i.e. adaptation of the doses and duration of the antithrombotic treatment according to the phase and severity of COVID-19).[89,91],[92] These technological tools will contribute to gather valuable data for both the users themselves, as well as health care providers and policy makers, who can use this data on a more aggregated level to assess the local or regional health status and (expected) pressure on the health care system.[93],[94],[95]

Spatial and social dimensions of SARS-CoV-2 pandemic and risk of COVID-19 worsening.

COVID-19, as all pandemics, have a spatial dimension that has to be managed. The burden of the COVID-19 crisis varies considerably not only across countries, but also across regions and municipalities within urban agglomerations. Areas with higher population density, environmental degradation, air pollution, poverty and social inequalities have been hit harder by the pandemic.[96],[97],[98],[99] Optimal temperature and humidity may also favor virus dissemination. On the other hand, rural areas and smaller islands are prone to be poorly equipped with fewer hospital beds and less health workers as compared to metropolitan areas. Even though frequently the virus first took hold in urban areas, over the past few months some countries experienced the health effect spread towards low-density areas. For example, in the USA, the highest augmentation in the number of deaths occurring in October 2020 was in rural counties not neighboring a metropolitan area. Spatial analysis is needed to determine clusters of the hardest-hit areas and to recognize the associations with circumstantial factors of vulnerability, like minority ethnic groups or low-income areas.[100] Spatial modeling has been a significant factor of the epidemiological toolkit guiding public health and government policy responses, and maps and charts that compare places have become key media for intensifying understanding of the pandemic.[101] Better information on such vulnerable groups and a more accurate picture of the parts of the population with the poorest health outcomes is important. Greater attention may offer a better selection for risk stratification, more adequately limiting the consequences of this outbreak. Being closer and more contextualized in our approach will allow for a localized and dedicated management of these preventive strategies involving a concentric manner with all of the health providers and not only the public hospitals.

Prevention, Detection, Anticipation

It is mandatory that national governments and the EU Commission explore all possible ideas and strategies in order to fulfill the difficult task of protecting the life and health of its citizens. There is an urgent need for a new, balanced, and integrated strategy for the management of the COVID-19 outbreak organized on the following three axes **(PDA)**.:

Prevention of the SARS-CoV-2 infection,

D*etection* and early diagnosis of patients at risk of disease worsening,

A*nticipation* of medical care

The PDA, as a global strategy, is complementary to individual "barrier measures" and aims to improve patients' care at home, to decrease hospital congestion and to prevent new severe lockdowns. The principles of the PDA strategy are organized for offering an equilibrated way to improve the quality of life and limit all the pandemic side-effects.

The PDA strategy, is articulated as follows:

Prevention. A master plan, for the prevention of SARS-CoV-2 infection, mitigation of virus spread and development of collective immunity on global level, (needs to be urgently launched and implemented by the WHO and the national governments (Figure 1).

- *Accelerated massive vaccination, epidemiological surveillance and tracing of contact cases* are prerequisites for effective and long-lasting control of the pandemic and the decrease of the likelihood of the appearance of more virulent viral strains.[102] Indeed, vaccines and tests accessible to all countries at affordable costs are of paramount importance both for ethical and practical reasons. Today, the function of public health systems, social and economic stability are linked to profit-based decisions regarding vaccines, diagnostic methods and therapies depends on the business plans of less than 10 pharmaceutical companies and a few states. China, Russia, India, and Western states, as major state players in the management of the pandemic, need to fully cooperate in terms of truly understanding the epidemiology of the pandemic and its

management. Pharmaceutical companies and consortiums having a pivotal role in the development of vaccines, diagnostic tests and treatments for COVID-19, need to cooperate and diffuse technological knowhow for massive production of the tools required for the control of the pandemic. According to the WHO and the World Trade Organization (WTO) there is an urgent need for "*global solidarity and unhindered global sharing of technology and knowhow*".[103],[104]. The recent recommendations of the Council for Trade-Related Aspects of Intellectual Property Rights of the World Trade Organization should be taken into consideration[105], without blind limitations of the Trade Related Aspects of the Intellectual Property Rights Agreement (TRIPS) especially in the light of a devastating pandemic. Unconditioned technology transfers should be eased so that the production and supply of COVID-19 medical goods, including vaccines and tests will be boosted and more global access to them will be available. In the same line, the elaboration of an enlarged industrial action plan coordinated by the WHO is required for the development and production of the 2nd generation vaccines, free of patent restrictions.

- *Improvement of sanitary conditions and setup of primary health care structures* dedicated for COVID-19, particularly in environmentally and socially sensitive urban zones, and also in areas where access to medical services is challenging. Analysis of the data from the epidemic waves of SARS-CoV-2 allows identification of the regions accumulating risk factors for enhanced viral spread and/or severe COVID-19 evolution. This information will allow a rationalized spatial - territorial distribution of primary health care structures dedicated to patients with COVID-19. Registration, at the community level, of the citizens exposed at high risk for virus infection or being at high risk of disease worsening if infected with SARS-CoV-2 will improve the efficacy of targeted actions for the control of the pandemic. A local patient pathway with all identified health actors and relays proposed to offer a closer and more

adapted strategy for on-site patient management and personalized care. It is time to set up a Global and Personalized Strategy (COVID-19 GPS network) considering all the dimensions of patient frailty facing this pandemic (physical, psychological, social, professional, cultural, economic).

- *Harmonization of Awareness Gaps*: While the COVID-19 pandemic has a catastrophic impact on public health and the economy globally, there remains an awareness gap among public sectors or there is a denial or lack of acceptance of the severe nature of this disease which is more evident in younger people. Therefore, generation-based gaps and uniform acceptance of the guidelines and the urgent need of vaccination is crucial in the control of this pandemic. Digitization approaches including social media such as Twitter, Instagram, and others may be helpful in facilitating this approach. Notably the generation-based gaps, especially for the younger groups can be planned by having advocacy platforms led by identified representatives of these groups with opinion impacts. Public personalities including politicians, movie stars and other artists, religious leaders, sports personalities, and other persons of public impact may contribute in defined programs to narrow the awareness gap and promote the development of global guidelines. Some such initiatives are already in place and have shown an impact in narrowing the awareness gaps in recognition of the severity of the COVID-19 pandemic.[106]

Detection of the dynamics of the virus circulation and detection of patients with COVID-19 and prompt identification of those at risk of disease worsening is acknowledged as a necessary step for the offer of effective medical care (Figure 2).

- *Monitoring and epidemiological surveillance with* wastewater-based survey network, *PCR and rapid screening tests for SARS-CoV-2 infection* are now available free of charge to many countries in order

to identify citizens with asymptomatic or early stages of infection and to reduce the spreading of the virus.

- *Intensive tracking* needs to be developed for each patient diagnosed with infection in the workplace, schools, and locally, when there are outbreaks. It is necessary to develop an epidemiological surveillance network at regional and national level involving virus tracing in the wastewaters (for the countries which are still missing it) to continuously and validly assess the course of the pandemic. To that respect it is important to underline that wastewater survey for SARS-CoV-2 is now considered as an essential tool to evaluate virus dissemination, notably in situations where massive testing is not possible. Very recently, the EU recommended each of its members to develop a wastewater-based survey network. Such a survey has to be implemented in a slightly different form in developing countries as well, notably when massive individual testing is not possible. Furthermore, appropriate bio-banking facilities for new SARS-CoV-2 strains and Global Observatories of population levels of protective immunity are prerequisite for the early detection of potential dangerous situations. In addition, e-applications are of help for continuous tracking. Importantly, tracking needs to be coupled with the rapid detection of positive cases and early patients' isolation. Therefore, quarantine conditions should be carefully examined – notably for people with low incomes - since they are a condition for an efficient acceptance. The problem of the implementation of digital tracking and population compliance are also major keys of their epidemiological interest.
- *Educational programs* must be elaborated (a) for citizens with risk factors or underlying diseases with increased risk of COVID-19 worsening, aiming their training on the application of physical and social distancing measures, early recognition of COVID-19 symptoms and communication with the medical staff at least by telemedicine and (b) for physicians, particularly general practitioners and family doctors, aiming their training on early

recognition of the risk of COVID-19 worsening in their patient list and the implementation of the recommendations for COVID-19 prompt diagnosis and ambulatory management. Patients with vascular disease or cardiovascular risk factors as well as patients with cancer, who represent a rather large part of the adult population in the community, should be under regular medical follow-up for the improvement of the adherence to the antihypertensive treatment (including ACE inhibitors or angiotensin receptor blockers), antithrombotic (antiplatelets or anticoagulant) and the lipid lowering treatment (i.e. statins) and the antihyperglycemic medications according to the recommendations of the relevant consensus statements and scientific societies. It is important to renew all of these prescriptions for avoiding any rupture and omission in these vulnerable patients.

Anticipation of medical treatment in patients with COVID-19 is essential for improved clinical outcome (Figure 3).[107]

- *Early diagnosis of COVID-19* with a simple and feasible methodology at the level of the primary health care structures are of major importance for prompt medical care. A regional procedure for prioritized hospitalization of patients at high risk or with early signs for disease worsening should be considered by health authorities since it is expected to improve the clinical outcomes.
- *Home-based medical care* of patients with COVID-19. Within the first 5 to 7 days after SARS-CoV-2 infection the symptoms of CVOID-19 are related principally with the viral load. Afterwards, the clinical evolution is determined by host reaction (cytokine storm, hypercoagulability, endothelial cell activation) which is amplified in patients at risk for disease worsening.[108],[109] Home based-medical care for patients at risk for disease worsening aims prompt administration of therapeutic agents targeting the viral load (those which are available and recommended today and that which will be at the future), the prevention and treatment of COVID-19

complications, the treatment of underlying diseases, the prevention of secondary infections, and the support of organ function in time.

- *Early treatment administration at out-patient receiving home based medical care as* is recommended today for the initial phase of COVID-19, (i.e. monoclonal antibodies against SARS-CoV-2, or other antiviral treatments available and approved by health authorities) and pharmacological thromboprophylaxis in patients at high risk for VTE or disease worsening. General, non-specific therapies such as strengthened supportive treatment, vitamin-D administration, adequate energy intake, evaluation of water and electrolyte balance, effective oxygen therapy measures are also important to be administered promptly by the general practitioner and home-based medical care.[110],[111]

Early administration of antithrombotic agents such as low molecular weight heparin (LMWH), direct orally active factor Xa inhibitors (apixaban, rivaroxaban) or sulodexide to patients at risk of disease worsening, reduces the risk of hospitalization, need for oxygen support or even mortality [112],[113],[114],[115],[116],[117],. Nevertheless, particularly for LMWHs, the optimal dose needs to be thoroughly evaluated.[118] The organization of the necessary framework for home-based medical care will be of major importance for the optimal administration of the forthcoming specific antiviral treatments which are currently under investigation or clinical development.[119]

- *Personalized therapeutic strategy and prompt identification of patients who need prioritized hospitalization* based on regular clinical follow up of the patients (i.e., by performing the recommended blood tests and applying the available risk assessment tools) will contribute to the improvement of the clinical outcome.[120]
- *Long-COVID-syndrome* is currently observed in patients who recovered from the acute disease. It has now been documented that one third of the COVID-19 patients suffer from varying degrees of behavioral and mental disorders with a wide range of

symptoms.[121],[122] Additionally, the behavioral impact of COVID-19 in the general public is well documented. This includes depression, anxiety, behavioral disorders requiring professional interventions.[123] The severity of these problems ranges widely with complex manifestations. Psychological programs for citizens are another approach to implement defined programs and solidarity networks to manage these issues.[124] The aggravation and prolongation of such a frail situation is leading to many other diseases (treatment omissions and diagnosis delays) and family fractures (violence, divorce, separation) as indirect consequences of this pandemic which has turned every facet of life upside down. Post-hospital discharge VTE may also be considered and prevented.

- *Homogenization of therapeutic protocols*. The COVID-19 pandemic has pressurized the medical community to make medical decisions and recommendations based on limited anecdotal, observational, and in some cases, a complete absence of evidence.[125],[126] Individual medical institutions have created their own institutional algorithms, presumably based on local individual expertise and consensus, as well as interim professional society and governmental recommendations[127] The ongoing clinical trials on antithrombotics and other treatments for patients with COVID-19 will offer guidelines supported by a high level of evidence. Nevertheless, the harmonization of diagnostic and therapeutic protocols principally at the levels of the primary healthcare structures needs to start and implemented rapidly.

Conclusions

The SARS-CoV-2 pandemic enters into a new phase which is characterized by the

1. Knowledge on the characteristics of variants of SARS-CoV-2, their pathophysiology and clinical courses of COVID-19.
2. Availability of high-quality diagnostic rapid screening tests for SARS-CoV-2 tests which allow accurate epidemiological surveillance and

tracing of contact cases with an affordable cost, which will allow effective mitigation of the pandemic.

3. Availability of vaccines is a fundamental element for accelerated development of worldwide collective immunity.
4. Description and identification of population groups which are at higher risk of COVID-19 infection and vulnerable to develop severe COVID-19 or a worsening disease.
5. Development and availability of validated risk assessment models which together with the clinical experience gained by physicians allow the earlier identification of patients at risk of disease worsening. This methodology is expected to be optimized in the forthcoming period and will allow its more systematic application
6. Development of therapeutic strategies and treatment guidance which include antiviral agents (i.e., monoclonal antibodies or other drugs) antithrombotic and anti-inflammatory agents, vitamins which may improve the clinical course of the patients with COVID-19 if they are administered as early as possible after symptom declaration and diagnosis of the disease.
7. Development of e-Health tools and artificial intelligence-based methodology can improve the benefit of the mitigation policies by decreasing the financial and social costs of the severe NPI and allows for prompt and personalized medicine in patients with COVID-19
8. Acquisition of a collective experience by the medical community, the citizens and the policy makers in the management of the pandemic will allow the adaptation of the strategies according to local customs and cultural characteristics of the populations.

The PDA strategy offers to policy makers the possibility for a rapid elaboration of concrete integrated and equitable program for the management of the next phases of the pandemic in order to preserve the health of peoples and the social cohesion.

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Conflict of interest

The authors have no conflict of interest to declare for this study

Figure 1. Illustration of the PDA strategy. Prevention of SARS-CoV-2 infection accelerated massive vaccination world-wide, epidemiological surveillance, masks, distancing, improvement of sanitary conditions and setup of primary health care structures are capital elements for the mitigation and the control of the pandemic.

Figure 2. Illustration of the PDA strategy. Detection of the dynamics of the virus circulation of patients with COVID-19 and prompt identification of those at risk of disease worsening are mandatory to preserve the health of citizens and society's cohesion.

Figure 3. Illustration of the PDA strategy. Anticipation medical treatment in patients with COVID-19 is essential for improved clinical outcome. Early identification of patients at risk of disease worsening and application of the recommended treatments at the level of the primary healthcare structures are related with improved clinical outcome and decreased mortality. The first 5 to 7 days after SARS-CoV-2 infection is a critical period for that requires identification of patients at risk of disease worsening and personalized *therapeutic strategy.*

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Table 1. Summary of vaccines which have been studied in Phase III trials and the results have been published or communicated in press releases of the companies (as of June 2021).

Vaccine	Developer	Vaccine Composition	Country of the Vaccine Producer	Vaccine Platform	Number of Doses & Schedule	Route of Administration	Storage Conditions	Current Status of Clinical Evaluation	Efficacy	Safety in Clinical Studies
mRNA-BNT162b2 - Comirnaty	Pfizer/BioNTech + Fosun Pharma	mRNA vaccine encoding for the RBD of the S1 protein. Vaccine contains single nucleoside incorporations of 1-methylpseudouridine. RBD antigen contains a T4 fibritin-derived fold-on trimerization domain. Encapsulated within an LNP.	USA Germany	-mRNA	2 Day 0 + 21	IM	Stored at –70°C Stored at -25 to -15°C for 2 weeks Stored 2-8 °C for 5 days	Phase 4	95%	Phase 3 results ahowed safety. (Published)
mRNA -1273	Moderna + National Institute of Allergy and Infectious Diseases	mRNA vaccine encoding for the profusion form of the S antigen that includes a transmembrane anchor and an intact S1-S2 cleavage site in its profusion form. Encapsulated within an LNP.	USA	mRNA	2 Day 0 + 28	IM	Stored at -20°C Stored 2-8 °C for 30 days	Phase 4	94,1%	Phase 3 results ahowed safety. (Published)
ChAdOx1-S - AZD1222	AstraZeneca + University of Oxford	Adenovirus derived from chimpanzee with E1 and E3 deletions, encoding for the full-length S protein with a tissue plasminogen activator signal peptide.	United Kingdom -Sweden	Non-replicating Viral Vector	1-2 Day 0 + 28	IM	Stored under refrigeration	Phase 4	79%	Phase 3 results ahowed safety. (Published)
Sputnik V	Gamaleya Research Institute + Health Ministry of the Russian Federation	Adenovirus based vaccine combining two adenoviruses: Ad5 and Ad26.	Russia	Non-replicating Viral Vector	2 Day 0 + 21	IM	The vaccine was manufactured as two formulations, frozen and lyophilized.	Phase 3	91,6%	Phase 3 results ahowed safety. (Published)

Ad26.COV2.S - JNJ-78436735	Johnson & Johnson + Janssen Pharmaceutical	Recombinant, replication incompetent adenovirus serotype 26 (Ad26) vector encoding a full length and stabilized SARS-CoV-2 spike (S) protein. The vaccine was derived from the first clinical isolate of Wuhan strain.	USA - Germany	Non-replicating Viral Vector	1-2 Day 0 + 56	IM	Stored at -20◦ C for 2 years Stored 2-8 °C for 3 months	Phase 3	72%	Phase 3 results ahowed safety. (Unpublished)
Convidecia	CanSino Biological Inc. + Beijing Institute of Biotechnology	Ad5 with E1 and E3 deletions encoding for the full-length S protein. Gene was derived from the Wuhan-Hu-1 sequence for SARS-CoV2 and contains a tissue plasminogen activator signal peptide.	China	Inactivated	1 Day 0	IM	Stored under refrigeration.	Phase 3	65,28	Phase 3 results ahowed safety. (Unpublished)
BBIBP-CorV	Sinopharm + China National Biotec Group Co	β-propionolactone inactivated vaccine of SARS-CoV-2	China	Inactivated	2 Day 0 + 21	IM	Stored under refrigeration.	Phase 3	80,6	Phase 3 results ahowed safety. (Unpublished)
CoronaVac	Sinovac Research and Development Co., Ltd	Formalin inactivated whole virus particles.	China	Inactivated	2 Day 0 + 14	IM	Stored under refrigeration.	Phase 4	50,38% - 83,5%	Phase 3 results ahowed safety. (Unpublished)
BBV152 – Covaxin	Bharat Biotech International Limited	BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine formulated with a Toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel- IMDG) or alum (Algel).	India	Inactivated	2 Day 0 + 14	IM	Stored under refrigeration. Stable in room temperature for 1 week.	Phase 3	80,6%	Phase 3 results ahowed safety. (Unpublished)
NVX-CoV2373	Novavax	Stable profusion, full-length S protein made from VLP nanoparticle technology, given with saponin-based adjuvant, Matrix-M ™.	USA	Subunit	2 Day 0 + 21	IM	Stored under refrigeration.	Phase 3	96%	Phase 3 results ahowed safety. (Unpublished)
EpiVacCorona	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	The vaccine contains small portions of viral proteins, known as peptides.	Russia	Subunit	2 Day 0 + 21	IM	Stored 2-8 °C for 2 years	Phase 3	Unknown	Phase 3 results ahowed safety. (Unpublished)

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