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Improved strategies to counter the COVID-19 pandemic: Lockdowns vs. primary and community healthcare

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ABSTRACT

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COVID-19 pandemic mitigation strategies are mainly based on social distancing measures and healthcare system reinforcement. However, many countries in Europe and elsewhere implemented strict, horizontal lockdowns because of extensive viral spread in the community which challenges the capacity of the healthcare systems. However, strict lockdowns have various untintended adverse social, economic and health effects, which have yet to be fully elucidated, and have not been considered in models examining the effects of various mitigation measures. Unlike commonly suggested, the dilemma is not about health vs wealth because the economic devastation of long-lasting lockdowns will definitely have adverse health effects in the population. Furthermore, they cannot provide a lasting solution in pandemic containment, potentially resulting in a vicious cycle of consecutive lockdowns with in-between breaks. Hospital preparedness has been the main strategy used by governments. However, a major characteristic of the COVID-19 pandemic is the rapid viral transmission in populations with no immunity. Thus, even the best hospital system could not cope with the demand. Primary, community and home care are the only viable strategies that could achieve the goal of pandemic mitigation. We present the case example of Greece, a country which followed a strategy focused on hospital preparedness but failed to reinforce primary and community care. This, along with strategic mistakes in epidemiological surveillance, resulted in Greece implementing a second strict, horizontal lockdown and having one of the highest COVID-19 death rates in Europe during the second wave. We provide recommendations for measures that will reinstate primary and community care at the forefront in managing the current public health crisis by protecting hospitals from unnecessary admissions, providing primary and secondary prevention services in relation to COVID-19 and maintaining population health through treatment of non−COVID-19 conditions. This, together with more selective social distancing measures (instead of horizontal lockdowns), represents the only viable and realistic long-term strategy for COVID-19 pandemic mitigation.

1. Introduction

As the world continues to navigate through the uncertainties of COVID-19, it becomes evident that the dynamic of the pandemic can easily overwhelm healthcare systems globally and impose serious adverse health, economic and social effects on the population. Even in Western, high-resource regions, such as Northern Italy or New York, hospitals and intensive care units (ICU) were under extreme pressure during the first pandemic wave in spring of 2020, resulting in difficult prioritization decisions about treatment based on factors such as age, comorbidities and functional status [1–3]. The risk of exceeding healthcare systems capacity has led to social (physical) distancing measures, which frequently mandate strict, horizontal lockdowns with universal restriction of movement affecting the whole population.

While using extreme lockdowns as the main strategy at the beginning of the pandemic was expected and defendable, considering the lack of preparedness in dealing with a public health crisis and the uncertainty over the case fatality rate, the second and third waves that are currently in full force throughout Europe and the US, respectively, have proven that lockdowns are not a measure with long-term and sustained mitigation effects, let alone a viable and definite solution. Instead, they could be used only as temporary measures to "buy time" and reorganize the healthcare and public health response, develop resources to effectively detect, isolate, test and care for all cases, as well as introduce other non-pharmacotherapeutic interventions and empower the population to develop an appropriate societal response, or even initiate plans for long-term pandemic prevention [4–7]. Lockdowns have been shown to reduce the effective reproduction number (R), i.e., the number of people infected by each infected person at short term [8]. However, strict lockdowns that include social distancing for the whole population, including younger people, might only confer temporary benefits and could result in more deaths long-term because the pandemic is prolonged and COVID-19 related mortality is highly skewed towards older age groups [9]. Therefore, intense and horizontal social distancing interventions may end-up causing more harm than good in terms of COVID-19 mortality, despite the best of intentions. But more importantly, all models analyzing the impact of lockdown on SARS-CoV-2 transmission and COVID-19 mortality fail to consider the potentially devastating adverse effects on other diseases. They also fail to consider the adverse economic and social consequences that can cause medium and long-term health harm on the whole population, particularly the younger and most productive population subgroups. This omission is in direct conflict with fundamental public health principles that dictate all decisions should be based on a holistic and careful assessment and weighing of intended benefits and unintended harms. Unintended adverse effects of lockdowns have already been observed. In Italy, the fatality rate in patients with myocardial infarction who presented to hospitals was increased by 3-fold with a parallel almost 2-fold higher risk for complications between March 12–19, 2020, during the period of lockdown, compared to the same week of 2019 [10]. Reduced rates of hospital admission for acute coronary syndrome were also observed, most likely due to patients' fear of being exposed to an environment with high risk of SARS-CoV-2 infection as well as delayed treatment [10–14]. In England and Wales, acute cardiovascular deaths at home were increased by 35 % compared to 2014–2019 [15]. Most of these deaths were not related to SARS-CoV-2 infection [15]. Besides the immediate effects on mortality, these issues are expected to have long-lasting, perhaps life-long, implications in patients who will end up with heart failure, leading to a reduction in life expectancy and a potentially dramatic decline in quality of life. Excess mortality has been observed in several countries, which is not solely attributed to COVID-19 [16,17]. Primary prevention strategies are expected to be disrupted. In the UK, approximately 1 million mammograms have been skipped, resulting in an estimated 8600 women who could be living with undetected breast cancer because of their diagnosis being delayed [18]. Other primary prevention programs are also expected to be impacted by the pandemic. The mental health impact of extreme social restrictions is also expected to be devastating, considering the impact observed in prior pandemics [19]. Mental disorders are associated with more than 2-fold higher relative risk for all-cause mortality, with the median years of potential life lost being 10 years [20]. In Switzerland, it was projected that approximately 180,000 people (2.1 % of the population) will be affected and 1.7 million life years may be lost as a result of lockdowns, due to mental health factors such as suicide, divorces, family violence, depression, and alcohol use disorder [21]. An important portion of the damage caused by stress-related issues may be hard or impossible to reverse, resulting in sustained suffering that is expected to last much longer than the physical health impact of the pandemic [21]. Children and adolescents are not expected to be spared from the adverse effects, and the disruption in education and socialization through school interactions is expected to cause even more problems [22,23]. Substance abuse is also increased during the stressful period of lockdowns, often stimulated by aggressive misleading "infosaturation" or "infoxication" regarding its supposed therapeutic benefits. [24,25]. Last but not least, the socioeconomic effects are expected to result in rising unemployment, poverty, and exacerbation of social and health inequalities that may be

long-lasting [26,27]. It should be mentioned that not all population subgroups carry the same risk for severe COVID-19 and death. Unlike the 1918 Spanish flu pandemic in which peak mortality was observed at the age of 28 [28], COVID-19-associated mortality is mainly affecting the elderly and people with comorbidities [29,30]. Specifically, epidemiological data suggest that factors such as obesity, cardiovascular risk factors and established vascular disease are associated with elevated risk for severe COVID-19, with microvascular thrombosis in the lungs and other systems being the main pathophysiological features [31]. At the same time, immune dysfunction, perhaps linked with environmental factors, toxin exposure as well as comorbidities seems to be a major determinant of severe COVID-19 severity. Besides people with comorbidities, socially disadvantaged groups have been shown to be disproportionately affected by COVID-19 [32–35]. These features led to the characterization of the COVID-19 global threat as a syndemic, instead of a pandemic, a synergistic interaction of an infectious disease with an array of non-communicable diseases as well as socioeconomic factors [36]. Therefore, measures such as strict lockdowns have the potential to create another potential form of "inequality" between population subgroups in terms of expected benefits and potential harms from public health measures and interventions relevant to COVID-19 mitigation. Even children are part of this "inequality". School closures, which are known to be associated with multiple harms [37], are not implemented in order to protect the health of children from SARS-CoV-2 infection (which is almost universally mild) but in order to reduce viral transmission to vulnerable groups. All these adverse effects are not necessarily acute and easily detectable but may evolve over time and may be long-lasting. For example, unemployment is associated with a 63 % higher mortality risk, adjusted for age and other covariates, and affects mainly those in their early and middle careers, which translates to younger age groups [38]. Furthermore, it should be emphasized that the decisions to implement strict, horizontal lockdowns are not a trade-off between health and wealth, with the interest of public health being favored over economic benefit. In fact, this represents a pseudo-dilemma since economic deprivation is closely and directly linked to public and population health deterioration.

While there is definitely the need to protect the vulnerable, careful planning and modelling are necessary so that the net positive outcomes of each intervention far outweigh the negative effects on a population level, not only in the short term but also in the long term. This has been largely ignored during this pandemic while it should have been at the forefront of the decision-making framework, with consideration for alternative interventions or effective strategies to mitigate their adverse impact [39,40]. Finally, while some concerns have been raised about human rights and democracy due to the measures of restricting movement, preventing people from working and socializing and other relevant government decisions [41], this is acceptable during public health crises. Still, it is important that such measures are of limited duration, based on scientific evidence, lawful, necessary, proportionate, non-discriminatory and least intrusive and restrictive possible in order to reach the objective [42]. At the same time, freedom of expression and access to critical information need to be protected [42].

All the above generate serious concerns about the use of horizontal lockdowns as the central and dominant measure to control and mitigate the impact of COVID-19 incidence, morbidity and mortality. In fact, we may have only recorded and witnessed "the tip of the iceberg" in terms of unintended harms of extreme lockdowns and other approaches in mitigating the pandemic, with the full extent and magnitude of adverse effects not yet being fully developed. Furthermore, lockdowns have been proven to have temporary effects only, since a second pandemic wave has occurred throughout Europe, while the benefit of horizontal, strict lockdowns, compared to partial lockdowns or curfew only, in preventing deaths remains unclear [43]. We are already seeing signs that this strategy could result in a vicious cycle of consecutive strict lockdowns, with short in-between breaks, especially during the winter when weather conditions facilitate viral spread. There is no doubt that social distancing measures and restrictions of movement are necessary as part of a mitigation strategy. Horizontal lockdowns for the whole population may be essential as a measure of last resort, either due to too many unknowns or out of despair because of uncontrollable viral spread and overwhelmed healthcare systems. However, considering the potentially harmful effects of such lockdowns, a more sustainable and realistic strategy is needed to effectively and holistically combat the pandemic. Additionally, a longer-term strategy to reduce morbidity and mortality from this and future pandemics is needed, focusing on environmental factors, toxin exposure and other risk factors for non-communicable diseases that potentially compromise the function of the immune system and increase infectious disease susceptibility and severity.

2. Hospital preparedness

Hospital preparedness is critical in organizing the national and local response to communicable disease epidemics. Increasing bed capacity, adjusting the infrastructure and re-allocating human and equipment resources, implementation of measures to protect staff, patients and visitors and training of personnel are important measures in dealing with a communicable disease crisis [44]. Such measures were the focus of interventions during the initial stages of the COVID-19 pandemic. On a European level, governments have been mobilizing special funds and used private donations to increase workforce capacity and to obtain additional equipment, including personal protective equipment and ventilators [45]. However, it soon became apparent that hospitals can easily be overwhelmed. In countries such as Spain and Italy, hospitals rapidly reached 100 % occupancy, despite efforts to place additional beds in improvised ward areas and repurpose post-anesthesia and cardiac care units into ICUs for COVID-19 cases [46–48]. This was expected since the virus is highly contagious and rapid transmission occurs in communities with no immunity to SARS-CoV-2. In fact, hospitals could become highly contaminated and thus become transformed into vectors of the disease, facilitating transmission to uninfected, vulnerable patients [47]. Hospital staff becomes exhausted, resulting in compromise of quality of care. Additionally, the elevated risk of being infected with a high viral load, which can even increase the risk of severe COVID-19 and death, may result in a further reduction of hospital capacity due to loss of personnel [49]. As expected, front-line healthcare workers are by far more likely to be infected with SARS-CoV-2 compared to the general population even when adjusting for the frequency of being tested. This can have significant implications in viral transmission to high-risk individuals seeking care for other health conditions [50]. Therefore, even if substantial financial and other resources were dedicated to hospital preparedness, it would still be inadequate to contain and mitigate the effects of the pandemic if no other measures are taken. Last but not least, national policies and national preparedness, both for organizing hospital services and for non-pharmacological intervention strategies, are needed so that the public health response is organized, the population receives consistent messages, and challenges such as resource capacity and local outbreaks are adequately addressed through cooperation and planning. At the same time, national policies should be flexible enough to accommodate for regional unique characteristics that would require policy adjustments.

3. Primary health care, community and home care

Fatality data were initially based on confirmed cases of SARS-CoV-2 infection. The case fatality rate was estimated at 3.4 % according to a World health Organization (WHO) briefing in early March 2020 [51]. However, as for many infectious diseases, this represented a gross overestimation because a substantial proportion of infected people are undetected due to being asymptomatic or oligo-symptomatic and thus typically not seeking medical assistance [52]. Massive under-testing was also a serious problem, particularly at the beginning of the pandemic but also more recently [53,54]. Serological studies allowed the calculation

of infection fatality rate, which turned out to be much lower than the case fatality rate, particularly for people < 65 years old and no serious comorbidities [55–57]. Large differences in death risk were found between different age groups and comorbidities [58,59]. Additionally, patients with poorly-controlled comorbidities may have a further increase in the risk for severe COVID-19 and death [58]. All the above indicate that a large proportion of COVID-19 patients will not need hospitalization, while, with appropriate interventions outside hospitals, and perhaps pharmacotherapies that are currently under investigation, the need to access secondary and tertiary healthcare services can be further reduced [60–63].

Primary healthcare and community care can have a central role in relieving the pressure from hospitals and maintaining population health. Previous data suggest that access to a family physician improves patient satisfaction, hospitalization rates, clinical outcomes and equity [64–66]. Therefore, primary care can essentially become the critical first line of defense through multiple primary and secondary prevention interventions in relation to COVID-19. Community education and risk communication, risk stratification and identification of vulnerable groups that need to be more aggressively protected from infection, pharmaceutical control of comorbidities that are recognized risk factors for severe COVID-19 and interventions to reduce health inequalities can only be achieved through a coordinated and well-planned action of primary and community health care. The usually long-lasting and trusted relationship between primary care physicians and patients ensures an open line of communication and may even prevent misinformation and misperceptions [67]. Differential diagnosis, testing and early detection of SARS-CoV-2 infection, contact tracing, supportive treatment, triage and risk assessment at individual, family and community levels are important secondary prevention measures. Coordination, motivation and monitoring of case isolation is another priority that can be handled by family physicians [68]. Home monitoring and care are also crucial, not only to reduce hospital admissions but also to timely identify worsening disease that would lead to prompt referral for hospitalized care before the development of irreversible health damage. For example, patients with vascular disease, who are at high risk for severe COVID-19, may need to be placed in close medical follow-up and assessed regularly by primary care physicians according to recommended guidelines [69]. Home visits, telephone and online health consultation, and delivery of simple equipment such as oxygen therapy and pulse oximeters are the main responsibilities of primary and community care interventions [47]. Additional services, such as delivery of medical and food supplies and domestic support can be provided by establishing local community care teams composed of community nurses, health visitors and social workers. Organized phone centers, dedicated to individuals with suspected or confirmed COVID-19, could be established locally, that will provide guidance, coordinate the testing and contact tracing process, and provide consulting and support for ambulatory patients with COVID-19. After hospitalization for COVID-19, primary care is crucial for rehabilitation, management of post-acute COVID-19 and community follow-up [70]. These measures contribute not only to rapid recovery and improvement in quality of life but also to shortening hospital stay and thus increasing available hospital resources. An additional pressing issue is the management of mental health problems that appear to be highly prevalent in patients recovering from COVID-19 [71,72]. Primary care is also responsible for maintaining the delivery of essential health services irrelevant to COVID-19, both in primary and secondary prevention, in order to reduce morbidity and mortality from other diseases. Finally, a key intervention in alleviating pressure to hospitals is to prioritize in the primary care setting conditions that could reduce non−COVID-19 related admissions to hospitals. It is well-established that a large proportion of hospital admissions are unplanned, i.e. non-elective, with a substantial proportion being considered unnecessary as most of these patients could have been cared for in the community [73,74]. Several health conditions, called ambulatory care sensitive conditions, have been identified, with hospital admissions potentially being prevented through primary care interventions. While previous studies have identified the important role of ambulatory care sensitive conditions as markers of accessibility, effectiveness and quality of primary care [75–77], it now becomes crucial to develop an effective strategy of safely reducing unplanned admissions through targeted primary and community care activities and services. Prioritizing interventions for conditions such as influenza, chronic obstructive lung disease, congestive heart failure and urinary tract infections appear promising in freeing up hospital capacity to deal with COVID-19 patients [78]. The role of primary care is indispensable particularly for underprivileged individuals and people with limited or distant access to hospital care such as those living in rural areas, which probably represent high risk groups for severe COVID-19.

It is now apparent that the battle against the pandemic cannot be won through a patient-centered care model driven by hospitals and intensive care [47]. Even the best hospital system would struggle to contain a pandemic of this scale. Instead, the key in managing this public health crisis is to reinforce but at the same time protect hospitals, by reducing the numbers of total and high-risk COVID-19 patients who will require hospitalized care. This can be a feasible goal. However, it needs a strong and coordinated effort by primary, community and home care so that it can be achieved safely and effectively, in addition to selective and carefully planned social distancing measures. An outline of the role of primary, community and home care in handling the pandemic is presented in Table 1.

4. Healthcare preparedness and interventions in Greece: a case example

The Greek national health system provides healthcare benefits/services through a network of public/state providers and contracted private providers of primary, hospital and ambulatory care [79]. The National Organization for the Provision of Health Services (Greek acronym: EOPYY) was formed in recent years by merging four of the largest social security organizations, being responsible for negotiating contracts and remunerates health professionals. Primary healthcare is provided by EOPYY-contracted private-practice physicians, diagnostic centers and

Table 1
The role of primary, community and home care in COVID-19 pandemic mitigation.

Primary prevention	Education/information/risk communication campaigns
	Risk stratification
	Prioritize high-risk individuals
	Pharmaceutical control of comorbidities which are risk factors for COVID-19
	Reduce health inequalities
	Managing mental health effects
Secondary Prevention	Differential diagnosis between SARS-CoV-2 and other infections
	Testing and early identification of cases
	Contact tracing
	Supportive treatment - delivery of simple equipment
	Home care
	Triage
	Coordination/motivation/monitoring of case isolation
	Phone/online consultation and support
	Timely identification of worsening COVID-19 disease
	Managing mental health effects
	Domestic support, food and medication supplies for those in quarantine
Post-COVID-19 Care	Rehabilitation
	Management of post-acute COVID-19
	Community follow-up
	Management of mental health effects
Managing other conditions	Delivery of essential health services
	Vaccinations
	Treating patients with ambulatory care sensitive conditions

private clinics, public National Primary Healthcare Network (now transformed into health centers), and State hospitals, health centers, rural and regional medical units. Hospital care is provided by EOPYY-contracted private clinics and state hospitals. There are about 3500 clinical and 2000 laboratory physicians who are contracted by EOPYY for providing health services, and about 800 family physicians (mostly general practitioners, internists and pediatricians). Characteristically, there are many prefectures that do not have any pediatrician or general practitioner contracted by EOPYY. Moreover, there are thousands of private doctors who provide services paid by the patients, but can also prescribe medications and diagnostic tests, with the cost being coveredςι (usually in part) by EOPYY. Private healthcare providers are prominent in primary care, especially in diagnostic technologies, private physicians' practice and pharmaceuticals [79]. The system is financed by the state budget, social insurance contributions and private payments.

The responsibility for developing a strategy for pandemic containment and mitigation and submit proposals for public health measures to the government was assigned to the National Public Health Organization (EODY). The initial response to the pandemic was mainly focused on enhancing hospital resources in terms of personal protective equipment, specialized care equipment such as ventilators, expansion of ICU beds and hiring healthcare personnel. Private donations also helped supporting the increased needs of the healthcare system. These were necessary steps considering the budget cuts during the recent economic crisis, particularly in public health expenditure and management, primary healthcare and critical care [80,81]. Social distancing measures were soon implemented in the country. With the first confirmed COVID-19 case being diagnosed on February 26, 2020, all schools were closed. On March 13, one day after the first death from COVID-19 was recorded, cafes, bars, museums, shopping centers, sports facilities and restaurants were closed, followed by retail shops on March 16. Finally, on March 23, restrictions on all non-essential movement throughout the country were implemented, with signed attestation or mobile phone SMS notification required for all movement outside the home for specific reasons such as health reasons, buying essential goods, assisting other people in need and exercising [82]. Restrictions were gradually lifted starting from May 4, after a 42-day lockdown. Until that time, 2632 confirmed cases and 146 deaths had been recorded. The beginning of the second wave of the pandemic occurred in August and increased still further after mid-October. The number of daily deaths started to rise in mid-September and further increased by early November to a 7-day moving average of 34 deaths per day (in November 11, 2020, from a maximum of 5 deaths per day in spring during the first wave of the pandemic). On that day, the second strict lockdown was announced, with schools retail, restaurants and nightlife closure, and with permission to leave home only for specific reasons (such as for work, health reasons, exercise, buying food supplies and to provide assistance to people in need) for which written attestation or mobile phone SMS notification was required (similarly to the first lockdown).

While efforts were focused on hospital re-organization and reinforcement, primary and community care were largely neglected. Characteristically, it was only on October 8, almost 7 months after the pandemic was declared by the WHO, that 160 health centers and 48 rural medical units were announced to participate in the management of patients suspected of having COVID-19 [83]. Patients with symptoms compatible with COVID-19 would need to schedule an appointment, either by phone or electronically, in order to be examined and tested at no cost [84]. It is still is unclear if everyone could be tested on the same day of asking for an appointment, while asymptomatic close contacts were apparently not included in the criteria for testing. Thus, the rapid identification and diagnosis of suspected COVID-19 cases and their closed contacts was in all likelihood compromised. No clear plan was announced about the role and the actions of primary care health centers and family physicians in triage, treatment and home care for individuals not needing hospital admission. Additionally, the testing capacity of primary healthcare centers is probably inadequate to handle the increased demand. As a result, people who want or need to be tested for SARS-CoV-2, mainly those who are ambulatory and either asymptomatic or with mild symptoms, have no other alternative but to visit hospitals which are on duty for emergencies in order to perform a diagnostic test. This represents a crucial, strategic mistake. It adds to the pressure already applied to hospitals and represents a waste of personnel and resources which should be mainly dedicated to the care of patients with severe disease. In fact, in a desperate effort to increase hospitals personnel capacity, healthcare professionals are being transferred from health centers to hospitals, further weakening primary care [85]. These may be preliminary signs of the hospital care system being close to its limits, and it is unclear how this situation has compromised the care for patients with other diseases. At the same time, the contamination burden of hospitals is expected to increase, resulting in higher viral exposure of the personnel and of non-infected (but high-risk) patients. Transmission may also be facilitated among people queuing for diagnostic tests. Hospitals can easily become "microbubbles" and major vectors of disease. An additional problem was that, according to media reports, hospitals were apparently used as isolation facilities for oligo-symptomatic COVID-19 patients who could not follow quarantine, social distancing and personal hygiene measures, such as migrants and refugees, further wasting valuable hospital resources [86]. Finally, some specialized infectious disease hospitals which were shut down in previous years were not re-opened during the pandemic. This represents a missed opportunity to at least isolate COVID-19 patients from non-infected patients who are hospitalized in general hospitals for other diseases.

No effort was made to reinforce the role of family physicians. There was no provision to provide them with personal protective and other equipment, or to accelerate the recruitment of more family physicians in an already-deficient system. Consequently, home care was largely neglected and unable to participate in the pandemic mitigation efforts. Private-practice physicians and diagnostic centers have been largely left out from the pandemic mitigation strategy. EOPYY does not compensate (neither fully nor in part) the diagnostic tests prescribed by private practice doctors. Even the large number of private laboratories which are contracted with EOPYY to provide services to patients (with the large part of the cost being compensated by EOPYY) do not receive any compensation for SARS-CoV-2 diagnostic tests. Therefore patients who make use of such diagnostic tests in private laboratories need to personally cover the whole cost. This represents a missed opportunity to increase testing capacity and alleviate the pressure from public hospitals and health centers which are overwhelmed by the current demand. Moreover, it results in delays in epidemiological surveillance, which should be based on the rapid identification and diagnosis of infected people and their close contacts so that isolation is implemented in a timely manner before transmitting the virus to other members of the community. Other efforts to increase testing capacity were mainly limited to initiatives by EODY, municipalities or peripheries to organize field testing for a limited number of days in major cities and towns. Anyone who wanted to be tested (irrespective of the presence or absence of symptoms) could perform a rapid antigen or a PCR test, even without physician prescription or recommendation. However, such initiatives lasted for a few days only, were not repeated in pre-defined periods of time and did not recruit random or population representative samples. Thus, they cannot be considered as sustained and lasting diagnostic interventions, and they could not provide any meaningful epidemiological data. Instead, they could be considered as blind population testing, which is unlikely to have any meaningful impact in controlling community transmission.

In the area of epidemiological testing and surveillance, we are aware of two published serological studies performed in Greece. In a study published in August 2020, 6586 blood samples collected in March and April were analyzed for SARS-CoV-2 IgG antibodies using a left-over sampling methodology (residual sera from the general population)

[87]. Seroprevalence was estimated at 0.02 % and 0.25 % in March and April, respectively, with an infection fatality rate of 0.54 %. Based on seroprevalence, for every laboratory-confirmed COVID-19 case there were approximately 10 additional cases. Although the study was planned to be repeated at monthly intervals, we were unable to find any publication presenting more recent data. Another seroprevalence study was performed among students and personnel of the National and Kapodistrian University of Athens in June and July, finding a weighted overall seroprevalence of 0.93 % [88]. In terms of using diagnostic tests (PCR or rapid antigen tests) for epidemiological surveillance purposes, to the best of our knowledge, no such studies have been performed in Greece. Such studies would be meaningful and important if they included population-representative samples and were repeated over time in order to timely identify increased transmission in specific areas and implement further local measures to contain and mitigate viral spread.

In conclusion, Greece represents a typical case of a country which was largely unprepared during the first wave of the pandemic. Additionally, no priority was given to primary and community healthcare reinforcement. The expectation that hospitals would be able to cope with the pressure of a highly transmissible virus was unrealistic. In fact, during the second pandemic wave, hospitals are under immense pressure and Greece now has one of the highest COVID-19 death rates in Europe. Still, even today, no strategy to introduce primary and community healthcare into a comprehensive plan to mitigate the pandemic has been announced. Instead, there are reports that a strategy of consecutive horizontal lockdowns, with short periods of partial easing of restrictions in-between, is considered. This could potentially have catastrophic consequences, not only by failing to prevent as many COVID-19-related deaths as possible but also by causing long-lasting social, economic and health damage to the population.

5. Recommendations for primary, community and home care reinforcement

Considering the need to i) implement social distancing measures but also avoid strict horizontal lockdowns due to unintended consequences, ii) reinforce hospital resources and protect them from patient overload, and iii) create a robust find-test-trace-isolate-support system [89], we propose the following measures to strengthen the participation of primary, community and home care in pandemic mitigation, which can be implemented in Greece and elsewhere.

1 Activation, expansion and support of primary health care, both of the public sector (health centers, rural and regional medical units in Greece) and of the private sector (private-practice physicians and family physicians contracted with EOPYY in Greece).
2 Creation of additional community care teams in every municipality, consisting of community care nurses, health visitors, social workers, domestic support staff and psychologists, who will work in collaboration with family physicians. These teams will provide support for COVID-19 patients who are in quarantine and for non-infected, especially the elderly, high-risk and socially deprived, individuals who are confined at home in order to avoid exposure to SARS-CoV-2 or are adversely affected by the implemented restrictions.
3 Development of a health network engaged in phone and online (using eHealth technologies) support for patients with COVID-19, with provisions for home visits by healthcare professionals, if needed. Such networks should ideally be developed locally in each municipality or prefecture, while additional similar networks may be created for the management of non-infected but high-risk patients who need aggressive primary prevention interventions to protect them from viral exposure and to manage comorbidities.
4 Disengagement of hospitals from the responsibilities of sample collection, diagnostic testing, treatment and isolation of people infected with SARS-CoV-2 who are ambulatory and do not need hospitalized care.
5 Cooperation between the national public health organizations (EODY for Greece) and regional medical associations to adopt protocols for the treatment and follow-up of ambulatory COVID-19 patients. This will protect hospitals from avoidable and unnecessary admissions.
6 Legislation for full compensation of the cost for SARS-CoV-2 diagnostic testing (rapid antigen and PCR tests) by social insurance or by the government (EOPYY for Greece) even if prescribed by private-practice physicians and performed in private laboratories. This will massively increase testing capacity, will ensure timely availability and accessibility to diagnostic tests for every person with an indication to be tested and will relieve hospitals from the responsibility to perform diagnostic tests.
7 Compensation of private-practice physicians for monitoring and treating patients with COVID-19, including home and distant (phone or online) care. This will increase healthcare professional resources by recruiting a large number of physicians who do not currently participate in pandemic mitigation in countries such as Greece.
8 Creation of a network of laboratories and contact tracing teams at regional or prefectural level. This will increase the speed of identification, diagnosis, contact tracing and isolation of infected people.
9 Implementation of frequent and repeated testing for the nursing home population and staff using rapid antigen tests or PCR tests. These are usually crowded facilities which favor viral transmission and exposure to high viral load, while people who live in these facilities are at high risk for severe COVID-19. Similar interventions should be organized for other facilities caring for high-risk individuals.
10 Provision for accommodation facilities for COVID-19 patients who need to be quarantined but do not have a place to isolate (e.g., homeless people, COVID-19 patients in nursing homes who need to be transferred in order to prevent transmission to others, refugees, COVID-19 patients who request accommodation because there have vulnerable family members who cannot be protected from viral exposure). Authorities could lease hotels or other buildings, and provide essential primary care support for these ambulatory patients.
11 Development of a plan for repeated, random or population-representative testing in each prefecture, using rapid antigen and antibody tests. It is essential to systematically monitor the epidemiological burden and population immunity so that timely and targeted interventions can be made at a local level.
12 Preparation of a comprehensive plan for the gradual lifting of the strict, horizontal lockdown as early as possible, which will include more selective social distancing measures focused on protecting vulnerable population subgroups, and additional restrictions implemented on a local level depending on the continuously-monitored epidemiological profile.

The above measures should be combined with other interventions such as social distancing measures in schools and public transport to prevent cluster infections [90]. Public education programs are also needed, which should provide information about COVID-19 related issues such as protective measures, but also emphasize on lifestyle and dietary modifications which could contribute to immune system health [91]. We cannot emphasize enough the need for schools, particularly primary schools, to remain open, since children have a very low risk for severe COVID-19 while, on the contrary, school closure can cause serious harms. Finally, it is important that all available epidemiological evidence should be accessible to the scientific community in full

transparency so that extensive analysis and a critical assessment of current and future decisions can be made. These principles and measures can be followed in many countries, adjusted according to local needs and unique characteristics of their healthcare system.

6. Conclusion

In anticipation of safe and effective vaccines, and given the uncertainty of both the magnitude and duration of their effectiveness as well as the expected delays in vaccinating large parts of the population, we need to become more creative, practical and effective. By carefully studying the unique epidemiological and clinical characteristic of the virus and the resulting pandemic, and by learning from past mistakes and from the experience of other countries, we can develop more effective strategies that will result in sustained suppression of community transmission. Strict, horizontal lockdowns cannot be used as the core of a long-term strategy for pandemic mitigation because of important adverse social, economic and health effects that have yet to be fully elucidated. A holistic approach is required, by recognizing the irreplaceable role of primary, community and home care, which should be at the forefront in managing the COVID-19 pandemic and the associated adverse effects for the population.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] L. Craxì, M. Vergano, J. Savulescu, D. Wilkinson, Rationing in a pandemic: lessons from Italy, Asian Bioeth Rev. 16 (June) (2020) 1–6, https://doi.org/10.1007/s41649-020-00127-1.
[2] Vergano M., Bertolini G., Giannini A., Gristina G., Livigni S., Mistraletti G., Riccioni L., Petrini F. SIAARTI Clinical Ethics Recommendations for the Allocation of Intensive Care Treatments in exceptional, resource-limited circumstances. Available at: https://bit.ly/2UyQ6I3. Accessed 12 November 2020.
[3] D. Petrakis, D. Marginã, K. Tsarouhas, F. Tekos, M. Stan, D. Nikitovic, D. Kouretas, D.A. Spandidos, A. Tsatsakis, Obesity - a risk factor for increased COVID-19 prevalence, severity and lethality (Review), Mol. Med. Rep. 22 (July(1)) (2020) 9–19, https://doi.org/10.3892/mmr.2020.11127.
[4] R.N. Kostoff, M.B. Briggs, A.L. Porter, M. Aschner, D.A. Spandidos, A. Tsatsakis, [Editorial] COVID-19: post-lockdown guidelines, Int. J. Mol. Med. 46 (August(2)) (2020) 463–466, https://doi.org/10.3892/ijmm.2020.4640.
[5] World Health Organization (WHO). Coronavirus disease (COVID-19): Herd immunity, lockdowns and COVID-19. Available at: https://www.who.int/news-room/q-a-detail/herd-immunity-lockdowns-and-covid-19. Accessed 12 November 2020.
[6] A. Tsatsakis, D. Petrakis, T.K. Nikolouzakis, A.O. Docea, D. Calina, M. Vinceti, M. Goumenou, R.N. Kostoff, C. Mamoulakis, M. Aschner, A.F. Hernández, COVID-19, an opportunity to reevaluate the correlation between long-term effects of anthropogenic pollutants on viral epidemic/pandemic events and prevalence, Food Chem. Toxicol. 141 (July) (2020), 111418, https://doi.org/10.1016/j.fct.2020.111418.
[7] R.N. Kostoff, M.B. Briggs, A.L. Porter, A.F. Hernández, M. Abdollahi, M. Aschner, A. Tsatsakis, The under-reported role of toxic substance exposures in the COVID-19 pandemic, Food Chem. Toxicol. 145 (November) (2020), 111687, https://doi.org/10.1016/j.fct.2020.111687.
[8] J.P.A. Ioannidis, S. Cripps, M.A. Tanner, Forecasting for COVID-19 has failed, Int. J. Forecast. (August) (2020) 25, https://doi.org/10.1016/j.ijforecast.2020.08.004.
[9] K. Rice, B. Wynne, V. Martin, G.J. Ackland, Effect of school closures on mortality from coronavirus disease 2019: old and new predictions, BMJ 7 (October) (2020) 371, https://doi.org/10.1136/bmj.m3588, m3588.
[10] S. De Rosa, C. Spaccarotella, C. Basso, M.P. Calabrò, A. Curcio, P.P. Filardi, M. Mancone, G. Mercuro, S. Muscoli, S. Nodari, R. Pedrinelli, G. Sinagra, Indolfi C; Società Italiana di Cardiologia and the CCU Academy investigators group. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era, Eur. Heart J. 41 (June (22)) (2020) 2083–2088, https://doi.org/10.1093/eurheartj/ehaa409.
[11] O. De Filippo, F. D'Ascenzo, F. Angelini, et al., Reduced rate of hospital admissions for ACS during covid-19 outbreak in northern Italy, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMc2009166 pmid:32343497.
[12] B. Metzler, P. Siostrzonek, R.K. Binder, A. Bauer, S.J. Reinstadler, Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage, Eur. Heart J. 41 (2020) 1852–1853, https://doi.org/10.1093/eurheartj/ehaa314, pmid:32297932.
[13] B. Ibáñez, Myocardial infarction in times of COVID-19, Rev Esp. Cardiol. (Engl Ed) (October) (2020) 30, https://doi.org/10.1016/j.rec.2020.09.023. S1885-5857(20)30461-30468.
[14] G. De Luca, M. Verdoia, M. Cercek, L.O. Jensen, M. Vavlukis, L. Calmac, et al., Impact of COVID-19 pandemic on mechanical reperfusion for patients with STEMI, J. Am. Coll. Cardiol. 76 (November (20)) (2020) 2321–2330, https://doi.org/10.1016/j.jacc.2020.09.546.
[15] J. Wu, M.A. Mamas, M.O. Mohamed, C.S. Kwok, C. Roebuck, B. Humberstone, T. Denwood, T. Luescher, M.A. de Belder, J.E. Deanfield, C.P. Gale, Place and causes of acute cardiovascular mortality during the COVID-19 pandemic, Heart (September) (2020) 28, https://doi.org/10.1136/heartjnl-2020-317912, heartjnl-2020-317912.
[16] A. Bilinski, E.J. Emanuel, COVID-19 and excess all-cause mortality in the US and 18 comparison countries, JAMA 12 (October) (2020), e2020717, https://doi.org/10.1001/jama.2020.20717.
[17] K. Docherty, J. Butt, R. de Boer, P. Dewan, L. Koeber, A. Maggioni, J. McMurray, S. Solomon, P.S. Jhund, Excess deaths during the Covid-19 pandemic: an international comparison, medRxiv (2020), https://doi.org/10.1101/2020.04.21.20073114, 04.21.20073114.
[18] Breast Cancer Now, Almost One Million Women in UK Miss Vital Breast Screening Due to COVID-19, 2020. September 30. Available at: https://breastcancernow.org/about-us/media/press-releases/almost-one-million-women-in-uk-miss-vital-breast-screening-due-covid-19. Accessed on 06 November 2020.
[19] L. Hawryluck, W.L. Gold, S. Robinson, S. Pogorski, S. Galea, R. Styra, SARS control and psychological effects of quarantine, Toronto, Canada, Emerg Infect Dis. 10 (July(7)) (2004) 1206–1212, https://doi.org/10.3201/eid1007.030703.
[20] E.R. Walker, R.E. McGee, B.G. Druss, Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis, JAMA Psychiatry 72 (April(4)) (2015) 334–341, https://doi.org/10.1001/jamapsychiatry.2014.2502. Erratum in: JAMA Psychiatry. 2015 Jul;72(7):736. Erratum in: JAMA Psychiatry. 2015 Dec;72(12):1259.
[21] D.A. Moser, J. Glaus, S. Frangou, D.S. Schechter, Years of life lost due to the psychosocial consequences of COVID-19 mitigation strategies based on Swiss data, Eur. Psychiatry 63 (May (1)) (2020) e58, https://doi.org/10.1192/j.eurpsy.2020.56.

[22] K. Magklara, H. Lazaratou, B. Barbouni, K. Poulas, K. Farsalinos, Coronavirus Greece Research Group. Impact of COVID-19 pandemic and lockdown measures on mental health of children and adolescents in Greece, medRxiv (2020), https://doi.org/10.1101/2020.10.18.20214643, 10.18.20214643.
[23] S. Singh, D. Roy, K. Sinha, S. Parveen, G. Sharma, G. Joshi, Impact of COVID-19 and lockdown on mental health of children and adolescents: a narrative review with recommendations, Psychiatry Res. 24 (August) (2020) 293, https://doi.org/10.1016/j.psychres.2020.113429, 113429.
[24] J. Marsden, S. Darke, W. Hall, M. Hickman, J. Holmes, K. Humphreys, J. Neale, J. Tucker, R. West, Mitigating and learning from the impact of COVID-19 infection on addictive disorders, Addiction 115 (June(6)) (2020) 1007–1010, https://doi.org/10.1111/add.15080.
[25] F. Pascual Pastor, M. Isorna Folgar, N. Carvalho, F. Carvalho, F. Arias Horcajadas, Therapeutic Cannabis and COVID-19: between opportunism and infoxication, Adicciones 32 (July (3)) (2020) 167–172, https://doi.org/10.20882/adicciones.1603. English, Spanish.
[26] M. Nicola, Z. Alsafi, C. Sohrabi, A. Kerwan, A. Al-Jabir, C. Iosifidis, M. Agha, R. Agha, The socio-economic implications of the coronavirus pandemic (COVID-19): a review, Int. J. Surg. 78 (June) (2020) 185–193, https://doi.org/10.1016/j.ijsu.2020.04.018.
[27] S. Sardar, I. Abdul-Khaliq, A. Ingar, H. Amaidia, N. Mansour, 'COVID-19 lockdown: a protective measure or exacerbator of health inequalities? A comparison between the United Kingdom and India.' a commentary on "the socio-economic implications of the coronavirus and COVID-19 pandemic: a review", Int. J. Surg. 29 (September 83) (2020) 189–191, https://doi.org/10.1016/j.ijsu.2020.09.044.
[28] A. Gagnon, M.S. Miller, S.A. Hallman, R. Bourbeau, D.A. Herring, D.J. Earn, J. Madrenas, Age-specific mortality during the 1918 influenza pandemic: unravelling the mystery of high young adult mortality, PLoS One 8 (August (8)) (2013), e69586, https://doi.org/10.1371/journal.pone.0069586.
[29] A.O. Docea, A. Tsatsakis, D. Albulescu, O. Cristea, O. Zlatian, M. Vinceti, S. A. Moschos, D. Tsoukalas, M. Goumenou, N. Drakoulis, J.M. Dumanov, V. A. Tutelyan, G.G. Onischenko, M. Aschner, D.A. Spandidos, D. Calina, A new threat from an old enemy: Re-emergence of coronavirus (Review), Int. J. Mol. Med. 45 (June(6)) (2020) 1631–1643, https://doi.org/10.3892/ijmm.2020.4555.
[30] A. Tsatsakis, D. Calina, L. Falzone, D. Petrakis, R. Mitrut, V. Siokas, M. Pennisi, G. Lanza, M. Libra, S.G. Doukas, P.G. Doukas, L. Kavali, A. Bukhari, C. Gadiparthi, D.P. Vageli, D.P. Kofteridis, D.A. Spandidos, M.M.B. Paoliello, M. Aschner, A. O. Docea, SARS-CoV-2 pathophysiology and its clinical implications: an integrative overview of the pharmacotherapeutic management of COVID-19, Food Chem. Toxicol. 146 (September) (2020) 111769, https://doi.org/10.1016/j.fct.2020.111769.
[31] G.T. Gerotziafas, T.N. Sergentanis, G. Voiriot, L. Lassel, C. Papageorgiou, A. Elabbadi, M. Turpin, P. Vandreden, L. Papageorgiou, T. Psaltopoulou, E. Terpos, M.A. Dimopoulos, A. Parrot, J. Cadranel, G. Pialoux, M. Fartoukh, I. Elalamy, Derivation and validation of a predictive score for disease worsening in patients with COVID-19, Thromb. Haemost. (September) (2020) 22, https://doi.org/10.1055/s-0040-1716544.
[32] B. Benjamin Wachtler, N. Michalski, E. Nowossadeck, M. Diercke, M. Wahrendorf, C. Santos-Hövener, T. Lampert, J. Hoebel, Socioeconomic inequalities in the risk of SARS-CoV-2 infection –First results from an analysis of surveillance data from Germany, J. Health Monit 5 (2020) 18–29, https://doi.org/10.25646/7057.
[33] E.G. Price-Haywood, J. Burton, D. Fort, L. Seoane, Hospitalization and mortality among black patients and white patients with Covid-19, N. Engl. J. Med. 382 (June (26)) (2020) 2534–2543, https://doi.org/10.1056/NEJMsa2011686.
[34] C.L. Niedzwiedz, C.A. O'Donnell, B.D. Jani, E. Demou, F.K. Ho, C. Celis-Morales, B. I. Nicholl, F.S. Mair, P. Welsh, N. Sattar, J.P. Pell, S.V. Katikireddi, Ethnic and socioeconomic differences in SARS-CoV-2 infection: prospective cohort study using UK Biobank, BMC Med. 18 (May (1)) (2020) 160, https://doi.org/10.1186/s12916-020-01640-8.
[35] Office for National Statistics, Deaths Involving COVID-19 by Local Area and Socioeconomic Deprivation: Deaths Occurring Between 1 March and 31 May 2020, Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsinvolvingcovid19bylocalareasanddeprivation/deathsoccurringbetween1marchand31may2020. Accessed on 06 November 2020, 2020.
[36] R. Horton, Offline: COVID-19 is not a pandemic, Lancet 396 (September (10255)) (2020) 874, https://doi.org/10.1016/S0140-6736(20)32000-6.
[37] R.M. Viner, C. Bonell, L. Drake, D. Jourdan, N. Davies, V. Baltag, J. Jerrim, J. Proimos, A. Darzi, Reopening schools during the COVID-19 pandemic: governments must balance the uncertainty and risks of reopening schools against the clear harms associated with prolonged closure, Arch. Dis. Child. (August) (2020) 3, https://doi.org/10.1136/archdischild-2020-319963, archdischild-2020-319963.
[38] D.J. Roelfs, E. Shor, K.W. Davidson, J.E. Schwartz, Losing life and livelihood: a systematic review and meta-analysis of unemployment and all-cause mortality, Soc. Sci. Med. 72 (March(6)) (2011) 840–854, https://doi.org/10.1016/j.socscimed.2011.01.005.
[39] I. Bavli, B. Sutton, S. Galea, Harms of public health interventions against covid-19 must not be ignored, BMJ 2 (November) (2020) 371, https://doi.org/10.1136/bmj.m4074, m4074.
[40] J. Wise, Covid-19: Experts divide into two camps of action-shielding versus blanket policies, BMJ 21 (September) (2020) 370, https://doi.org/10.1136/bmj.m3702, m3702.
[41] Ottavio Marzocchi. Policy Department for Citizens' Rights and Constitutional Affairs. European Parliament. The Impact of COVID-19 measures on democracy, the rule of law and fundamental rights in the EU. Policy Department for Citizens' Rights and Constitutional Affairs. European Parliament. Available at: https://www.europarl.europa.eu/RegData/etudes/BRIE/2020/651343/IPOL_BRI(2020)651343_EN.pdf. Accessed on 06 November 2020.
[42] Human Rights Watch. Human Rights Dimensions of COVID-19 Response. Available at: https://www.hrw.org/news/2020/03/19/human-rights-dimensions-covid-19-response. Accessed on 06 November 2020.
[43] R. Chaudhry, G. Dranitsaris, T. Mubashir, J. Bartoszko, S. Riazi, A country level analysis measuring the impact of government actions, country preparedness and socioeconomic factors on COVID-19 mortality and related health outcomes, EClinicalMedicine. 25 (August) (2020), 100464, https://doi.org/10.1016/j.eclinm.2020.100464.
[44] Hospital Preparedness for Epidemics, World Health Organization, 2014. Available at:Accessed on 06 November 2020, https://apps.who.int/iris/bitstream/handle/10665/151281/9789241548939_eng.pdf.
[45] F. D'Ambrosio, A.G. de Belvis, A. Morsella, G. Castellini, G. Graffigna, P. Laurenti, Life After COVID-19: rethinking the healthcare system and valuing the role of citizens' engagement in health prevention, Front. Psychol. 11 (2020), 589249, https://doi.org/10.3389/fpsyg.2020.589249.
[46] E. Condes, J.R. Arribas, COVID19 MADRID-S.P.P.M. group. Impact of COVID-19 on Madrid hospital system, Enferm. Infecc. Microbiol. Clin. 25 (June) (2020), https://doi.org/10.1016/j.eimc.2020.06.005. S0213-005X(20)30236-6.
[47] M. Nacoti, A. Ciocca, A. Giupponi, P. Brambillasca, F. Lussana, M. Pisano, G. Goisis, D. Bonacina, F. Fazzi, R. Naspro, L. Longhi, M. Cereda, C. Montaguti, At the epicenter of the Covid-19 pandemic and humanitarian crises in Italy: changing perspectives on preparation and mitigation, NEJM Catal (2020), https://doi.org/10.1056/CAT.20.0080.
[48] A. Remuzzi, G. Remuzzi, COVID-19 and Italy: what next? Lancet 395 (April (10231)) (2020) 1225–1228, https://doi.org/10.1016/S0140-6736(20)30627-9.
[49] S. Nava, R. Tonelli, E.M. Clini, An Italian sacrifice to the COVID-19 epidemic, Eur. Respir. J. 55 (June (6)) (2020) 2001445, https://doi.org/10.1183/13993003.01445-2020.
[50] L.H. Nguyen, D.A. Drew, M.S. Graham, A.D. Joshi, C.G. Guo, W. Ma, R.S. Mehta, E. T. Warner, D.R. Sikavi, C.H. Lo, S. Kwon, M. Song, L.A. Mucci, M.J. Stampfer, W. C. Willett, A.H. Eliassen, J.E. Hart, J.E. Chavarro, J.W. Rich-Edwards, R. Davies, J. Capdevila, K.A. Lee, M.N. Lochlainn, T. Varsavsky, C.H. Sudre, M.J. Cardoso, J. Wolf, T.D. Spector, S. Ourselin, C.J. Steves, A.T. Chan, COronavirus pandemic epidemiology consortium. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study, Lancet Public Health 5 (September(9)) (2020) e475–e483, https://doi.org/10.1016/S2468-2667(20)30164-X.
[51] World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 3 March 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—3-march-2020. Accessed on 06 November 2020.
[52] H. Nishiura, T. Kobayashi, T. Miyama, A. Suzuki, S.M. Jung, K. Hayashi, R. Kinoshita, Y. Yang, B. Yuan, A.R. Akhmetzhanov, N.M. Linton, Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19), Int. J. Infect. Dis. 94 (May) (2020) 154–155, https://doi.org/10.1016/j.ijid.2020.03.020.
[53] H. Lau, T. Khosrawipour, P. Kocbach, H. Ichii, J. Bania, V. Khosrawipour, Evaluating the massive underreporting and undertesting of COVID-19 cases in multiple global epicenters, Pulmonology (June) (2020) 6, https://doi.org/10.1016/j.pulmoe.2020.05.015. S2531-0437(20)30129-X.
[54] S. Anand, M. Montez-Rath, J. Han, J. Bozeman, R. Kerschmann, P. Beyer, J. Parsonnet, G.M. Chertow, Prevalence of SARS-CoV-2 antibodies in a large nationwide sample of patients on dialysis in the USA: a cross-sectional study, Lancet. 396 (September (10259)) (2020) 1335–1344, https://doi.org/10.1016/S0140-6736(20)32009-2.
[55] G. Molenberghs, C. Faes, J. Aerts, H. Theeten, B. Devleesschauwer, N.B. Sierra, T. Braeye, F. Renard, S. Herzog, P. Lusyne, J. Van der Heyden, H. Van Oyen, P. Van Damme, Hens N. Belgian Covid-19 mortality, excess deaths, number of deaths per million, and infection fatality rates (8 March - 9 may 2020), medRxiv (2020), https://doi.org/10.1101/2020.06.20.20136234, 06.20.20136234.
[56] COVID-19 Pandemic Planning Scenarios, Centers for Disease Control and Prevention, 2020. September 10. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html. Accessed on 06 November 2020.
[57] J.P.A. Ioannidis, Infection Fatality Rate of COVID-19 Inferred from Seroprevalence Data. Bulletin of the World Health Organization, 2020. BLT.20.265892. Available at: https://www.who.int/bulletin/online_first/BLT.20.265892.pdf. Accessed on 06 November 2020.
[58] E.J. Williamson, A.J. Walker, K. Bhaskaran, S. Bacon, C. Bates, C.E. Morton, H. J. Curtis, A. Mehrkar, D. Evans, P. Inglesby, J. Cockburn, H.I. McDonald, B. MacKenna, L. Tomlinson, I.J. Douglas, C.T. Rentsch, R. Mathur, A.Y.S. Wong, R. Grieve, D. Harrison, H. Forbes, A. Schultze, R. Croker, J. Parry, F. Hester, S. Harper, R. Perera, S.J.W. Evans, L. Smeeth, B. Goldacre, Factors associated with COVID-19-related death using OpenSAFELY, Nature 584 (August(7821)) (2020) 430–436, https://doi.org/10.1038/s41586-020-2521-4.
[59] T.V. Giannouchos, R.A. Sussman, J.M. Mier, K. Poulas, K. Farsalinos, Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an analysis of 89,756 laboratory-confirmed COVID-19 cases, Eur. Respir. J. 30 (July) (2020), 2002144, https://doi.org/10.1183/13993003.02144-2020.
[60] A.V. Skalny, L. Rink, O.P. Ajsuvakova, M. Aschner, V.A. Gritsenko, S.I. Alekseenko, A.A. Svistunov, D. Petrakis, D.A. Spandidos, J. Aaseth, A. Tsatsakis, A.A. Tinkov, Zinc and respiratory tract infections: perspectives for COVID-19 (Review), Int. J. Mol. Med. 46 (July(1)) (2020) 17–26, https://doi.org/10.3892/ijmm.2020.4575.

[61] C. Sarkar, M. Mondal, M. Torequl Islam, M. Martorell, A.O. Docea, A. Maroyi, J. Sharifi-Rad, D. Calina, Potential therapeutic options for COVID-19: current status, challenges, and future perspectives, Front. Pharmacol. 15 (September) (2020) 572870, https://doi.org/10.3389/fphar.2020.572870, 11.
[62] M. Torequl Islam, M. Nasiruddin, I.N. Khan, S.K. Mishra, M. Kudrat-E-Zahan, T. Alam Riaz, E.S. Ali, M.S. Rahman, M.S. Mubarak, M. Martorell, W.C. Cho, D. Calina, A.O. Docea, J. Sharifi-Rad, A perspective on emerging therapeutic interventions for COVID-19, Front. Public Health 3 (July) (2020) 8, https://doi.org/10.3389/fpubh.2020.00281, 281.
[63] G.M. Nitulescu, H. Paunescu, S.A. Moschos, D. Petrakis, G.M. Nitulescu, G.N.D. Ion, D.A. Spandidos, T.K. Nikolouzakis, N. Drakoulis, A. Tsatsakis, Comprehensive analysis of drugs to treat SARS-CoV-2 infection: mechanistic insights into current COVID-19 therapies (Review), Int. J. Mol. Med. 46 (August(2)) (2020) 467–488, https://doi.org/10.3892/ijmm.2020.4608.
[64] M.L. Parchman, S.K. Burge, The patient-physician relationship, primary care attributes, and preventive services, Fam. Med. 36 (January(1)) (2004) 22–27.
[65] Lj Weiss, J. Blustein, Faithful patients: the effect of long-term physician-patient relationships on the costs and use of health care by older Americans, Am. J. Public Health 86 (December(12)) (1996) 1742–1747, https://doi.org/10.2105/ajph.86.12.1742.
[66] J. Kearon, C. Risdon, The role of primary care in a pandemic: reflections during the COVID-19 pandemic in Canada, J. Prim. Care Community Health 11 (Jan-Dec) (2020), https://doi.org/10.1177/2150132720962871, 2150132720962871.
[67] T.C. Voo, B. Capps, Influenza pandemic and the duties of healthcare professionals, Singapore Med. J. 51 (April(4)) (2010) 275–281.
[68] A. Lee, A.A. Chuh, Facing the threat of influenza pandemic - roles of and implications to general practitioners, BMC Public Health 2 (November) (2010) 10, https://doi.org/10.1186/1471-2458-10-661, 661.
[69] G.T. Gerotziafas, M. Catalano, M.P. Colgan, Z. Pecsvarady, J.C. Wautrecht, B. Fazeli, D.M. Olinic, K. Farkas, I. Elalamy, A. Falanga, J. Fareed, C. Papageorgiou, R.S. Arellano, P. Agathagelou, D. Antic, L. Auad, L. Banfic, J.R. Bartolomew, B. Benczur, M.B. Bernardo, F. Boccardo, R. Cifkova, B. Cosmi, S. De Marchi, E. Dimakakos, M.A. Dimopoulos, G. Dimitrov, I. Durand-Zaleski, M. Edmonds, E. A. El Nazar, D. Erer, O.L. Esponda, P. Gresele, M. Gschwandtner, Y. Gu, M. Heinzmann, N.M. Hamburg, A. Hamadé, N.A. Jatoi, O. Karahan, D. Karetova, T. Karplus, P. Klein-Weigel, E. Kolossvary, M. Kozak, E. Lefkou, G. Lessiani, A. Liew, A. Marcoccia, P. Marshang, G. Marakomichelakis, J. Matuska, L. Moraglia, S. Pillon, P. Poredos, M. Prior, D.R.K. Salvador, O. Schlager, G. Schernthaner, A. Sieron, J. Spaak, A. Spyropoulos, M. Sprynger, D. Suput, A. Stanek, V. Stvrtinova, A. Szuba, A. Tafur, P. Vandreden, P.E. Vardas, D. Vasic, M. Vikkula, P. Wennberg, Z. Zhai, Scientific reviewer committee. Guidance for the management of patients with vascular disease or cardiovascular risk factors and COVID-19: position paper from VAS-European independent foundation in Angiology/Vascular medicine, Thromb. Haemost. (September) (2020) 13, https://doi.org/10.1055/s-0040-1715798.
[70] T. Greenhalgh, M. Knight, C. A'Court, M. Buxton, L. Husain, Management of post-acute covid-19 in primary care, BMJ 11 (August) (2020) 370, https://doi.org/10.1136/bmj.m3026, m3026.
[71] M. Taquet, S. Luciano, J.R. Geddes, P.J. Harrison, Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA, Lancet Psychiatry (November) (2020) 9, https://doi.org/10.1016/S2215-0366(20)30462-4. S2215-0366(20)30462-30464.
[72] G. McDonald, L.L. Clark, Mental health impact of admission to the intensive care unit for COVID-19, Br. J. Community Nurs. 25 (November (11)) (2020) 526–530, https://doi.org/10.12968/bjcn.2020.25.11.526.
[73] A. Huntley, D. Lasserson, L. Wye, R. Morris, K. Checkland, H. England, C. Salisbury, S. Purdy, Which features of primary care affect unscheduled secondary care use? A systematic review, BMJ Open 4 (May (5)) (2014) e004746, https://doi.org/10.1136/bmjopen-2013-004746.
[74] S. Purdy, T. Griffin, C. Salisbury, D. Sharp, Ambulatory care sensitive conditions: terminology and disease coding need to be more specific to aid policy makers and clinicians, Public Health 123 (February(2)) (2009) 169–173, https://doi.org/10.1016/j.puhe.2008.11.001.
[75] A.B. Bindman, K. Grumbach, D. Osmond, M. Komaromy, K. Vranizan, N. Lurie, J. Billings, A. Stewart, Preventable hospitalizations and access to health care, JAMA 274 (July (4)) (1995) 305–311.
[76] J. Caminal, B. Starfield, E. Sánchez, C. Casanova, M. Morales, The role of primary care in preventing ambulatory care sensitive conditions, Eur. J. Public Health 14 (September(3)) (2004) 246–251, https://doi.org/10.1093/eurpub/14.3.246.
[77] C. Sanderson, J. Dixon, Conditions for which onset or hospital admission is potentially preventable by timely and effective ambulatory care, J. Health Serv. Res. Policy 5 (October(4)) (2000) 222–230, https://doi.org/10.1177/135581960000500407.
[78] C. Stavropoulou, V.J. Palmer, A. Burls, E. Ansuategi, N. Del Mar Ubeda Carrillo, S. Purdy, What Conditions Could We Prioritise in the Primary Care Setting to Reduce non-COVID-related Admissions to Hospital? The Centre for Evidence-based Medicine, 2020. https://www.cebm.net/covid-19/what-conditions-could-we-prioritise-in-the-primary-care-setting-to-reduce-non-covid-related-admissions-to-hospital/.
[79] National Contact Point. The Greek Health System. Available at: https://eu-healthcare.eopyy.gov.gr/en/2_1.aspx. Accessed on 06 November 2020.
[80] E. Simou, E. Koutsogeorgou, Effects of the economic crisis on health and healthcare in Greece in the literature from 2009 to 2013: a systematic review, Health Policy. 115 (April(2-3)) (2014) 111–119, https://doi.org/10.1016/j.healthpol.2014.02.002.
[81] M. Mpouzika, E. Mpouzika, E. Papathanassoglou, The effect of the Greek financial crisis on the operation of public intensive care units, Connect World Crit. Care Nurs. 12 (2) (2017) 48–51, https://doi.org/10.1891/1748-6254.12.2.48.
[82] Wikipedia. COVID-19 pandemic in Greece. Available at: https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Greece. Accessed on 8 November 2020.
[83] Coronavirus: detailed list of health Centers and rural medical units. The 24-hour duty centers. Available at: https://www.skai.gr/news/ygeia/koronoios-analytika-i-lista-me-ta-kentra-ygeias-kai-ta-perifereiaka-iatreia-ta-24ora. Accessed on 06 November 2020 (in Greek).
[84] Coronavirus. Health Centers where you can be tested for COVID-19 at no cost. Available at: https://ygeiamou.gr/%CE%B5%CE%B9%CE%B4%CE%AE%CF%83%CE%B5%CE%B9%CF%82/%CF%80%CE%BF%CE%BB%CE%B9%CF%84%CE%B9%CE%BA%CE%AE-%CF%85%CE%B3%CE%B5%CE%AF%CE%B1%CF%82/137190/koronoios-se-pia-kentra-igias-borite-na-kanete-dorean-test-covid-19/. Accessed on 06 November 2020 (in Greek).
[85] Diavgeia. Transfer of medical personnel from Health Centers of Nigrita and Strymoniko to Serres General Hospital for November 2020. Available at: https://diavgeia.gov.gr/doc/%CE%A8%CE%9B%CE%9F%CE%9F%CE%9F%CE%A11%CE%9F-%CE%967%CE%9B?inline=true. Accessed on 06 November 2020.
[86] Coronavirus – Attica: Half of hospitalized patients with coronavirus infection in the three major hospitals are foreigners. Available at: https://www.iatropedia.gr/eidiseis/koronoios-attiki-allodapoi-oi-misoi-nosilevomenoi-me-koronoio-sta-tria-megalytera-nosokomeia-anaforas/134608/. Accessed on 06 November 2020.
[87] Z. Bogogiannidou, A. Vontas, K. Dadouli, M.A. Kyritsi, S. Soteriades, D.J. Nikoulis, V.A. Mouchtouri, M. Koureas, E.I. Kazakos, E.G. Spanos, G. Gioula, E.E. Ntzani, A. A. Eleftheriou, A. Vatopoulos, E. Petinaki, V. Papaevangelou, M. Speletas, S. Tsiodras, C. Hadjichristodoulou, Repeated leftover serosurvey of SARS-CoV-2 IgG antibodies, Greece, March and April 2020, Euro Surveill. 25 (August(31)) (2020), 2001369, https://doi.org/10.2807/1560-7917.ES.2020.25.31.2001369.
[88] O.E. Tsitsilonis, D. Paraskevis, E. Lianidou, V. Pierros, A. Akalestos, E. Kastritis, P. Moutsatsou, A. Scorilas, T. Sphicopoulos, E. Terpos, N. Thomaidis, A. Tsakris, N. Voulgaris, C.C. Daskalaki, Z. Evangelakou, C. Fouki, D.D. Gianniou, S. Gumeni, E.G. Kostaki, I.V. Kostopoulos, M.S. Manola, N. Orologas-Stavrou, C. Panteli, E. D. Papanagnou, P. Rousakis, A.D. Sklirou, S. Smilkou, D. Stergiopoulou, I. P. Trougakos, S. Tsiodras, P.P. Sfikakis, M.A. Dimopoulos, Seroprevalence of antibodies against SARS-CoV-2 among the personnel and students of the national and Kapodistrian university of Athens, Greece: a preliminary report, Life (Basel). 10 (September (9)) (2020) 214, https://doi.org/10.3390/life10090214.
[89] S. Rajan, J. D Cylus, M. Mckee, What do countries need to do to implement effective' find, test, trace, isolate and support' systems? J. R. Soc. Med. 113 (July (7)) (2020) 245–250, https://doi.org/10.1177/0141076820939395.
[90] T. Liu, D. Gong, J. Xiao, J. Hu, G. He, Z. Rong, W. Ma, Cluster infections play important roles in the rapid evolution of COVID-19 transmission: a systematic review, Int. J. Infect. Dis. 99 (October) (2020) 374–380, https://doi.org/10.1016/j.ijid.2020.07.073.
[91] F. Tekos, Z. Skaperda, N. Goutzourelas, D.S. Phelps, J. Floros, D. Kouretas, The importance of redox status in the frame of lifestyle approaches and the genetics of the lung innate immune molecules, SP-A1 and SP-A2, on differential outcomes of COVID-19 infection, Antioxidants (Basel). 9 (August (9)) (2020) 784, https://doi.org/10.3390/antiox9090784.