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Review

The Experience of Greece as a Model to Contain COVID-19 Infection Spread

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Abstract. *The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) emerged in late 2019 and has caused a pandemic known as corona virus disease 2019 (COVID-19), responsible for the death of more than 2 million people worldwide. The outbreak of COVID-19 has posed an unprecedented threat on human lives and public safety. The aim of this review is to describe key aspects of the bio-pathology of the novel disease, and discuss aspects of its spread, as well as targeted protective strategies that can help shape the outcome of the present and future health crises. Greece is used as a model to inhibit SARS-COV-2 spread, since it is one of the countries with the lowest fatality rates among nations of the European Union (E.U.), following two consecutive waves of COVID-19 pandemic. Furthermore, niche research technological approaches and scientific recommendations that emerged during the COVID-19 era are discussed.*

Since its initial zoonotic spillover event in China (November 2019), severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has been affecting humans on a global scale. Health care systems worldwide have been challenged at an unprecedented scale, leading governments to the adoption of draconian social isolation measures (such as lockdowns). Despite these efforts, global spread of the virus remains uncontrollable. The present review portrays key aspects of the corona virus disease 2019 (COVID-19) bio-pathophysiology and summarizes important pandemic management lessons learned through the lens of the Greek case.

Origin of SARS-CoV-2

There are seven human coronaviruses (HCoVs) genera currently identified and clustered as alphacoronaviruses and betacoronaviruses. Out of the seven genera, four strains are circulating in the human population and in animals are known to cause 10-15% of cases of the common cold (alphacoronaviruses - HCoV-NL63, HCoV-229E, HCoVOC-43 and HCoV-HKU1). Three zoonotic betacoronaviruses have emerged in the human population due to species jumping or zoonotic transfer; SARS-CoV, MERS-COV and SARS-CoV-2, all of which have common ancestors in bat viruses (1). SARS-COV and MERS-COV probably originated from bats but entered the human population through one or more intermediate animal hosts. Regarding SARS-CoV the intermediate host was civets (*Paguma larvata*) and for MERS-COV-1 the intermediate host was the dromedary camels (*Camelus dromedarius*). In these intermediate hosts the virus underwent rounds of RNA replication leading to mutations that allowed the virus to efficiently transmitted to the human population. Regarding SARS-CoV-2, the intermediate host (if there is one) between bats and humans remains unknown and controversial.

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Pathobiology/Pathophysiology

Our knowledge on how HCoVs affect humans is relatively new, and most data became available after the outbreak of SARS-CoV in China in 2002 (2, 3). HCoVs are pleomorphic single-stranded, positive-sense RNA viruses with a helical nucleocapsid and a lipid envelope derived from the host cell (4). In humans, these viruses cause primarily respiratory tract infections of variable severity.

Coronaviruses have the largest genomes among RNA viruses with approximately 30 Kb coding 20 proteins (5). At the molecular level, coronaviruses infect host cells by attaching to their surface and binding to membrane receptors, through the spike (S) proteins of the viral cone. In particular, SARS-CoV-2 entry in the cell is driven by interactions between the viral S protein and human angiotensin-converting enzyme 2 (ACE2), a cellular membrane receptor. A transmembrane serine protease (TMPRSS4) has been identified to be highly interactive with ACE2. TMPRSS4 facilitates viral entry into host cells by priming the S protein and augmenting its fusogenic activity (6). Binding of the virus to ACE2 causes a cascade of events, starting with deposition of the nucleocapsid into the cell cytoplasm, while the viral genome becomes subject to translation. Subsequently, the genome cap is methylated at two positions, N methylation of the first-base guanidine and C-O methylation of the following nucleotide (5). These methylations make the SARS-CoV-2 genome resemble the host mRNA and protect the viral genome from intracellular host defenses. Thereafter, the first translated protein, replicase, uses the viral genome to construct all structural and accessory proteins of the new virus, inside the endoplasmic reticulum and Golgi apparatus. Initially, the structural proteins M, S and E are formed, and then nucleocapsids are constructed with the assistance of the N protein, ultimately leading to the formation of virions. Viral proteins nop14 and ASP16 function as methyltransferases in conjunction with ASP10. Virions are finally exported from infected cells in Golgi sacs, a process that helps them evade human immune surveillance (7). The viral proteins are potential drug targets, especially the methyltransferases which may be inhibited by methionine restriction of the host (8).

At clinical level SARS-CoV-2 infection causes variable clinical syndromes ranging from asymptomatic or mild respiratory infection to severe acute respiratory disease and multi-organ injury. Among those with symptomatic disease, pneumonia appears to be one of the most prevalent and lethal manifestations; common symptoms include fever, tiredness, dry cough, dyspnea, headache, olfactory and gustatory dysfunction while bilateral ground glass lung opacities are often seen in computed tomography (CT) scans (9). Furthermore, upper-respiratory-tract symptoms and signs (such as rhinorrhea) are relatively uncommon (10). However, symptoms of viral infection may vary significantly among individuals, as there are cases where patients initially reported gastrointestinal symptoms (nausea, vomiting and diarrhea) prior to having fever and lower respiratory tract signs (11).

Pathogenicity of severe and critical COVID-19 disease has been linked with a great increase of pro-inflammatory cytokines, a phenomenon termed "cytokine storm". This can result in hyperactivation of the immune system and lead to pulmonary and multi-organ damage. Some COVID-19 patients have exhibited both leucopenia and lymphopenia (white cells $<4\times10^9/l$ and lymphocytes $<10^9/l$, respectively) with initial interleukin values (IL1B, IL1RA, IL7-10) as well as interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα) and vascular endothelial growth factor (VEGF) concentrations much higher than normal (12). SARS-CoV-2 infection causes systemic disease, involving multiple organs and systems (13). Cytokine storm leads to extensive vascular damage and eventual multi-organ organ failure. Several pathways have been described regarding this hyperinflammatory response; briefly, cytokine production is promoted *via* the NLRP3 inflammasome, a molecular platform shown to participate in disease pathophysiology as well as being a marker correlated to severity of disease (14, 15).

Activation of coagulation pathways through direct viral endothelial damage as well as due to overproduction of cytokines, results in a defective procoagulant-anticoagulant balance that is responsible for thrombosis, disseminated intravascular coagulation, and ultimately multi-organ failure (16).

Chest CT scan of COVID-19 patients demonstrate bilateral lobular areas of consolidation as well as bilateral ground glass opacities. The CT imaging findings of SARS-CoV-2-infected patients do not differ from those with other causes of viral pneumonia. However, there have been reports of symptomatic cases having negative CTs. This is because despite its high sensitivity (86.2%), CT has a very low specificity (18.1%). Therefore, the prognostic value of radiology is questioned in the case of COVID-19 as it may lead to false negatives (17, 18).

Currently, there are insufficient data on the disease's pathological aspects. In this respect, relevant studies involving post-mortem biopsies seem to provide useful insight on the systemic status of the disease. A study used core needle biopsies of the lung, heart and liver from patients who succumbed to COVID-19, to investigate the pathological aspects of affected organs that led to fatality. The patients were 51-89 years old with previous underlying health conditions. The organs mainly affected were the lungs, showing damage in alveolar epithelial cells, hyaline formation and hyperplasia, while damage in the liver and heart was limited, most likely linked to underlying conditions (19). Varga *et al.* identified viral inclusion structures in the kidney of a renal transplant patient by electron microscopy. A post-mortem histological examination of another patient revealed lymphocytic endotheliitis in the lung, heart, kidney and liver, as well as liver-cell necrosis. Endotheliitis was also observed in the small intestine of a patient; the authors emphasized the presence of diffuse endothelial inflammation caused by SARS-CoV-2, since the ACE2 receptor is present in epithelial cells of multiple organs. The widespread endothelial dysfunction leading to apoptotic death of these cells may be caused by either direct viral insult or as a result of hyper-activated immune response (20).

Transmission

There are numerous reports on how SARS-CoV-2 is transmitted, with contradictory findings. The general consensus is that viral transmission occurs mainly through droplet transmission during direct and close interaction with an infected individual, or *via* airborne transmission during aerosol-producing procedures or indirectly through contact with viral emissions from the individual, such as droplets remaining on surfaces, or through fomites on surfaces that the individual has touched (21-24). Several other reports have, in fact, revealed that the air is the main transmission route for CoV in indoor settings (25, 26). Indeed, a recent study revealed that aerosol and fomite transmission of SARS-CoV-2 occurs and the virus can remain active in aerosols for hours, and on surfaces for days after excretion from an infected individual (27). Important findings estimate a person to be most infectious when viral shedding is at its maximum; this happens on or before symptom onset. Accordingly, the use of facial mask is essential to prevent spread of the disease (28). Compulsory use of masks has therefore been implemented in most countries, following the Chinese model to control spreading events.

Another crucial aspect, related to COVID-19 epidemiology is the role of children in disease transmission. Importantly, very low rates of pediatric COVID-19 patients have been reported compared to adults. This population is potentially under-represented in this pandemic due to specific mechanisms existing in children that regulate the interaction between the respiratory and immune system, which could potentially lead to milder or even asymptomatic phenotypes. However, the low prioritization of children in COVID-19 testing due to the asymptomatic nature of the infection as well as the low risk for disease progression, may also contribute to an underestimated incidence of SARS-CoV-2 infection among the pediatric population (29, 30). A study showed that children are clearly susceptible to SARS-CoV-2 infection, and therefore they are able to transmit the virus. Another study investigating a large primary dataset of cases and close contacts with sufficient documentation of surveillance modes, showed that 7% of close contacts younger than age 10 became infected, a percentage that is roughly the same as in the overall population (31, 32). The exact role of children in the onwards transmission of the virus remains controversial (33, 34), and school policies greatly vary from country to country.

With regard to sex predilection for severe disease, remarkable differences have been observed in immune response between men and women, underlining the key role of immune regulatory genes encoded by the X chromosome in females leading to lower viral load levels, and less inflammation compared to men (35).

Since a superspreading event of SARS-CoV that occurred within a housing block in Hong Kong in 2003, the World Health Organization (WHO) published a report stating that the wastewater plumbing system can facilitate viral transmission (36). In this respect, the existence of adequate viral load in wastewater systems inside high-risk transmission settings, such as health care centers and hospitals, in combination with the ability of SARS-CoV-2 to be transmitted through droplet nuclei (airborne transmission), should be dealt with caution and taken into consideration in order to minimize disease spread (37).

Another important issue is whether the virus can pass between domestic animals and humans. It is important to understand if cats and dogs are susceptible to the virus since these animals are in close contact to humans. A research group showed that cats can be infected by SARS-CoV-2, but the animals did not show any symptoms of the disease; the mode of viral spread between animals remains unclear, but contaminated feaces and urine is a possible route of viral spread (38). Already, several cases have been associated with farmed minks, which can act as a reservoir of SARS-CoV-2, passing the virus between them, posing a risk for virus spill-over to humans (39). This highlights the need to further study the role of animals in disease transmission.

Finally, with regard to how environmental factors may affect the spread of COVID-19, a large study across four European countries, showed that both cold and dry environment are likely to facilitate viral transmission (40).

Epidemiological Aspects – The Greek Experience

"First Pandemic Wave": March-June 2020. Greece has a population of 11,184,000 with an average life expectancy of 79 and 84 years for males and females, respectively (41). The median age of Greek inhabitants is 44.9 years. Importantly, 21.3% of Greeks are over the age of 65 years old, thus Greece has the second oldest population among other European Union countries, right below Italy (22%). The high percentage of aged inhabitants inevitably sets Greece among the countries with the most susceptible population for severe COVID-19 disease and poor outcomes.

The first COVID-19 case was reported in Greece on February 26th, 2020. As of June 20th, 2020 (the estimated date of the first pandemic wave waning in Greece), Greece had

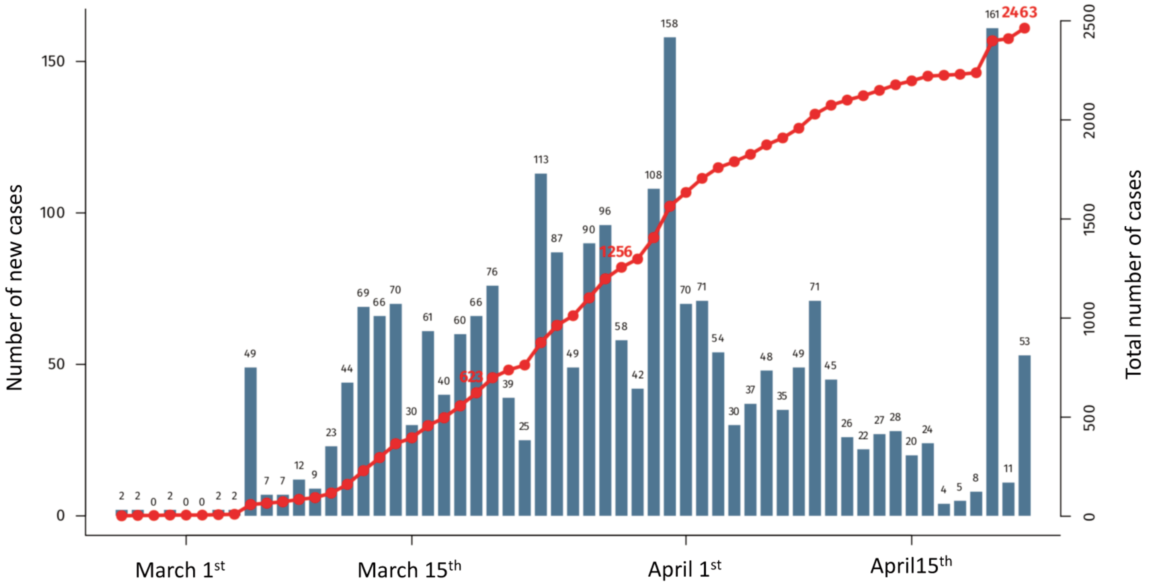

Figure 1. *Number of confirmed COVID-19 cases in Greece as of April 23rd 2020.*

Table I. *Age distribution of patients diagnosed with COVID-19 in Greece as of April 23rd, 2020.*

	Total COVID-19 cases (percent of total)	Number of deaths	Patients in intensive care units (ICU)
0-17 years	80 (3.6%)	0 (0%)	1 (1.9%)
18-39 years	694 (30.9%)	2 (1.6%)	0 (0%)
40-64 years	984 (43.8%)	30 (24%)	25 (48.1%)
>65 years	490 (21.8%)	93 (74.4%)	26 (50%)

3,256 confirmed cases of SARS-CoV-2 infection (Figure 1). This is a 29.11 rate of cases per 100,000 population compared to 878.4 in Sweden, a country with comparable population (42). Among a total of 278,895 tests performed for SARS-COV-19, in Greece, the positivity rate was 1.9% (43). Confirmed cases had a mean age of 49 years old (Table I), while 55.6% were males. A total of 580 cases were related to travelling abroad, and 1,560 cases were close contacts of confirmed cases; no known source of infection was found for the remaining ones.

At the end of first wave, there were 48 COVID-19 patients being treated in intensive care units (ICU) across the country (13 women and 35 men). Their mean age was 67 years and 88% had at least one underlying comorbidity factor and/or advanced age (>70 years old). Moreover, 190 deaths of patients with COVID-19 (38 women and 92 men) with a mean age of 74 years (Table I) were recorded at that time. About 90% of the fatal cases had previous serious health conditions and/or age >70 years (43).

Greece's most affected area was the prefecture of Attica including the capital city, Athens, where almost half of its population resides. The second most affected region was that of central Macedonia (Figure 2) including Greece's second largest city, Thessaloniki. Few clusters of infected individuals were scattered across Central Greece and the prefecture of Thessaly, in the north-eastern part of the Peloponnese and the region of Evros including the Greek-Turkish border. Interestingly, no cases of SARS-COV-2 infection have been recorded in the prefecture of Sterea Ellada, the entire region of Khalkidhiki, as well as the island of Chios, until the end of the first wave.

The Greek approach to contain the pandemic was shaped by the country's financial capacity and the national healthcare system's readiness; during the first wave, Greece was not capable of scaling-up COVID-19 testing to a massive population-based approach, like *e.g.* Germany (44) or to ensure a sufficient number of ventilators and intensive

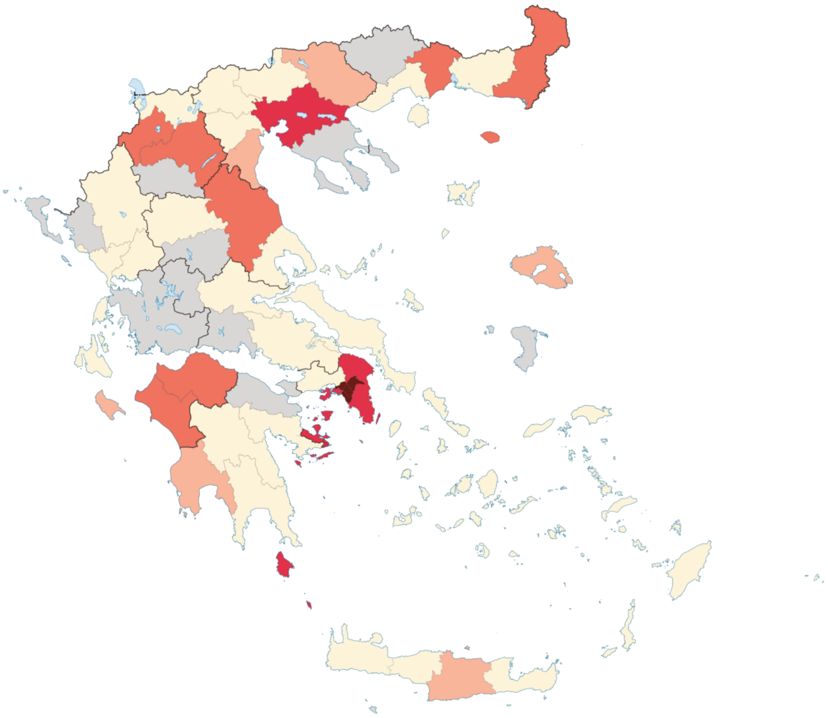

Figure 2. *Map of COVID-19 cases distributed in Greece as of April 15th 2020 per regional unit (prefecture). Light pink: 1-4 confirmed cases; pink: 5-9 confirmed cases; light red: 10-49 confirmed cases; red: 50-99 confirmed cases; light brown: 100-199 confirmed cases; brown: >200 confirmed cases.*

care infrastructure to care for all patients with COVID-19 requiring critical care (45). On this basis, COVID-19 pandemic would have been devastating in Greece, if effective public health and physical/social distancing measures were not implemented early enough.

Effective Adopted Protective Strategies During the "First Pandemic Wave" in Greece

In Europe, most governments dealt promptly with the COVID-19 pandemic, by imposing restrictions on social interactions and public transportation, but in some countries, such as Italy and Spain, restriction measures were delayed, resulting in catastrophic numbers of casualties.

In Greece, containment measures were implemented as early as the first case of COVID-19 was discovered. Control measures began with cancelation of public festivities and followed by the closure of schools and universities, on March 10th, 2020 and two days later, malls, cafeterias and restaurants were locked down. Finally, on March 23rd a nationwide travelling restriction was enforced. Of note, Greece declared a national lockdown when the number of active COVID-19 cases was as low as 695 patients across the country.

This strategy of acting swiftly and adopting containment policies before any casualties, along with the willingness of Greek communities to adopt and support the imposed measures, led to a highly successful result against the COVID-19 pandemic, at least during the first wave. Importantly, Greece had the third lowest case fatality rate (5%) amongst European countries with a comparable population, and the lowest actual number of deaths (Table II) during the first wave.

Following the end of the "first wave" (end of June 2020), several factors contributed to an increased number of cases and deaths in Greece were: (i) more than 5 million tourists visited Greece in the next 4 months; (ii) Greece has the second oldest population in the E.U., as discussed above; (iii) poorly-equipped hospitals – approximately only 1,000 ICU beds in hospitals across the country (10 beds per 100,000 people, although the number has now increased significantly); (iv) a health care sector ravaged by austerity and an economy being nearly 40% smaller than what it was in 2008, before the last global financial crisis.

The epidemiological data of COVID-19 in Greece, for the first half of 2020, can be regarded as a great success, and model for the world, compared to other EU countries. Upon exiting the lockdown on May 5th 2020, Greece entered the next phase of dealing with an anticipated COVID-19 second wave; as in many other countries in the northern hemisphere, the challenge of the national healthcare system's

Table II. *Comparative depiction of case fatality rates of COVID-19 in European countries of similar population sizes (data of first wave Jan-June 2020).*

Country	Population	Deaths from COVID-19	Confirmed COVID19 cases	Case fatality rate
Netherlands	17,127,246	5,288	41,774	0.13
Belgium	11,585,253	8,415	51,420	0.16
Greece	10,434,585	148	2,678	0.05
Czech Republic	10,708,072	270	8,031	0.03
Sweden	10,088,474	3,040	24,463	0.12
Portugal	10,202,245	1,105	26,715	0.04

sustainability as well as the re-implementation of social distancing and other preventative strategies to restrain viral spread until population vaccination, were revisited.

Vaccines and Vaccination Strategies

At present BNT162b2, from Pfizer-BioNTech, a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes a prefusion-stabilized, membrane-anchored SARS-CoV-2 full-length spike protein is a two-dose regimen vaccine that shows 95% effectiveness in preventing Covid-19 illness (46). Similarly, the mRNA-1273 vaccine from Moderna has thus far shown 94.1% efficacy in preventing COVID-19 while AZD1222, a vector-based vaccine from Astrazeneca, has thus far shown 62-90% efficiency (47, 48). These vaccines were recently approved by the US Food and Drug Administration and/or the European Medicines Agency and mass vaccination programmes have started or are about to start.

The COVID-19 experience is shaping the future of vaccine research and development. Since December 2020, the developers of several vaccines had announced very promising results in large trials, and over time more trials confirmed initial enthusiasm. These results have indicated that the vaccine development process can be significantly accelerated, but the major requirement is to not compromise on safety. Since allergic reactions in people who received the COVID-19 vaccine produced by Pfizer and BioNTech in December 2020 were reported (49), concerns were raised regarding its safety. The compound most possibly responsible for these anaphylactic episodes is polyethylene glycol (PEG), found in the packaging of the mRNA that forms the vaccine's main ingredient (also present in Moderna’s vaccine) (50, 51). Although PEGs have never been used before in vaccines, they are found in many drugs, some of which have been shown to trigger anaphylaxis (52), a potentially life-threatening reaction if left untreated. The exact mechanism of PEG-induced anaphylaxis remains unknown; since a small number of people previously exposed to PEG may have increased levels of antibodies against it, these vaccines could potentially put them at risk of an anaphylactic reaction. Although anaphylaxis is a rare risk of drug administration and has a good prognosis when diagnosed and treated promptly and correctly, vaccination centres should have trained staff and the necessary equipment and medicine available to treat such episodes. With the necessary precautionary measures, the benefits of the COVID-19 vaccines have thus far outweighed the risks.

However big the political and media scrutiny on vaccines under development may be, the goal should always remain to achieve efficacy outcomes, critically evaluated with strict scientific merit aimed at clear clinical significance.

The New Era of “Epidemiomics”

The COVID-19 era, undoubtedly gave rise to novel perspectives on how scientists and governments perceive and deal with matters of public health. Analytical technologies that have been maturing for decades are now sufficiently developed to provide reliable answers on the epidemiological surveillance and determination of genetic variants on disease susceptibility and severity. Genomics, proteomics, epigenomics and metabolomics are in the frontline against infectious diseases, studying the phylogenetic lineage of viruses, tracing the genotypic variation of viral transmission paths, and understanding the evolutionary biology and spread of communicable diseases. Such approaches may provide new opportunities for epidemiological studies to understand the correlation between the genetic basis of predisposition and the dismal or favourable prognosis to an infectious disease within a population as well as the course of this same disease within an individual patient (53). Research of this type has already started showing promising results; in the UK a genome-wide association study was conducted, comparing critically ill COVID-19 patients with controls form various genetic cohorts, towards understanding the host mechanisms leading to a more severe disease phenotype. Five host genes (FNAR2, TYK2, OAS1, DPP9 and CCR2) have been discovered thus far that are associated with disease severity (54).

Omics and epidemiology (“epidemiomics”), in a symbiotic relationship, will allow the implementation of personalised medicine based on individual omic data of patients: “omics” centres can screen large numbers of samples leading to discovery of susceptibility alleles that in combination with phylogenetic scores will predict disease outcome (55). This could lead to individualisation of protective measures and treatments. Through evidence-based identification of population groups at risk and patient stratification based on individualised profiling, an effective targeted preventive strategy can be crafted (56, 57).

An effective global strategy against pandemics is necessary. The need for collective societal response on this behalf is more important than ever. Pathogens of zoonotic or agricultural origin with high mutation and gene recombination rates, constitute a huge pool of global health threats (58). The human–animal interphase in the context of disease generation must be thoroughly reconsidered, even if this means that a ban on selling wild-caught animals in wet markets must be imposed. Although vaccines and therapeutic alternatives are good responses to the problem, they are still responses; prevention is much more effective and should precede them.

Take Home Messages

Epidemiological studies are highly anticipated to produce accurate infection rates and shed light on many questions such as the transmissibility of the virus in the Greek climate (high summer temperature, increased UV from sunlight, vitamin D synthesis, and temperate climate).

Whilst examining the case of Greece, it becomes clear that in order to adopt preventive strategies that work, health care systems worldwide must rely on case-specific multi-parametric predictive models. To address the multi-phased aspects of the COVID-19 pandemic, key factors such as the real number of infected persons in each country as well as the exact personalised characteristics of individuals predisposed to severe disease forms, need to be taken in consideration.

In Greece, as in many other countries worldwide, the lack of nation-wide testing strategies during the first wave, could have led to an underestimation of the actual number of reported cases. Population-wide access to molecular (and/or accurate antigen-based) COVID-19 tests, that could facilitate the prompt isolation of confirmed cases and the precise contact tracing, might have accelerated the exiting strategy from the lockdown that had a huge economic burden for societies. In Greece, the shortage of consumables globally due to the pandemic, the lack of sufficient infrastructure, healthcare facilities and logistics across the country, the limited number of personnel trained to perform such laboratory-based molecular testing and the insufficient evidence on the accuracy of non-approved tests, led to the adoption of a very effective symptom-based isolation and the implementation of strict social distancing measures during the first wave. It should be noted, however, that both models compel huge financial sacrifices, and it still remains unclear which testing/prevention strategy works better in terms of a bearable socioeconomic burden with the lowest possible loss of human lives. Surely, one size does not fit all; hence, the implementation of different approaches to combat this and (maybe) future pandemics/epidemics on a country-wide basis, should comply with the available resources, the specific cultural traits of each population and the social/economic needs of each country. Undoubtedly, the ultimate goal for all prevention models should be the prioritization of human lives and the society's well-being.

No matter how efficient a model may be in theory, the success is ultimately defined by the willingness of each society to comply with the necessary measures. To this end, public sharing of information and precise justification of the role and purpose of such measures by authorities, encourage the development of mutual trust that is paramount for the successful implementation of each strategy. This approach, which was followed by the Greek government, proved unequivocally rewarding in terms of population compliance. However, the era of social media domination and information overload in general, has unavoidably led not only to excessive anxiety and depression phenomena, but also to misinformation and conspiracy theories globally. The latter, and more importantly the economic and emotional exhaustion of the population from the prolonged lockdown, generated different degrees of public distrust to the measures. This has been augmented by the inconsistency of the data shared with the public during the different phases of the pandemic; although this phenomenon is well-known to the scientific community, which acknowledges that evidence evolves and parallels research, for some lay people such messages seem conflicting and amplify their suspicion and sense of uncertainty. Thus, it is imperative to assemble special crisis response groups comprising of experts that can efficiently articulate and communicate the need for each measure to the public. Each decision needs to be explained, dissected and analyzed to the extent needed to counterbalance the organic opposition the population is bound to lean towards, especially given a financial crisis similar to the one that preceded COVID-19 in the Greek society.

Furthermore, retrospective analysis of data is required to adjust for future epidemic scenarios, in order for prediction to be more accurate. The combination of multi-professional expertise such as laboratory medicine, omics research, epidemiology, virology and all other disciplines of science can help achieve targeted prevention. The example of Greece suggests that strategic measures and trust amongst the population can reduce COVID-19 spread while avoiding draconian measures similar to the ones taken in China.

Compliance With Ethical Standards

The article follows international standards on ethics: only officially published data on Covid-19 have been considered for the publication.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

GJD and AKA conceived the project, supervised the study and did most of the writing. PCF wrote the commentary section regarding the socioeconomic burdens and future ways to act. AMG performed bibliographical search and assisted in editing and writing. RMH contributed in the structure of the manuscript and critically revised it at all stages. GT revised the final draft. All Authors have read and approved the final version of the manuscript.

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