

The state of COVID-19 in Greece: Vigilance in the face of unpredictability

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ABSTRACT

A new COVID-19 reality is emerging globally. Despite the 'global health emergency' being downgraded to a global health threat by the World Health Organization, several countries around the world promote COVID-19 vaccination programs by months, in response to changes in the virus due to the new emerging variants. New hospital admissions and number of beds occupied by COVID-19 patients are globally on the rise. Where do we stand amidst all this, in Greece? In this narrative review, we bring forward five immediate priorities for our scientific societies, our health care colleagues and the State, in order to stay vigilant in the face of COVID-19 unpredictability. A team of experts put the minimum of measures in place to ensure a level of readiness that would allow our healthcare system to sustain the management of the COVID-19 challenge. We hope that our action-oriented proposals can contribute to the discussion on how we can strengthen our responses and sustain our successes in fighting COVID-19, for the winter ahead of us and beyond.

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INTRODUCTION

The coronavirus SARS-COV-2, the cause of COVID-19, swarmed our lives at the beginning of 2020 and within a few months caused the collapse of global economies and healthcare systems, ultimately claiming over 7 million lives globally¹. Three and a half years later, despite vaccines and

antivirals being made widely available, especially in the high-income countries, and many political declarations about the end of the pandemic, the future impact of COVID-19 remains largely unpredictable. Willingly or not, this forces governments, healthcare organizations, scientific societies, academia, and the media, to remain vigilant.

Greece had reported about 5.4 million cases and 37572 deaths by 18 October 2023¹. By the time this review was developed, and according to the Hellenic National Public Health Organization, on the week beginning 13 November 2023, the number of COVID-19 admissions (n=787) showed an 11% decrease compared to the average weekly number of new admissions during the previous 4 weeks; the number of new intubations (n=13) decreased compared to the previous week and compared to the average weekly number of new intubations during the previous 4 weeks (n=20), while the viral load surveillance in municipal wastewater showed an increase in SARS-CoV-2 virus circulation in 3 out of 9 areas participating in the network. Mortality rates have been steadily declining while deaths are increasingly concentrated amongst the most vulnerable populations, especially the unvaccinated, and elderly patients with multiple comorbidities. Current prevalent variants, much like the rest of Europe, are XBB.1.5 (Kraken), EG.5.1 (Eris), and XBB.1.16 (Arcturus), classified as Variants of Interest (VOI) that belong to the Omicron family, and, as such, display characteristics of high contagiousness and low severity, in terms of impact on hospitalizations and mortality. According to the Hellenic National Public Health Organization, 163 positive samples of the newly emerged BA.2.86 Omicron sub-variant have been recorded between 5 September and 3 November 2023, in Greece. But the epidemiology of COVID-19 changed rapidly towards the end of 2023 leading to a higher number of recorded cases, hospitalizations, and deaths².

Overall, and despite the previous variability in waves with surges coming and going over the last 12 months, it appears that the epidemiological situation has largely stabilized; we are probably irreversibly transitioning into what is called an endemic situation, where the mortality from the virus is expected to decline substantially. In reality, we are moving towards a phase where COVID-19 will become endemic, dictated by the evolution of the virus itself. It is already clear that the thought of SARS-CoV-2 behaving as a seasonal virus like influenza is not at all accurate; this has not happened yet. COVID-19 and flu are both contagious respiratory diseases, but SARS-CoV-2 appeared to be rapidly evolving, contagious for a longer time and spreading more quickly than the flu. COVID-19 can cause different complications and become more severe than the flu. And, as long as the SARS-COV-2 is rapidly evolving with numerous variants already presented, how can we best prepare to effectively respond to the upcoming phases of COVID-19? Readiness is clearly declining, the last update of the dedicated website (<https://covid19.gov.gr/>) dates back to February 2023³. Still, the question remains: do we need to develop an evidence-based approach by identifying and implementing new actions based on our prior experience in COVID-19 management?

In this narrative review, we outline our point of view as to the priorities we need to collectively consider, building on our successes and achievements of the past years, as we remain

hopefully sufficiently vigilant towards a still unpredictable future of COVID-19.

PRIORITIES FOR VIGILANCE IN COVID-19 MANAGEMENT

Guidance principle: No room for complacency

The proportion of people estimated to be infected has varied over time, yet COVID-19 appears to be ever present, and people are being infected, maybe increasingly as they return to work after holidays, schools open, and the weather grows chillier. Long COVID prevalence estimates range from 15.2% to 53.1% in studies based on self-report data, and from 1.8% to 8.3% in studies considering those with a diagnosis or referral for long COVID⁴. The cumulative risk of acquiring long COVID grows the more times people are reinfected with COVID-19⁵.

However, COVID-19 projections for the future are becoming increasingly harder. As more parameters need to be allowed into our modelling exercises, such as hybrid immunity, reduced surveillance of virus and people, declining testing rates, and individualization of behaviors and interpretation of risk, which is no longer mandated by the State, together with a possible concurrent surge with other respiratory viruses, it will become even harder to predict how and how much COVID-19 will impact on public health in the coming months.

It is therefore critical to maintain the minimum of measures in place to ensure a level of readiness that would allow our healthcare system to sustain its successful management of the COVID-19 challenge, in the winter and beyond.

Priority 1: Vaccination

In Greece, 74.8% of the total population (82.6% aged ≥ 18 years, and 89.8% aged ≥ 60 years) completed the primary series of vaccination, while only 55.7% (66.7% aged ≥ 18 years, and 79.2% aged ≥ 60 years) of the total population returned for one booster or additional dose (3rd) of the COVID-19 vaccine. One should also note the decreasing percentage (26.7%) of a 2nd booster in those aged >60 years⁶. It is an absolute priority to convince people, especially those at high risk for severe disease, such as the elderly and those with comorbidities, to vaccinate against the virus.

Recent vaccine effectiveness data reveal waning protection conferred by the outgoing bivalent vaccines against infection and hospitalization as the XBB sublineage becomes more prevalent, although the durability of protection against intensive care admission or mortality remains relatively high. The newly introduced monovalent and updated COVID-19 vaccines 2023–2024 specifically target XBB.1.5, a subvariant of Omicron, which is currently widespread in Greece and worldwide. The revised vaccines are expected to be effective against the XBB sublineage variants such as XBB.1.5 and XBB.1.16, as well as variants closely related to it, such as BA.2.86 and EG.5, which are

currently co-circulating in Greece⁷.

More concerning is the impact of the increasing 'vaccine fatigue'. In Greece, the percentage of the eligible general population that was vaccinated with the fourth dose, that is, the second booster dose of the bivalent omicron vaccine, is unknown. The frequency of vaccination and the number of different vaccination schedules for the general population, the elderly population, and the immunocompromised population, are some reasons that led to the vaccine fatigue. The vaccine fatigue behavior has exposed them to an increased risk for severe disease. Some months down the line and with the media emphasis on COVID-19 receding, how likely is it for these people to return to vaccination centers? Probably very unlikely; therefore, it becomes even more relevant and urgent to mobilize people at risk of serious disease to vaccinate against COVID-19. This would require free access to the vaccine and healthcare providers supporting vaccinations for these people, through education, scheduling appointments and phasing other relevant vaccines, such as flu, pneumococcus. Similarly, awareness campaigns to the public for vaccines as an important tool to ensure public health and controlling the disease should be prioritized. Organizing collaboration forums for scientific societies and the state, can also best support immunizations programs overall.

Priority 2: Testing and diagnosis

There has been criticism for creating a 'false reality' with COVID-19, due to the extensive testing, which were also partially used as a means of epidemiological surveillance. As testing rules have eased or completely relaxed, asymptomatic patients or patients with symptoms that have not been tested or confirmed with COVID-19, can challenge the transmission of the virus amongst the most vulnerable. Moreover, the overall impact of respiratory virus co-infections in the present and upcoming seasons remains highly unknown in terms of morbidity burden, clinical severity, and outcome⁸. Though widespread testing of symptomatic individuals cannot be enforced nor justified, agreeing on a reasonable testing protocol for all respiratory viruses would make sense, especially within hospitals, so that we can identify coinfections and optimize treatment for patients.

Priority 3: Treatment

The value of antiviral treatments for eligible patients with COVID-19 is indisputable, validated by clinical trials and real-world evidence. This value is becoming increasingly relevant in the face of vaccination fatigue, which is expected to negatively impact the willingness of the population to return for their annual booster shots. Especially amongst vulnerable, at-risk patients, such as elderly patients with comorbidities in the community, immunocompromised patients, patients on dialysis and patients residing in healthcare facilities (psychiatric, geriatric or end-of-life), who may choose not to vaccinate, availability of treatment is of utmost importance.

Besides antiviral availability, the urgency of treatment should also be emphasized so all eligible patients to initiate and complete appropriate antiviral therapy, unlike of what we currently observe mainly due to patients lack of willingness to receive antiviral treatment but also due to physicians. The implementation of antiviral therapy should have two objectives: timely administration of antivirals to outpatients, and timely administration of antivirals in any spread that occurs in a hospital environment. The above could only be optimized when combined with robust infrastructure for hospital and healthcare facilities and aligning HCP education with patient education through medical societies and the state, to optimize patient and healthcare outcomes.

Elderly patients with comorbidities in the community

Currently there are patients who are eligible for antiviral treatment based on their risk profile and their clinical status who are not yet prescribed antivirals. This is a critical point in our care response that we need to tackle urgently. Our priority is to ensure that vulnerable, at-risk patients, living in the community, access antiviral treatment early, before any hospital admission, precisely to avert hospitalizations. This is, equally to the standard of care of the early administration of antivirals during hospitalization, the backbone of our treatment approach. This will help minimize duration of hospitalization, avert other hospital infections and, ultimately, reduce mortality.

Immunocompromised patients and patients on dialysis

A target group of special importance are immunocompromised patients with COVID-19. Essentially, this is the group at highest risk for severe disease and for whom there is pressing need for updated clinical management guidelines and standardization of clinical practice. We can safely estimate a 2–3% of the total population as being immunocompromised (including cancer and hematological patients, patients with rheumatoid arthritis, inflammatory bowel diseases, organ transplant patients, those on various immunosuppressives and patients under hemodialysis) with only around 10000 of them being severely immunocompromised. These are the patient populations that should be absolutely prioritized for early antiviral treatment without exception and for whom specific treatment guidance can support physicians to optimize therapeutic options.

Patients in various non-hospital healthcare settings

A critical priority for the healthcare system is to deliver early treatment with antivirals in stand-alone psychiatric, geriatric and palliative healthcare facilities, as well as facilities for people with disabilities. In such cases, it is advisable that the patient is not transported to other healthcare facilities to receive the appropriate early treatment. This optimizes the delivery of care to the patient and improves the pressure on the general healthcare system. General practitioners or

internists, who already manage a series of therapies, regularly monitor patient vitals, and respond to any adverse events within these facilities, are well equipped to administer parenteral antiviral treatments, especially as these have a well-established safety profile in populations and settings over the past three years. This ‘decentralization’ of care delivery in such settings has already been stipulated in an Autumn 2022 circular from the Ministry of Health⁹ – yet its implementation lags. To speed up and standardize response, it is imperative that physicians in such units are educated on the importance of early antiviral treatment. It is equally important to remove barriers in primary care settings (applicable to elderly patients with comorbidities, and immunocompromised patients and patients on dialysis, as well). The clear communication of the framework in place in the respective settings, would aid the implementation of early treatment for eligible patients.

Integration of treatment guidelines

A key step in the appropriate management is the early administration of an antiviral to the clinically appropriate patient. There is a significant need to focus on preventing adverse outcomes (such as hospitalization and/or death) in the at-risk population. The diversity of the population at-risk requires customized solutions to each patient profile that adhere to the prescribing labels and safety precautions, and align with the standards of care dictated by evidence-based therapeutic algorithms. To facilitate the achievement of our treatment response goals, it is critical that we move towards simple and holistic therapeutic protocols designed and issued jointly by all involved scientific societies, which incorporate any specific guidance on special populations. Jointly issued and commonly implemented guidelines would also help educate colleagues of all specialties on the management of COVID-19 among the most critical patients.

Priority 4: Long COVID-19

Long COVID-19 is used to describe a situation in which a patient sustains, for example chronic fatigue, depression, dyspnea, stress, hair loss, tachypnea, and cachexia three months after his/her COVID-19 infection, symptoms that affect primarily the cardiovascular, respiratory and nervous system. Although the Omicron variant and its subvariants appear to lead less frequently to long COVID, nonetheless, a substantial number of patients in Greece are currently suffering from the debilitating symptoms of long COVID, with a formal patient association being established amongst them. A nationwide system of recording and monitoring such patients at the point-of-care would help to both increase our understanding of the burden of long COVID and to actively and effectively support patients and carers. Considering the term ‘Long Covid’, we should also focus on a particular group of patients, which consists of those who, although they have previously been infected, cannot reduce their viral load, so they continue to have

symptoms and imaging burden. The majority of these patients are immunocompromised. It is imperative to find specific protocols in these patients and, above all, to strictly avoid further immunosuppression through therapeutic interventions.

Priority 5: Pediatric population

Pediatric populations should be another priority for vigilance. Given the lack of randomized controlled trials in pediatric patients and an increasing need to acquire evidence on outcomes, it would be critical to support real world evidence studies to assess treatment effectiveness in this population, which, in Greece, is relatively small and well defined. It should be noted that amongst immunocompromised adolescents (aged ≥ 12 years), treatment entails the same options as those targeted to immunocompromised adults.

CONCLUSION

COVID-19 is still here and will be for a very long time, mutating as it goes along, stretching healthcare resources and affecting people’s lives. Its current status according to the WHO is ‘global health risk’, downgraded in May 2023 from a ‘public health emergency’¹⁰. Yet, the situation is still evolving, with a number of variants growing in ‘concern’ and both science and policy trying to figure out how to respond. In this context, we are putting forward five actionable priorities and urge our colleagues and the State to stay vigilant in the face of uncertainty.

CONFLICTS OF INTEREST

The authors have each completed and submitted an ICMJE form for Disclosure of Potential Conflicts of Interest. The authors declare that they have no competing interests, financial or otherwise, related to the current work. S. Loukidis reports receiving payments for presentations and support for meetings/travel from Pfizer Gilead. V. Sypsa reports receiving grants from Greek Shipowners’ Social Welfare Company SYN-ENOSIS, to cover the cost of social contact surveys during the COVID-19 pandemic; paid to an institution she is affiliated to. She also reports participating on a Data Safety Monitoring Board or Advisory Board of Gilead. G. Touloumi reports receiving grants from Gilead Europe and UCL, UK, which were paid to her institution. She also reports receiving consulting fees from Gilead Europe and payment for presentations from Gilead.

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ETHICAL APPROVAL AND INFORMED CONSENT

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DATA AVAILABILITY

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authors on reasonable request.

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DISCLAIMER

N. Tzanakis reports that he is an Editorial Board Member of Pneumon. He had no involvement in the peer-review or acceptance of this article, and had no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to a handling editor of the journal.

REFERENCES

1. WHO COVID-19 dashboard. World Health Organization. 2023. Accessed November 27, 2023. <https://covid19.who.int/>
2. Epidemiological Surveillance of Respiratory Infections: Weekly overview, Week 46/2023 (13/11/2023 – 19/11/2023). Report in Greek. National Public Health Organization. Accessed November 27, 2023. <https://eody.gov.gr/ekthesi-epitirisi-anapneustikon-ion-2023-46/>
3. Health. Website in Greek. covid19.gov.gr. Accessed November 27, 2023. <https://covid19.gov.gr/ygeia-covid19/>
4. International review of the epidemiology of long COVID. Health Information and Quality Authority. May 31, 2023. Accessed November 27, 2023. <https://www.hiqa.ie/reports-and-publications/health-technology-assessment/international-review-epidemiology-long-covid>
5. Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nat Med*. 2022;28(11):2398-2405. doi:[10.1038/s41591-022-02051-3](https://doi.org/10.1038/s41591-022-02051-3)
6. COVID-19 Vaccine Tracker. European Centre for Disease Prevention and Control. Accessed November 27, 2023. <https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html>
7. Regan JJ, Moulia DL, Link-Gelles R, et al. Use of Updated COVID-19 Vaccines 2023–2024 Formula for Persons Aged ≥6 Months: Recommendations of the Advisory Committee on Immunization Practices — United States, September 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(42):1140-1146. doi:[10.15585/mmwr.mm7242e1](https://doi.org/10.15585/mmwr.mm7242e1)
8. Maltezou HC, Papanikolopoulou A, Vassiliu S, Theodoridou K, Nikolopoulou G, Sipsas NV. COVID-19 and Respiratory Virus Co-Infections: A Systematic Review of the Literature. *Viruses*. 2023;15(4):865. doi:[10.3390/v15040865](https://doi.org/10.3390/v15040865)
9. Fouseki E. G. Kotsiopoulos at ANA-MPA: We are adapting the NHS to the pandemic data. The changes in the management of covid incidents. Article in Greek. Athens - Macedonian News Agency. October 11, 2022. Accessed November 2023. <https://www.amna.gr/health/article/680359/G-Kotsiopoulos-sto-APE-MPE-Prosarmozoume-to-ESY-sta-dedomena-tis-pandimias-Oi-allages-sti-diacheirisi-ton-peristatikon-covid>
10. Statement on the fifteenth meeting of the IHR (2005)

Emergency Committee on the COVID-19 pandemic. World Health Organization. May 5, 2023. Accessed November 27, 2023. [https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-\(2005\)-emergency-committee-regarding-the-coronavirus-disease-\(covid-19\)-pandemic](https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic)