Mandatory vaccinations, the imposing of fines, the segregation of citizens and promotion of inequality in the modern democracy of Greece. Is science allowed to "enforce" or silently back-up such policies?

Charalampos Mavridis[1], Georgios Aidonidis, Dimitrios Arapoglou, Athanasios Kalogeridis

1 University of Crete

Funding: The author(s) received no specific funding for this work.

Potential competing interests: The author(s) declared that no potential competing interests exist.

Abstract

Not applicable

Undoubtedly COVID-19 is one of the most important health issues with more than 5,000,000 deaths worldwide to date. Each country's government was tasked with taking several measures to protect public health, without causing direct or indirect harm, either in the short or the long term, to its citizens. It is the responsibility of science to provide without any bias or partiality the direction to ensure the maintenance of public health at the least cost. The MEDLINE database contains over 240,000 articles on COVID-19 and about 2000 related meta-analyses. As we are still in a period of "learning", during which a massive amount of medical data is constantly added on a daily basis, not to mention the associated legal, social, and psychological implications, it is utterly inappropriate to create mandates out of any guidance that emerges. The proportionate degree of the measures against the pandemic, which can include the use of masks, COVID passes, lockdowns, fines, and mandatory vaccination, varies considerably from country to country. However, the global trends tend to merge on the fact that transparency in the conveying of information and the promotion of educated self-choice provide more rational, humane and effective management of the pandemic[1]. The opinion of experts as displayed on television and the media carries the least degree of scientific credibility and recommendation, as defined in evidence-based medicine. Contrary to that, we should take into serious consideration, the degree of evidence that form the basis of the large study by Subramanian et. Al, where it was shown that vaccination for COVID-19 cannot control its spread regardless of the level of vaccination coverage, with data from 68 countries and 2947 counties in the US[2].Initial data from phase 3 clinical trial showed that the number needed to vaccinate (NNTV) to prevent case of COVID-19 was about 119 and especially to prevent severe disease, about 2380 (figure 1)[3].

Vaccinated health care workers (HCWs) are now known to transmit COVID-19, with publications even showing over-transmission of the disease[4-8]. Even after the 4th dose, HCWs who were infected were infectious, with a relatively high viral load, as the vaccination showed very low efficacy against covid-19[10]. So, the definitive argument against vaccine mandates comes very recently in the form of a shocking Letter to the Editor of the New England Journal of Medicine by

Israeli Healthcare Officials, who underline the low effectiveness of the vaccines in HCWs.

A careful review of the weekly COVID-19 Vaccine Surveillance Reports of the UK Health Security Agency (UKHSA), beginning from Week 37 of 2021[11], which is based on data from 18/8/2021 – 3/9/2021 and moving on, unfortunately displays clearly a constant and repeating pattern, which is that in the age groups from 30-80 years old, after the prevalence of the delta strain, the new covid-19 cases per 100,000 of the respective population (case rate) are invariably more, sometimes even twice as many in the fully vaccinated individuals compared to the unvaccinated. The case rate among vaccinated individuals was also increased in the remaining age groups, with the exception of <30 and >80 years old. One can verify this pattern by running through the following weekly reports: Week 37 (p.13), Week 38 (p.13), Week 39 (p.14), Week 40 (p.13), Week 41 (p.13), Week 42 (p.13), Week 43 (p.19), Week 44 (p.20), Week 45 (p.22), Week 46 (p.23), Week 47 (p.33), Week 48 (p.44), Week 49 (p.35), Week 50 (p.39), Week 51 (p.40)[11, 12]. As far as we know, there was never a lockdown affecting only the unvaccinated in the UK, as compared to Greece. Beginning at Week 3 2022 (p. 38), the UKHSA started to produce these tables by counting only on people who had undergone booster vaccination, 3 doses in total, in the vaccinated group, and still the same pattern is observed. Moreover, moving forward to the most recent reports in 2022, Week 9 (p,45), Week 10 (p. 45), Week 11 (p.45), the pattern seems to become even worse, since the case rate among booster-vaccinated individuals in the aforementioned age groups climbs to three or even four times more than among the unvaccinated. Unfortunately, it seems that mass vaccinating of the population could have actually produced over-transmitters of the disease, instead of working towards the fallacy of creating an immunity wall. The aforementioned tables correctly point out that the proportionate rate of ER admissions and deaths are definitely lower in the vaccinated group compared to the unvaccinated, progressively increasing in proportion with age, although this difference has blunted considerably and has even gotten to even terms with the prevalence of the omicron strain. Consequently, taken all the facts in consideration, vaccination against COVID-19 is clearly an individual protective measure, and not a collective one. In accordance with this, reports from Robert Koch Institute (RKI) in Germany mentioned that breakthrough infections are possible also among vaccinated staff at a similar viral load[13].Data of the last month from RKI underline that vaccinated were 66% out of new cases and died more frequently than unvaccinated[14], although vaccine effectiveness against hospitalization and ICU-treatment was preserved. In Israel, a new in-hospital outbreak has recently occurred where the source was a fully vaccinated patient with COVID-19[15]. The US Centers for Disease Control and Prevention (CDC) announced four of the top five counties with the highest percentage of fully vaccinated population (84.3 - 99.9%) as "high" transmission counties[15].Consequently the Lancet has published a correspondence where it is noted that after the prevalence of Delta and ongoing Omicron variant and the waning of immunity over a few months, “stigmatizing unvaccinated people is unjustified” according to the cumulative data of the pandemic[15].

Last but not least regarding mandatory HCWs vaccination against COVID-19, a House of Lords committee in a dramatically written newsletter refused to acknowledge the need for a mandate, since it is not economically, scientifically and morally confirmed[16]. This has led to the total revoking of the measures of mandatory HCWs vaccination and the vaccination-as-condition-of-deployment (VCOD) in the UK, as officially stated in the Government resolution of 01/03/2022[17].Consequently, the UK has not suspended or sacked a single HCW in the NHS, during the massive winter outbreak. The same rationale was followed by other western countries, such as Sweden and other Scandinavia, who

never even considered mandatory vaccinations in HCWs or other population groups, and they have definitely managed to keep the pandemic's toll to a far better level than in Greece. The green pass of convalescent patients in Greece is valid for 3 months. This is totally incomprehensible, as the superiority of naturally-acquired immunity has been recently demonstrated by the CDC (19-01-2022)[18]. In this report, by studying the 18% of the population of the United States, it has been shown that naturally-acquired immunity was more potent, up to 5 times, and longer-lasting compared to vaccine-acquired immunity against delta variant. The systematic review and meta-analysis by Chivese T. et al. in a total of 18 countries and 12,011,447 patients showed strong immune memory in covid-19 patients for at least 8 months, with a 0.2% probability of reinfection[19], and there are studies showing protection against reinfection for 1.5-2 years, as well as protection for severe infection for many years, even in asymptomatic covid-19 infected individuals[20, 21].The hesitancy to acknowledge the superior duration and quality of naturally-acquired immunity seems totally unreasonable and out of alignment with global expert opinions and evidence-based studies[22]. The same applies to the undeniably more benign epidemiologic course of the omicron variant, which seems to increase the hazard ratio of breakthrough infection among vaccinated[18]. Moreover, relying solely on mass vaccination with an imperfect vaccine, as defined by its inability to control the horizontal and vertical transmission of the infection disease, carries significant public health issues, eventually negating any expected benefits[23, 24].

The translation product of the new vaccine technologies, spike protein (S) alone, which as it is not inactivated, appears to modify the normal function of ACE2 receptors and trigger several molecular mechanisms via signal transduction pathways. Briefly could be mentioned, that S protein alone could cause either impairing of the DNA repair mechanism, inducing dysfunction of the tumor suppressor proteins, p53 and BRAC1,2[25-27] or downregulation of ACE2 receptor and inhibition of mitochondrial function resulting in serious damages of vascular endothelial cells.

While it was initially thought that the spike protein would remain in deltoid muscle cells, we now know that it migrates and circulates for at least 4 months after vaccination[28], with higher levels even than severely ill COVID-19 patients[29]. It was also initially thought that the mRNA contained in the respective vaccines cannot affect the cell's DNA in any way, but this again has been overthrown by a recent study[30] in which the presence of DNA as a product of reverse transcription, as well as up-regulation of endogenous reverse transcriptase LINE-1 (long interspersed nuclear element-1) gene, is demonstrated in a hepatic cellular line as early as 6 hours after vaccination. Although the probability of this phenomenon is low, it is generally known that through the nuclear pore complexes, molecules are transported to and from the nucleus. In particular, transport of various proteins and RNAs can take place through binding with importin-b[31]. Furthermore, since vaccine mRNA can be detected up to 60 days post vaccination in lymph nodes, there are multiple questions arising in regards to accuracy, quantity and quality of the ongoing mRNA translation[29].

During the pandemic, the antibody-dependent enhancement (ADE) of infection is crucial since the present strains are different from the first one with disastrous consequences[32].

In the meantime, myocarditis, predominantly in young males, due to direct toxic effects[9], detection of unusual thrombotic events such as cerebral sinus thrombosis (implicating blood-brain barrier penetration)[33], cardiovascular deaths, including sudden cardiac deaths attributed to the particular pathophysiology of the well-described Kounis syndrome[34], as well as miscellaneous other adverse events with common feature the activated inflammatory and thrombogenic process[35], compose a dynamic profile of vaccines requiring a continuous alert of safety[36].

The questions that arise need to be clarified transparently by properly structured randomized clinical trials, with the investigation of molecular pathways in more samples. Along with this, the deadlines for the completion of studies by pharmaceutical companies are 2023 and 2024[37].

A major issue, arising from the reduction in number available of HCWs in countries where mandatory vaccinations are implemented, is the quantitative and qualitative understaffing of health care units. The availability and lack of training and specialization of health personnel are clear factors in increasing mortality[38, 39]. Department understaffing results in an increase in mortality for each inpatient by 3% daily[40]. On the contrary, countries which invested in the steady improvement of medical services achieved a reduction in ICU mortality over time[41]. Politics is a completely different science from medicine. Transparency does not reduce the intention to vaccinate[1], so there is no need to use extreme pressures measures.

Stigmatization and segregation are not appropriate in civilized societies as they can lead by themselves to further major public health issues[42]. There has already been an increase in domestic violence and suicide attempts among young people[43, 44].

Under the current laws in Greece, from six months now, there is an ongoing social occlusion of the unvaccinated citizens who cannot eat indoors in a restaurant, cannot attend a cinema, cannot enter a stadium, and cannot visit a shopping mall or bar even with a negative PCR or rapid test.

It is important to research additional pharmacological and non-pharmacological prevention options to establish health and social equilibrium, to avoid the nightmare that is setting in with general confidence in medicine constantly declining[45]. Authorities should be flexible in renewing guidelines and adapting new concepts about COVID-19 [46]. They should also be aware of the outcomes of major legal actions against vaccine mandates, in order to review their nation's policies. Foremost amongst them is the decision of the U. S. District Courts for the Western District of Louisiana and the Eastern District of Missouri, which both found the HCWs mandatory vaccination rule in the USA defective and entered preliminary injunctions against its enforcement. [Louisiana v. Becerra, 2021 WL 5609846 (Nov. 30, 2021); Missouri v. Biden, 2021 WL 5564501 (Nov. 29, 2021)]. In each case, the Government moved for a stay of the injunction from the relevant Court of Appeals, which was DISMISSED by the Supreme Court of the USA on 13 January 2022 [Nos. 21A240 and 21A241, Cite as 595 U. S. ____ (2022)].

Ultimately, science exists only through transparent dialogue and the use of reliable methods, under the rationale of proposing rather than imposing solutions. Healthcare has many dimensions as there is a social dimension in addition to the physical, mental and spiritual. The fight against any health crisis, regardless of its source, is about multidimensional healthcare, looking forward to the future.

As can be concluded, the policy of putting unvaccinated HCWs on suspension, has not only failed to improve the pandemic's outcomes, but on the contrary has produced a significant shortage of experienced staff, increasing inpatient mortality and leading the remaining staff to physical and emotional exhaustion. For more than seven months unpaid HCWs have been facing serious issues with survival, and there have been colleagues on an ongoing hunger strike. The proper course of action to promote safe healthcare, in addition to upholding the relevant preventive measures, would be to ensure that the HCW come to work healthy, which means not being infected by or even asymptomatic carriers of the virus, which can be established only through regular diagnostic testing on both vaccinated and unvaccinated individuals of

the institution's staff. Consequently, as the pandemic tends to wane, even these measures will eventually become obsolete.

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
	(N=18,198)		(N=18,325)			
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
	(N=19,965)		(N=20,172)			
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

A) 162/18325 = 0,0088 , B) 8/18198 = 0,0004 Γ) 0,0088-0,0004 = 0.0084 Δ) 1/0,0084 = 119

Efficacy Endpoint Subgroup	BNT162b2 (30 µg) (N[a]=21669) n1[b]	Surveillance Time[c] (n2[d])	Placebo (N[a]=21686) n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
Severe COVID-19 occurrence after Dose 1	1	4.021 (21314)	9	4.006 (21259)	88.9	(20.1, 99.7)
After Dose 1 to before Dose 2	0		4		100.0	(-51.5, 100.0)
Dose 2 to 7 days after Dose 2	0		1		100.0	(-3800.0, 100.0)
≥7 Days after Dose 2	1		4		75.0	(-152.6, 99.5)

A) 9/21686=0,00046 , B) 1/21669=0,00004 Γ) 0,00046-0,00004=0.00042 Δ) 1/0,00042=2.380

Figure 1. Calculation of the Number Needed to Vaccinate (NNTV) for covid-19 occurrence (first table) and for severe illness (second table). Data from phase 3 clinical trial of BNT16b2[3].

References

1 Kerr JR, Freeman ALJ, Marteau TM et al. Effect of Information about COVID-19 Vaccine Effectiveness and Side Effects on Behavioural Intentions: Two Online Experiments. Vaccines (Basel) 2021; 9 (4).

2 Subramanian SV, Kumar A. Increases in COVID-19 are unrelated to levels of vaccination across 68 countries and

2947 counties in the United States. Eur J Epidemiol 2021; 36 (12): 1237-1240.

3 Polack FP, Thomas SJ, Kitchin N et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020; 383 (27): 2603-2615.

4 Pollett SD, Richard SA, Fries AC et al. The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) mRNA Vaccine-Breakthrough Infection Phenotype Includes Significant Symptoms, Live Virus Shedding, and Viral Genetic Diversity. Clin Infect Dis 2022; 74 (5): 897-900.

5 Hetemäki I, Kääriäinen S, Alho P et al. An outbreak caused by the SARS-CoV-2 Delta variant (B.1.617.2) in a secondary care hospital in Finland, May 2021. Euro Surveill 2021; 26 (30).

6 Shitrit P, Zuckerman NS, Mor O et al. Nosocomial outbreak caused by the SARS-CoV-2 Delta variant in a highly vaccinated population, Israel, July 2021. Euro Surveill 2021; 26 (39).

7 Ioannou P, Karakonstantis S, Astrinaki E et al. Transmission of SARS-CoV-2 variant B.1.1.7 among vaccinated health care workers. Infect Dis (Lond) 2021; 53 (11): 876-879.

8 Keehner J, Horton LE, Binkin NJ et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. N Engl J Med 2021; 385 (14): 1330-1332.

9 Diaz GA, Parsons GT, Gering SK et al. Myocarditis and Pericarditis After Vaccination for COVID-19. Jama 2021; 326 (12): 1210-1212.

10 Regev-Yochay G, Gonen T, Gilboa M et al. Efficacy of a Fourth Dose of Covid-19 mRNA Vaccine against Omicron. New England Journal of Medicine 2022.

11 Agency UHS. COVID-19 vaccine surveillance reports (weeks 19 to 38) 2021.

12 Agency UHS. COVID-19 vaccine weekly surveillance reports (weeks 39 to 11, 2021 to 2022) 2021, 2022.

13 Koch-Institut R. Wöchentlicher Lagebericht des RKI zur Coronavirus-Krankheit-2019 (COVID-19). 14-10-2021 ed.; 2021:32.

14 Koch-Institut R. Wöchentlicher Lagebericht des RKI zur Coronavirus-Krankheit-2019 (COVID-19) 17.03.2022 – AKTUALISIERTER STAND FÜR DEUTSCHLAND. 2022:39.

15 Kampf G. The epidemiological relevance of the COVID-19-vaccinated population is increasing. Lancet Reg Health Eur 2021; 11: 100272.

16 Kmietowicz Z. Evidence is insufficient to back mandatory NHS staff vaccination, says House of Lords committee. BMJ 2021; 375: n2957.

17 Care DoHaS. Revoking vaccination as a condition of deployment across all health and social care: consultation response 2022.

18 León TM, Dorabawila V, Nelson L et al. COVID-19 Cases and Hospitalizations by COVID-19 Vaccination Status and Previous COVID-19 Diagnosis - California and New York, May-November 2021. MMWR Morb Mortal Wkly Rep 2022; 71 (4): 125-131.

19 Chivese T, Matizanadzo JT, Musa OAH et al. The prevalence of adaptive immunity to COVID-19 and reinfection after recovery - a comprehensive systematic review and meta-analysis. Pathog Glob Health 2022: 1-13.

20 Wei J, Matthews PC, Stoesser N et al. Anti-spike antibody response to natural SARS-CoV-2 infection in the general population. Nat Commun 2021; 12 (1): 6250.

21 Le Bert N, Clapham HE, Tan AT et al. Highly functional virus-specific cellular immune response in asymptomatic SARS-CoV-2 infection. J Exp Med 2021; 218 (5).

22 Kojima N, Klausner JD. Protective immunity after recovery from SARS-CoV-2 infection. Lancet Infect Dis 2022; 22 (1): 12-14.

23 Read AF, Baigent SJ, Powers C et al. Imperfect Vaccination Can Enhance the Transmission of Highly Virulent Pathogens. PLoS Biol 2015; 13 (7): e1002198.

24 Gandon S, Mackinnon MJ, Nee S et al. Imperfect vaccines and the evolution of pathogen virulence. Nature 2001; 414 (6865): 751-756.

25 Singh N, Bharara Singh A. S2 subunit of SARS-nCoV-2 interacts with tumor suppressor protein p53 and BRCA: an in silico study. Transl Oncol 2020; 13 (10): 100814.

26 Jiang H, Mei YF. SARS-CoV-2 Spike Impairs DNA Damage Repair and Inhibits V(D)J Recombination In Vitro. Viruses 2021; 13 (10).

27 Lei Y, Zhang J, Schiavon CR et al. SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2. Circ Res 2021; 128 (9): 1323-1326.

28 Bansal S, Perincheri S, Fleming T et al. Cutting Edge: Circulating Exosomes with COVID Spike Protein Are Induced by BNT162b2 (Pfizer-BioNTech) Vaccination prior to Development of Antibodies: A Novel Mechanism for Immune Activation by mRNA Vaccines. J Immunol 2021; 207 (10): 2405-2410.

29 Röltgen K, Nielsen SCA, Silva O et al. Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination. Cell 2022; 185 (6): 1025-1040.e1014.

30 Aldén M, Olofsson Falla F, Yang D et al. Intracellular Reverse Transcription of Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 In Vitro in Human Liver Cell Line. Current Issues in Molecular Biology 2022; 44 (3): 1115-1126.

31 Oka M, Yoneda Y. Importin α: functions as a nuclear transport factor and beyond. Proc Jpn Acad Ser B Phys Biol Sci 2018; 94 (7): 259-274.

32 Yahi N, Chahinian H, Fantini J. Infection-enhancing anti-SARS-CoV-2 antibodies recognize both the original Wuhan/D614G strain and Delta variants. A potential risk for mass vaccination? J Infect 2021; 83 (5): 607-635.

33 Wittstock M, Walter U, Volmer E et al. Cerebral venous sinus thrombosis after adenovirus-vectored COVID-19 vaccination: review of the neurological-neuroradiological procedure. Neuroradiology 2022: 1-10.

34 Kounis NG, Koniari I, de Gregorio C et al. Allergic Reactions to Current Available COVID-19 Vaccinations: Pathophysiology, Causality, and Therapeutic Considerations. Vaccines (Basel) 2021; 9 (3).

35 Guardiola J, Lammert C, Teal E et al. Unexplained liver test elevations after SARS-CoV-2 vaccination. J Hepatol 2022.

36 Edler C, Klein A, Schröder AS et al. Deaths associated with newly launched SARS-CoV-2 vaccination (Comirnaty®). Leg Med (Tokyo) 2021; 51: 101895.

37 ClinicalTrials.gov. Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals; A Study to Evaluate Safety and Immunogenicity of mRNA-1273 Vaccine to Prevent COVID-19 in Adult Organ Transplant Recipients and in Healthy Adult Participants; A Study of Ad26.COV2.S for the Prevention of SARS-CoV-2-Mediated COVID-19 in Adult Participants (ENSEMBLE). 2022.

38 Tourangeau AE, Cranley LA, Jeffs L. Impact of nursing on hospital patient mortality: a focused review and related policy implications. Qual Saf Health Care 2006; 15 (1): 4-8.

39 Aiken LH, Clarke SP, Sloane DM et al. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. Jama 2002; 288 (16): 1987-1993.

40 Griffiths P, Maruotti A, Recio Saucedo A et al. Nurse staffing, nursing assistants and hospital mortality: retrospective longitudinal cohort study. BMJ Qual Saf 2019; 28 (8): 609-617.

41 Karagiannidis C, Windisch W, McAuley DF et al. Major differences in ICU admissions during the first and second COVID-19 wave in Germany. Lancet Respir Med 2021; 9 (5): e47-e48.

42 Yuan K, Huang XL, Yan W et al. A systematic review and meta-analysis on the prevalence of stigma in infectious diseases, including COVID-19: a call to action. Mol Psychiatry 2021: 1-15.

43 Kourti A, Stavridou A, Panagouli E et al. Domestic Violence During the COVID-19 Pandemic: A Systematic Review. Trauma Violence Abuse 2021: 15248380211038690.

44 Yard E, Radhakrishnan L, Ballesteros MF et al. Emergency Department Visits for Suspected Suicide Attempts Among Persons Aged 12-25 Years Before and During the COVID-19 Pandemic - United States, January 2019-May 2021. MMWR Morb Mortal Wkly Rep 2021; 70 (24): 888-894.

45 Hellerstein M. What are the roles of antibodies versus a durable, high quality T-cell response in protective immunity against SARS-CoV-2? Vaccine X 2020; 6: 100076.

46 Ioannidis JPA. Infection fatality rate of COVID-19 inferred from seroprevalence data. Bull World Health Organ 2021; 99 (1): 19-33f.