UF COM Faculty Council Committee on
Dr. Joseph Ladapo's Analysis of COVID-19 Vaccination
Detailed Critique

On October 7, 2022, Dr. Joseph Ladapo, announced new guidance from the Florida Department of Health (FDOH) that recommends against vaccination with COVID-19 mRNA vaccines for males aged 18-39 years of age. As a basis for this recommendation, he put forward a non-peer-reviewed and unauthored analysis of FDOH surveillance data that suggested an increase in the risk of cardiac deaths amongst males aged 18-39 who had received the COVID-19 mRNA vaccine. The analysis, which appears to have served as a key driver for the Ladapo/FDOH guidance, has substantial limitations.

Below we review the major critiques of Dr. Ladapo's analysis and detail how Dr. Ladapo's associated public policy raises concern for violations of section 3.B.3 of the UF faculty policy on research integrity. Specifically, Section 3.B.3 of the UF policy on Research Integrity (UF Regulation 1.0101) notes: *"Reports of careless, irregular, or contentious research practices, as well as authorship disputes, may not meet the standard for research misconduct but may be a research integrity violation*."

Our committee finds concern for research integrity violations based on Dr. Ladapo's "*careless, irregular, or contentious research practices".*

In his guidance, Dr. Ladapo:

1. **Reports the relative incidence estimate for cardiac death among males, ages 18-39, as statistically significant, when the estimate would likely be non-significant if best-practice corrections for multiple testing were used.**

The confidence limits around the relative incidence estimate for '18-39 year-old males, mRNA vaccine' has a lower bound of 1.05, meaning that it is statistically significant, but barely so. If the authors had followed standard statistical practice and corrected this estimate for the large number of tests that were performed (multiple testing), it is highly likely that the confidence interval would have included 1.00, i.e., not be significant. Multiple testing refers to situations where a dataset is subjected to statistical testing multiple times - either at multiple time-points or through multiple subgroups or for multiple end-points. This amplifies the probability of a false-positive finding. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4840791/).

2. **Uses a method that cannot usefully inform public policy.**

This is because policy recommendations must be based not only on the risks of public health programs like vaccination, but also its benefits. The fundamental problem with his using the Self-Controlled Case Series (SCCS) method as a basis for recommending against vaccinating a specific age/sex group is that it only estimates the risk of vaccine-associated mortality without estimating the benefit of vaccination due to averted mortality from COVID-19. The SCCS relative-

incidence methodology as applied to COVID-19 vaccination produces estimates only of the potential vaccine risks, without considering its benefits. According to the Centers for Disease Control and Prevention (CDC), between 2020-2022 (the same time period as the DOH analysis), there were 1,165 deaths involving COVID-19 among 18-39 year-old males in Florida. The fundamental problem in using the DOH analysis as a basis for recommending against vaccinating a specific age/sex group is that it only estimates the risk of vaccine-associated mortality, without estimating the benefit of vaccination due to averted mortality from COVID-19.

3. Establishes a hypothesis based on a retrospective analysis of a data set and then tests that hypothesis on the same data.

When one creates and tests a hypothesis on the same dataset, they are retrospectively first informally analyzing the data for something that looks unusual and then asking if what was seen is unusual. The creating and testing of hypotheses needs to be performed on different datasets. This is a misuse of statistics and further demonstrates "careless, irregular, or contentious research practices."

4. Forms conclusions on the basis of exceptionally small event rates that distort magnitude of risk and do not consider magnitude of benefit.

For example, Table 1 in the FLDOH report explicitly shows that the estimate of cardiac-related deaths in the 18-24 year old age group is crude due to sparse data (see Figure 1). Given the other acknowledged flaws in the analysis a mischaracterization of just a few events would have resulted in a loss of any statistical significance. This again, in a situation where the benefits of vaccination were overlooked and exemplifies "careless, irregular, or contentious research practices."

Cardiac-related deaths			
≥ 18			
Baseline period	16406	2923.10	Ref
Risk period	3479	556.78	1.07 (1.03 - 1.12)
18 - 24*			
Baseline period	17	3.23	Ref
Risk period	5	0.62	1.54 (0.57 - 4.19)
25 - 39			
Baseline period	75	15.29	Ref
Risk period	29	2.91	2.16 (1.35 - 3.47)
40 - 59			
Baseline period	1034	183.46	Ref
Risk period	214	34.94	1.07 (0.91 - 1.26)
≥ 60			
Baseline period	15280	2721.12	Ref
Risk period	3231	518.31	1.05 (1.01 - 1.10)
*Crude due to sparse data			

Figure 1: Excerpt from Table 1 in the analysis entitled "Relative incidence following COVID-19 vaccination or infection for all-cause and cardiac-related deaths during the risk period vs baseline period"

5. Commits reporting bias by cherry picking results; focusing only on evidence that supports his stance, ignoring contradicting evidence, and failing to appropriately acknowledge the limitations of his own data set.

The main conclusions of Dr. Ladapo's own analysis are ignored, namely: 1) "In this statewide study of vaccinated Florida residents aged 18 years or older, COVID-vaccination was not associated with an elevated risk for all-cause mortality." 2) "The risk associated with mRNA vaccination should be weighed against the risk associated with COVID-19 infection."

The analysis states that: "These data are preliminary, based on surveillance data, and should be interpreted with caution. The results have several limitations."

Below are the limitations listed in the analysis:

a. ***Sources of bias***. "While this method has been used to assess risk of death following COVID-19 vaccination, it violates the assumption that an event does not affect subsequent exposure (for mRNA vaccines), which may introduce bias. Further, it does not consider the multidose vaccination schedule required for mRNA vaccination." While these limitations are noted in FDOH report, they are effectively ignored in the associated public policy guidance as no apparent consideration for time period associated with infection versus vaccination, vaccine dose, or previous vaccination status was made.

b. ***Inaccuracy in cause of death: Cause of death may be wrongly attributed as cardiac-related***. "This study cannot determine the causative nature of a participant's death. We used death certificate data and not medical records. COVID testing status was unknown for those who did not die of/with COVID. Cardiac-related deaths were ascertained if an ACME code of I3-I52 were on their death certificate, thus, the underlying cause of death may not be cardiac-related." Specifically, cases were defined as being "cardiac related" if the death certificate contained a diagnosis that was coded using one of 22 ICD10 codes (I30-I52) for "other forms of heart disease." No effort was made to break down results by specific diagnosis codes, to assess medical records, or contact physicians to confirm cause of death. Of note, death certificate diagnoses such as cardiac arrest (ICD10 code I46) may include persons who do not have underlying cardiac illnesses. Once again this represents "careless, irregular, or contentions research practices" in which there are concerns of "knowingly publishing material that will mislead readers."

c. ***Confounding***. "The finding that the Janssen vaccine was more protective than mRNA vaccine against mortality within 28 days of vaccination could be due to confounding and needs to be further evaluated. It is likely that the populations who received COVID-19 mRNA vaccine and the Johnson vaccine are different, something we were not able to ascertain in this analysis. It is possible that the population who received the Johnson vaccine was younger and healthier than those receiving the mRNA vaccines. The Pfizer and Moderna mRNA vaccines were released more than 2 months earlier than the Janssen vaccine when the recommendations were limited to those 65 and older." Once again, while

these confounding issues are acknowledged in the report they are ignored in associated policy which brings into question "a significant departure from the accepted practices of the relevant research community."

d. ***Analysis did not include benefits of COVID-19 vaccines***. "Additional studies should be conducted to further understand the risks and benefits of vaccination of males between 25-39." Failing to include the benefit of an intervention when analyzing the purported risk of the intervention leads to particularly biased and unsupported findings and is clearly a deviation from accepted research practice.

e. ***Small sample size in the primary analysis for the 25 - 39 age group***. "Increased risk in the primary analysis for the 25 - 39 age group was based on a small sample size." Given the aforementioned sample size limitations these data are not appropriate for informing public policy. Despite these limitations, Dr. Ladapo's associated guidance fails to objectively and appropriately balance risk versus benefit. Again this calls into question potential violations of the UF policy regarding research integrity with specific concerns regarding "misleading readers."

f. ***Unknown COVID-19 mortality among asymptomatic or undiagnosed COVID-19 infection*.** "Additionally, significant mortality from diagnosed COVID-19 infection occurred among all adult age groups. COVID-19 mortality among asymptomatic or undiagnosed COVID-19 infection is less clear. However, excess overall mortality among 25–44-year-old Americans was significant in a study looking at mortality from January 2020-October 2020. The largest increases were among Hispanic and Latino. It is unclear what the contribution of asymptomatic or undiagnosed COVID-19 infection is to mortality risk, and how this contributes to excess mortality."

Cherry picking findings that support one position, ignoring data that contradicts it, and failing to acknowledge the limitations of his own research report raise further concerns that Dr. Ladapo has performed "careless, irregular, or contentious research practices."

6. Ignores the total body of evidence regarding risk versus benefit of vaccination.

Given Dr. Ladapo's emphasis on the potential for cardiac death following COVID-19 vaccination, the lack of consideration for benefit associated with COVID-19 vaccination is a major flaw and represents a significant deviation from the standards of epidemiologic and public health research.

For example: Two Years of U.S. COVID-19 Vaccines Have Prevented Millions of Hospitalizations and Deaths. **Findings:** From December 2020 through November 2022, we estimate that the COVID-19 vaccination program in the U.S. prevented more than 18.5 million additional hospitalizations and 3.2 million additional deaths. Without vaccination, there would have been nearly 120 million more COVID-19 infections. The vaccination program also saved the U.S. $1.15 trillion (Credible Interval: $1.10 trillion–$1.19 trillion) (data not shown) in medical costs that would otherwise have been incurred. December 13, 2022.

7. Ignores published findings on the relationship between myocarditis and COVID-19 vaccines.

Below is a brief list of peer reviewed publications from major, peer-reviewed publications:

a. Myocarditis with COVID-19 mRNA Vaccines, *Circulation*, August 10, 2021. **Conclusion:** In summary, >177 million people have received at least 1 dose of COVID-19 vaccine (>300 million doses) in the United States, and CDC and other international organizations continue to monitor the safety of COVID-19 vaccines for any health problems including rare cases of myocarditis after vaccination. Despite rare cases of self-limited myocarditis, the benefit-risk assessment for COVID-19 vaccination shows a favorable balance for all age and sex groups; therefore, COVID-19 vaccination is currently recommended for everyone 12 years of age and older.

b. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization, *New England Journal of Medicine*, December 2, 2021. **Conclusion:** Among patients in a large Israeli health care system who had received at least one dose of the BNT162b2 mRNA vaccine, the estimated incidence of myocarditis was 2.13 cases per 100,000 persons; the highest incidence was among male patients between the ages of 16 and 29 years. Most cases of myocarditis were mild or moderate in severity.

c. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021, *Journal of the American Medical Association*, January 25, 2022. **Conclusion:** Based on passive surveillance reporting in the US, the risk of myocarditis after receiving mRNA-based COVID-19 vaccines was increased across multiple age and sex strata and was highest after the second vaccination dose in adolescent males and young men. This risk should be considered in the context of the benefits of COVID-19 vaccination.

d. Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases, *Lancet*, June 11, 2022**. Conclusion:** In conclusion, the risk of myocarditis or pericarditis events in people who received COVID-19 mRNA vaccines was elevated in younger populations; however, the incidence was rare [sic, with only 411 events occurring in 15 million recipients of 16 912 716 doses of BNT162b2 and 10 631 554 doses of mRNA-1273]. Our study showed that, in the period of 1–7 days after receipt of the second dose, the highest risk was in men aged 18–25 years. A head-to-head comparison of myocarditis and pericarditis risk for the mRNA-1273 and BNT162b2 vaccine brands did not indicate a statistically significant difference, but also could not rule out that a difference might exist. Studies with additional data sources are needed to further evaluate the risk.

In summary, Dr.Ladapo's FDOH analysis has serious shortcomings that Dr. Ladapo has been made aware of and has responded to on his official Twitter account and in the Wall Street Journal (wherein he is identified as a University of Florida Faculty member). Importantly, the study on which Dr. Ladapo's subsequent analysis is mirrored, that of Nafilyan et al., came to the opposite conclusion and found that "although there is a risk of myocarditis or pericarditis with COVID-19, there is no evidence of increased risk of cardiac or all-cause mortality following COVID-19 vaccination in young people aged 12-29." Numerous analyses (Nafilyan, CDC, etc.) have demonstrated the risk of cardiac death following SARS-CoV-2 infection, whose risk is greatly reduced by receiving COVID-19 vaccines. Therefore, there are a number of reasons to be skeptical of the claim that mRNA COVID-19 vaccines increase cardiac death by 84% in young men. The analysis does not weigh benefits against risks, as the guidance purports to do.

A recommendation to withhold COVID-19 mRNA vaccines for certain age groups, should be supported by a careful risk-benefit analysis. Such an analysis could have been performed, and indeed has been performed by the US and other governments, and by academics. Conversely, Dr. Ladapo's FDOH analysis and associated policy are of highly questionable merit. Importantly, Dr. Ladapo's report and policy have furthered the dubious claim that mRNA vaccines are leading to vastly increased numbers of cardiac death in young men, a claim which has been repeated and defended by Dr. Ladapo despite its shortcomings. These statements further elevate our concerns that he has "knowingly published material that will mislead readers".

In summary, the committee has concerns that Dr. Ladapo may have violated Sections 3.B.3 of the UF faculty policy on research integrity and has referred the matter to the University of Florida Research Integrity Officer (RIO).

References

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Cherry Picking: When People Ignore Evidence that They Dislike, (https://effectiviology.com/cherry-picking).