Comment on "Protection from COVID-19 vaccination and prior SARS-CoV-2 infection among children aged 6 months - 4 years..."

Siguna Mueller*

Center for Research in Medical Pharmacology, University of Insubria, Varese, Italy
Correspondence:
smuellermueller@uninsubria.it

Abstract

In the United States, mRNA COVID-19 vaccines were first authorized in June 2022 for children aged 6 months - 4 years with the aim to prevent severe outcomes from COVID-19. However, data on the actual safety and efficacy to prevent infection or severe disease, also in the context of prior exposure to the virus and the emergence of new viral variants, are scarce. To address this extremely urgent issue, Feldstein et al. [4] recently published merged data from 3 prospective cohort studies in children <5 years of age. The information provides valuable insights into the real-world performance of the injections in this age group. In contrast to the author's highlights of their potential to reduce severe disease, here, an independent analysis that examines the totality of data, identifies important insights missed before. The critique done here is exclusively based on the information provided in [4] and identifies the radically opposing narrative given by Feldstein et al., in sharp contradiction to their own findings. This investigation concludes with potential underlying mechanisms to explain some of the underappreciated data by Feldstein and collaborators.

Keywords: COVID-19 mRNA vaccines, children, CHD study, prior infection, vaccine efficacy

1 Motivation

A recent publication by Feldstein et al. [4], in collaboration with the Centers for Disease Control and Prevention (CDC), provided indispensable study data on the impact of COVID-19 mRNA vaccines on children. The study was conducted from Sept 1, 2022 to April 30, 2023 in the United States in a prospective manner. Examined were children aged 6 months to 4 years who received various types and doses of these injections. The median follow-up time was 154 days, during which vaccinated kids were compared to the unvaccinated peers in terms of their risk of either contracting (1) SARS-CoV-2 infection or (2) symptomatic COVID-19. The impact of prior infection was also examined.

In light of the importance of the new information provided for guiding and adapting public health policies and informing doctors and parents, this article provides an independent analysis of the published

*ORCID ID: 0000-0002-2016-5027

data. Even though the authors conclude that, based on their data, "COVID-19 vaccines are recommended to reduce severe illness; the overall risk of infection may not differ substantially between vaccinated and unvaccinated naïve children <5 years," it is found this conclusion is not supported by the information provided in the article. On the other hand, the data provided demonstrate important insights and raise additional questions.

2 Appraisal and Evaluation of the Study Findings

The data provided in [4], especially in Table 2, are noteworthy. The outcome of various study interventions was first determined in terms of incidence per 1000. To further highlight the impact of vaccination, these data are then converted into their respective hazard ratios (HR). These measures delineate the relative risk of an event occurring in one, compared to another, group, such as a control group and a treatment group. (For example, an HR of 3 means that three times the number of events are seen in the treatment group, whereas an HR of 0.333 indicates that the hazard rate in the treatment group is one-third of that in the control group.) In the study, while some of the HR values were smaller than 1, the majority, including those with greatest relevance, were substantially greater than 1, demonstrating the substantial elevated risk that the vaccinated kids experienced relative to their unvaccinated peers.

The critique below is solely and exclusively based on the data of [4]. Specifically, the HR values of Table 2 in Ref. [4], relative to the respective baseline conditions indicated therein are summarized in Fig. 1 below.

2.1 Strong natural immunity, but explicit sequelae for consecutive vaccination not assessed

One of the key study insights was the strength of natural immunity. In the paper, prior infection with SARS-CoV-2, "was defined as laboratory confirmation of infection by RT-PCR from a study-collected specimen, positive anti-N SARS-CoV-2 antibody, or self-report of infection prior to enrollment or September 1, 2022 (whichever occurred later)." The authors warn that "contracting a primary infection in a naïve immune system poses a risk of severe events such as hospitalization and death." However, their data show the opposite.

As had been expected for natural immunity in general, prior infection was associated with a lower incidence of both SARS-CoV-2 infection and symptomatic COVID-19 also for children aged 6 months-4 years. However, in Table 2 of their paper, the authors did not distinguish the vaccinated from the vaccinated when estimating the protective effect of prior infection with SARS-CoV-2. Throughout the study, natural immunity resulted in a substantial lowering of risk of infection, so that the Adjusted HR (95% CI) relative to (a) SARS-CoV-2 infections and (b) Symptomatic COVID-19 were, (a) 0.58 (0.25, 1.35) and (b) 0.47 (0.10, 2.16), respectively. This means that infection lowered by more than half the risk of contracting symptomatic COVID-19.

Moreover, natural immunity was both strong and durable, and assessed for much longer than the general study period. Remarkably, after 365 days, the adjusted HR for any SARS-CoV-2 infection was still 0.29. This is a firm indicator that natural infection provides lasting immunity that also facilitates

cross-protection against emerging SARS-CoV-2 variants (Figure 1(a)). Although natural immunity was still strong after 1 year, the durability of hybrid- or vaccine-only immunity was not determined.

2.2 Efficacy Data

This section provides some of the main insights and controversial results that can be derived from the article. The data are all taken from Table 2 in the paper by Feldstein et al. [4]. For simplicity, the actual HRs are given without their confidence intervals (which can be found in that table). Only those comparisons are discussed for which the estimates rely on a baseline that is reasonably justified (see below).

2.2.1 Important comparisons are not provided

As mentioned, in the study, natural immunity was highly protective for the overall study population. The impact of prior infection on the study and control group was substantial, in both cases lowering their risk of (symptomatic) infection. Unfortunately, the article does not provide any data on the extent to which prior infection changed the outcome in the vaccinated group. For these, rather than contrasting the risk for subsequent infections in relation to the presence or absence of prior infection, the risk estimate is given relative to a different baseline (the unvaccinated). In that case, vaccination plus prior infection resulted in an HR of 0.31. While this looks impressive, this is compared to the unvaccinated without prior infection. Apparently, this data point prompted the authors to conclude that "prior infection plus vaccination may provide the strongest immunity." Yet, critical comparisions, such as between vaccinated/naive and vaccinated/prior infection are missing.

2.2.2 Several measures rely on inappropriate baselines

As just noted, the paper frequently relies on comparisons between cohorts that do not seem justified whilst excluding others. For example, the article says nothing about how prior infections impacted later vaccination. We only know the combined effect ("hybrid immunity) relative to those who had neither been vaccinated nor infected with the virus. We are not told the degree to which infection alone impacts vaccination.

Table 2 in the paper contains several other comparisons with an inappropriate baseline. These are excluded here from the discussion. Specifically, Table 2 in the paper also compares the unvaccinated/naive with the vaccinated/prior infection, further broken down relative to vaccine manufacturer or timing of vaccination. In all these cases, the HR values are less than 1, making it appear as if the intervention (vaccination) had a very protective effect, especially for those with prior infections. Again, these assertions were made relative to a different baseline whereas the actual effects of prior immunity in the vaccinated group or its subgroups were not measured.

Likewise, the authors also do not contrast the durability of natural immunity compared to vaccination or hybrid immunity. Thus, overall, only some group comparisons were made and others were omitted (Figure 2).

Given the strong natural immunity in the unvaccinated cohort, one may wonder to what extent the protective effect of hybrid immunity is attributable more to natural infection than injection. Related comparisons could have been, but were not made, for instance between the unvaccinated/prior infection with the vaccinated/prior infection.

2.2.3 Vaccination either led to minimal or substantially negative protection

As indicated in Table 2 in the paper by Feldstein et al. [4], for the most part, vaccination had no protective effect at all. An overall summary, by manufacturer and time since last the most recent shot, is given in Figure 1(b) below.

As is obvious from Figure 1(b), with the exception of Moderna's vaccine which marginally lowered the risk for (symptomatic) infection, overall, those who were vaccinated had an increased risk and were therefore more likely to get sick than those who were not vaccinated!

2.2.4 Compared to Moderna, the Pfizer-BioNTech injection showed an even more negative outcome

As summarized in Figure 1(b) overall, and further in Figure 1(c), kids who got the vaccine by Pfizer-BioNTech were much more likely than the unvaccinated to get a (symptomatic) COVID-19 infection. Figure 1(c) summarizes only individuals without prior infection ("naïve") irrespective of their vaccination status and thus eliminates the protective impact of natural immunity.

Interestingly, while the protective effect relative to any SARS-CoV-2 infection was overall negative, for Moderna, kids without prior infection seemed to experience a slightly positive protective effect for symptomatic infections. Albeit, as the Adjusted HR (95% CI) was 0.67 (0.16, 2.83), the very large CIs indicate a wide range of responses, including negative protection for some. Given the known decline of vaccine efficacy over time, this finding of negative protection for some within the short study period does not justify the efficacy of Moderna, and much less Pfizer-BioNTech.

The drastically increased risk for both infection and symptomatic COVID-19 for Pfizer-BioNTech is a serious red flag but not highlighted by the authors. The reasons for this enormous discrepancy between the two manufacturers must be urgently investigated. Possible explanations include quality differences and manufacturing problems related to contaminants such as DNAs or RNA/DNAs [9,13,22] or aberrant proteins resulting from the mRNA modification [15].

Another plausible reason for the highly elevated negative protection for Pfizer may lie in the increased number of shots. In the study, the vaccinated were those who had completed at least their primary series: whereas for Moderna, this was at least 2 doses, for Pfizer-BioNTech, this was at least 3. The higher risk of infection with a higher number of COVID-19 vaccine doses received is inline with what is known for adults [21]. Apparently, the same tragic pattern also applies to children.

For those without prior infection, the impact of vaccination was essentially always negative Despite the seemingly positive effect against symptomatic COVID-19 in the "naïve" subgroups, overall, for those without natural immunity, those who had received any vaccine were not better protected against (symptomatic) infection than their unvaccinated peers. As summarized in Figure 1(d), for those without prior

infection, even bivalent boosters could not remediate the non-existing or even negative protection.

2.2.5 Ongoing vaccination and bivalent boosters obfuscate the durability of vaccine-immunity

Inherently, the prospective nature of the study obfuscates insights into the waning of vaccine protection. It is important to emphasize that whilst the main study period covered 8 months, the median follow-up time was only 154 days. Yet, as kids continued to get vaccinated, this is not the same as the median time-span since the last injection. This may be significantly shorter. Especially with the bivalent boosters, due to their rollout later in the study, the follow-up time is clearly reduced.

Bivalent boosters were limited to the time they became available during the study. Given that this time (December 17, 2022 to May 6, 2023) is 2 months shorter than the general study period, and that the new approval will have accelerated booster uptake during the study period, this will likely shorten the median follow-up for the bivalent boosters to much less than 100 days.

2.2.6 The bivalent boosters did not help

According to the authors, bivalent boosters could have been instrumental to counteract the negative findings seen otherwise which they believe, results from viral evolution. They emphasize this by saying: "Interestingly, among participants without evidence of prior infection, those vaccinated with Pfizer-BioNTech were more likely to have SARS-CoV-2 infection and COVID-19 compared to those who were naïve and unvaccinated. This may be partly due to the fact that only 28% of children who were vaccinated with Pfizer-BioNTech received a bivalent Omicron-containing Pfizer-BioNTech vaccine, either as the third dose of the primary series (80.6%) or as an additional booster (19.4%)."

However, the purportedly strong protective effect of bivalent boosters is not supported by the study data. Even though Table 2 in their paper indicates an Adjusted HR (plus 95% CI) in this case of 0.74 (0.37, 1.48), this reduction compared to the unvaccinated was only seen for "any" SARS-CoV-2 infection, including those who were asymptomatic and merely "laboratory confirmed".

Yet, the authors themselves emphasize the importance of COVID-19 vaccines to "reduce severe illness." Nonetheless, their own data reveal that bivalent boosters do not minimize the risk of symptomatic disease as their HR (plus 95%) compared to the unvaccinated was actually 1.04 (0.37, 2.96). For those with no prior infection, receiving a bivalent booster resulted in a further elevated risk compared even to those who did not get such a booster (summarized in Figure 1(d)).

Thus, the predicament of vaccine waning because of viral evolution and escape is not remediated by bivalent boosters which instead seem to make the situation even worse.

2.2.7 The waning of vaccine immunity is re-established in the study

The rapid waning of COVID-19 vaccine immunity is a well-established fact and also confirmed in this study. As summarized in Figure 1(b), the risk for (symptomatic) infection is even greater after 60 than within 60 days of receipt of the last injection. Moreover, as just noted, it is not known for how much longer than 60 days the majority of participants were followed. Despite the limited follow-up time, the

study data showed that with time, the protective effect against symptomatic disease further decreased and their propensity for negative protection further increased (summarized in Figure 1(b,d)).

2.2.8 Gigantic Confidence Intervals

The troubling findings of vaccination engendering negative protection are further heightened when one considers the confidence intervals as provided in Table 2 in the paper. In all cases where vaccination has a demonstratively negative effect related to the prevention of symptomatic infection, the respective CIs are humongous, with upper limits of 5, 6, 7, or even over 11.

2.3 The negative effect may be worse for "prevention of symptomatic COVID-19" than that of SARS-CoV-2 infection alone.

Some estimates, e.g. as depicted in Figure 1(b), indicate the increase in elevated risk is further pronounced when assessed in the context of symptomatic COVID-19 compared to the inability of the injections to prevent any SARS-CoV-2 infection.

This, along with the enormous differences seen in the CI upper limits is unexpected for homogeneous pharmaceuticals and instead suggests enormous product differences, tremendous variations in the mechanism of actions, and other underappreciated patient differences. Products with such a wide range of negative immune protection are not in line with what the public expects from vaccines.

3 Conclusion

The study by Feldstein et al. [4] provides valuable insights into the immune-protective effects of COVID-19 mRNA vaccines on children aged 6 months to 4 years. The analysis done above belies the main conclusions made by the authors:

- "There was no difference in incidence by vaccination status." This assertion does not align with the study data which clearly demonstrates the opposite.
- "While COVID-19 vaccines reduce severe disease, they may not reduce overall SARS-CoV-2 infections in young children." Even though the latter part somewhat resembles their actual findings, it is a huge understatement. The data in the paper highlight the antagonistic effects of the injections, displaying negative immune protection.
- Likewise, the assertion about severe disease prevention is contradicted by the data provided as the study even showed a further increase in the risk of contracting symptomatic COVID-19 than merely indicating a positive SARS-CoV-2 test. The impact on "severe" disease was not even studied in the paper as "symptomatic" COVID-19 was merely defined as "a positive RT-PCR test and $\geq$2 COVID-like illness symptoms reported within seven days before or after the specimen collection date). Moreover, as explicitly stated in the paper, "Importantly, the outcomes of infection and symptomatic COVID-19 as defined in these cohorts represent predominantly non-severe disease," meaning that the authors repudiate their own conclusion.

The detailed study data yield important insight not mentioned by the authors. The negative effect on protection overall, seemingly even further pronounced against symptomatic COVID-19, including the bivalent boosters, and the marked differences between Moderna and Pfizer/BioNTech are strong indicators of additional factors beyond the anticipated antibody-mediated immunity, suggesting a common underpinning via their commonality to what is known mostly for adults. These include:

- Immune tolerance and negative protection [1, 7, 10, 14, 23],
- Immune impairment of heterologous coronavirus infections or prior immunity [5],
- Ill-defined and variable immune responses due to mRNA modification, codon optimization, the inflammatory nature of the lipid nanoparticles, and the biocorona, [14, 17, 20],
- Vaccine-induced pathologies and aberrant health effects [2, 8, 11, 16],
- Lot variations and variations in vaccine composition [6, 12, 18, 19],
- Generation of aberrant vaccine-antigens [15],
- Product variations due to design as well as manufacturing and contaminants, supply-chain, storage, and dosing challenges [9, 13, 14, 22],
- Inherent unpredictability due to the nature of the injections as pro drugs and active pharmaceuticals [3].

In all, despite the preeminence of the funder (the CDC), potential COIs, and faulty conclusions and recommendations, the authors have provided invaluable data about the real-world impact of mRNA vaccines on kids and key insights that still paint a sobering picture: these products do not deliver the protection as intended, their mechanisms of action remain insufficiently understood, and their real-word impact is rapid immune waning, at best, and a seemingly unavoidable risk increase with time and number of doses delivered. The conclusion in [4] as it currently stands requires significant revision.

Figures

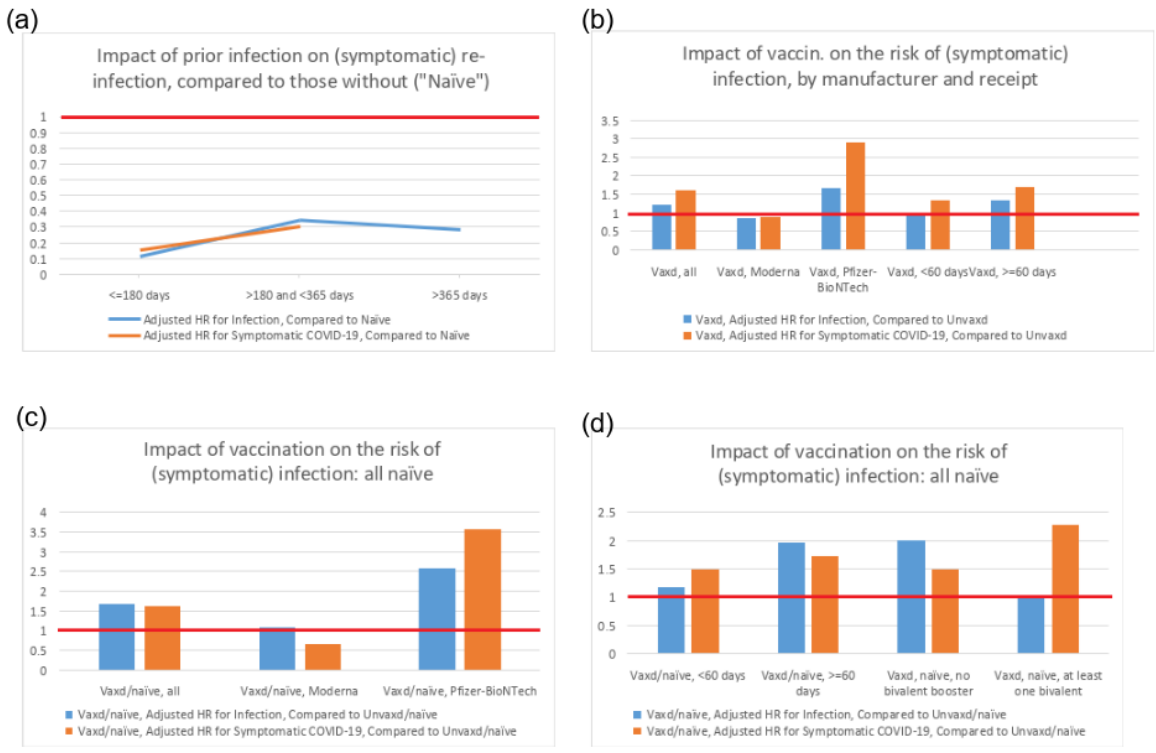

Figure 1: **Summary of the main findings by Feldstein et al. [4].** Data are exclusively taken from [4] and depicted here graphically. Overall, the y-axes illustrate the Adjusted Hazard Ratios (HR) of [4] relative to the respective unvaccinated comparator groupsn indicated therein. For details, including the corresponding CIs, see Table 2 in [4]. (a) HRs following prior exposure, by time since the most recent infection: Infection with SARS-CoV-2 prior to the study resulted in lasting and strong natural immunity (regardless of vaccination status) when compared with those without evidence of prior infection ("Naïve", regarded as reference). This was essentially true for all study participants (the upper limits of the 95% CIs are less than or comparable to 1). (b) By manufacturer and time since last injection: The HRs explicitly show how "vaccination" decreased or increased the frequency of getting(symptomatic) COVID-19 when contrasted with the unvaccinated (baseline indicated in red). (c) Analogous to (b), with no participants having any prior immunity ("naïve"). The HRs explicitly show how "vaccination" of kids without prior infection decreased or increased the frequency of getting (symptomatic) COVID-19 when contrasted with the unvaccinated without prior infection (baseline indicated in red). (d) Analogous to Figure (c), involving immune "naïve" participants, by the timing of receipt/utilization of bivalent boosters.

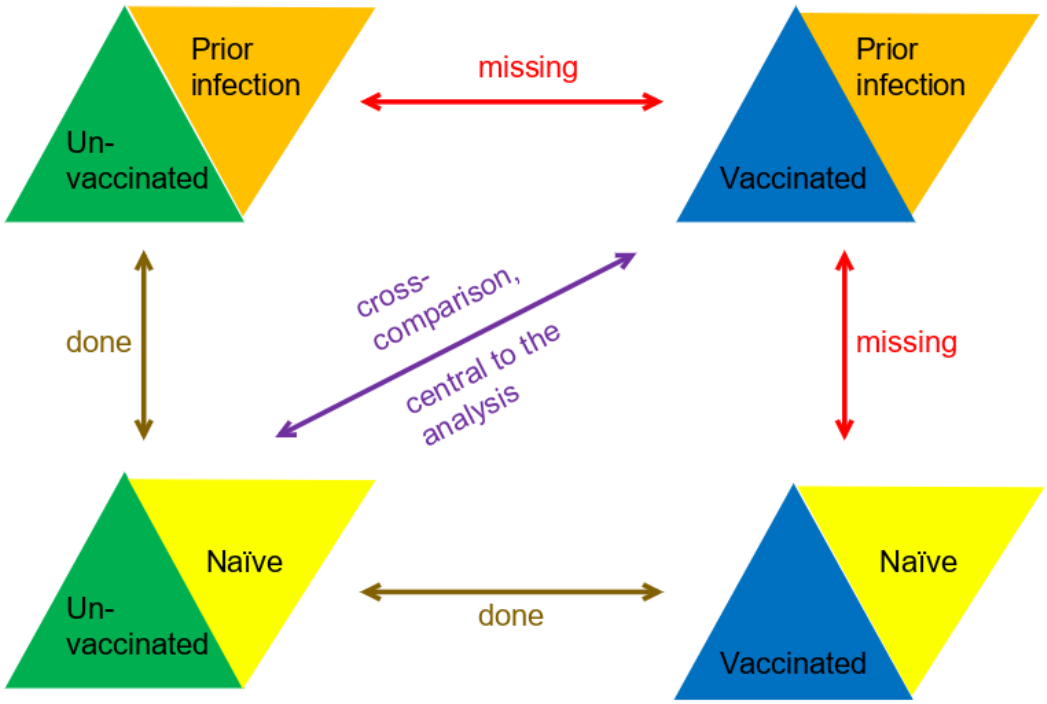

Figure 2: **Baselines used in the study by Feldstein and colleagues [4].** The main findings of the article by Feldstein et al. are detailed in their Table 2 (titled "Incidence and adjusted hazard ratios of laboratory-confirmed SARS-CoV-2 infection and symptomatic COVID-19 among children aged 6 months – 4 years by vaccine type and interval since receipt of a bivalent vaccine dose"). Other than for the natural immunity estimates (see Figure 1 above), the reference population is either the vaccinated or, more specifically, the vaccinated without prior infection. Yet, when comparing to the vaccinated cohort, the comparators often involve those with prior immunity. Overall, not all possible comparisons are given (missing ones are in red) while some use an inappropriate reference population (indicated in violet).

Declarations

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CONFLICT OF INTEREST STATEMENT

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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AUTHOR CONTRIBUTION

The author is responsible for the conception of the study, literature review and interpretation, drafting and writing the manuscript, and has approved it for submission.

AUTHOR INFORMATION

The author is an experienced independent transdisciplinary researcher with a Masters in Mathematics/Statistics (with highest distinction, University of Klagenfurt, Austria), a PhD in Mathematics (summa cum laude, Univ. of Klagenfurt), 'Habilitation' in Mathematics, Data Security and Cryptography (Univ. of Klagenfurt), and a PhD in Biomedical Sciences (GPA of 4.0, University of Wyoming, USA). She has been a member of The European Network of Scientists for Social and Environmental Responsibility (ENSSER) since 2020, is also the author of "Challenges and Opportunities of mRNA Vaccines Against SARS-CoV-2 – A Multidisciplinary Perspective" Springer 2023, and has been volunteer contributor to several open-ended online Forums of the Convention on Biological Diversity. After years of independent work, in October 2024, she joined the Center for Research in Medical Pharmacology, University of Insubria, Varese, Italy as a PhD student in Clinical and Experimental Medicine and Medical Humanities.

The author's ORCID ID is: 0000-0002-2016-5027

CODE AVAILABILITY

This work did not use any computer code or mathematical algorithms. It is entirely logical and rational analysis.

DATA AVAILABILITY

Not applicable. This work is a logical and rational analysis.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable. This is a theoretical analysis only.

INCLUSION AND ETHICS IN GLOBAL RESEARCH

Not applicable. This is a theoretical analysis only.

ADDITIONAL POLICY CONSIDERATIONS

This work did not include any macromolecular structural data, biological materials, research on animals and/or animal-derived material, human embryos, gametes and/or stem cells, human research participants, clinical data, or any archeological, geological, or palaeontological materials.

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