Legitimate questions on "Real-World Immunogenicity and Reactogenicity of Two Doses of Pfizer-BioNTech COVID-19 Vaccination in Children Aged 5–11 Years"

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Abstract

This paper poses some legitimate questions on the contents of a paper dealing with the issue of children vaccination against COVID-19 with the BioNTech product. As a result of the COVID-19 pandemic, it is becoming urgently needed to make a clear distinction between scientific and marketing communication. The questions posed may help the reader to clarify the actual contribution and nature of the referred study. Hence, this paper does not follow the conventional structure of a scientific paper. For instance, we do not give specific conclusions, because we do not know in advance the potential answers to the posed questions. However, we expect that future readers of the referred paper may benefit from a critical reading using this paper to draw their own conclusions and to take it as a starting point for further enquiries.

1 Introduction

Posing legitimate questions is the cornerstone of knowledge generation, specifically critical for scientific development. Specifically, the scientific community must be free to attack and confirm or falsify scientific statements [17]. The COVID-19 pandemic has been characterized by the denial of such simple rights. The denial of the right to question is often grounded by the authorities on the obligation to trust without question. It is paradoxical that the public is forced into trusting corporations whose only liability is regarding the profit of the stakeholders. Specifically, in the USA, under the National Childhood Vaccine Injury Act of 1986 (42 U.S.C. §§ 300aa-1 to 300aa-34)[1] companies manufacturing products under the label of vaccines are not liable and can not be brought to court

[1] https://www.congress.gov/bill/99th-congress/house-bill/5546

for lack of effectivity or serious adverse effects (SAE). All responsibility lies on the government institutions that must guarantee the public safety. Moreover, the contract[2] for the purchase of Pfizer-Biontech *successful vaccines* deviates all liabilities to the Member States that are responsible for the administration of the doses purchased by the European Commission. The same institutions that survey the vaccine products safety are liable for any damage caused by them. The public is forced into automatic compulsory trust on companies that work for profit and on Member State institutions that might well be protecting them (the companies) in order to protect themselves to answer for lack of effectivity or SAEs.

In its influential book [4] Edward Barnay set the basics for the control of the masses, mostly with commercial and financial goals in mind. One of the keystones of the propaganda machine is the use of well known and well respected persons to promote the product. Of special interest are scientists which can endorse the product with scientific like reasoning. This strategy has been and is being exploited by the tobacco industry and the ultra-processed food and sugar industries [2, 3, 14, 8, 16, 15, 18, 9, 5, 20]. In this context, it is important for the reader to discriminate marketing papers from scientific papers, specially when the papers are trying to influence public policies or set mandates.

Therefore, we assert our right to pose legitimate questions and to receive clarifying responses, ... or silence (that is better than wild dogs barking at the moon).

This paper follows an unusual structure. We focus on a succession of aspects of the paper [10], discussing each one and stating specific questions that we find relevant in order to achieve a correct understanding of the study and its results, as well as of its implications in the formation of public policies that the authorities claim to be sustained by Science, despite contradicting evidences. For each aspect we pose specific questions

2 Conflicts of interest

The authors [10] declare no conflict of interests and no funding to carry out the research. However, it is immediate to find in an internet search that the Sheba Medical Center has been a showcase for Pfizer at several stages of the COVID-19 pandemic. Recently, it has been publicized by the institution itself that it was the single site outside USA running the observational studies on the immunogenicity of combined Omicron boosters, and studies relating the relative immunogenicity of the Moderna and Pfizer products as second boosters. It is difficult to understand that these works would have been done for free when the Sheba Medical Center is a private for profit company and Pfizer has huge financial interest in the outcome of the observational studies. It would be highly clarifying to know if there is any kind of institutional contract or agreement between the Sheba Medical Center and Pfizer, under whose umbrella the employees of the Sheba Medical Center may be compelled to participate

[2] published by the Italian RAI https://www.rai.it/dl/doc/2021/04/17/1618676600910_APA%20BioNTech%20Pfizer___.pdf

or carry out the study. It would be of special interest to know if the potential agreement includes professional help to write and publish the article, something that would ease the burden from the already overwhelmed authors. Specifically, it would be quite clarifying to assess to what extent the recruitment process has been true to the Helsinki declaration to know if the refusal by parents to participate in the study would somehow conflict with any standing agreement between the Sheba Medical Center and Pfizer. It would be enlightening to know the actual number of employees with children in the target age range, and the relative success of the call to participate, as well as the actual message conveyed for recruitment. The conflicts of interest of reviewers and editors should also be stated when an approved paper is to be used in the marketing strategy of a company. To summarize, we pose the following legitimate questions on potential for conflicts of interest:

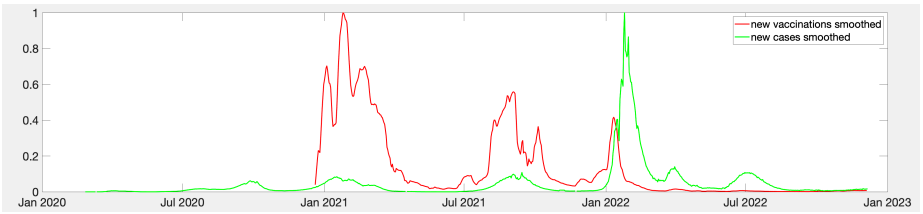
- Is there any framework contract between Sheba Medical Center and Pfizer that covers the work reported in [10].? Are the costs of the study covered exclusively by the authors?
- Could the Sheba Medical Center employees be/feel compelled or coerced into participating in the study either as researchers or parents.?
- Have significant parts of the paper been written by professional writers hired by Pfizer, Biontech, or the Sheba Medical Center ?
- Have the reviewers and paper editors any undeclared conflicts of interest?

3 Early bird infections after vaccinations

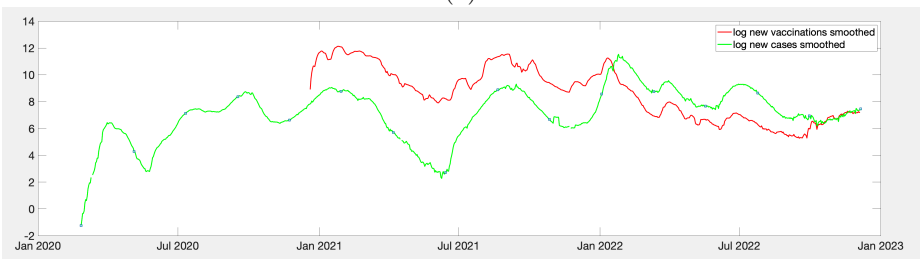
The first paragraph of Section 3 [10] includes the statement "Of them, 10 children were found positive between day 0 and day 21 and were excluded from the analysis." This exclusion has not been stated in section 2.2 of the paper. Besides, the Table 1 has no mention of the 10 children excluded from the study because they tested positive in the period 0 to 21 days. Exclusion of these patients is noted as casual and irrelevant for the main analysis. However, we note that 93 infections out of 120 recruited children is quite close to 78% of infections in a vaccinated population. We think that some question about vaccine efficacy can be posed even if the study was not designed to measure efficacy.

A well known but poorly understood phenomenon is the Antibody-dependent enhancement (ADE) of virus infection and disease [19], which has been warned against for COVID-19 vaccines [13]. A legitimate question is whether ADE is mechanism responsible for these early infections after vaccination, which amount to almost 10% of the original cohort. We have not found any effort by manufacturing companies and vaccination advocates to check out this hypothesis by clinical or biochemical analysis, only plain denial of the evidence by simply dropping the data out of any study, like the authors do in this paper.

To shed some light on the issue, we would like to put into consideration the relation between vaccination efforts, COVID-19 cases and deaths in Israel



(a)



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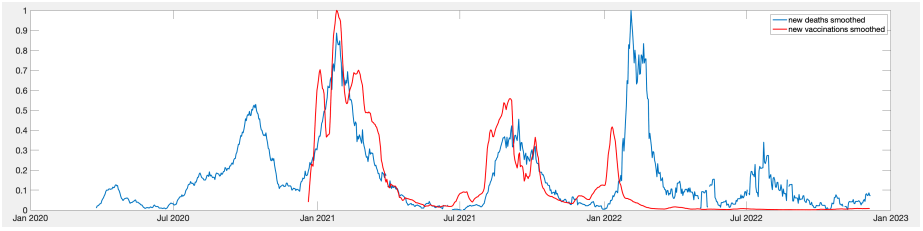

(c)

Figure 1: Graphical Relation between vaccination efforts and COVID cases and deaths. Extracted from `https://ourworldindata.org/explorers/coronavirus-data-explorer`.

visualized in Figure 1. The data has been downloaded from ourworldindata.org. The data and the matlab code is available at zenodo.org [7]. Figure 1(a) plots together the vaccination doses and the detected cases, both time series normalized in the [0,1] interval[3]. The exponential explosion of cases of the Omicron wave in early 2022 diminishes the scale of previous waves of cases. Israel reporting of testing efforts in ourworldindata.org stopped in June 2022, at the time the number of tests per case was in the order of 5, conversely the share of positive tests was over 30%. These two values can be interpreted as an endemic situation of the COVID-19 after a massive intervention that achieved fully vaccination of 65% of the population, as reported in ourworldindata.org. Therefore, the end of the Omicron wave appears to be due to the end of massive testing efforts, rather than the end of the endemic propagation of the virus.

In Figure 1(a) it can be appreciated that each wave of vaccination effort correlates to or anticipates a wave of cases. In order to highlight this correlation/anticipation, we plot the logarithms of cases and doses in Figure 1(b), where a nice correlation can be observed in two periods (a) since the beginning of vaccination until the end of 2021, and (b) after March 2022 until the end of the series. In the middle of these two periods, there is a wave of doses at the end of 2021 that anticipates the Omicron wave of cases. A time series causal analysis, i.e. applying Granger causality test, should conclude the causal connection between doses and cases in this time period. Finally, Figure 1(c) plots together the COVID-19 deaths and doses. During the year 2021 there is a nice correlation between doses and deaths. Again, the wave of booster doses at the end of 2021 may have a causal relation (using Granger causality tests) to the greatest COVID-19 mortality peak in Israel by the Omicron wave. Detailed quantitative analysis should confirm our qualitative observations.

These observations may point out to the fact that the early bird infections after vaccination may not be a casual isolated event. Consequently, we believe that the following are legitimate questions:

- Why have been removed the early bird infections from the reported results?
- Could early bird infections be a rather generalized epidemiological response that explains the observed correlation of treatment waves and deaths and cases?
- Could early bird infections be due to ADE effects?
- In view of how the wave of doses at the end of year 2021 appears to anticipate/predict the surge of cases and deaths in early 2022, could ADE explain the success of the Omicron variant?
- In several parts of the manuscript, authors refer to the "high immune scape" of Omicron VOCs, as well as their high transmissibility in a strongly

[3]This normalization to the [0,1] interval has the inconvenience of reducing the visual impact of the waves previous to the Omicron wave, because of its sheer scale. Local plots should highlight the correlation between cases and vaccine doses in these early waves.

vaccinated population. Have the authors considered that instead of "escaping the vaccine" Omicron may have been boosted by the vaccine?

- What could be the public health impact of a massive pharmacological intervention based on the same technology used to develop the COVID-19 vaccines to treat the AIDS pandemic, i.e. to attack the HIV virus?

4 Efficacy

Authors of [10] acknowledge that the study was not designed to measure efficacy of the treatment, however their definition of efficacy remains hidden and blurry. In the abstract, we find the following phrase "Of the 110 vaccinated children, 75.5% were infected, with only mild COVID-19 infection symptoms." This phrase is constructed in a way that suggests that the vaccination is the cause of the mild symptoms. However, in the discussion section authors recall that during the worst of the Omicron wave, the risk of moderate/severe/critical hospitalization for children was $3.2/10^5$ without referring comorbidities that may be explanatory of the outcome and in absence of information about vaccination status[4]. This fact does not support the suggested association between vaccination and mild symptoms. Moreover, 37% of children in the age range of the study were infected during the Omicron wave while the rate of infections in this study is over 75% in vaccinated children. We can formulate the following legitimate question:

- Is it possible to assert the efficacy of the vaccine in reducing the number of infections when the ratio between infections in the vaccinated sample and in the (most likely unvaccinated) population in the same age range is 2.04? I.e. the risk of infection in vaccinated children appears to be twice to the general (unvaccinated) population.

In the discussion section [10], authors refer to the safety and efficacy study for children in the age range 5-11 years carried out in the USA by Pfizer and Biontech [21]. This study reports a relative efficacy of 90% of the vaccine (infection ratios 16/736 for placebo and 3/1450 for vaccinated). However, in the vaccinated population infections in the period between the first dose and seven days after the second dose went unrecorded and unreported. This information was missing even in the supplementary material. Notice that in [21] the count of infections for the placebo cohort starts the same day of the first dose. Let us consider that the same ratio of infections observed in [10] (10 out of 120) in the period between the first and second dose happened in [21]. This would amount to 120 infections that went unreported in [21], so the corrected relative risk increase **due to taking** the vaccine would be 290% (almost a 3 fold increase in risk for the vaccinated), conversely relative risk reduction achieved by **not**

[4]It is not clear if vaccination was recommended in this period of time for children in the age range of the study, thus the vaccination status is very likely negative for most or all of these children.

taking the vaccine would be 74%. These results are so different to the desired conclusions that hiding the data should have appear the only natural course of action to the people in charge of [21]. It becomes self-evident that the data should be public and available to independent researchers when the decision about an intervention over a sensitive population is based on the data analysis results.

5 Poor adherence

Table 1 [10] gives some details of the adherence to the study by the children/parents. The number of tested children at day 180 is a mere 26% of the original cohort of 110. There is no specification of how many infected vs. uninfected children assisted to the testing sampling in days 90 and 180.

- Is the lack of adherence to the study related to the emergence of infections?

Another surprising data in Table 1 is the increasing adherence to fill the questionnaires that reach 100% in the two last visits. We can assume that they are online responses and that the participants were actively encouraged to respond, but there is no explanation in the paper.

6 Immunogenicity, natural immunity, and infections.

In Section 3.1 and supplementary tables S3 and S4 the summary results regarding immunogenicity are reported. A salient fact is that, despite increase in immunogenicity markers, 75.5% of the children were infected. This raises the following questions:

- How relevant are the immunogenicity markers to measure protection against infection, when their positive increase is uncorrelated with the actual infections?
- Are immunogenicity marker processes and instruments so tightly calibrated to the ancestral Wuhan virus that they are useless to predict protection against even minor variants?
- Taking into account that the ancestral Wuhan virus is no longer in circulation (unless there is some redistribution of it into the general population from laboratory samples), is it reasonable to think that the generation of specific antibodies for the ancestral Wuhan virus may have no impact on the protection against new variants?

Another salient fact is that the increase in immunogenicity markers is greater, and sustained longer, in infected children than in uninfected children. The difference is not statistically significant at visit 3 (day 90) but it becomes significant at visit 4 (day 180). Note that the log scale in figure 1 of [10] does

hinder the visual observation of this fact. If we deny natural immunity, then we deny that vaccines may work in any form. Given that children's infections are usually short lived, (two weeks appear to be considered as long covid by the authors), it is remarkable that the effects extend until day 180 into the study. This observation raises the following question:

- Is natural immunity acquired by infection with the Omicron variant boosting the immunogenicity markers of vaccinated children, even when these immunogenicity markers are sharply focused on the the ancestral Wuhan virus?

The question is relevant, because the phenomenon goes in the opposite direction of the recommendations of health authorities in most countries, that state that having a dose after a natural infection "would increase the protection against new variants". The immunogenicity results in [10] can be interpreted as "having an infection after vaccination, your natural immunity will boost the protection against the ancestral Wuhan virus intended by the vaccine". Of course, infection will protect you against the last variant, otherwise no vaccine will be effective in any way. This leads to the following question:

- Is there any scientific (independent of financial interests) reason to impede children to acquire natural immunity via natural infection with the latest variants that are in circulation.?

Authors recall in the discussion section [10] that, despite the extremely high incidence of Omicron in early 2022 (over 37% of children in the age range of the study), the risk of moderate/severe/critical hospitalization was $3.2/10^5$ without referring comorbidities that may be explanatory of the outcome. It is not unreasonable to think that the risk from natural COVID-19 infection for **healthily developed children** is some orders of magnitude lower than this figure. Hence, the above question can be reshaped as follows:

- Is the risk from the vaccination significantly greater or lower than the risk from natural COVID-19 infection.?

In other words, for a population that has no adverse outcome from natural infection (i.e. children), measuring the reduction in the number of infections by the vaccine should be irrelevant for the establishment of a vaccination mandate or for personal decision. Moreover, it has been publicly stated by Pfizer representatives that the clinical trials did not measure transmission, hence the "do it to stop transmission" argument must be put on hold until there is clear and sound proof that the products effectively stop transmission. We can rephrase the above question as follows:

- Is the vaccine safer than natural infection.?

Recently there is a wave of publication that try to show that "yes, (some) vaccine is safer than natural infection" in some specific way. But the study under analysis [10] does not provide convincing proof, first because there is no

control unvaccinated population, second because safety signals that are evident from the data (to be discussed in the next Section) are ignored by the authors in the conclusions and discussion.

Finally, in Section 2.2 [10], an exclusion criteria that authors have considered is "history of SARS-CoV-2 in the previous 2 weeks". After noticing the long term effect of natural infections on immunogenicity markers (increase after 180 days), it is reasonable to expect some long term effects of previous infections. For instance, it would be interesting to know if the uninfected children had some history of previous infections that may have protected them additionally.

- Why previous history of infections (before previous 2 weeks) has been neglected in the study.?

7 Safety: Lymphadenopathy

Table 3 of [10] contains a summary of reported adverse events. Seven events of Lymphadenopathy were reported, i.e. 6% of the vaccinated children suffered Lymphadenopathy symptoms. Duration of the events was short, three days after the first dose, one day after the second dose. It is interesting to note that Lymphadenopathy is absent in Table 4. The acknowledged ratio of Lymphadenopathy events for the Pfizer-BioNTech COVID-19 vaccine is 0.3% [11]. Moreover, it is considered as a serious adverse event. The American CDC acknowledges an incidence of 0.9% in the range of age of the study [1]. A recent case report on the accelerated progression of a specific lymphoma which acknowledges a causality link with the BNT162b2 mRNA vaccine booster shot [6] should be a strong note of caution about the unknown effects of the vaccine on the lymphatic system. The specific question raised by these observations is the following:

- Why an observation of 6% incidence of lymphadenopathy (versus 0.3% or 0.9% in other literature sources) does not raise a safety signal.?

The study in [10] is short lived and can not give information about these risks. The study in [21] comments on a two year follow up, in an imprecise protocol.

- Why the manufacturing companies have not established a proactive long term screening of the health status of the participants.?
- If the companies are having profits in the order of billions, why they can not spare some money for a thorough follow up of study participants?
- Moreover, why this caution is not extended to the entire population that has been treated with an experimental product?

8 Open science: open access data and code

There is a new policy in Europe regarding the accessibility of scientific instruments enabling third parties to check, reproduce and falsify the published claims,

that goes under the name of Open Science[5]. It includes new resources for open access paper publishing, but also resources to publish data and code that allows reproducibility and falsifiability. In fact, all material related to this paper is being published in a zenodo entry [7], including data, code, referred documents and papers, and the paper itself. Following this philosophy, any claim that is not supported by Open Science best practices must be considered inconclusive and speculative. Moreover, if the paper is intended to influence public policies, then lack of Open Science standards should put the paper conclusions on hold. Sometimes, papers refer to a public repository that is empty in order to give the impression of sharing data and code [12]. The paper [10] gives no access link to the data (which could have been easily anonymized) nor the code. There is not a single reference of which software tools were used for the analysis in [10].

9 Conclusions

We have revised and proposed legitimate questions raised by the paper [10] with the aim of clarifying its contents and contribution to the improved understanding of the effects of the massive vaccination campaign. Israel is a very special case, because it was set as a case study for the Pfizer-Biontech product. As such, it has produced a great quantity of high quality epidemiological and clinical data that should be exploited to start searching for the answers to the questions posed here and elsewhere.

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Conceptualization and writing MG

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Conflict of interest

The author does not have any conflict of interest.

[5] https://research-and-innovation.ec.europa.eu/strategy/strategy-2020-2024/our-digital-future/open-science_en

Institutional Review Board Statement

Does not apply

Informed Consent Statement

does not apply

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