Concerns regarding the efficacy and safety for BNT162b2 mRNA coronavirus disease (COVID-19) vaccine through six months

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Summary of concerns

Efficacy

- Important limitations of the stated efficacy claims were not discussed
- Only the relative risk reductions were stated; absolute risk reduction metrics were not presented
- Integration of adult and adolescent cohorts with differing follow-up periods were presented without explanation
- Large number of discontinued or missing participants comparable to primary end-point event numbers
- Prior SARS-CoV-2 infections screened only in a subset of trial participants, and determined only by an antibody test with severe sensitivity limitations
- Cut-offs of the RT-PCR positivity tests were not reported; no confirmatory functional virology assays were performed
- Absence of systematic testing and unbiased testing framework for the detection of SARS-CoV-2-infected participants

Safety

- Trial participants were healthier than the average population
- Monitoring of adverse events were limited in time and scope
- Number of severe adverse events in the vaccine arm were much higher than the numerical reduction in severe COVID-19 cases between vaccine and placebo arms
- Superficial evaluation of the most clinically relevant end-point - survival; no independent assessment of the causes of death provided
- Cardiovascular adverse vaccine events are now widely recognized, yet no systematic monitoring of cardiovascular health was carried out
- Substantially higher number of solicited and unsolicited adverse events, most of which presented as COVID-19-like symptoms, in the vaccine arm yet study claims efficacy against symptomatic COVID-19
- Increase in cardiac-related deaths in the vaccine arm compared to placebo arm
- Inability to assess long term safety within the trial due to unblinding and participant crossover to the vaccine arm

Other concerns

- Multiple conflicts of interest of a large majority of study authors
- Multiple trial irregularities reported by Thacker *et al.* (1) published in the British Medical Journal

Article

We present several concerns regarding the recent article by Thomas *et al.* (2) on the efficacy and safety of the BNT162b2 mRNA coronavirus disease (COVID-19) vaccine, which was published in the New England Journal of Medicine (NEJM) on November 4, 2021. An abbreviated version of this letter was submitted to the NEJM on November 15, 2021 and declined for publication on November 29, 2021 due to limited space. The study assessed the BNT162b2 in individuals that were healthy or had stable chronic medical conditions and concluded that, "through 6 month follow up, despite a gradual decline in vaccine efficacy, BNT162b2 had a favorable safety profile and was highly efficacious at preventing COVID-19." We present numerous concerns regarding the reported safety and efficacy of this injection.

Efficacy

First, Thomas *et al.* (2) reported BNT162b2 efficacy as a relative risk reduction of contracting symptomatic reverse-transcriptase-polymerase chain reaction (PCR)-confirmed COVID-19 of 91.3% (77 vs 850 cases) and severe symptomatic PCR-confirmed COVID-19 of 96.7% (1 vs 30 severe cases). Thomas *et al.* (2) should have reported efficacy as an absolute risk reduction as per the communicating risks and benefits guidelines issued by the United States Food and Drug Administration (FDA) (3), which would have highlighted the modest absolute risk reductions provided by the vaccine in both symptomatic (3.7%) and severe symptomatic (0.7%) PCR-confirmed COVID-19.

Second, this analysis is the only published account of the BNT162b2 phase I – III trial efficacy outcomes among adults ≥16 years of age through six-month follow-up after immunization. In a trial amendment, a cohort of adolescents aged 12 to 15 years was added to the phase III study for which there was a shorter follow-up period. In this analysis, Thomas *et al*. (2) combined the two cohorts in providing efficacy outcomes after a six month follow up and departed from the initial analysis without providing a reasonable explanation for doing so. Given that vaccine efficacy wanes over time, by combining the older and younger cohorts, Thomas *et al.* (2) obfuscated the efficacy of the older group at six months. The authors should have provided efficacy outcomes for both groups and explicitly state the two reporting time periods in their conclusion.

Third, when discussing their findings, Thomas *et al.* (2) did not mention that a larger proportion of participants in the placebo group discontinued the trial compared to the vaccine group; 40% more after the first dose (271 vs 380 participants) and 63% more after the second dose (167 vs 273 participants). Discontinuations consisted mostly of "voluntary withdrawals", "no longer meeting the eligibility criteria" and "lost to follow-up." Additionally, there were a high number of participants missing from the CONSORT diagram between 2nd dose and the open-label period with more participants missing in the vaccine arm (1,258 vs 583 missing). These imbalances, which were in the order of the number of primary end-point events (77 and 850, for vaccine and placebo, respectively) call into question the reliability of these findings. Thomas *et al*. (2) should have disclosed the details related to the nature of these losses and discussed the impact they may have had on overall findings.

Fourth, Thomas *et al.* (2) used inappropriate tests when assessing current or prior infections due to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). The authors screened 10,453 serum samples for COVID-19 infections up to 6 weeks prior to enrollment using the Roche Elecsys® Anti-SARS-CoV-2 antibody test, which tests for only the nucleocapsid protein of SARS-CoV-2 and has high sensitivity 14 days after infection when antibodies tend to peak (4). However, as antibody levels wane over time despite persisting immunity, it is unlikely that this test alone could identify prior immunity to SARS-CoV-2 or distinguish between prior immunity to other coronaviruses, which express similar proteins. Additionally, testing for the SARS-CoV-2 was done with the Cepheid Xpert Xpress SARS-CoV-2 RT-PCR rather than the gold-standard functional virology assay, looking for cytopathic effect in permissive cells. FDA specifications for PCR testing at that time the trial was conducted tended toward cycle thresholds beyond 20-30 cycles (5), which are now widely recognized as being unreliable in detecting an active COVID-19 infection (6-8). Given these limitations, Thomas *et al.* (2) should have used better screening for natural immunity, used a functional virology assay, and discussed the implications of these testing limitations in their findings.

Fifth, we noted an absence of systematic testing and an objective testing framework for the detection of SARS-CoV-2-infected participants. In this study, it was left to the discretion of the investigator to send a patient presenting with COVID-19-like symptoms for laboratory confirmation of SARS-CoV-2 infection, a task which would be particularly difficult given that reactogenicity events consisted principally of COVID-19-like symptoms (Thomas *et al.* (2), Figure S1). This lack of systematic testing introduced a concerning level of variability and subjectivity associated with the identification of both symptomatic cases and disease severity (9,10). Thomas *et al*. (2) should have discussed the implications of this lack of objective and systematic virological assessment on their study findings as well as presented data related to asymptomatic testing that was conducted at "selected sites." Overall, the emphasis on relative risk reductions, the combining efficacy outcomes from the adult and adolescent cohorts, the large number of people who were excluded from the analysis, and the use of inappropriate tests and lack of objective testing framework call into question the authors' conclusions regarding vaccine efficacy.

Safety

First, Thomas *et al.* (2) concluded their article by stating that BNT162b2 showed a "favorable safety profile," and in their abstract stated that "BNT162b2 continued to be safe and have an acceptable adverse-event profile." However, Thomas *et al.* (2) Figure S1 summarized solicited adverse events reported within 7 days of the first dose in the reactogenicity subset, which represented a mere 22% of the randomized population. A considerably higher rate of local and systemic adverse events was reported among vaccine recipients with a marked increase in adverse events with the second dose. The preponderance of systemic effects in both arms were COVID-19-like symptoms and occurred at higher rates than in the vaccine compared to the placebo group, despite the vaccine group having a higher number of identified symptomatic COVID-19 cases (77 vs 850, vaccine vs placebo, respectively). The very need for this trial is predicated on the importance and clinical relevance of eradicating COVID-19 symptoms. How is it then that such consistent increases in COVID-19-like symptoms among vaccine recipients are described as "favorable"?

Second, Thomas *et al*. (2) provided a descriptive analysis of vaccine safety. To better compare the benefits and the risks of this vaccine, we calculated absolute and relative risk reductions/increases (ARR/ARI and RRR/RRI, respectively) associated with the vaccine for efficacy events seven days after the second dose (i.e., corresponding to full vaccination for those in the vaccine group) and for safety events during the respective data collection period (starting with the first-dose). These calculations were based on the eligible population for each relevant safety and efficacy events without adjusting for surveillance time as that data was not published for safety events. A simple chi-square calculator was used to assess the significance of the difference in event numbers between groups (Table 1) (11).

Table 1. Differences in the number of efficacy and safety events in eligible populations[¥] reported in the 6-month update of the BNT162b2 mRNA Covid-19 vaccine

Event	BNT162b2 (n)	Placebo (n)	Absolute Difference (p-value)[?]	Absolute Risk Change* (%)	Relative Risk Change* (%)
Cases Adults and Adolescents 7 days after 2nd dose[$]	77	850	-773 (p<0.00001)	-3.7	-90.9
Any Unsolicited Treatment-Related Adverse Event Adults[#]	5,241	1,311	+3,930 (p<0.00001)	+17.9	+299.7
Any Severe Event Adults[/]	390	289	+101 (p=0.0001)	+0.5	+34.9
Severe Cases in Adults 7 days after 2nd dose[&]	1	23	-22 (p<0.00001)	-0.1	-95.7
Unsolicited Severe Adverse Events~ Adults Prevents daily routine activity or requires intervention or worse	262	150	+112 (p<0.00001)	+0.5	+74.6
Serious Adverse Event Adults[§] Requires hospitalization or results in permanent injury or death	127	116	+11 (p=0.5)	+0.05	+9.5
Deaths during placebo-controlled period [additional deaths during open-label period in vaccine recipients or placebo-only][%]	15 [+5]	14 [NR]	+1 [+5] (p=0.9)	+0.005	+7.1
Deaths due to cardiovascular events^	9	5	+4		

[¥] For the purpose of this table and in accordance with the terminology used in the study report, adult and adolescent populations are defined as ≥16 years old and 12-15 years old, respectively.
[?] Significance figures (p-values) estimated using chi-square calculator available at https://www.socscistatistics.com/tests/chisquare. P-values are without the Yates correction. This procedure was applied following the framework used by Classen (11) in his analysis of "All Cause Severe Morbidity" based on data from the initial reports of the vaccine Phase III trials
** Authors estimated vaccine efficacy using total surveillance time as denominator, however, as this value was unavailable for all the events analyzed, our calculations used the common statistical definition, i.e., number of events relative to total number of eligible patients for each event analysis reported[29] similar to previous analyses of this nature (11-30);*
[$] ≥7 Days after dose 2 among participants without evidence of previous infection
[#] Adverse events reported outside of the reactogenicity subgroup and assessed by the investigator as related to investigational product
[/] In calculations combining efficacy and safety events, the number of patients randomized that received any dose of vaccine or placebo was used as the study population in the statistical calculations, following the framework used by Classen (11) in his analysis of "All Cause Severe Morbidity". Differences in the total (event-incident) population (randomized vs efficacy vs safety) used as denominator are relatively small and are expected to have minimal impact on the relative differences between groups. Without access to individual patient data, these calculations were performed under the assumption that efficacy and safety events were non-overlapping
[&] ≥7 Days after dose 2; confirmed severe COVID-19 defined as PCR-positivity and "presence of at least one of the following: • Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg); • Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO); • Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors); • Significant acute renal, hepatic, or neurologic dysfunction;• Admission to an ICU; • Death"
~ Severe (grade ≥3) adverse events were generally defined as those that interfere significantly with participant's usual function, those that affect daily living or require medical care; grade 4 events were generally defined as those that required emergency room visit or hospitalization
[§] Serious adverse events were defined as any untoward medical occurrence that, at any dose: a. Results in death; b. Is life-threatening; c.

Requires inpatient hospitalization or prolongation of existing hospitalization; d. Results in persistent disability/incapacity.
% Deaths during the open-label period were reported only in vaccine recipients, 3 participants in the BNT162b2 group and 2 in the original placebo group who received BNT162b2 after unblinding
^Those with reported cause of death due to: aortic rupture, arteriosclerosis, cardiac arrest, cardiac failure congestive, cardiorespiratory arrest, hypertensive heart disease, or myocardial infarction

Our findings showed that the increase in unsolicited adverse events in vaccine recipients, which included at least one adverse event up to 1 month post the second dose, was greater (RRI of 299.7% and ARI of 17.9%; p<0.00001) than the reduction in identified symptomatic COVID-19 cases observed in fully-vaccinated individuals for the duration of the trial (RRR of 90.9% and ARR of 3.7%; p<0.00001).

A similar pattern was observed for severe and serious adverse events. The study concluded that "vaccine efficacy against severe disease was 96.7%." However, our analysis showed that the vaccine was associated with a significant increase in severe adverse events defined as an adverse event that interferes significantly with daily activity or requires medical care (RRI of 74.6% and ARI of 0.5%; p<0.00001) and a numerical increase in serious adverse events, defined as any untoward medical occurrence that was life-threatening, required hospitalization or resulted in persistent disability up to 6 months (RRI of 9.5% and ARI of 0.05%; p=0.5) compared to placebo. These increases were greater than the reduction in severe COVID-19 cases observed in fully-vaccinated individuals for the duration of the trial (RRR of 95.7% and ARR of 0.1%; p=0.00002). When severe COVID-19 events were pooled with severe or serious adverse events to determine the likelihood of experiencing any severe event (11), there was an overall increase in severe events among vaccine recipients compared with placebo (RRI of 34.9% and ARI of 0.5%, p=0.0001). Given these findings, Thomas *et al.* (2) should have revised their conclusion to state, "the vaccine was associated with a concerning and clinically meaningful increase in severe events relative to placebo."

Third, Thomas *et al.* (2) conducted minimal monitoring of adverse events (12). Firstly, the solicited reactogenicity data was collected for only a small portion of trial participants (9,839/44,047 or 22.3%), for a limited 7 days after each dose, and for only a short pre-specified list of systemic and injection site reactions with no monitoring of sub-clinical effects. Secondly, unsolicited adverse events were collected for a mere 1 month and serious adverse events for only 6 months following the second dose. This means that severe vaccine related cardiac, neurological or immunological injuries that took more than a month to diagnose and were not considered serious, would not be reflected in the findings. Thirdly, unblinding and subsequent crossover of those on the placebo arm to the vaccine arm, will certainly attenuate any safety signals coming from this trial as well as preclude insights into long-term safety which were to be monitored for 2 years. Thomas *et al.* (2) should have commented on the implications their abbreviated monitoring schedule may have on safety underreporting as well as the implications of unblinding on short- and long-term safety outcomes. Given the increase in severe events (RRI of 34.9% and ARI of 0.5%) and cardiovascular deaths associated with the vaccine (n= 9 vs 5, vaccine vs placebo, respectively), The authors should have more closely monitored safety and provided a detailed discussion of the severe and serious adverse events along with a discussion of their potential long-term implications.

Fourth, given the inclusion of adolescents and "healthy participants who had stable chronic medical conditions" in the study population, we noted very little discussion of death, the most clinically

relevant end-point of this trial. Thomas *et al.* (2) Table S3 showed a slightly higher number of deaths in the vaccine group (n=15 vs n=14 in the placebo group during the blinded period). However, the manuscript text (Thomas *et al*. (2), page 7) stated that five additional deaths occurred in vaccine recipients after unblinding (two of which were initially allocated to the placebo group) for a total of 20 deaths in vaccine recipients. Thomas *et al.* (2) Table S4 also showed that although only 3 study deaths were attributed to COVID-19 or COVID-19 pneumonia (n=1 vs n=2, vaccine vs placebo, respectively) a total of 14 deaths were cardiovascular in nature (aortic rupture, arteriosclerosis, cardiac arrest, cardiac failure congestive, cardiorespiratory arrest, hypertensive heart disease) with the almost twice as many occurring in the vaccine arm (n=9 vs n=5, vaccine vs placebo, respectively). There is currently an abundance of real-world evidence to support an association between cardiovascular adverse events and the vaccines (13-17). Thomas *et al.* (2) reported that "none of these deaths were considered to be related to BNT162b2 by the investigators" without describing the objective framework of testing that allowed them to arrive at that conclusion or whether their findings were independently evaluated. Given the seriousness of these adverse events in an otherwise healthy population, Thomas *et al.* (2) should have provided a detailed description of how they arrived at their conclusion, these evaluations should have undergone independent assessment, and all ongoing study protocols investigating BNT162b2 should be immediately amended to include systematic short- and long-term clinical and sub-clinical monitoring of cardiovascular health. Overall, the increased rates of COVID-like symptoms, unsolicited adverse events as well as severe and serious adverse events in the vaccine compared to the placebo arm, as well as the net increase in deaths in vaccine recipients compared with those who were unvaccinated present serious concerns regarding the safety of these biological agents.

Conflicts of Interest

The disconnect between author conclusions, our analysis of the data, and the NEJM rejection of our letter to the editor led us to examine author disclosures for potential conflicts of interest (COI) (Table 2). Our analysis revealed multiple direct conflicts of interest. The article was supported by BioNTech and Pfizer, the corresponding author, Judith Absolon, and the senior author, Kathrin Jansen were employees of Pfizer and owned company stock, and the first author Stephen Thomas was a consultant to Pfizer. Of the 32 authors, 21 (66%) were employees of Pfizer or BioNtech and 26 (81%) had Pfizer/BioNtech-related conflict of interests. We also noted that one of NEJM's senior editors is also a co-principal investigator of the related Moderna-Vaccine COVE-trial (18,19).

Table 2. Conflicts of interest related to Pfizer/BioNTech

Title	Author
Corresponding author	Judith Absalon: Pfizer employment and stock holder
First author	Stephen Thomas: Pfizer consultancy
Last author	Kathrin Jansen: Pfizer employment and stock holder
Other 29 authors (66% employees, 81% had some COI)	Pfizer/ BioNTech employment and stockholder, n=15; Pfizer/ BioNTech employment (without stock) n=4; Pfizer grant/contract n=3; Pfizer clinical trial n=1; Other company consultancy n=1; No COI n=5

Conclusion

Our critique of the Thomas *et al*. (2) publication revealed multiple concerns regarding author claims of BNT162b2 safety and efficacy as well as a high number of direct conflicts of interest in the publication authors. These, coupled with multiple reports indicating that vaccine efficacy wanes within months of administration (20-23), reduced effectiveness of BNT162b2 with respect to emerging variants (24-26), record rates of serious adverse events (122,833) and deaths (17,128) reported in the US passive Vaccine Adverse Event Reporting System, VAERS by October 16, 2021, and problems with data integrity in the conduct of this trial reported recently by Thacker (1) in the British Medical Journal, raise further concerns regarding both the efficacy and safety of this agent. We did not find sufficient evidence to support use of these agents in the healthy adults studied or in specific unstudied demographics that are being mandated to comply with vaccination including the naturally immune, the frail elderly, those with multiple co-morbidities, the immunocompromised, and pregnant women. It also calls into question use in adolescents and children given that companion trials conducted in those populations suffered from similar design flaws, including underpowered in participant numbers and that recommendations for use were based on minimal safety follow up (27,28).

Conflicts of Interest

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Ilidio Martins, none to disclose
Claudia Chaufan, none to disclose
Julian Northey, none to disclose
Niel A. Karrow, none to disclose
Steven Pelech is the majority shareholder and president and Chief Scientific Officer of Kinexus Bioinformatics Corporation, which has been developing serological tests for detection of antibodies against SARS-CoV-2 proteins and testing of drugs to inhibit SARS-CoV-2 replication
Bonnie Mallard, none to disclose
Christopher A. Shaw has been an expert witness in Vaccine Court twice
David Speicher, none to disclose
Ondrej Halgas, none to disclose
Deanna McLeod, none to disclose

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