Serious adverse events of special interest following mRNA vaccination in randomized trials

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ABSTRACT

Introduction. In 2020, prior to COVID-19 vaccine rollout, the Coalition for Epidemic Preparedness Innovations and Brighton Collaboration created a priority list, endorsed by the World Health Organization, of potential adverse events relevant to COVID-19 vaccines. We leveraged the Brighton Collaboration list to evaluate serious adverse events of special interest observed in phase III randomized trials of mRNA COVID-19 vaccines.

Methods. Secondary analysis of serious adverse events reported in the placebo-controlled, phase III randomized clinical trials of Pfizer and Moderna mRNA COVID-19 vaccines (NCT04368728 and NCT04470427), focusing analysis on potential adverse events of special interest identified by the Brighton Collaboration.

Results. Pfizer and Moderna mRNA COVID-19 vaccines were associated with an increased risk of serious adverse events of special interest, with an absolute risk increase of 10.1 and 15.1 per 10,000 vaccinated over placebo baselines of 17.6 and 42.2 (95% CI -0.4 to 20.6 and -3.6 to 33.8), respectively. Combined, the mRNA vaccines were associated with an absolute risk increase of serious adverse events of special interest of 12.5 per 10,000 (95% CI 2.1 to 22.9). The excess risk of serious adverse events of special interest surpassed the risk reduction for COVID-19 hospitalization relative to the placebo group in both Pfizer and Moderna trials (2.3 and 6.4 per 10,000 participants, respectively).

Discussion. The excess risk of serious adverse events found in our study points to the need for formal harm-benefit analyses, particularly those that are stratified according to risk of serious COVID-19 outcomes such as hospitalization or death.

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Keywords: SARS-CoV-2; COVID-19; vaccines; COVID-19 vaccines; mRNA vaccines; Pfizer-BioNTech COVID-19 vaccine BNT162b2; Moderna COVID-19 vaccine mRNA-1273; NCT04368728; NCT04470427; serious adverse events; adverse events of special interest; Brighton Collaboration; Coalition for Epidemic Preparedness Innovations; Safety Platform for Emergency vACcines

Conflicts of interest:
JF, JE, MJ, SG, PW, RK: none to declare. **PD** has received travel funds from the European Respiratory Society (2012) and Uppsala Monitoring Center (2018); grants from the FDA (through University of Maryland M-CERSI; 2020), Laura and John Arnold Foundation (2017-22), American Association of Colleges of Pharmacy (2015), Patient-Centered Outcomes Research Institute (2014-16), Cochrane Methods Innovations Fund (2016-18), and UK National Institute for Health Research (2011-14); was an unpaid IMEDS steering committee member at the Reagan-Udall Foundation for the FDA (2016-2020) and is an editor at The BMJ. The views expressed here are those of the authors and do not necessarily reflect those of their employers.

INTRODUCTION

In March 2020, the Brighton Collaboration and the Coalition for Epidemic Preparedness Innovations partnership, Safety Platform for Emergency vACcines (SPEAC), created and subsequently updated a "priority list of potential adverse events of special interest relevant to COVID-19 vaccine trials."[1] The list comprises adverse events of special interest (AESIs) based on the specific vaccine platform, adverse events associated with prior vaccines in general, theoretical associations based on animal models, and COVID-19 specific immunopathogenesis.[1] The World Health Organization's Global Advisory Committee on Vaccine Safety endorsed and recommended the reporting of AESIs based on this priority list. To our knowledge, however, the list has not been applied to serious adverse events in randomized trial data.

We sought to investigate the association between FDA-authorized mRNA COVID-19 vaccines and serious adverse events identified by the Brighton Collaboration, using data from the phase III randomized, placebo-controlled clinical trials on which authorization was based. We then use the results to illustrate the need for formal harm-benefit analyses of the vaccines that are stratified according to risk of serious COVID-19 outcomes, as well as contextualize the findings against post-authorization observational data.

METHODS

Pfizer and Moderna each submitted the results of one phase III randomized trial in support of the FDA's emergency use authorization of their vaccines. Two methodologist reviewers searched journal publications and trial data on the FDA's and Health Canada's websites to locate serious adverse event results tables for these trials. The Pfizer and Moderna trials are expected to follow participants for two years. Within weeks of the emergency authorization, however, the sponsors began a process of unblinding all participants who elected to be unblinded. In addition, those who received placebo were offered the vaccine. These self-selection processes may have introduced nonrandom differences between the vaccine and unvaccinated participants, thus rendering the post-authorization data less reliable. Therefore, to preserve randomization, we used the interim datasets that were the basis for emergency authorization in December 2020, approximately 4 months after trials commenced.

The definition of a serious adverse event (SAE) was provided in each trial's study protocol and included in the supplemental material of the trial's publication.[2–4] Pfizer and Moderna used nearly identical definitions, consistent with regulatory expectations. An SAE was defined as an adverse event that results in any of the following conditions: death; life-threatening at the time of the event; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; a congenital anomaly/birth defect; medically important event, based on medical judgment.

In addition to journal publications, we searched the websites of the FDA (for advisory committee meeting materials) and Health Canada (for sections of the dossier submitted by sponsors to the

regulator).[5] For the FDA website, we considered presentations by both the FDA and the sponsors.[6] Within each of these sources, we searched for SAE results tables that presented information by specific SAE type; we chose the most recent SAE table corresponding to the FDA's requirement for a safety median follow-up time of at least 2 months after dose 2.

For each trial, blinded SAE tables (containing SAE types without results data) were prepared. Using the blinded SAE tables, two clinician reviewers (JF and JE) independently judged whether each SAE type was an AESI.

Our project used an AESI list derived from the work of Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC) Project. This effort created an AESI list which categorizes AESIs into three categories: those included because they are seen with COVID-19, those with a proven or theoretical association with vaccines in general, and those with proven or theoretical associations with specific vaccine platforms. The first version was produced in March 2020 based on experience from China. Following the second update (May 2020), the WHO Global Advisory Committee on Vaccine Safety (GACVS) adopted the list, and Brighton commenced a systematic review process "to ensure an ongoing understanding of the full spectrum of COVID-19 disease and modification of the AESI list accordingly."[7] This resulted in three additional AESIs being added to the list in December 2020. The subsequent (and most recent fourth) update did not result in any additional AESIs being added to the list.

We matched SAEs recorded in the trial against an expanded list of AESIs created by combining Brighton's SPEAC COVID-19 AESI list with a list of 29 clinical diagnoses Brighton identified as "known to have been reported but not in sufficient numbers to merit inclusion on the AESI list."[7] Sensitivity analysis was used to determine whether the original versus expanded list had an effect on identifying a safety concern. For SAEs that described symptoms, not diagnoses, the clinician reviewers independently judged whether each SAE type was likely to have been caused by an AESI. For example, the SAE "abdominal pain" is a symptom based diagnosis, which was judged as fitting within the SPEAC clinical diagnosis of "colitis/enteritis." Disagreements were resolved through consensus; in two cases, consensus could not be reached and were resolved by the judgment of a third clinician reviewer (PW) to create a majority opinion. For each included SAE, we recorded the corresponding Brighton Collaboration AESI category and organ system.

Risk ratios and risk differences between vaccine and placebo groups were calculated for the incidence of SAEs. We excluded SAEs that were efficacy outcomes (i.e. COVID-19). Because we did not have access to individual participant data, to account for the occasional multiple SAEs within single participants, we reduced the effective sample size by multiplying standard errors in the combined SAE analyses by the square root of the ratio of the number of SAEs to the number of patients with an SAE. This adjustment increased standard errors by 10% (Pfizer) and 18% (Moderna), thus expanding the interval estimates. We estimated combined risk ratios and risk differences for the two mRNA vaccines by averaging over the risks using logistic regression models.

We used a simple harm-benefit framework to place our results in context. The analysis compared risks of excess serious AESIs against reductions in serious complications of COVID-19.

RESULTS

Serious adverse event tables were located for each of the vaccine trials submitted for EUA in the United States: Pfizer-BioNTech COVID-19 vaccine BNT162b2 (NCT04368728)[2,8,9] and Moderna COVID-19 vaccine mRNA-1273 (NCT04470427).[3,10,11] **(Table 1)**

Reporting windows and all-cause serious adverse events

Moderna reported SAEs from dose 1 whereas Pfizer limited reporting from dose 1 to 1 month after dose 2. Both studies reported all data at the time of data cutoff.

The Pfizer trial reported a 36% higher risk of serious adverse events unrelated to COVID-19 in vaccinated participants than placebo recipients: 67.5 per 10,000 versus 49.5 per 10,000; risk ratio 1.36 (95% compatibility[1] interval, CI 1.02 to 1.83). The Moderna trial reported a 5% higher risk of SAEs unrelated to COVID-19 in vaccinated individuals compared to those receiving placebo: 136 per 10,000 versus 129 per 10,000; risk ratio 1.05 (95% CI 0.83 to 1.32). Combined, there was a 15% higher risk of SAEs unrelated to COVID-19 in mRNA vaccine recipients than placebo recipients: 98 per 10,000 versus 85 per 10,000; risk ratio 1.15 (95% CI 0.96 to 1.38). **(Table 2)**

Serious adverse events of special interest

Regarding whether each SAE type was included on the SPEAC derived AESI list, agreement between the two independent clinician reviewers was 86% (281/325); 40 of the 44 disagreements were resolved through consensus, and only four disagreements necessitated a third clinician reviewer. **Supplemental Table 1** includes a full list of included and excluded SAEs across both trials.

In the Pfizer trial, 52 serious AESI (27.7 per 10,000) were reported in the vaccine group and 33 (17.6 per 10,000) in the placebo group. This difference corresponds to a 57% increased risk of serious AESI (RR 1.57 95% CI 0.98 to 2.54) and an absolute risk increase of 10.1 serious AESI per 10,000 vaccinated participants (95% CI -0.4 to 20.6). In the Moderna trial, 87 serious AESI (57.3 per 10,000) were reported in the vaccine group and 64 (42.2 per 10,000) in the placebo group. This difference corresponds to a 36% increased risk of serious AESI (RR 1.36 95% CI 0.93 to 1.99) and an absolute risk increase of 15.1 serious AESI per 10,000 vaccinated participants (95% CI -3.6 to 33.8). Combining the trials, there was a 43% increased risk of

[1] A compatibility interval is identical to a confidence interval, but relabeled to emphasize that it is not a Bayesian posterior interval (as is improperly suggested by the "confidence" label).[12,13]

serious AESI (RR 1.43; 95% CI 1.07 to 1.92) and an absolute risk increase of 12.5 serious AESI per 10,000 vaccinated participants (95% CI 2.1 to 22.9). **(Table 2)**

Of the 236 serious AESIs occurring across the Pfizer and Moderna trials, 97% (230/236) were adverse event types included as AESIs because they are seen with COVID-19. In both Pfizer and Moderna trials, the largest increase in absolute risk occurred amongst the Brighton category of coagulation disorders. Cardiac disorders have been of central concern for mRNA vaccines; more cardiovascular AESIs occurred in the vaccine group in the Pfizer trial, but cardiovascular AESI events were balanced in the Moderna trial. **(Tables 3 and 4)**

Sensitivity analysis

In a sensitivity analysis, we restricted the serious AESI analysis to those AESIs listed in SPEAC's COVID-19 AESI list (i.e. separating out Brighton's list of 29 clinical diagnoses "known to have been reported but not in sufficient numbers to merit inclusion on the AESI list.") This reduced the total number of AESIs across the two trials by 48 (35 vaccine group, 13 placebo group). There was still a higher risk of serious AESI when limited to the SPEAC COVID-19 AESI list, but the magnitude of the increase (in both relative and absolute terms) was smaller than when using the larger AESI list. **(Supplemental Table 2)**.

Harm-benefit considerations

In the Moderna trial, the excess risk of serious AESIs (15.1 per 10,000 participants) surpassed the risk reduction for COVID-19 hospitalization relative to the placebo group (6.4 per 10,000 participants).[3] In the Pfizer trial, the excess risk of serious AESIs (10.1 per 10,000) surpassed the risk reduction for COVID-19 hospitalization relative to the placebo group (2.3 per 10,000 participants).

Comparison with FDA reviews and post-authorization studies

In their review of SAEs that supported the authorization of the Pfizer and Moderna vaccines, the FDA concluded that SAEs were, for Pfizer, "balanced between treatment groups,"[14] and for Moderna, were "without meaningful imbalances between study arms."[15] In contrast to the FDA analysis, we found an increased risk of all cause SAEs in the Pfizer trial. While our analysis excluded SAEs related to COVID-19 (because it is an efficacy outcome), this exclusion did not explain the difference given the low risk of SAEs attributed to COVID-19 (0 in the vaccine arm, 1 in the placebo arm). Instead, the difference in findings may in part be explained by the fact that the FDA analyzed the total number of participants experiencing any SAE, whereas our analysis was based on the total number of SAE events. Given that approximately twice as many individuals in the vaccine group experienced multiple SAEs than the placebo group (there were 24 more events than participants in the vaccine group, compared to 13 in the placebo group), FDA's analysis of only the incidence of participants experiencing any SAE would not reflect the observed increase in multiple SAEs in the vaccine group.

A more important factor, however, may be that FDA's review of non-fatal SAEs used a different analysis population with different follow-up windows. The FDA reported 126 of 21621 (0.6%) of vaccinated participants experienced at least one SAE at data cutoff compared to 111 of 21631 (0.5%) of placebo participants. In contrast, our analysis found 127 SAEs among 18,801 vaccine recipients versus 93 SAEs among 18,785 placebo recipients.[14] While summary results for the population we analyzed was provided in a table, FDA did not report an analysis of them. The substantially larger denominators in FDA's analysis (5,666 more participants) reflect the fact that their analysis included all individuals receiving at least one dose (minus 196 HIV-positive participants), irrespective of the duration of post-injection follow-up time. In contrast, our analysis was based on the study population with median follow-up ≥2 months after dose 2 (minus 120 HIV-positive participants), of which 98.1% had received both doses.[2,16] The FDA's analysis of SAEs thus included thousands of additional participants with very little follow-up, of which the large majority had only received 1 dose.

Although the randomized trials offer high level evidence for a causal association, the sparsity of their data necessitates that harm-benefit analyses also consider observational data. Since their emergency authorization in December 2020, hundreds of millions of doses of Pfizer and Moderna COVID-19 vaccines have been administered and post-authorization observational data offer a complementary opportunity to study AESIs. Post-authorization observational safety studies include cohort studies (which make use of medical claims or electronic health records) and disproportionality analyses (which leverage spontaneous adverse event reporting systems). In July 2021, the FDA reported detecting four potential adverse events of interest: pulmonary embolism, acute myocardial infarction, immune thrombocytopenia, and disseminated intravascular coagulation following Pfizer's vaccine based on medical claims data in older Americans.[17] Three of these four serious adverse event types would be categorized as coagulation disorders, which is the Brighton AESI category which showed the largest absolute increase in the vaccine group in both the Pfizer and Moderna trials. FDA stated it would further investigate the findings but at the time of our writing has not issued an update. Similarly, spontaneous-reporting systems have registered serious adverse reactions including anaphylaxis (all COVID-19 vaccines), thrombocytopenia syndrome among premenopausal females (Janssen vaccine), and myocarditis and pericarditis among younger males (Pfizer and Moderna vaccines).[18,19]

Using data from three postmarketing safety databases for vaccines (VAERS, EudraVigilance, and VigiBase), disproportionality studies have reported an increase in many of the same SAE types found in the present study.[20–22] For example, a study using VAERS and EudraVigilance comparing the disproportionality of adverse event reports between the influenza vaccine versus the mRNA COVID-19 vaccines reported increased relative risk of the following Brighton AESIs: cardiovascular events, coagulation events, hemorrhages, gastrointestinal events, and thromboses. While CDC published a protocol[23] in early 2021 for using proportional reporting ratios for signal detection in the VAERS database, the agency has not yet reported such a study.[24] Among self-controlled case series, one reported an incidence rate ratio of 1.38 (95% CI 1.12-1.71) for hemorrhagic stroke following Pfizer vaccine,[25] another reported 0.97 (95% CI 0.81-1.15),[26] while a cohort study[27] reported 0.84 (95% CI 0.54-1.27).

DISCUSSION

Using a prespecified list of AESI identified by the Brighton Collaboration, an increase in serious AESI was found in the mRNA COVID-19 vaccine group in both the Pfizer and Moderna adult phase III trials, from 10.1 (Pfizer) to 15.1 (Moderna) additional events for every 10,000 individuals vaccinated.

Comparing the excess of serious AESI against the reduction of serious complications of COVID-19 among the vaccinated is essential for harm-benefit analyses. The results show an excess risk of serious AESIs greater than the reduction in COVID-19 hospitalizations in both Pfizer and Moderna trials. These results are compatible with a recent preprint analysis of COVID-19 vaccine trials by Benn et al., which found no evidence of a reduction in overall mortality in the mRNA vaccine trials based on data from the later, March 2021 BLA (Biologics License Application) timepoints that underpinned subsequent regulatory approval (31 deaths in the vaccine arms versus 30 events in the placebo arms; RR 1.03, 95% CI 0.63 to 1.71).[28] Our analysis as well as Benn et al. point to the need for formal harm-benefit analyses especially in individuals at low risk of COVID-19 hospitalization or death. Using VAERS data, Krug et al. attempted such an analysis, albeit focused on just one SAE (myocarditis)[19] Individual participant data for all SAEs is not publicly available at present, but would help identify factors (e.g. age and comorbidities) that may elevate the risk of serious AESIs. It would also be essential to compare long-term outcomes of vaccinated and unvaccinated groups, e.g., for symptoms identified with "long covid."

Adverse events detected in the post-marketing period have led to the withdrawal of several past vaccines. An example is intussusception following one brand of rotavirus vaccine: around 1 million children were vaccinated before identification of intussusception, which occurred in around 1 per 10,000 vaccinees.[29] Despite the unprecedented scale of COVID-19 vaccine administration, the AESI types identified in our study may still be challenging to detect with observational methods. Most cohort study designs crucially depend upon comparing the risks of adverse events "observed" against a background (or "expected") risk. However, background incidence risks display great variation, by database, age group, and sex.[30] If the risk ratio of 1.4 estimated in our analysis were the actual effect size, it could be quite difficult to unambiguously replicate it with observational data given concerns about systematic as well as random errors.[31–33]

In addition, disproportionality analyses following COVID-19 vaccination also have limitations, particularly with respect to the type of adverse events seen in our study. The majority of SAE types that contributed to our results are relatively common events, such as ischemic stroke, acute coronary syndrome, and brain hemorrhage. This complicates signal detection because clinical suspicion of an adverse vaccine reaction following an event commonly seen in clinical practice will be lower than for less commonly observed SAEs like myocarditis. For this reason, the basic ingredient for effective pharmacovigilance--clinical suspicion leading to the filing of an individual case safety report--may be far less common in the post-authorization setting. At the

same time, heightened awareness about COVID-19 vaccines can result in over- and under-reporting. Public health messages assuring vaccine safety may lower clinical suspicion of potential causal relationships, whereas messages about potential harms can conversely stimulate reports that otherwise may not have been made. There are thus factors that can lead to bias in either direction, further complicating analysis and interpretation. In contrast to these problems, in the randomized clinical trials used in this analysis, all SAEs were to be recorded, irrespective of clinical judgment regarding potential causality.

Although our analysis is secondary, reanalyses of clinical trial data have led to the detection of adverse events well after the market entry of major drugs such as rofecoxib and rosiglitazone.[34,35] Our analysis has an advantage over postmarketing observational studies in that the data are from blinded, placebo-controlled randomized trials vetted by the FDA, and uses the Brighton Collaboration AESI list, which was pre-specified, endorsed by WHO, and established well before the availability of the clinical-trial results, and designed for use in COVID-19 vaccine trials.

Limitations of our study include that Pfizer's SAE table did not include SAEs occurring past 1 month after dose 2. This reporting threshold may have led to an undercounting of serious AESIs in the Pfizer study, and for both studies, the limited follow up time prevented an analysis of harm-benefit over a longer time period. It should also be recognized that all SAEs in our analysis are those that met the regulatory definition of a serious adverse event. However, many adverse event types which a patient may themselves judge as serious may not meet this regulatory threshold.

Another limitation is our lack of access to individual participant data, which forced us to use a conservative adjustment to the standard errors. The 95% CI[12,13] calculated are therefore only approximate because we do not know which patients had multiple events. Furthermore, despite our attempt to remove efficacy endpoints from our analysis (i.e., SAEs labeled as COVID-19, COVID-19 pneumonia, and "SARS-CoV-2 test positive"), it was not possible to identify and remove SAEs that occurred in patients with serious complications of COVID-19 (e.g., acute respiratory failure, cardiac arrest, and acute kidney injury), which are common. Of 18 total efficacy SAEs removed from our analysis, 17 were in the Moderna trial, and of these, 16 were in the placebo arm. This suggests the possibility that SAEs were overcounted in the placebo arm of our analyses, primarily for Moderna's vaccine, due to our inability to remove COVID-19-related SAEs. These study limitations all stem from the fact that the raw data from COVID-19 vaccine clinical trials are not publicly available.[36,37] Given the global public health implications, there is an urgency to make all COVID-19 trial data public, particularly regarding serious adverse events, without any further delay.

Finally, we emphasize that the elevated risk of serious AESIs in the vaccine group represents an average across the group. SAEs may not be distributed equally across the demographic subgroups enrolled in the trial, and the risks may be substantially less in some groups compared to others. Thus, knowing the actual demographics of those who experienced an increase in serious AESI in the vaccine group is necessary for a proper harm-benefit analysis.

A systematic review and meta-analysis using individual participant data should be undertaken to address questions of harm-benefit in various demographic subgroups. Full transparency of the COVID-19 vaccine clinical trial data is needed to properly evaluate these questions. Unfortunately, well over a year after widespread use of COVID-19 vaccines, participant level data remain inaccessible.[36,37]

Author Contributions: All authors had full access to all of the data in the study (available at https://doi.org/10.5281/zenodo.6564403), and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors
Acquisition of data: Doshi
Analysis and interpretation: All authors
Statistical analysis: Jones, Greenland
Drafting of the manuscript: Fraiman, Doshi
Critical revision of the manuscript for important intellectual content: All authors

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Conflicts of interest:
JF, JE, MJ, SG, PW, RK: none to declare. **PD** has received travel funds from the European Respiratory Society (2012) and Uppsala Monitoring Center (2018); grants from the FDA (through University of Maryland M-CERSI; 2020), Laura and John Arnold Foundation (2017-22), American Association of Colleges of Pharmacy (2015), Patient-Centered Outcomes Research Institute (2014-16), Cochrane Methods Innovations Fund (2016-18), and UK National Institute for Health Research (2011-14); was an unpaid IMEDS steering committee member at the Reagan-Udall Foundation for the FDA (2016-2020) and is an editor at The BMJ. The views expressed here are those of the authors and do not necessarily reflect those of their employers.

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Table 1. Data sources for phase III trials				
Trial	**Data cutoff date**	**Journal articles**	**FDA sources**	**Health Canada sources**
Pfizer trial in ages 16 and above (NCT04368728)	14 Nov 2020 (supported Dec 2020 EUA)	Aggregate data only	**Table 23 in sponsor briefing document**	**Table 55 in sponsor document C4591001 Final Analysis Interim Report Body**
Moderna trial in ages 18 and above (NCT04470427)	25 Nov 2020 (supported Dec 2020 EUA)	Table S11 in publication	Table 27 in sponsor briefing document	**Table 14.3.1.13.3 in sponsor document mRNA-1273-P301 Unblinded Safety Tables Batch 1 (DS2)**
Note: bolded font indicates dataset chosen for analysis; EUA = Emergency Use Authorization				

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Table 2. Serious adverse events

Trial	Events[a]		Risk difference per 10,000 participants (95% CI)	Risk ratio (95% CI)
	Vaccine	Placebo		
All serious adverse events[b]				
Pfizer	127	93	18.0 (1.2 to 34.9)	1.36 (1.02 to 1.83)
Moderna	206	196	6.4 (-23.9 to 36.8)	1.05 (0.83 to 1.32)
Combined	333	289	12.9 (-0.4 to 29.3)	1.15 (0.96 to 1.38)
Serious adverse events of special interest[c]				
Pfizer	52	33	10.1 (-0.4 to 20.6)	1.57 (0.98 to 2.54)
Moderna	87	64	15.1 (-3.6 to 33.8)	1.36 (0.93 to 1.99)
Combined	139	97	12.5 (2.1 to 22.9)	1.43 (1.07 to 1.92)

[a] Denominators for Pfizer were 18,801 in the vaccine group and 18,785 in the placebo group, and for Moderna were 15,185 in the vaccine group and 15,166 in the placebo group.
[b] All SAEs are included in the calculations except for efficacy outcomes which were included in certain SAE tables: "COVID-19" and "COVID-19 pneumonia" (Moderna) and "SARS-CoV-2 test positive" (Pfizer). "All SAEs" for Moderna was calculated using the "Number of serious AEs" row in Moderna's submission to FDA.[10]
[c] Standard errors used to estimate 95% CIs were inflated by the factor √[#SAE]/[#patients with SAE] to account for multiple SAE within patients.

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Table 3. Serious AESIs, Pfizer trial

Brighton category	Vaccine	Placebo	Vaccine events per 10,000	Placebo events per 10,000	Difference in events per 10,000	Risk ratio
Association with immunization in general						
Anaphylaxis	1	1	0.5	0.5	0.0	1.00
Association with specific vaccine platform(s)						
Encephalitis/encephalomyelitis	0	2	0.0	1.1	-1.1	0.00
Seen with COVID-19						
Acute kidney injury	2	0	1.1	0.0	1.1	N/A
Acute liver injury	0	1	0.0	0.5	-0.5	0.00
Acute respiratory distress syndrome	2	1	1.1	0.5	0.5	2.00
Coagulation disorder	16	10	8.5	5.3	3.2	1.60
Myocarditis/pericarditis	2	1	1.1	0.5	0.5	2.00
Other forms of acute cardiac injury	16	12	8.5	6.4	2.1	1.33
Subtotal	39	28	20.7	14.9	5.8	1.39
Brighton list of 29 clinical diagnoses seen with COVID-19						
Abscess	4	1	2.1	0.5	1.6	4.00
Cholecystitis	4	2	2.1	1.1	1.1	2.00
Colitis/Enteritis	1	1	0.5	0.5	0.0	1.00
Diarrhea	1	0	0.5	0.0	0.5	N/A
Hyperglycemia	1	1	0.5	0.5	0.0	1.00
Pancreatitis	1	0	0.5	0.0	0.5	N/A
Psychosis	1	0	0.5	0.0	0.5	N/A
Subtotal	13	5	6.9	2.7	4.3	2.60
Total	**52**	**33**	**27.7**	**17.6**	**10.1**	**1.57**

Table 4. Serious AESIs, Moderna trial

Brighton category	Vaccine	Placebo	Vaccine events per 10,000	Placebo events per 10,000	Difference in events per 10,000	Risk ratio
Association with specific vaccine platform(s)						
Bell's Palsy	1	0	0.7	0.0	0.7	N/A
Encephalitis/encephalomyelitis	1	0	0.7	0.0	0.7	N/A
Seen with COVID-19						
Acute kidney injury	1	3	0.7	2.0	-1.3	0.33
Acute liver injury	1	0	0.7	0.0	0.7	N/A
Acute respiratory distress syndrome	7	4	4.6	2.6	2.0	1.75
Angioedema	0	2	0.0	1.3	-1.3	0.00
Coagulation disorder	20	13	13.2	8.6	4.6	1.54
Generalized Convulsions	2	0	1.3	0.0	1.3	N/A
Myelitis	0	1	0.0	0.7	-0.7	0.00
Myocarditis/pericarditis	4	5	2.6	3.3	-0.7	0.80
Other forms of acute cardiac injury	26	26	17.1	17.1	0.0	1.00
Other rash	1	1	0.7	0.7	0.0	1.00
Rhabdomyolysis	0	1	0.0	0.7	-0.7	0.00
Single Organ Cutaneous Vasculitis	1	0	0.7	0.0	0.7	N/A
Subtotal	65	56	42.8	36.9	5.9	1.16
Brighton list of 29 clinical diagnoses seen with COVID-19						
Abscess	1	0	0.7	0.0	0.7	N/A
Arthritis	3	1	2.0	0.7	1.3	3.00
Cholecystitis	4	0	2.6	0.0	2.6	N/A
Colitis/Enteritis	6	3	4.0	2.0	2.0	2.00

Diarrhea	2	1	1.3	0.7	0.7	2.00
Hyperglycemia	1	0	0.7	0.0	0.7	N/A
Hyponatremia	1	1	0.7	0.7	0.0	1.00
Pancreatitis	2	0	1.3	0.0	1.3	N/A
Pneumothorax	0	1	0.0	0.7	-0.7	0.00
Psychosis	1	1	0.7	0.7	0.0	1.00
Thyroiditis	1	0	0.7	0.0	0.7	N/A
Subtotal	22	8	14.5	5.3	9.2	2.75
Total	**87**	**64**	**57.3**	**42.2**	**15.1**	**1.36**

Supplemental Table 1. Included and excluded SAE types across both trials

Included SAE types (matching AESI list): Abdominal pain, Abdominal pain upper, Abscess, Abscess intestinal, Acute coronary syndrome, Acute kidney injury, Acute left ventricular failure, Acute myocardial infarction, Acute respiratory failure, Anaemia, Anaphylactic reaction, Anaphylactic shock, Angina pectoris, Angina unstable, Angioedema, Aortic aneurysm, Aortic valve incompetence, Arrhythmia supraventricular, Arteriospasm coronary, Arthritis, Atrial fibrillation, Atrial flutter, Axillary vein thrombosis, Basal ganglia haemorrhage, Bile duct stone, Blood loss anaemia, Bradycardia, Brain abscess, Cardiac failure, Cardiac failure acute, Cardiac failure congestive, Cardiac stress test abnormal, Cardio-respiratory arrest, Cerebral infarction, Cerebrovascular accident, Chest pain, Cholecystitis, Cholecystitis acute, Cholelithiasis, Colitis, Coronary artery disease, Coronary artery dissection, Coronary artery occlusion, Coronary artery thrombosis, Deep vein thrombosis, Dermatitis bullous, Diabetic ketoacidosis, Diarrhoea, Diplegia, Dyspnoea, Embolic stroke, Empyema, Facial paralysis, Fluid retention, Gastroenteritis, Gastrointestinal haemorrhage, Haematoma, Haemorrhagic stroke, Hemiplegic migraine, Hepatic enzyme increased, Hyperglycaemia, Hyponatraemia, Hypoxia, Ischaemic stroke, Laryngeal oedema, Multiple sclerosis, Myocardial infarction, Non-cardiac chest pain, Oedema peripheral, Pancreatitis, Pancreatitis acute, Pericarditis, Peripheral artery aneurysm, Peritoneal abscess, Pleuritic pain, Pneumothorax, Post procedural haematoma, Post procedural haemorrhage, Postoperative abscess, Procedural haemorrhage, Psychotic disorder, Pulmonary embolism, Rash, Rash vesicular, Respiratory failure, Retinal artery occlusion, Rhabdomyolysis, Rheumatoid arthritis, Schizoaffective disorder, Seizure, Subarachnoid haemorrhage, Subcapsular renal haematoma, Subdural haematoma, Tachyarrhythmia, Tachycardia, Thrombocytopenia, Thyroid disorder, Toxic encephalopathy, Transaminases increased, Transient ischaemic attack, Traumatic intracranial haemorrhage, Type 2 diabetes mellitus, Uraemic encephalopathy, Uterine haemorrhage, Vascular stent occlusion, Ventricular arrhythmia

Excluded SAE types (not matching AESI list): Abdominal adhesions, Abortion spontaneous, Abortion spontaneous incomplete, Accelerated hypertension, Adenocarcinoma gastric, Adrenal gland cancer, Alcohol abuse, Alcohol poisoning, Alcohol withdrawal syndrome, Animal bite, Ankle arthroplasty, Ankle fracture, Anxiety, Anxiety disorder, Aortic stenosis, Appendicitis, Appendicitis perforated, Arteriosclerosis, Asthma, Atelectasis, Autonomic nervous system imbalance, B-cell small lymphocytic lymphoma, Back injury, Back pain, Benign prostatic hyperplasia, Bipolar disorder, Breast cancer, Breast cancer stage I, Breast hyperplasia, Bronchitis, Cartilage injury, Cellulitis, Cervical radiculopathy, Cervical spinal stenosis, Cervical vertebral fracture, Choroidal neovascularisation, Chronic kidney disease, Chronic lymphocytic leukaemia, Chronic myeloid leukaemia, Chronic obstructive pulmonary disease, Clostridium difficile colitis, Clostridium difficile infection, Colon cancer stage III, Colon injury, Colorectal cancer, Completed suicide, Complicated appendicitis, Concussion, Confusional state, Constipation, Cough, Craniocerebral injury, Dehydration, Depression, Diplopia, Diverticular perforation, Diverticulitis, Dizziness, Drug hypersensitivity, Duodenal ulcer, Duodenal ulcer haemorrhage, Emphysema, Facial bones fracture, Fall, Feeling hot, Femoral neck fracture, Femur fracture, Fibromuscular dysplasia, Flail chest, Flank pain, Food poisoning, Foot fracture, Foot operation, Forearm fracture, Fracture nonunion, Gastric cancer, Gastric perforation, Gastrooesophageal reflux disease, Gout, Gun shot wound, Head injury, Heart disease congenital, Hepatic cancer metastatic, Hepatic mass, Hepatitis A, Hernia, Hiatus hernia, Hip arthroplasty, Hip fracture, Humerus fracture, Hypertension, Hypertensive emergency, Hypertensive urgency, Hypoglycaemia,

Hypokalaemia, Hypomagnesaemia, Hypotension, Idiopathic intracranial hypertension, Immunisation anxiety related reaction, Incarcerated hernia, Incision site pain, Influenza like illness, Intentional self-injury, Interstitial lung disease, Intervertebral disc degeneration, Intervertebral disc protrusion, Intestinal obstruction, Intestinal perforation, Intraductal proliferative breast lesion, Invasive ductal breast carcinoma, Invasive lobular breast carcinoma, JAMMED RIGHT INGUINAL HERNIA@@, Jaw operation, Joint injury, Knee arthroplasty, Large intestine perforation, Lead dislodgement, Leiomyosarcoma metastatic, Leydig cell tumour of the testis, Ligament rupture, Loss of consciousness, Lower limb fracture, Lung cancer metastatic, Lymphadenopathy, Major depression, Malignant melanoma, Meningioma, Mental disorder, Metabolic acidosis, Metastases to central nervous system, Migraine, Multiple injuries, Musculoskeletal chest pain, Nausea, Neck pain, Nephrolithiasis, Neutropenia, Obstructive pancreatitis, Oesophageal carcinoma, Oesophageal food impaction, Organising pneumonia, Orthostatic hypotension, Osteoarthritis, Osteochondritis, Osteomyelitis, Ovarian cyst, Ovarian mass, Overdose, Pancreatic mass, Papillary thyroid cancer, Paraesthesia, Pelvic neoplasm, Penile cancer, Penile neoplasm, Peritonitis, Pharyngitis streptococcal, Pleural effusion, Pneumonia, Pneumonia aspiration, Pneumonia staphylococcal, Pneumonitis, Polymyalgia rheumatica, Postoperative wound infection, Precancerous condition, Prostate cancer, Prostate cancer metastatic, Pulmonary mass, Pyelonephritis, Pyelonephritis acute, Rectal prolapse, Renal cancer, Renal cell carcinoma, Renal colic, Retinal detachment, Retinal tear, Rib fracture, Road traffic accident, Salivary gland calculus, Salpingitis, Sepsis, Septic shock, Sexual abuse, Shoulder injury related to vaccine administration, Skin laceration, Small intestinal obstruction, Speech disorder, Spinal cord injury cervical, Spinal fusion surgery, Spinal stenosis, Staphylococcal infection, Streptococcal sepsis, Suicidal ideation, Suicide attempt, Suspected COVID-19, Swelling face, Syncope, Systemic inflammatory response syndrome, Tendon rupture, Thoracic vertebral fracture, Thyroidectomy, Toxic shock syndrome, Toxicity to various agents, Transient global amnesia, Traumatic liver injury, Ulna fracture, Umbilical hernia, Unevaluable event, Urinary bladder polyp, Urinary tract infection, Urosepsis, Uterine leiomyoma, Uterine prolapse, Vertigo, Viral pharyngitis, Volvulus, Vomiting, Wound infection, Wrist fracture

Excluded SAE types (efficacy-related endpoints): COVID-19, COVID-19 pneumonia, SARS-CoV-2 test positive.

Note: Pfizer and Moderna coded all SAEs using the MedDRA coding dictionary; terms here are reproduced verbatim from the SAE tables. Preferred terms with @@ denote uncoded terms.

Supplemental Table 2. Sensitivity analysis				
	Events[a]		Risk difference per 10,000 participants (95% CI)	Risk ratio (95% CI)
Trial	Vaccine	Placebo		
Serious adverse events of special interest[b]				
Pfizer	52	33	10.1 (-0.4 to 20.6)	1.57 (0.98 to 2.54)
Moderna	87	64	15.1 (-3.6 to 33.8)	1.36 (0.93 to 1.99)
Combined	139	97	12.5 (2.1 to 22.9)	1.43 (1.07 to 1.92)
SAEs matching Brighton's SPEAC COVID-19 AESI list[c,d]				
Pfizer	39	28	5.8 (-3.5 to 15.2)	1.39 (0.82 to 2.37)
Moderna	65	56	5.9 (-10.9 to 22.6)	1.16 (0.76 to 1.77)
Combined	104	84	5.9 (-3.2 to 15.0)	1.24 (0.89 to 1.72)

[a] Denominators for Pfizer were 18,801 in the vaccine group and 18,785 in the placebo group, and for Moderna were 15,185 in the vaccine group and 15,166 in the placebo group.
[b] This analysis, presented in the main paper, is reproduced here for ease of interpreting the sensitivity analysis.
[c] This list does not include the 29 clinical diagnoses Brighton identified as "known to have been reported [in conjunction with COVID-19] but not in sufficient numbers to merit inclusion on the AESI list."
[d] Standard errors used to estimate 95% CIs were inflated by the factor √[#SAE]/[#patients with SAE] to account for multiple SAE within patients.