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Research Article

COVID-19 Vaccination from First Dose to Booster: New Insights into the Frequency of Most Common Systemic Adverse Events and Possible Booster Nocebo Effects based on a Systematic Review

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ABSTRACT

Background: Based on placebo data, it has been recently demonstrated that the frequencies of most common adverse events (AEs) of COVID-19 vaccination are overestimated due to negative expectation bias of vaccine recipients (nocebo effect). Since booster studies lack comparators, estimating the extent of the nocebo effect is difficult. We aimed to overcome this obstacle through a systematic comparison of most common AE frequencies across vaccine doses (first, second, booster), age groups, and vaccine *vs.* placebo arms.

Methods: We systematically assessed systemic AEs in approved COVID-19 vaccines according to the PRISMA guidelines. All documents regarding COVID-19 vaccines with a booster dose authorized by the FDA (cutoff date 19 November 2021) were systematically searched on PubMed and the FDA website. Solicited systemic AEs from all documents supporting approval/authorization were collected. After standardization of doses and age groups, AE frequencies were compared between vaccine and placebo.

Findings: Two trials were identified for BNT162b2 (n=21,785 participants), two for mRNA-1273 (n=22,324), and one for Ad26.COV2.S (n=4,085). Fever cases dropped to about half with the booster dose in all vaccines, whereas all other AE frequencies were similar to the preceding dose. Almost no fever cases occurred with placebo (first/second dose); all other systemic AEs occurred at high frequencies. After subtracting placebo arm values from vaccine values, the frequencies for the various AEs were roughly comparable within each dose for each vaccine.

Interpretation: Fever is the only solicited systemic AE that can be assessed objectively. It occurs about 50% less often with the booster than with the preceding dose. This may indirectly indicate a considerable overestimation of systemic AEs in the case of booster vaccinations and a pronounced nocebo effect. The nocebo effect appears to substantially contribute to the differences in the frequencies of the various systemic AEs.

Keywords: COVID-19; Vaccination; Booster; Adverse events; Nocebo

INTRODUCTION

Vaccination is an important tool to combat viral infections. In the case of COVID-19, the approved vaccines are well tolerated and most adverse events (AEs) are only mild [1]. Even more, the results of a recent study suggest that a substantial proportion of the AEs following COVID-19 vaccination may be due to a negative expectation bias of participants, the so-called nocebo effect [2] assessed in placebo arms. This study was based on the initial approval Randomized Controlled Trials (RCTs), which are the best sources of efficacy and safety data, as they provide control data as reference points. Therefore, these studies are essential to better estimate the relevance of more frequent AEs.

In this sense, the evaluation of AE frequencies after booster COVID-19 vaccines with a current Emergency Use Authorization (EUA) in the USA (BNT162b2, mRNA-1273 and Ad26.COV2.S) is particularly challenging, since the booster studies are not controlled and the reported AEs thus lack any reference parameter.

We have recently published the results of the first approach that enables an indirect comparison of approved COVID-19 vaccines using all available RCT data [3]. Here we apply the same approach to AEs occurring after the booster dose. This may help to objectify the current discussions around the safety of booster vaccines against COVID-19 and reduce the hesitancy among the public towards

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receiving a booster dose. Moreover, it serves as an outstanding example of how an indirect comparison among different clinical studies can be accomplished by means of systematic, standardized assessments of the biomedical literature that goes beyond traditional reviews.

MATERIALS AND METHODS

Study selection

The PRISMA 2020 Statement [4] was adopted for study selection and data collection. A systematic search on PubMed and FDA website was performed. Three vaccines with a booster dose have a EUA in the USA: the mRNA vaccines BNT162b2 (Comirnaty) by Biontech/Pfizer and mRNA-1273 (Spikevax) by Moderna, and the adenovirus vector vaccine Ad26.COV2.S by Janssen. All journal articles and regulatory documents which formed the basis for the EUA of the booster dose were identified. All publications available as of 19 November 2021 reporting results of these trials were considered and included in the assessment. Study identification was performed independently by two authors, according to the predefined eligibility criteria, and corroborated by other two authors; any arising disagreements were solved through discussion among all authors. Risk of bias was negligible, since all publications containing available data were included in the analysis.

Data collection and standardization

Every data point of interest (i.e. study design, demographics, safety outcomes) was systematically identified and compiled in a specialized, relational SQL database by two authors. For all studies, systemic AE data from the first, second and booster doses were collected. In order to allow a clear readout, only homologous vaccination strategies were included in this booster vaccination assessment; no further filters or limits were applied. Placebo arms were examined where available (i.e. first dose in all three vaccines; second dose for BNT162b2 and mRNA-1273). In all selected studies, solicited AEs (i.e. AEs actively sought after vaccination) [5] were reported by participants using electronic diaries within seven days of vaccine administration. Solicited systemic AEs were identified and entered into the database. Subsequently, AEs were standardized according to the Medical Dictionary for Regulatory Activities (MedDRA version 22.1, English) and age groups were standardized according to pre-established criteria (Table 1). Only AEs occurring with at least two vaccines were analyzed. The data was standardized in order to identify most comparable subgroups across the three vaccines. The data was analyzed and the results visualized with the software TIBCO Spotfire (version 11.4.0).

Table 1: Age groups as reported in journal articles and regulatory documents and their standardization for analysis.

Age as reported (years)	Standardized age groups
16-55	Middle-aged
18-55	
18-59	
18-64	
18-95	Overall
≥ 18	
55-70	Senior
>55	
≥ 60	
≥ 65	
≥ 70	

RESULTS

The selection process is depicted in Figure 1. After exclusion of non-approved dosages and dosing schedules, ten publications reporting on clinical trials were identified (Table 2), including seven journal articles [6-13] and three regulatory Food and Drug Administration (FDA) documents [10,14,15]. The entire data compiled in the SQL database amounted to 71 different study arms, corresponding to all information relevant for vaccine safety after first, second and booster doses at the time of analysis.

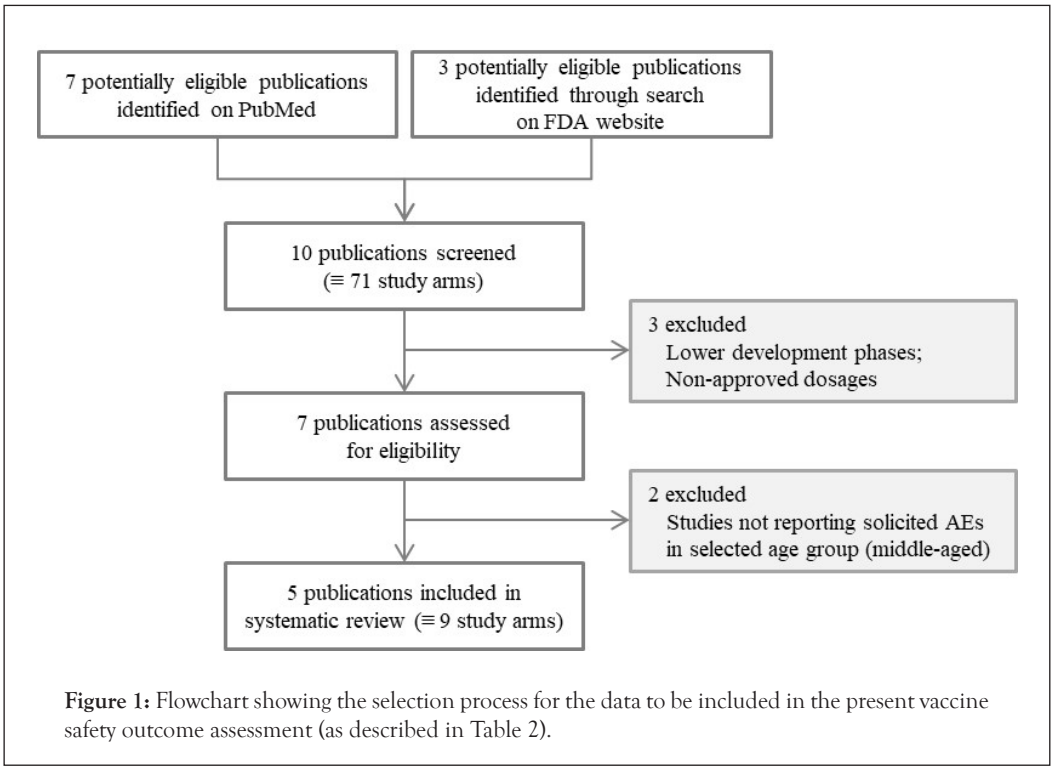

Figure 1: Flowchart showing the selection process for the data to be included in the present vaccine safety outcome assessment (as described in Table 2).

Table 2: Stepwise selection of publications (i.e. sources) containing relevant information to be included in the safety assessment of COVID-19 vaccines (first, second and booster dose) approved or authorized in the USA. Ten publications were initially identified and compiled in a SQL database. A) All ten identified publications containing relevant information (i.e. prospective data from clinical trials) about the safety of COVID-19 vaccines approved or authorized in the USA (first, second and booster dose). B) Standardization step to identify comparable age groups among all trials. C) Publications with comparable safety outcomes reported separately for the first, second and booster vaccine doses in middle-aged participants.

Vaccine	Clinical trials.gov ID	Trial phase	(A) Identified data sources	(B) Standardization of age groups	C) Publications with middle-aged subjects
BNT162b2	NCT04380701	Phase I/II	(6)	✓	
	NCT04368728	Phase I/II/III	(7)	✓	
			(8)	✓	✓
			(9)	✓	
			(10)	✓	✓
mRNA-1273	NCT04283461	Phase I	(11)	✓	
			(12)	✓	
	NCT04470427	Phase III	(13)	✓	✓
	NCT04405076	Phase II	(14)	✓	✓
Ad26.COV2.S	NCT04505722	Phase III	(15)	✓	✓
	NCT04535453	Phase II		✓	✓

The data structure showed three trial phases (I–III) (Table 2), various numbers of subjects depending on trial phase (Table 3), and three distinct dose analysis sets (first dose *vs.* second dose *vs.* booster dose). Moreover, eleven age ranges were identified across the three analyzed vaccines; a standardization step as shown in Table 1 allowed their clustering into three age groups: Overall, middle-aged, and senior participants. The overall group would best represent the general population; however, data was available in all studies only for the groups of middle-aged and senior participants. Therefore, for this assessment, only the middle-aged group was included, as it is believed to represent the general population better than the senior group (Tables 3 and 4). Accordingly, five publications were found suitable for safety analysis per administration dose (Table 3), reporting data on five trials: One phase I–III study was assessed for BNT162b2 (reported in one original article and one FDA document), whereas for mRNA-1273 and Ad26.COV2.S one phase II and one phase III study each were included (one original article and one FDA document for mRNA-1273; one FDA document for Ad26.COV2.S). The entire data was compiled in the SQL database, amounting to nine different study arms corresponding to all relevant vaccine safety information for first, second and booster doses at the time of analysis.

It must be considered that different numbers of participants were included in the trials for each vaccine (BNT162b2: 21,785; mRNA-1273: 22,324; Ad26.COV2.S: 4,085) (Table 3). In addition, the publications regarding booster vaccinations only reported on rather few participants (BNT162b2: 290; mRNA-1273: 129; Ad26.COV2.S: 89) in comparison to the verum arms of the initial trials. Therefore, different numbers of participants were analyzed for different vaccine doses, representing a statistical limitation of this assessment.

The systemic AEs can be divided in three groups according to their frequency with the three vaccines across doses: Particularly common AEs (headache, fatigue), practically non-occurring AEs (fever), and AEs somewhere between the first two groups (arthralgia, myalgia, chills). The most common AEs with the booster dose of any vaccine were fatigue, headache and myalgia, as already seen in the pre-booster doses (Figure 2). Fever was the systemic AE with the lowest frequency across all vaccines and doses. In the case of the mRNA vaccines (mRNA-1273 and BNT162b2), systemic AEs occurred less frequently after the first dose and more frequently after the second dose. The AE frequencies for the booster dose lied between those of the first and second doses, with the exception of arthralgia, myalgia and fatigue for BNT162b2, which had slightly higher frequencies with the booster. It is noteworthy that the frequency of fever decreased to about half from the preceding dose (i.e. second dose for BNT162b2 and mRNA-1273, first dose for Ad26.COV2.S) to the booster dose for all vaccines. Because the vector vaccine Ad26.COV2.S only requires a single initial dose, we compared the data for the first dose with that of the booster vaccination. With the exception of fatigue, the systemic AE rates were lower with the booster dose than with the first vaccine dose. No data is available for Ad26.COV2.S on chills and arthralgia (Figure 2).

Table 3: Details of the five publications selected for inclusion in the safety outcome assessment per administration dose after data standardization.

Label	Dose	Study arm	Number of participants	Age groups	Clinical trials.gov ID	Sources
BNT162b2	First	Placebo	10,896	16-55 years	NCT04368728	(8)
		Verum	10,889			
	Second	Placebo	10,896			
		Verum	10,889			
	Booster	Verum	290	18-55 years		(10)

mRNA-1273	First	Placebo	10,918	18-64 years	NCT04470427	(13)
		Verum	11,406			
	Second	Placebo	10,918			
		Verum	11,406			
	Booster	Verum	129		NCT04405076	(14)
Ad26.COV2.S	Single-dose	Placebo	2,049	18-59 years	NCT04505722	(15)
		Verum	2,036			
	Booster	Verum	89	18-55 years	NCT04535453	

Table 4: Age groups reported in publications providing safety data for each vaccine. Please note that the overall group would best represent the general population; however, data was available in all studies only for the groups of middle-aged and senior participants. Therefore, for this assessment, only the middle-aged group was included, as it is believed to represent the general population better than the senior group.

		Vaccines			Age groups included in assessment
		BNT162b2	mRNA-1273	Ad26.COV2.S	
Age Groups	Middle-aged	✓	✓	✓	✓
	Overall		✓	✓	
	Senior	✓	✓	✓	

Figure 2: Most common systemic adverse events occurring after the first, second and booster doses of anti-SARS-CoV-2 vaccines in verum arms. The highest frequencies for each adverse event occurring with each vaccine are shown. No data was reported for chills or arthralgia for Ad26.COV2.S. The Janssen vaccine is approved with a single dose before the booster dose.

To further illustrate the differences between the individual vaccine doses, we plotted the changes in the frequency of AEs for all vaccines. The comparison of the frequencies between the first and second doses showed that the AEs for the mRNA vaccines increased by 10% to about 39% (Figure 3), but decreased for almost all AEs in the placebo arms between the same doses (Figure 4). When comparing the frequencies of the AEs associated with the booster dose with those of the previous doses (i.e. second dose for BNT162b2 and mRNA-1273, first dose for Ad26.COV2.S) (Figure 5), all rates decreased for mRNA-1273 (clearly with myalgia by-12%). BNT162b2 displayed similar results for the booster and the second dose (slightly lower for chills and headache; slightly higher for arthralgia, fatigue and myalgia). For Ad26.COV2.S, a slight increase was noted in the frequency of fatigue from the previous dose to the booster dose (7.9%).

High frequencies were observed for most of the systemic AEs in the placebo arms, with the exception of fever, which was practically absent in all three vaccines (Figure 6).

If the frequencies of the individual systemic AEs in the placebo arms are subtracted from those in the vaccine arms, the ranges within each vaccine remain similar except for fever (first dose: 5%–14% for BNT162b2, 2.8%–9.6% for mRNA-1273, 19.6–27% for Ad26.COV2.S-Figure 7; second dose: 17%–36% for BNT162b2, 34.8%–48.7% for mRNA-1273; no second dose for Ad26.COV2.S -Figure 8). With this approach, the main AE frequency groups previously described are no longer detectable.

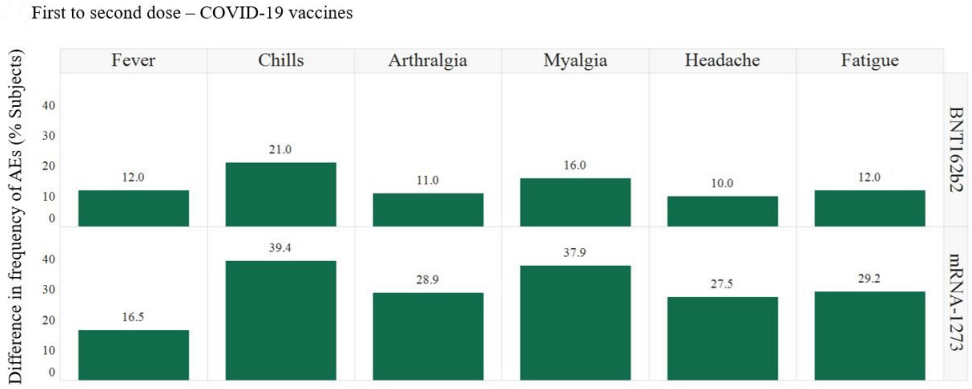

Figure 3: Differences in the frequencies of most common systemic AEs between doses: from first to second vaccine dose in the verum group. The highest frequencies for each AE occurring with each vaccine are shown. The Janssen vaccine is approved with a single dose before the booster dose.

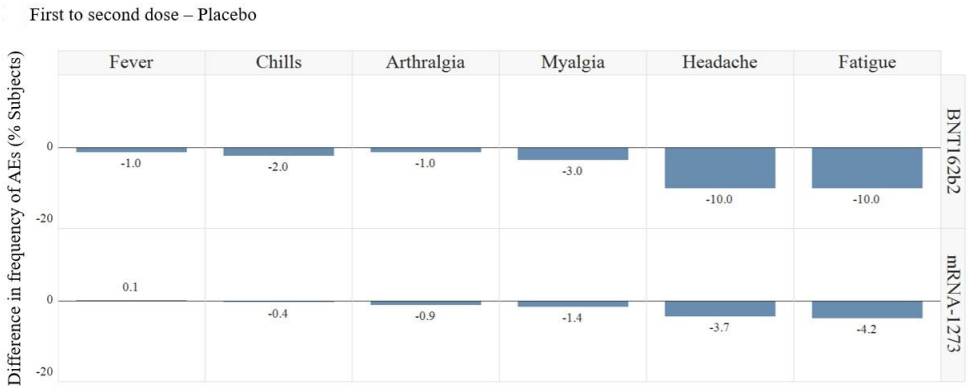

Figure 4: Differences in the frequencies of most common systemic AEs between doses: from first to second vaccine dose in the placebo group. The highest frequencies for each AE occurring with each vaccine are shown. The Janssen vaccine is approved with a single dose before the booster dose.

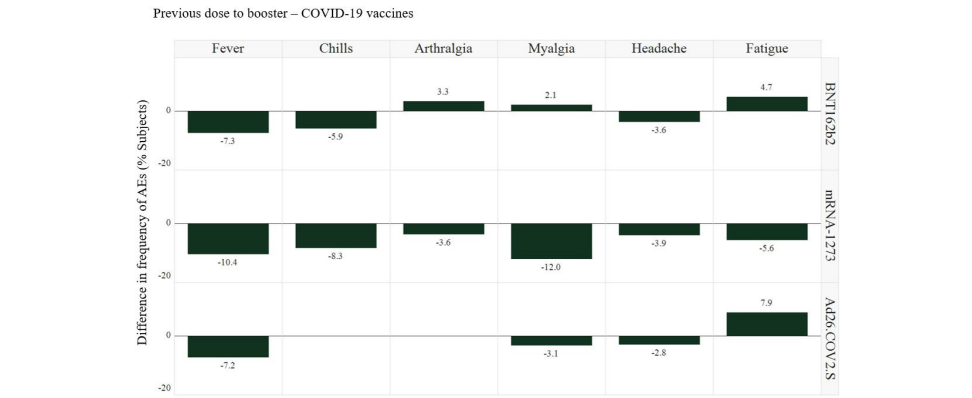

Figure 5: Differences in the frequencies of most common systemic AEs between doses: between booster and previous dose (i.e. second dose for BNT162b2 and mRNA-1273, first dose for Ad26.COV2.S). The highest frequencies for each AE occurring with each vaccine are shown. No data was reported for chills or arthralgia for Ad26.COV2.S. The Janssen vaccine is approved with a single dose before the booster dose.

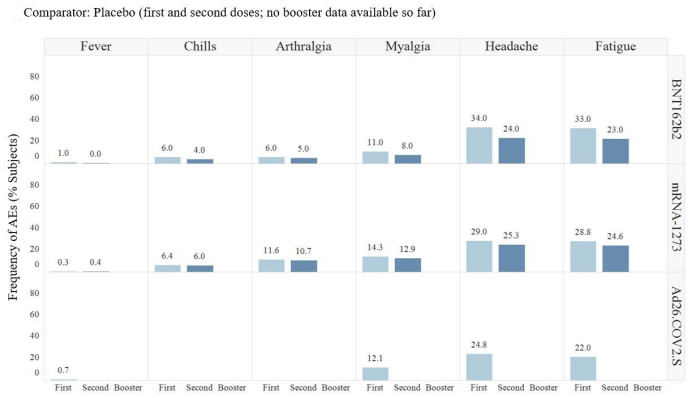

Figure 6: Most common systemic adverse events occurring after the first, second and booster doses of anti-SARS-CoV-2 vaccines in placebo arms. The highest frequencies for each adverse event occurring with each vaccine are shown. No data was reported for chills or arthralgia for Ad26. COV2.S. The Janssen vaccine is approved with a single dose before the booster dose.

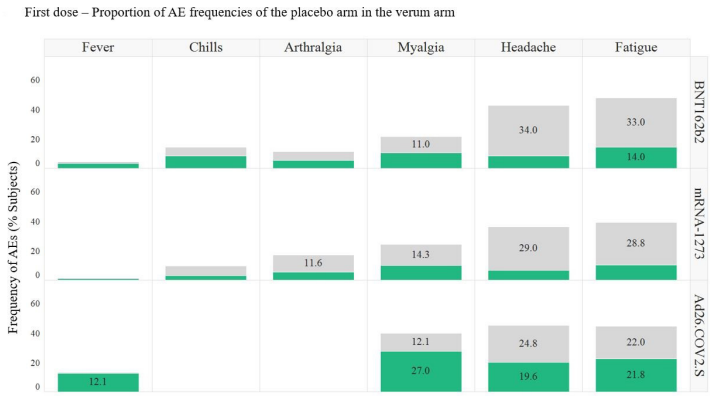

Figure 7: Graphic visualization of the nocebo effect in COVID-19 vaccination. The values for AE frequencies in the placebo arm in relation to the verum arm are represented in with the first vaccine dose. The gray portion represents the AE percentages in the placebo arm; the green portion corresponds to the remaining proportion of AEs occurring in the verum arms after subtraction of the values observed for the same AEs in the placebo arm.

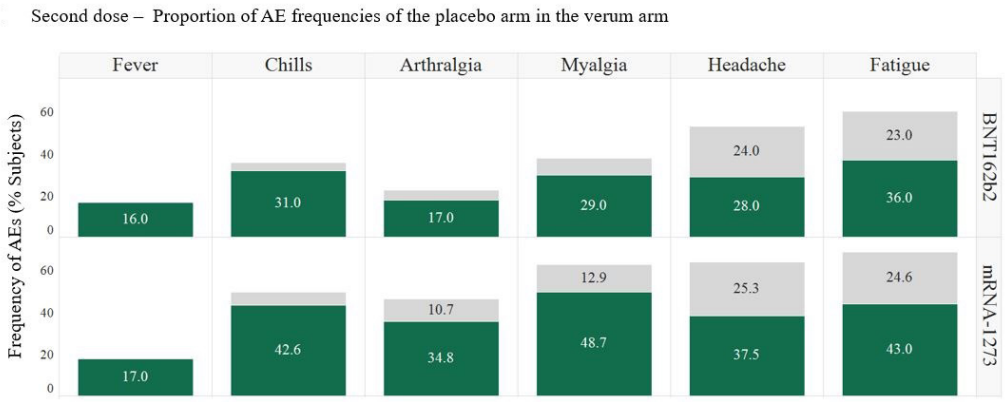

Figure 8: Graphic visualization of the nocebo effect in COVID-19 vaccination. The values for AE frequencies in the placebo arm in relation to the verum arm are represented with the second vaccine dose; Ad26. COV2.S is approved without a second dose. The gray portion represents the AE percentages in the placebo arm; the green portion corresponds to the remaining proportion of AEs occurring in the verum arms after subtraction of the values observed for the same AEs in the placebo arm.

DISCUSSION

Comparisons between different clinical trials can have a major impact on both individual treatment decisions as well as on decisions during the pharma Research and Development (R&D) process. However, head-to-head comparisons are rarely conducted; instead, indirect comparisons are performed (e.g. Cochrane analyses, review articles). Here, we indirectly compare trial data for COVID-19 vaccines which currently have a EUA in the USA for booster vaccination. We investigated all systemic, solicited AEs (i.e. those AEs actively sought after vaccination) [5] reported for each vaccine after the first, second and booster dose.

Overall, the systemic AEs can be divided in three groups according to their frequency with the three analyzed vaccines across doses: Particularly common AEs (headache, fatigue), practically non-occurring AEs (fever), and AEs with a frequency somewhere between the first two groups (arthralgia, myalgia, chills). Upon subtracting AE frequencies observed with placebo from those reported with the vaccines, these main AE frequency groups are no longer detectable.

Safety outcomes after the first and second vaccine doses have been reported recently [3]. Overall, as for the first and second doses, the authorized booster vaccine doses are well tolerated, and most AEs are only mild. Fatigue, headache and myalgia prevailed as the most common AEs. Fever was the AE with the lowest frequency across all vaccines and doses.

Various patterns could be verified in the AE frequencies. In the case of the mRNA vaccines (mRNA-1273 and BNT162b2), systemic AEs occur less frequently after the first dose and more frequently after the second dose. With few exceptions, the frequencies for the booster dose lie between those of the first and second doses. For Ad26.COV2.S, only one initial dose is needed. Most systemic AEs are lower with the booster dose than with the first dose.

AEs arising from drug therapy are the most common reasons provided by patients who do not accept medication or fail to adhere to treatment. Whereas this may primarily have individual consequences, in the case of a pandemic the refusal to accept vaccination rises to a social problem [16].

For the analyzed COVID-19 vaccines, the nocebo effect with mRNA-1273 and BNT162b2 decreased from the first to the second dose for all subject-reported systemic AEs; there were almost no fever cases in any of the three placebo arms. One can speculate whether the nocebo effect would decrease even more significantly with a booster-placebo control arm.

In contrast to all other common systemic AEs, fever was barely reported in the placebo arms. A possible explanation for this is that fever can be measured objectively. In contrast, all other assessed systemic AEs are subject-reported, and therefore prone to a negative perception bias. This observation is in accordance with a nocebo effect, defined as AEs occurring during sham treatment. The nocebo effect has been reported in usual drug treatments, particularly for pain [17]. In addition, it has been recently reported for several AEs in COVID-19 vaccination [2]. The nocebo effect in vaccination is of particular interest since a high frequency of non-objectively measurable AEs may negatively impact vaccination willingness [18]. Therefore, fever as an objectively measurable parameter could help to better understand the extent of the nocebo effect of subjective AEs during vaccination. It is interesting that the frequency of fever decreases to about half with the booster dose of the three vaccines in comparison to the respective previous dose. In contrast, the frequencies of the other systemic AEs only decrease slightly in the same comparison, and for some AEs these values even increase.

CONCLUSION

Even though distinct AEs may develop differently between vaccine doses, it can be speculated that the frequency of all systemic AEs, also with the booster dose, may be strongly influenced by a nocebo effect. Ultimately, this question can only be answered with placebo-controlled vaccine studies of the booster dose.

The systemic review presented here is only a small excerpt from a larger systematic COVID-19 vaccine safety assessment based on the most relevant trial data (safety and efficacy). The multidimensional assessment of vaccine data presented here may serve as basis for a public awareness campaign to combat hesitancy in receiving a booster dose of the approved anti-SARS-CoV-2 vaccines.

LIMITATIONS OF THE STUDY

The trials analyzed here included considerably different numbers of participants, in particular for the booster dose, representing a statistical limitation of this assessment.

DECLARATION OF COMPETING INTEREST

The authors declare that the analysis was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The present systematic review was not registered in any international database.

REFERENCES

1. WHO website. COVID-19 advice for the public: Getting vaccinated. 2021.
2. Amanzio M, Mitsikostas DD, Giovannelli F, Bartoli M, Cipriani GE, Brown WA. Adverse events of active and placebo groups in SARS-CoV-2 vaccine randomized trials: A systematic review. Lancet Reg Heal Eur. 2021;12:100253.
3. Behrens C, Gasperazzo T, Samii-Moghadam M, Lampe JB. An objective systematic comparison of the most common adverse events of COVID-19 vaccines. Medrxiv. 2021.
4. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;18(3):e1003583.
5. Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F. The how's and what's of vaccine reactogenicity. NPJ Vaccines. 2019;4:39.
6. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T-cell responses. Nature. 2020;586(7830): 594-599.
7. Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020;586(7830):589-593.
8. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the bnt162b2 mrna covid-19 vaccine. N Engl J Med. 2020;385(19):1761-1773.
9. Walsh EE, Frenck Jr RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. New Eng J Med. 2020;383(25):2439-2450.

10. FDA Fact Sheet: Emergency use authorization (EUA) of the Pfizer-biontech covid-19 vaccine to prevent coronavirus disease 2019 (Covid-19). 2021.
11. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and immunogenicity of sars-cov-2 mrna-1273 vaccine in older adults. N Engl J Med. 2020;383(25):2427-2438.
12. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 - Preliminary report. N Engl J Med. 2020;383(20):1920-1931.
13. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mrna-1273 sars-cov-2 vaccine. N Engl J Med. 2020;384:403-416.
14. FDA Fact Sheet: Emergency use authorization (EUA) of the Moderna (Covid-19) vaccine to prevent coronavirus disease 2019 (covid-19). 2021.
15. FDA Fact Sheet: Emergency use authorization (EUA) of the Janssen (Covid-19) vaccine to prevent coronavirus disease 2019 (covid-19). 2021.
16. Sever PP. Nocebo affects after COVID-19 vaccination. Lancet Reg Heal Eur. 2021;12: 100273.
17. Wolters F, Peerdeman KJ, Evers AWM. Placebo and nocebo effects across symptoms: From pain to fatigue, dyspnea, nausea, and itch. Front Psychiatry. 2019;10:470.
18. Häuser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. Dtsch Arztebl Int. 2012;109(26):459-465.