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Severe side effects to SARS-CoV-2 vaccinations may be missed by questionaires

We eagerly read the article by Borroni et al. about the side effects after vaccination with the mRNA BNT162b2 vaccine in 3659 healthcare workers [1]. It was concluded that adverse reactions to the second jab of the Moderna vaccine are usually mild and of short duration [1] and that "adverse events in specific subgroups, such as pregnant females, elderly or young subjects, and those with severe comorbidities should be assessed in different settings" [1]. The study is appealing but raises concerns, which require discussion.

The study deforms the true spectrum of side effects. According to table 2 only mild side effects were reported. However, SARS-CoV-2 vaccinations can be complicated by severe, even lethal, side effects [2]. One reason why only mild side effects were registered could be the methods applied. Only patients who were able to fill in the form were included. Those unable to attend and to fill in the form were lost. Those, being unable to attend because of being hospitalised for side effects were thus excluded. Severe side effects in response to a SARS-CoV-2 vaccination include venous sinus thrombosis (SVT), Guillain-Barre syndrome (GBS), immune encephalitis, transverse myelitis, small fiber neuropathy, reversible, cerebral vasoconstriction syndrome (RCVS), multiple sclerosis, neuromyelitis optica spectrum disorder, and several others [2]. We should be told which treatment did those patients require, which were hospitalised and their outcome.

We do not agree with the conclusion that the provided results allow to assess the applied vaccine as safe for all vaccinees. There is a proportion of patients that experiences severe side effects and it is the duty of health care workers and researchers to find out which mechanisms and risk factors predispose for severe adverse reactions. One risk factor for severe side effects, in particular GBS, is previous GBS [3]. There are also patients with myasthenia or previously diagnosed multiple sclerosis who are at risk to experience exacerbation of myasthenia, myasthenic crises, or flares and exacerbation of multiple sclerosis relapses.

Interestingly, 432 vacciness had a previous SARS-CoV-2 infection. We should be told why these subjects received a vaccination despite having experienced a previous SARS-CoV-2 infection. Were these patients tested for neutralising antibodies prior to the vaccination? Did those with a previous SARS-CoV-2 infection experience less or more frequently side effects from the vaccination than those without a previous infection?

Sixty-three vaccines required help by a physician and ten of the included vaccinees were admitted to the intensive care unit (ICU) [1]. We should be told which type of side effects these 10 patients experienced, which diagnosis was established, which therapy they received, and which their outcome was.

In line with previous studies headache was highly prevalent, reported by 1380 patients. We should be told in how many of these patients headache underwent further work-up to detect the cause of headache and how many of these patients had ICB, SAB, RCVS, VST or dissection of an intracranial artery.

Overall, the interesting study has some limitations which challenge the results and their interpretation. Diagnosis, treatment and outcome of those that required hospitalisation because of side effects should be provided.

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AUTHORS' REPLY

Finsterer and Matovu [1] raised concerns about our article [2] on the side effects after vaccination with the mRNA BNT162b2 vaccine. They stated that "the study deforms the true spectrum of side effects" because "only patients who were able to fill in the form were included", leading to an exclusion of most-severe cases. We disagree with their opinion.

First, our objective was the evaluation of the safety profile after second vaccination dose among health-care workers (HCWs) of our hospital, not the safety of BNT162b2 in general. The studies among HCWs we quoted in our paper had the same aim. It is well known that severe adverse reactions are extremely rare and can only be reported to vaccine safety vigilance systems covering very large populations. For example, the most recent (9th) report of the Italian Medicines Agency (AIFA) for the period from 27 December 2020 to 26 September 2021 covered 84 million of administered vaccine doses (71.2% regarding BNT162b2) and recorded 101,000 suspected adverse reactions (69.0% regarding BNT162b2). The number of severe events correlated with BNT162b2 was 4 per 100,000 administered doses (4.5 per 100,000 after the first and 3.5 per 100,000 after the second dose). The number of cases of myocarditis/pericarditis was 6 per million administered doses, of anaphylactic reactions 3 per million, and of facial nerve paralysis 2 per million [3]. Of note, "severe" adverse events after BNT162b2 vaccination in the AIFA report include fever, lymphadenopathy, headache, paresthesia, joint and muscle pain, gastrointestinal symptoms, skin rashes, fatigue, and dizziness, but none of the severe diseases or syndromes quoted by Finsterer and Matovu (which were reported after vaccination with other non-mRNA vaccines). The severe "adverse reactions" mentioned by Finsterer and Matovu were only described in case-reports [4-6].

Second, the form to collect adverse events was administered to our HCWs at the time of blood sampling for anti-spike antibody measurement, so a selection bias is unlikely. Of course, there is the possibility that very ill individuals did not come for blood sampling. However, this appears not be the case (see below).

Finsterer and Matovu also stated that they "do not agree with the conclusion that the provided results allow to assess the applied vaccine as safe for all vaccinees". In fact, our conclusions ("In interpreting these results, one should consider that our study was limited to a working population in relatively good health.") were different.

Finsterer and Matovu asked why previously infected subjects received vaccination. The reason is that in Italy only on 3 March 2021 the Italian Government stated that previously infected subjects could be considered fully vaccinated with only one dose if infection had occurred between 3 and 6 months before. Before that date workers received two doses even if previously infected.

Finsterer and Matovu asked whether those with a previous SARS-CoV-2 infection experienced less or more frequently side effects than those without a previous infection. That information is reported in Table 2 and page 481 of our paper ("subjects previously infected with SARS-CoV-2 were at lower risk if they had a recent infection history (≤180 days), while workers who had a previous infection occurred more than 180 days before the second dose were at increased risk") [2].

Finsterer and Matovu asked about "Sixty-three vaccines required help by a physician and ten of the included vaccines were admitted to the intensive care unit (ICU)" [1]. This is incorrect. In fact, we stated that "63 consulted a physician, including 10 subjects who were admitted to an emergency department" (not ICU). Moreover, we described diagnoses (esophageal gastric pain, suspected severe allergic reactions, flu-like symptoms, hemifacial paresthesia, cochleo-vestibular neuritis, and hemithoracic pain) and stated that "None of them required hospitalization".

Finally, Finsterer and Matovu asked about "how many patients with headache underwent further work-up to detect the cause of headache and how many of these patients had severe diseases or syndromes". We responded above that none of the subjects who consulted a physician did that because of headache.

In conclusion, we think our study provided a fair description of safety of BNT162b2 vaccine among HCWs in our hospital.

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