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Research Letter

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High anaphylaxis rates following vaccination with the Pfizer BNT162b2 mRNA vaccine against COVID-19 in Japanese healthcare workers: a secondary analysis of initial post-approval safety data

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To contain the coronavirus disease 2019 (COVID-19) pandemic, vaccine development and rollout have progressed rapidly around the world. After successful COVID-19 vaccine development, following the past examples of vaccine-preventable diseases,[1] nationwide vaccination programmes have been under way swiftly on a global scale. The BNT162b2 mRNA COVID-19 vaccine (Comirnaty, Pfizer-BioNTech, USA) is one of the vaccines granted earliest regulatory approval globally.[2,3] In Japan, fast-track approval was granted to the vaccine on 14 February 2021, with the scheduled provision of ∼140 million doses. The vaccine was the sole approved product as of May 2021, and the Japanese government set to prioritize vaccination in 4.84 million healthcare workers (HCWs) due to the sequential supply of limited doses.

The first round of Japan's vaccination programme against COVID-19 was initiated at 100 medical institutions eligible for priority vaccination for an estimated 40 000 HCWs from 17 February 2021.[4] However, from early March 2021, the vaccination programme was extended to additional 4.8 million HCWs at other medical institutions before disclosing the initial safety data including anaphylaxis observed at preceding institutions. As of 16 March 2021, >350 000 HCWs had received the first dose of the vaccine, and >9000 HCWs had received the second dose. Belatedly, on 12 March 2021, the Ministry of Health, Labour, and Welfare (MHLW) disclosed preliminary data of serious adverse reactions to the vaccine.

Therefore, using publicly available data by the MHLW, we conducted a secondary analysis of initial post-approval safety data concerning serious adverse reactions of anaphylaxis based on the vaccination programme in Japanese HCWs. For the diagnosis of anaphylaxis, each medical institution voluntarily reported possible cases based on their own judgement. Subsequently, the expert committee of the MHLW evaluated them based on the Brighton Collaboration case definition criteria (hereafter Brighton criteria).[5] Statistical analysis was not performed due to the small number of subjects with anaphylaxis. Ethical considerations were not applied to this study.

The data included 181 184 HCWs who received one or more doses of vaccination by 11 March 2021.[6] As shown in Table 1, 37 cases of anaphylaxis were observed, equating to 204.2 cases per million doses administered. Among them, only 17 (45.9%) cases were evaluated based on the Brighton criteria. Of which seven (41.1%) cases met the Brighton criteria 1, 2 or 3, resulting in 38.6 cases per million doses administered. The mean age of 37 cases was 40.4 years old, and a predominant cases were females (35, 94.5%). Twenty-one patients (56.8%) had a history of allergy as shown in Table 1. Within 30 min of vaccination, 31 (83.8%)

Table 1. The Characteristics of anaphylaxis cases

	All $N = 37$	Allergy histories	
		Yes ($N = 21$)	No ($N = 16$)
Mean age [range]	40.4 ∓ 11.0 [23–58]	41.2 ∓ 11.3	39.4 ∓ 10.5
Female sex, *N* (%)	35 (86.5)	20 (95.2)	15 (93.8)
Time from vaccination to onset of anaphylaxis, min			
0–5	9	5	4
6–10	3	2	1
11–20	12	7	5
21–30	7	3	4
31–	6	4	2
Mean ($N = 36$)[a]	18.2 ∓ 13.1	19.7 ∓ 14.5	16.2 ∓ 10.5
Brighton Collaboration case definition criteria			
1	2		2
2	4	1	3
3	1	1	
4, 5	10	7	3
Unevaluated	20	12	8
		Details of allergies[b]	
Overall drugs and vaccines		15	
Of these, influenza vaccine		5	
Analgesics or NSAIDs		4	
Antibacterial agents		2	
Hepatitis vaccine		2	
Contrast agents		2	
Overall foods		10	
Of these, egg		4	
Crustaceans (shrimps, crabs, etc.)		3	
Mackerel, buckwheat or wheat		Each 1	
Animal (Cat)		2	
Cosmetics		4	

Using data published by the Ministry of Health, Labour and Welfare as of 11 March 2021.[5]
All cases were the first dose of vaccination.
[a]One person who took 145 min to develop anaphylaxis (no history of allergy) was considered an outlier affecting the mean and was excluded from this analysis.
[b]The total does not necessarily add up to 21 because some patients have multiple allergy histories.

cases developed anaphylaxis. Those with allergic history had a longer onset time and a larger standard deviation than those without (19.7 ∓ 14.5 vs 16.2 ∓ 10.5 min). The outcomes were reported as recovery or mild improvement in all cases.

In Japan, the estimated cases per million doses administered were as high as 204.2 based on the spontaneous report, and they were 38.6 even when limited to the cases evaluated as level 1, 2 or 3 of the Brighton criteria. According to the US CDC, among a total of 9 943 247 doses of the BNT162b2 mRNA vaccine administered from 14 December 2020 to 18 January 2021, the anaphylaxis cases per million doses administered were 4.7.[3] The underlying reasons of such high incidence of anaphylaxis in Japan are unknown, but the presence of polyethylene glycol (PEG) additive,[7] which is also used in many cosmetic and pharmaceutical products is considered to be one of the reasons for inducing anaphylaxis by the BNT162b2 mRNA vaccine. Of the 37 HCWs who developed anaphylaxis, 57% had some history of allergy, and four patients had a history of cosmetics allergy, suggesting the potential involvement of PEG.

In Japan, based on 'Immunization Act and the Pharmaceuticals and Medical Devices Act', a spontaneous reporting system for adverse reactions is already in place, but the information on the safety of the BNT162b2 mRNA vaccine after approval is still limited. We found that the MHLW had not fully evaluated vaccine anaphylaxis at the early phase of the vaccination programme, and it is understandable that the Japanese government tried to make up the delayed vaccine rollout compared with other high-income countries under the uncontrolled spread of COVID-19 in the country. However, precautious measures should be paid to vaccine hesitancy prevailing in Japan, as illustrated in the past human papillomavirus vaccine controversy.[8] One of the first medical institutions that joined the vaccination programme is planning to conduct a safety survey (COV-Safe) using a social networking service for HCWs, and some hospitals have started their safety verification efforts.[9] Also, the US CDC[3] and the European Medicines Agency[10] continue to monitor and publicize the safety of coronavirus vaccines on an ongoing basis. In order to promote the vaccination programme, further effort should be directed domestically and internationally to ensure the safety of vaccines with prompt evaluation and timely publication.

There are several limitations. First, the data about anaphylaxis were based on spontaneous reports without exact

definition from medical institutions, and some reported cases were not evaluated by the MHLW using the Brighton criteria. This might have led to over or underestimation of the effect. Second, although the high proportion of women experiencing adverse reactions is consistent with previous studies,[3] a factor of gender bias is possible because all participants were HCWs. Third, we could not perform joint research with the MHLW using raw data, and our study included the publicly available data only, preventing us from conducting in-depth exploration of subject.

In conclusion, this study suggests that the incidence of anaphylaxis by the BNT162b2 mRNA vaccine may be higher in certain populations, such as the Japanese. Further safety studies that take into account ethnicity and race are necessary. Further global efforts should be directed to ensure the safety of vaccines with prompt evaluation and timely publication to promote effective vaccination programmes.

Authors' contributions

Takanao Hashimoto wrote the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and approved the final manuscript.

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Conflicts of interest

Dr Ozaki reports personal fees from Medical Network Systems, MNES Inc. outside the submitted work. Dr Tanimoto reports personal fees from Medical Network Systems, MNES Inc., and Bionics co. ltd, outside the submitted work.

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