Research Letter

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

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Highlight

In the initial post-approval safety data among Japanese healthcare workers who received the BNT162b2 mRNA COVID-19 Vaccine, the incidence of anaphylaxis was approximately 1 in 4,897, which was higher than the previous reports among non-Japanese population. This finding suggests a different vaccine safety signal depending on ethnic and racial characteristics.

(50 words)

Text

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 programs 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.²³ In Japan, fast-track approval was granted to the vaccine on February 14, 2021, with the scheduled

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provision of about 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 health care workers (HCWs) due to the sequential supply of limited doses.

The first round of Japan's vaccination program against COVID-19 was initiated at 100 medical institutions eligible for priority vaccination for an estimated 40,000 HCWs from February 17, 2021. However, from early March 2021, the vaccination program 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 March 16, 2021, more than 350,000 HCWs had received the first dose of the vaccine, and more than 9,000 HCWs had received the second dose.

Belatedly, on March 12, 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 program in Japanese HCWs. For the diagnosis of anaphylaxis, each medical institution voluntarily reported possible cases based on their own judgment. Subsequently, the expert committee of the MHLW evaluated them based on the Brighton Collaboration case definition criteria (hereafter Brighton criteria). 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 March 11, 2021. As shown in Table, 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 (18.9%) 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 higher proportion of cases 35 (94.5%) were females. Twenty-one patients (56.8%) had a history of allergy as shown in Table. Within 30 minutes of vaccination, 31 (83.8%) 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. Anaphylaxis reporting rate, including “unevaluated”, was 204.2 cases per million doses administered for entire 37 cases and 38.6 cases per million doses administered for subjects evaluated according to the Brighton criteria.

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 December 14, 2020, to January 18, 2021, the anaphylaxis cases per million doses administered were 4.7. The underlying reasons of such high incidence of anaphylaxis in Japan are unknown, but the presence of polyethylene glycol (PEG) additive, 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 program, and it is understandable that the Japanese government tried to make up the delayed vaccine rollout compared to 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. One of the first medical institutions that joined the vaccination program 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. Also, the US CDC and the European Medicines Agency continue to monitor and publicize the safety of coronavirus vaccines on an ongoing basis. In order to promote the vaccination program, 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 programs.

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Table. 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
| Age (years) | N=9 | N=5 | N=4 |
|------------|-----|-----|-----|
| 0-5        | 3   | 2   | 1   |
| 6-10       | 12  | 7   | 5   |
| 11-20      | 7   | 3   | 4   |
| 21-30      | 6   | 4   | 2   |
| Mean (N=36) | 18.2±13.1 | 19.7±14.5 | 16.2±10.5 |

**Brighton Collaboration case definition criteria**

1. 2
2. 4
3. 1
4. 1
5. 10
6. 7
7. 3

**Overall drugs and vaccines**

- Analgesics or NSAIDs: 4
- Antibacterial agents: 2
- Hepatitis Vaccine: 2
- Contrast Agents: 2

**Overall foods**

- 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 March 11, 2021. All cases were the first dose of vaccination.
*1 One person who took 145 minutes to develop anaphylaxis (no history of allergy) was considered an outlier affecting the mean and was excluded from this analysis.

*2 The total does not necessarily add up to 21 because some patients have multiple allergy histories.