

Letter to the Editor

Safety of SARS-CoV-2 BNT162b2 Vaccine in Elderly Patients from Japan - A Preliminary Assessment and A Call on Careful Pharmacovigilance

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Seguridad de la Vacuna contra SARS-CoV-2 BNT162b2 en Pacientes Ancianos de Japón – Una evaluación preliminar y un Llamado a una Cuidadosa Farmacovigilancia

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Vaccines are efficacious, effective and safe measures to control COVID-19. Despite phase 3 and 4 studies, some concerns should be addressed in certain populations regarding its specific vaccine safety. One of them is the safety of the elderly. The majority of enrollees in clinical studies on COVID-19 vaccines have been young to middle-aged individuals, with few exceptions [1].

For example, the median ages of enrollees in the two clinical trials using the mRNA vaccines are 51.4 and 52.0 years [2,3]. Then, it is challenging to discuss the safety of these vaccines in the elderly based on the results of these clinical studies, then also needing real-world observations outside them and effectiveness assessments.

In Japan, the eldest country globally, vaccination using the BNT162b2 mRNA COVID-19 vaccine began in February 2021 for healthcare workers, and in April 2021, for the elderly. In this country, as in most places, when serious adverse events occur after vaccination, physicians are obligated to report them to Japan's Ministry of Health, Labour and Welfare (MHLW), which promptly discloses information on them publicly.

Then, we reviewed the clinical features of individuals who died closely after vaccination using the database published by MHLW.

A total of 9,783,387 doses of the vaccine were administered in Japan from February 17 to June 18, 2021. As of June 23, only 355 deaths have been reported, representing 3.63 deaths per 100,000 doses. Of those 355 fatalities, 322 (90.7%) occurred in people older than 65, but 278 (78.3%) had underlying diseases. As of June 13, 2021, causes of death have been published in 277 of the 355 cases, including heart failure (n=37), hemorrhagic stroke (n=30) and cardiopulmonary diseases (n=30). According to the Ministry of Health, a causal relationship between death and vaccination was only suspected in 26 (7.3%). Such a relationship was ruled out in 39, remaining unknown in 290 cases.

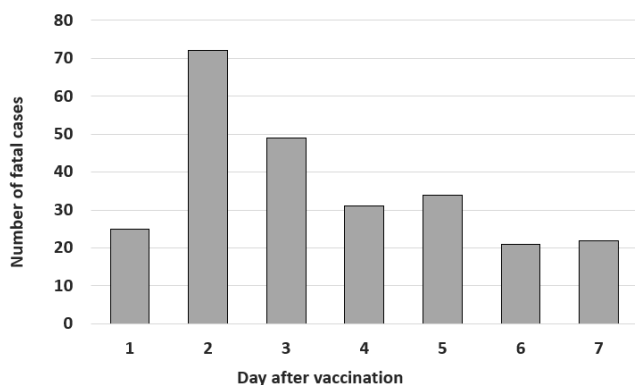
Most of the deaths occurred within a week of vaccination (n=254, 71.5%) (Figure 1), especially on the second (n=72, 20.3%) and third day (n=49, 13.8%). Although the possibility of reporting bias cannot be denied, some deaths among elderly Japanese people after vaccination were also reported during the 2009 H1N1 pandemic [4].

Furthermore, the number of deaths might not have peaked immediately after vaccination if vaccination had not been associated with their deaths.

There are several possibilities as to why many elderly people in Japan have died after vaccination. Besides the elderly have low organ reserves, they might

have been "overdosed" with the vaccine. Compared to Caucasians, Asians weigh approximately 20% less than them [5]. Despite that, the vaccine dose used in Japan and Western countries is the same, 30 µg. In phase 1 clinical trial of the vaccine, 10, 20, and 30 µg doses were administered, and a dose-dependent relationship was observed in adverse reactions [6]. Fever was observed in 0% in the 10 and 20 microgram groups, but 8% in the 30 µg group after the second dose, in those aged 65 to 85 years.

Figure 1. Number of deaths within the seven days following BNT162b2 mRNA COVID-19 vaccination.



Although this would be considered a superficial and preliminary analysis with many broad conclusions, suppositions and speculations, which could be controversial, our call is directed to raise the awareness on the constant need of the enhanced assessment of vaccine safety, which requires detailed and careful analysis by experts in the field, when occur.

These findings led us to consider that acute inflammatory reactions may be associated with the vaccine, exacerbating underlying diseases, increasing the possibility of fatal complications. Although these data may suggest that deaths were related to the vaccine due to the time relationship, also the findings would be explained by the expected death rate in the population.

Therefore, further studies are needed to improve the safety of vaccine administration in the elderly. Especially more safety studies on the elderly, as well as enhanced and careful pharmacovigilance of vaccinated population, is deserved [7], particularly in the context where COVID-19 vaccination is needed in the highest possible proportion of the world population to achieve efficient control of the pandemic, together with already fully deployed non-pharmacological interventions.

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