

# **Overview of mortality and pharmacoepidemiologic assessment after COVID-19 vaccination : a population-based overview and proposal**

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## **Abstract:**

Since COVID-19 vaccination started in Japan, the Ministry of Health, Labour and Welfare (MHLW) has accumulated clinically significant information on post-vaccination deaths voluntarily reported by physicians all over Japan. This information has been periodically reviewed by a committee established in MHLW, and the review data have been published each time. From a global perspective, this nationwide real-world data is considered to be invaluable.

Focusing on these published data, we organized, visualized and discussed them along with other officially published data from the Japanese authorities in order to clarify the progression of the number of deaths against the number of people vaccinated against COVID-19, the pattern of deaths after vaccination, and the causes of death in a way that reveals clinical medical implications. We also pointed out that the frequency of deaths and adverse reactions after vaccination followed an almost identical pattern over time when histograms are compared. With these findings, as well as the six-month follow-up results in the clinical trial of Comirnaty published in July, this article describes the facts of deaths after COVID-19 vaccination, in which mRNA-containing lipid nanoparticles have been administered to humans for the first time, and proposes what should be done in light of the need for follow-up of long-term adverse effects of vaccination.

## **Keywords:**

SARS-CoV-2, mRNA vaccine, vaccine mortality rate, COVID-19 vaccine, vaccine toxicity

Japanese Abstract :

Since the start of COVID-19 vaccination in Japan on February 17, 2021, the Ministry of Health, Labor and Welfare has been accumulating clinically relevant information on post-vaccination deaths voluntarily reported by physicians. This information has been periodically reviewed by the MHLW Review Committee, and the data have been published as needed. Globally, it is invaluable as real-world data on a national basis. In this editorial, we focus on this published data and describe the transition in post-COVID-19 vaccine deaths relative to vaccine doses in Japan, the pattern of post-vaccination deaths, and the causes of death in a way that brings together and visualizes clinical implications. In addition, it was pointed out that the pattern of death occurrence after vaccination and the pattern of adverse reaction occurrence after vaccination almost coincide with each other by comparison of histograms. It was summarized as a proposal on what should be done from the perspective of the need for follow-up on long-term side effects due to vaccination, by describing the actual state of death after vaccination with COVID-19 vaccine, which is the first mRNA-containing nanoparticle administered to mankind, with reference to data such as the 6-month follow-up of a paper on a clinical trial of Harmoni published in July.

Keywords :

SARS-CoV-2, mRNA vaccine, post-vaccination mortality, COVID-19 vaccine, vaccine toxicity

## INTRODUCTION

Eight months have passed since vaccination began in Japan on February 17, 2021, late in the Western industrialized countries. Initially, priority was given to health professionals, and in mid-April, it was expanded to include people over 65. As of 15 October 2021, 94599325 people had received one or more doses of vaccine, representing 75% of the population. Of these, 83656184 people, almost 66% of the population, have completed two doses. 1

The efficacy and safety of this vaccine have already been reported in many papers, but there are few population-based, nationwide reports of deaths after vaccination. As is well known, formal clinical trials of COVID-19 vaccines are still ongoing. According to clinical registration, Phase I / II trials of Pfizer Inc's Coniati vaccine and Takeda Pharmaceutical Co.'s Moderna vaccine are ongoing in Japan, 2 and 3, with completion expected in November 2021 and March 2022, respectively. Phase 3 clinical trials in the US are expected to be completed in May 4, 2023 for Comuniti and in October 2022 for Moderna. 5 In other words, these vaccines were granted emergency use authorization in the United States when the results of early clinical trials in the United States were available, and vaccination was started in Japan with special approval 6, 7 after review by the regulatory authority PMDA.

In Japan, since May 26, cases of death after vaccination spontaneously reported to MHLW by physicians have been periodically summarized and reviewed by committees set up in MHLW (Adverse Reaction Review Committee, Vaccination and Vaccine Subcommittee, Health Science Council ; Safety Measure Investigation Committee, Drug Safety Measure Committee, Pharmaceutical Affairs and Food Sanitation Council), and details of reported cases have been published at 1-2 week intervals. According to the report published on October 1, 2020, the cumulative number of deaths after vaccination was 1233 (1198 at Community and 35 at Moderna). The problem is that cases reported by physicians as being causally related to vaccination were also classified as "not assessable (NE)" 8, 9.

Japan has a terrible history of drug harm. 10 As a lesson from this, strict postmarketing surveillance after approval of new drugs is required for MAHs. 11 Regarding the use of the novel coronavirus vaccine, although the MAH requested early post-marketing phase vigilance, information on post-marketing safety evaluation seems to be based only on spontaneous reports from healthcare professionals and MAH collected to MHLW 8, 9. It is still fresh in our memory that over 7000 deaths due to adverse drug reactions occurred with gefitinib because Japan's world-class post-marketing all-case surveillance and legal pharmacovigilance were not applied. 12 Against this background, this article provides a multifaceted assessment of the post-vaccination deaths published by MHLW and recommends a rigorous scientific investigation.

## 1. Number of Vaccinated and Post-Vaccination Deaths

The number of people vaccinated reached 1,230,000 within two months of the start of vaccination of healthcare workers, and since the start of vaccination of the elderly, the number of people vaccinated has increased exponentially, surpassing 30,000,000 in July. On the other hand, reporting of post-vaccination deaths began with the start of vaccination. The post-vaccination death rate relative to the number of people vaccinated (those who received at least one dose of vaccine) was 0.0012% based on the report on May 24, 2020, when vaccination was mainly limited to medical personnel, then rose to 0.0022% as of July 7 and to 0.0020% as of July 21 (Figure 1). For comparison, the mortality rate of amyotrophic lateral sclerosis (ALS) in Japan is 1.07 / 100,000 (0.00107%). 13

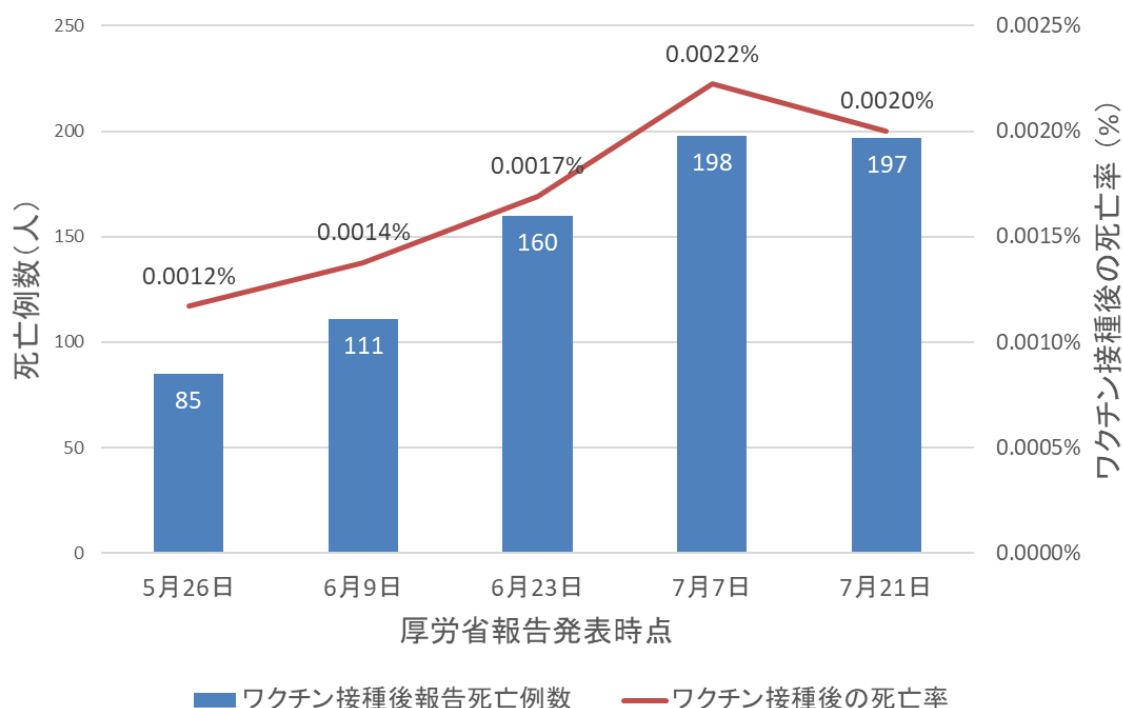


Figure 1. Post-vaccination deaths and mortality

Deaths and mortality rates based on MHLW reports as of July 21 are shown. Data sources and calculations are described in Supplementary Information A-2-1.

Prepared by the author from the following sources :

Summary of events reported as deaths after new corona vaccination : Adverse Reaction Review Committee, Immunization and Vaccine Subcommittee, Health Science Council (60th to 64th meetings) ; Safety Investigation Committee, Committee on Drug Safety, Pharmaceutical Affairs Committee, Pharmaceutical Affairs and Food Sanitation Council (8910th to 13th meetings in 2021) Report Document SA-1-SA-8

According to the Ministry of Health, Labor and Welfare reports as of July 21, 2020, the cumulative number of deaths (cumulative death rate) by the number of vaccinations was 488 (0.0012% ; number of people vaccinated, 41245144) after the first vaccination, 214 (0.0008% ; 27071471) after the second vaccination, and 44 unknown number of deaths. With Moderna, there were five deaths after the first dose (0.0002% ;

2286339) and no deaths after the second dose (0.0000% ; 544368). As of 15 October deaths as of October 15, 8 and 9. 1233

## 2. Number of days before and number of deaths after vaccination

A histogram with the number of days between vaccination and death on the horizontal axis and the number of deaths on the vertical axis based on reports from the Ministry of Health, Labor and Welfare (Figure 2) shows a characteristic pattern that peaks on the 2nd day after vaccination, then decreases and becomes almost constant. This pattern is also similar to the histogram of adverse reactions to vaccines (especially erythema, swelling, and induration at the injection site) (Fig. 3) 14, suggesting an association between these deaths and vaccination. It is important to note that deaths on the day of vaccination have reached a peak of 35% on day 2. About 57% of deaths occur within 5 days of vaccination. About 70% of patients die within 10 days after 2 days, and about 20% die after 11 days.

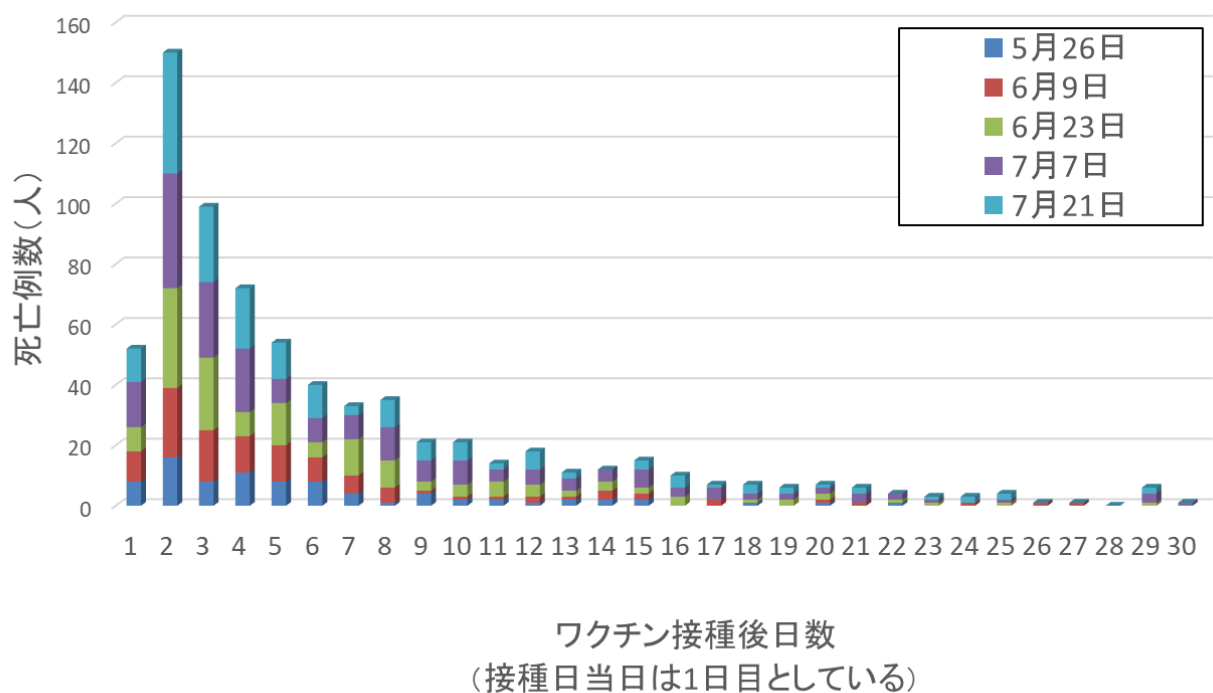


Figure 2. Number of days until death after vaccination and number of deaths

In the MHLW reports of 26 May, 9 June, 23 June, 7 July and 21 July, deaths are indicated by the colored histograms at each time point of reporting. The day of vaccination is designated day 1. These data are based on Supplementary Information A-2-1 and the number of deaths after 31 days (38, 29 unknown) has been omitted.

Prepared by the author from the following sources :

Summary of events reported as deaths after new corona vaccination : Adverse Reaction Review Committee, Immunization and Vaccine Subcommittee, Health Science Council (60th to 64th meetings) ; Safety Investigation Committee, Committee on Drug Safety, Pharmaceutical Affairs Committee, Pharmaceutical Affairs and Food Sanitation Council (8910th to 13th meetings in 2021) Report Document SA-1-SA-8

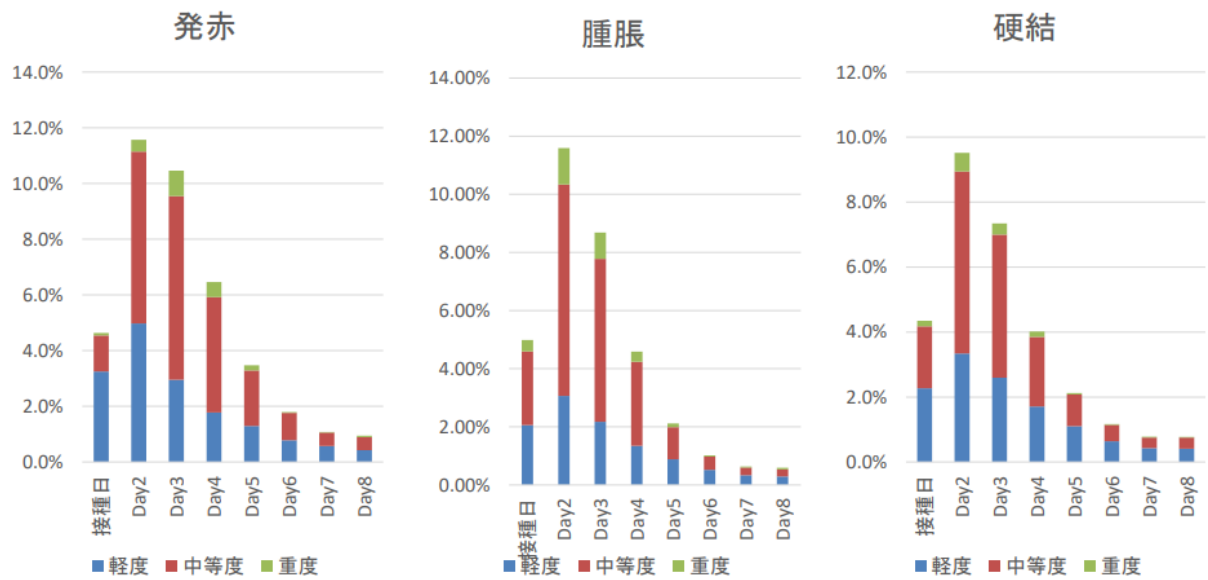


Figure 3 : Vaccination site response in the initial intensive investigation (cohort study) of the first dose of novel coronavirus vaccine

Source : Focused survey in early stage of COVID-19 vaccine administration (cohort survey) ; interim report of health observation diary tabulation after the 1st dose ; Committee on Safety Measures, Committee on Adverse Reactions and Committee on Drug Safety, Committee on Immunization and Vaccines ; MHLW, 3 / 12 / 2021 ; Cited August 24, 2021.14

### 3. Clinical Features of Death after Vaccination in Single-Cause Cases

We will describe the clinical features of post-vaccination deaths, focusing on the single death case, which accounts for 82% (548) of the total. A striking feature of reports of deaths after vaccination in single-cause cases is cardiovascular disease involving the heart, brain and lungs (vascular disease), which accounts for about 30% of cases and cardiac disease, including cardiorespiratory arrest, accounts for slightly more than 20% of cases (Figure 4). Vascular lesions were found in 41% of the brain, 31% of the heart, 4% of the GI tract, 4% of the lungs and 20% of other sites. More than 80% of patients had underlying disease, 9% had no underlying disease, and 9% had no underlying disease. Of the patients with multiple causes of death, those with two causes accounted for 15% (99 patients) of the total, but those with both causes classified as vascular or cardiac disorder or a combination accounted for 38% and those with either vascular or cardiac disorder as the cause of death accounted for 31% (see Supplementary Material a- 2 2-3).

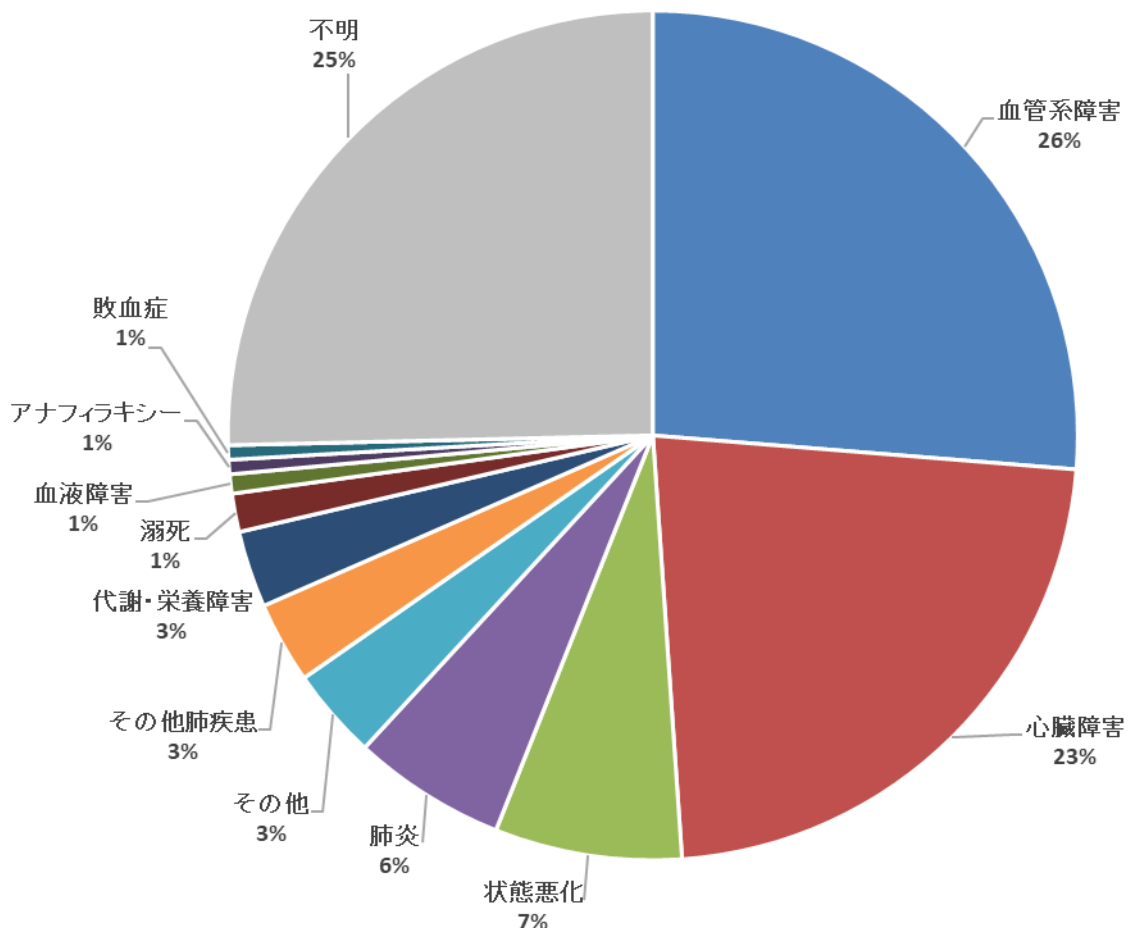


Figure 4 Number of patients by cause of death (as announced July 21, 2020) : Single cause of death only

This chart breaks down the causes of death after vaccination based on the data in Supplementary Information A-2-2-2, with single-cause cases accounting for 82% of the total.



Prepared by the author from the following sources :

Summary of events reported as deaths after new corona vaccination : Adverse Reaction Investigation Committee, Immunization and Vaccine Subcommittee, Health Science Council (the 64th meeting) ; Safety Investigation Committee, Drug Safety Committee, Pharmaceutical Affairs Department, Pharmaceutical Affairs and Food Sanitation Council (the 13th meeting in 2021) ; Report Documents SA-7, SA-8

In addition, in a paper on clinical trials of the Conianti vaccine published on July 28, 2021, 15 deaths in the vaccine group and 14 deaths in the placebo group were reported in Table S4 of Supplementary Information. Notably, cardiac arrest was the cause of four deaths in the vaccine group (compared with one in the placebo group), accounting for 26% of vaccine deaths. Vascular and cardiac disorders caused eight deaths in the vaccine group (compared with three in the placebo group), accounting for half of deaths caused by vaccines. These points are consistent with the trend of causes of death after vaccination in Japan described above.

#### 4. Deaths per 100,000 people by cause of death

It is possible to calculate mortality after COVID-19 infection and after vaccination. These are summarized in Table 1.

Cause of death, etc	Deaths per 100,000 population	Notes
Death due to novel coronavirus infection		
Overall	10.088	*1
~ 50 s	0.573	*1
& gt ; 60 s	27.859	*1
Death due to influenza		
Overall	2.900	*2
Death after coronavirus vaccination	1.725	*3
Death due to influenza vaccination	0.011	*4

\* 1 : See Supplemental Information B-2-1

\* 2 : 2019 (2019) Summary of Monthly Vital Statistics Annual Report (Approximate), Table 6. Excerpt from Ministry of Health, Labour and Welfare 16

\* 3 : See Supplementary Information A-2-3

\* 4 : See Supplemental Information B-2-2

Table 1 Deaths per 100,000 people by cause of death : COVID-19 and post-vaccination deaths and influenza and vaccination deaths

## DISCUSSION

To get an overview of deaths after vaccination, this article organizes and visualizes the Ministry of Health, Labor and Welfare report on deaths after COVID-19 vaccination.

Official figures from the Ministry of Health, Labor and Welfare show a gradual increase in post-vaccination deaths, averaging 1.725 deaths per 100,000 people as of July 21, 2020 and 2.4 deaths per 100,000 people as of August 4, 2021 (Supplementary Information A-2-4). Since the death reported to the MHLW was a sudden death after vaccination, it is easy to infer that the doctor who diagnosed the death would have reported the death because he had some causal relationship with vaccination in mind. In other words, it is unlikely that the doctor randomly reported death close to the date of vaccine administration. Thus, in the post-vaccination death histogram (Figure 2), the fact that more than half of reported cases of post-vaccination death are gone within a few days suggests a close relationship between vaccination and death.

Although mortality increases with age, there is no correlation between age and the number of days before death. Vascular damage to the heart, brain and lungs and thrombosis account for nearly 30% of deaths, which is not surprising given the vaccine's mechanism of action. However, most of the committee's decisions were NE in terms of causality, and some cases were NE despite reports of causality (44 of 668 completed cases as of August 4, 2021 [Supplementary Information SA1-9, SA1-10]). The NE's decision means abandoning scientific thinking and will certainly lead to future problems. As a matter of course, post-vaccination deaths should, whenever possible, be subjected to autopsy to better understand the pathogenic process.

Given that cancer deaths in Japan are 1031 / day 16 and that more than 5 months have elapsed since vaccination began, the reported post-vaccination deaths could have been much higher if simple death reporting of any cause had been imposed. In addition, physician reporting of deaths after vaccination is voluntary, not total. At the end of October, 6 people died within 7 days of vaccination, 12 between 8 and 14 days, 10 between 15 and 21 days, 20 between 22 and 28 days, and 196 after 1 month, according to the answer of the Director of Health and Welfare Department to the questions of Niki Itome at the Koka City Council (December 8, 2021). It is unclear whether these deaths after vaccination have been reported to the MHLW, which is itself puzzling. However, the number of deaths after vaccination in Koka City strongly suggests that the number of deaths after vaccination published by the MHLW is only the tip of the iceberg. Vaccine registration and physician follow-up are essential for an accurate count of post-vaccination deaths.

In addition, it should be assumed that any damage to vascular endothelium caused by vaccination may increase the risk of vascular events and other events, including neurologic disease, over time, even after more than a month. From this report alone, almost 1 in 100,000 people die of cardiovascular abnormalities within a few days of vaccination, and with accurate follow-up, this number would be much higher. For patients with underlying cardiovascular disease, vaccination should be given with extreme caution. Because vaccination may precipitate subsequent cardiovascular events, close surveillance should continue. We strongly request

that a protocol be developed and a large prospective controlled cohort study be conducted with unvaccinated people as controls.

It is not too late to suggest that accurate data be collected. This can be accomplished by :

#### **A. Retrospective survey of vaccine recipients**

- The survey should be conducted using a thorough protocol and a well-designed questionnaire.
- Grade ADRs and conduct a thorough investigation of hospital admissions for grade 3 or higher.
- Deaths should be accompanied / interviewed by family members and a thorough all-case medical record review from the time of presentation to death.

#### **B. Prospective surveys of vaccine recipients**

- Collect data prospectively with careful monitoring of grade 3 or higher ADR for signal detection. Deaths after vaccination should be followed, whenever possible, by pathologic autopsy to elucidate the pathogenic process. To this end, a detailed pathology research plan should be developed and followed closely.
- Investigate infection rates \*, severity, mortality and cause of death for post-vaccination novel coronavirus infections (so-called breakthrough infections).
- Because there is no evidence of long-term toxicity of mRNA vaccine, surveillance will continue for several years after vaccination. Careful and long-term follow-up is needed, especially for the development of autoimmune diseases, neurodegenerative diseases, tumors and infections.
- The frequency and extent of viral mutations and adverse events in infections after vaccination should be prospectively investigated.

#### **C. Retrospective and Prospective Studies in Unvaccinated Populations**

- Examine infection rate \*, severity, mortality and cause of death and compare results with those in A and B.

\* It is critical to consider how infection is diagnosed after vaccination (Supplementary Information C).

Finally, recent studies have shown that binding of an infection-enhancing antibody to a specific site in the N-terminal domain of the SARS-CoV-2 spike protein directly enhances binding of ACE2 to the spike protein, resulting in increased infectivity of SARS-CoV-2. 17 This justifies these suggestions.

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Figure Title

Figure 1. Changes in the number and rate of deaths after vaccination.

Figure 2. Number of reported deaths on each day after vaccination.

Figure 3. Vaccination site reaction on each day after vaccination.

Figure 4. Percentage of patients by single cause of death (as of July 21).

Table 1. Number of deaths per 100,000 people by cause of death: COVID-19 vs influenza