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Editorial

Trick of clinical trials

New Products

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Trick of clinical trials

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Large-scale randomised controlled trials (RCTs) are of paramount importance to support the efficacy and safety of pharmaceutical candidates and to provide the base of approval. The role of the national regulator is to identify falsified data in the dossier of approval and approve only effective and safe medicines through careful examination. The reason why we emphasize such an obvious thing here is that we were surprised at the complexity of the tricks of RCTs of baricitinib (p27).

We have never encountered such strange phenomena as in the RCTs of baricitinib: the incidences of almost all adverse events were significantly lower in baricitinib group. Incidence of acute kidney injury was 33% lower, although dose-dependent nephrotoxicity was evident in animal studies.

At first, we suspected the difference in the baseline characteristics of renal failure, but we found no difference. Proportion of corticosteroid users was slightly lower without significance. After careful examination the mystery was solved. Infections were halved by baricitinib, although it is a strong immunosuppressant and should increase infections (p27).

Clinical trials should not have any tricks at first place as they are not a magic. In reality, however, we have noticed that tricks are included intentionally in quite a few clinical trials. For example, among the 14 RCTs investigating mortality effects of antipyretic therapy in patients with severe infections, in 11 RCTs improper study design and/or real biases (not a risk of bias) in baseline characteristics (such as renal failure) were found. Meta-analysis results using data from 3 remaining studies showed that antipyretic treatment significantly increased mortality by 4.4 times (unpublished data).

Review by the national regulatory bodies has also been exhibiting complicated aspects. U.S. Food and Drug Administration (FDA) approved aducanumab (anti-amyloid β agent for Alzheimer disease) even though almost all experts in the advisory panel concluded against approval due to insufficient evidence. U.S. Public Citizen Health Research Group, one of the members of International Society of Drug Bulletins (ISDB) says " FDA's decision to approve aducanumab for Alzheimer's disease shows reckless disregard for science, severely damages agency's credibility".

New products approved not only in Japan, but also in the United States, can be unreliable. Therefore, we have to carefully examine tricks in clinical trials and in the review process by regulators.

Baricitinib for the treatment of COVID-19 (trade name Olumiant)

Data are seriously inconsistent and unreliable

Translated and revised from Med Check (in Japanese) July 2021 ; 21 (96):82-85

Med Check Editorial Team

Abstract

- Remdesivir and dexamethasone have already been approved for the treatment of COVID-19, but only dexamethasone for severe cases is useful.
- In April 2021, the emergency use of a potent immunosuppressant, baricitinib in combination with remdesivir was approved for COVID-19.
- In a randomized controlled trial (RCT) using remdesivir in all adult patients with COVID-19, baricitinib and placebo were compared as concomitant medications (ACTT-2 trial). The primary outcome (the median number of days to recovery) is reported to be significantly shorter for baricitinib by 1 day as compared to 8 days in the placebo group. However, the patients who had the significantly shorter number of days to recovery were only those with severity level 6 (using high-flow oxygen inhaler or non-invasive ventilator) at baseline, and no significant difference was found in other patients. This is an unnatural result.
- Since baricitinib is an immunosuppressant, infectious diseases other than COVID-19 should increase as adverse events in baricitinib group as warned in the package insert. However, in baricitinib group, the incidence of infection was only about half of that in the placebo group (odds ratio 0.54). This is totally incomprehensible.
- In this study, corticosteroid users were about 5.7 times more likely to have infections and 6.6 times more likely to die from adverse events than non-users. It is inferred that the number of corticosteroid users was smaller in baricitinib group, although the difference was not significant, and it is likely to have contributed to the unnatural result.
- In the first place, ACTT-1 trial, which is supposed to be the evidence for the effect of remdesivir is not valid. Moreover, it was also proven ineffective in the meta-analysis including the largest WHO trial. ACTT-2 study cannot be the evidence for the efficacy of baricitinib as it involved concomitant use of the ineffective medicine.

Conclusion: Data manipulation is suspected. This study does not provide a basis for efficacy and safety.

Keywords: immunosuppressants, steroids, infectious diseases, renal disorders, remdesivir

Introduction

Baricitinib (trade name: Olumiant) was approved in April 2021 for the treatment of COVID-19, following remdesivir and dexamethasone, on the condition that it is used in combination with remdesivir [1].

Baricitinib was already approved for the indication of "rheumatoid arthritis (including prevention of structural damage to joints) for which existing treatments are inadequate [2]" in Japan in July 2017. In December 2020, an indication of refractory atopic dermatitis, in which corticosteroids and tacrolimus had been ineffective, was added. Strictly speaking, it is not a drug with a new ingredients, but with an expanded indication

(new indication).

Usually, infectious diseases heal naturally because the body develops fever and releases cytokines, such as interferon, to kill the virus. However, in COVID-19, the causative virus, SARS-CoV-2 (novel coronavirus), may have a property to escape the attack of cytokines, and cytokines are overproduced, causing cytokine storms. It is thought that it may attack the host's tissues and lead to aggravation [3].

Baricitinib inhibits the action of a protein called Janus kinase (JAK), which is deeply involved in the action of a protein and one of the cytokines called interleukin-6 (IL-6). This JAK inhibitory effect is thought to suppress cytokine storms and inflammation [1].

It is expected that this effect will contribute to the prevention of COVID-19 aggravation, and an international joint clinical trial (ACTT-2) was launched in May 2020. Six months later, in November, in the United States, Food and Drug Administration (FDA) granted an emergency use authorization and baricitinib was began to be used in critically ill patients as "a drug that may help prevent the aggravation of COVID-19." In Japan, it was approved as a COVID-19 therapeutic agent based on the results of the ACTT-2 study [1].

ACTT-2 study [1,4] reported that the efficacy outweighed the harm for COVID-19. However, baricitinib has already been used for rheumatoid arthritis, and the following adverse reactions related to immunosuppressive action have been reported; serious infections including herpes zoster and tuberculosis, malignant tumors, cytopenia, lipid abnormalities, venous thromboembolism and diverticulitis [2]. It never is a safe drug.

In addition, infliximab and etanercept were used unsuccessfully to prevent cytokine storms in severe sepsis. Many clinical trials have been conducted to investigate the effect of tocilizumab for COVID-19, but no efficacy has been proven [5].

It is thought that corticosteroid, dexamethasone is effective not because it suppresses immune function, but because it temporarily replaces glucocorticoid that has declined to be excreted in spite of increased demand due to aggravation [6].

This article analyzes the result of ACTT-2 and evaluates the efficacy and safety for COVID-19.

What is ACTT-2 trial?

ACTT-2 trial is a randomized placebo controlled trial (RCT), involving 1033 adult in-patients with COVID-19 (**Note**). Baricitinib or placebo was used in 515 patients and 518 patients, respectively, for up to 14 days, and the efficacy and safety were compared [1,4].

The primary outcome was time to recovery, and the secondary outcome was clinical symptoms at day 14.

"Recovery" in the primary outcome was defined as scores 1 (not hospitalized, no limitations on activities) to 3 (hospitalized, not requiring supplemental oxygen and no longer requires ongoing medical care) in an 8-point ordinal scale (**Table**).

In addition, there is a risk of developing venous thromboembolism (VTE) due to SARS-CoV-2 infection itself. Moreover, the results of clinical trials for other indications, such as rheumatoid arthritis, have shown that baricitinib has a risk of developing VTE. For these reasons, in ACTT-2 study, prophylactic measures for VTE were taken in all patients unless they have contraindications, such as an active bleeding event or a history of heparin-induced thrombosis. At baseline or during the study period, heparin (including small molecule heparin) was mainly used in 495/507 patients (97.6%) in baricitinib group and 498/509 patients (97.8%) in placebo group for the purpose of preventing thrombosis.

Note : The patients included were those who had at least one of the following conditions, were moderately or severely ill, and fall under scores 4-7 in Table; (1) Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), (2) SpO2 ≦ 94% on room air, (3) Requiring supplemental oxygen, (4) Requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

Table: Ordinal scale for severity

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitations on activities and/or requiring home oxygen
3. Hospitalized, not requiring supplemental oxygen required, no longer requires ongoing medical care
4. Hospitalized, not requiring supplemental oxygen required, requiring ongoing medical care (COVID-19 related or otherwise)
5. Hospitalized, requiring supplemental oxygen
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices
7. Hospitalized, on invasive mechanical ventilation or ECMO
8. Death

Effective only for score 6 (if no bias in baseline characteristics)

The primary outcome, median time to recovery (28 days after randomization), was 7 days in baricitinib group and 8 days in placebo group, and it was reported that baricitinib significantly shortened the time to recovery by 1 day. The hazard ratio was 1.16 (95% CI: 1.01-1.32).

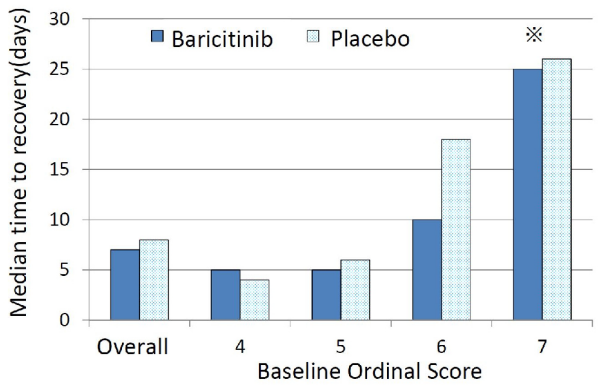
However, when time to recovery was compared based on the severity at enrollment, it was shortened only in patients with a score of 6 (hospitalized, on non-invasive ventilation or high flow oxygen devices) in baricitinib group. Time to recovery was 10 days in baricitinib group and 18 days in placebo group.

In patients with milder (scores 4 and 5) or severer (score 7) conditions at enrollment, there was no difference in time to recovery between baricitinib group and placebo group. In patients with score 4 (no supplemental oxygen required), time to recovery was shorter in placebo group: 5 days in baricitinib group and 4 days in placebo group. In patients with score 5 (supplemental oxygen only), it was 5 days in baricitinib group and 6 days in placebo group. In patients with score 7 (invasive mechanical ventilation or ECMO), there was no significant difference (hazard ratio: 1.08, 95% CI: 0.59-1.97) (Figure 1).

Furthermore, exactly the same tendency was observed in one of the secondary outcomes, "clinical status using ordinal scale at 14 days after randomization".

Mortality rate at day 28 from the start of the study was 5.1% in baricitinib group, and 7.8% in placebo group (hazard ratio:0.65, 95% CI :0.39-1.09), which showed lower tendency in baricitinib group, although it was not significant.

Figure1: Time to recovery (median days at the time point of day 28)



* Since the median cannot be estimated for severity score 7 group at baseline, the lower limit of the 95% CI is shown.

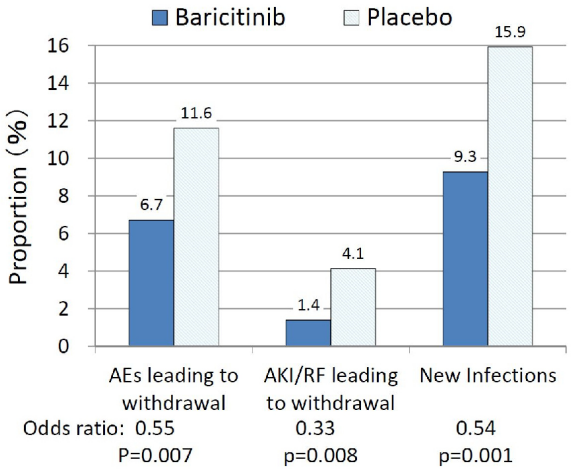
Adverse events and bias in baseline characteristics

The incidence of all adverse events in ACTT-2 study was significantly lower in baricitinib group: 41.4% in baricitinib group and 47.5% in placebo group (p = 0.0495). The incidence of adverse events that had led to death was 3.7% and 6.1%, respectively, and no significant difference was found. However, the incidence of adverse events that had led to discontinuation was reported to be significantly lower in baricitinib group (6.7% vs. 11.6%, odds ratio:0.54, p = 0.007). The difference in the incidence of acute renal injury or renal failure was particularly marked (1.4% vs. 4.1%, odds ratio:0.33, p=0.008) (Figure 2).

In general, if the baseline characteristics of treatment group and control group are similar, even if the targeted outcome, reduction of a disease, is achieved in the former, the incidence of adverse events tend to be similar in both groups or slightly higher in treatment group. Moreover, even if the incidence of minor adverse events is significantly higher in treatment group, if there is no significant difference in the incidence of major adverse events, it is considered that benefit outweighs harm.

However, in ACTT-2 study, how adverse events occurred is totally different from the general tendency mentioned above. The study showed unprecedented results, in which all serious adverse events, particularly

Figure2: Infectious diseases are reduced by an immunosuppressant?



AEs: Adverse Events, AKI/RF: Acute kidney injuries or Renal failure,
Immunosuppressants usually increase new infections, but baricitinib showed the opposite results.
There is a possibility of substantial bias in any baseline characteristics. That may be the reason why there were fewer important adverse events in baricitinib group.

Figure3: Corticosteroid users are at high risk of new infections and death

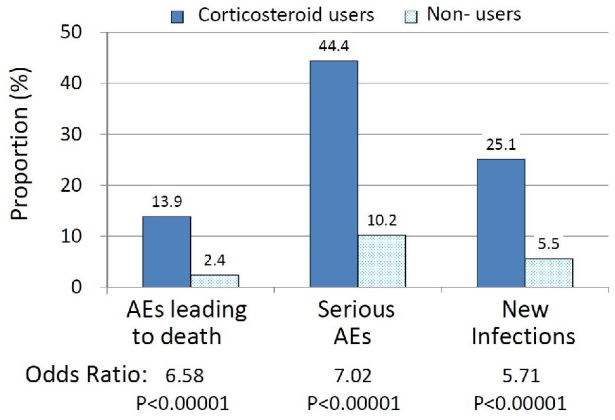


Figure 3 is made by using the data from Table 18 in p.25 of the examination report by PMDA [1]. The proportion of corticosteroid users tended to be lower in baricitinib group (20.8% vs. 23.2% , odds ratio: 0.87, p = 0.31). Even though this is a slight difference, if presence or absence of corticosteroids has produced difference in prognosis as shown in this figure, it may affect the course of the diseases and may result in the differences of adverse events as shown in the Figure 2.

that led to discontinuation including acute renal injury and renal failure, occurred significantly less frequently in treatment group. At the time of initial examination of the study, we strongly suspected that baseline renal function may be seriously biased. However, we found totally no bias in the baseline renal function.

Among all the adverse events reported, infection is the most problematic. Since baricitinib is a potent immunosuppressant, it usually increases infection in treatment group. This is also warned in the package insert. However, the incidence of infection was also significantly lower in baricitinib group: 47 cases (9.3%) in baricitinib group and 81 cases (15.9%) in placebo group (odds ratio:0.54, 95%CI:0.37-0.7 p=0.0014)(**Figure 2**). The original data were not included in the main report [4a], and this is calculated based on the total number of infection-related adverse events in Table S11 in Supplement of the published paper [4b].

At baseline, the number of corticosteroid users was smaller in baricitinib group, although the difference was not significant: 20.7% in baricitinib group and 23.2% in placebo group. However, the analysis of the data from the examination report by Pharmaceuticals and Medical Devices Agency (PMDA) [1] revealed that the risk of fatal adverse events and serious adverse events is 6.6 times and 7 times higher in corticosteroid users than in non-corticosteroid users, respectively (**Figure 3**). Furthermore, the analysis of the data in the supplementary appendix of the published paper [4] showed that the risk of new infection was 5.7 times higher in corticosteroid users (**Figure 3**).

Therefore, the slight difference in the number of corticosteroid users in baricitinib group has reduced new infection and its complication, such as sepsis and acute renal failure, and has slightly shorten the time to recovery apparently. As a result, it helped to produce favorable result for baricitinib group.

In addition, a toxicity study conducted with baricitinib for the indication of rheumatoid arthritis showed dose-dependent increase in renal toxicities in animals [2]. Considering these, it is extremely unnatural that acute renal disorder occurred markedly less frequently in baricitinib group.

Further examination revealed that no difference was observed in baseline renal function in both groups. However, as explained above, suppose that the slight difference in the number of corticosteroid users has greatly affected the outcome, the difference in all adverse events and apparent efficacy can be explained. This strongly implies the possibility of data manipulation.

Venous thromboembolism (VTE) can also occur as a complication of COVID-19 itself [7]. In addition, baricitinib increases the risk. Therefore, thrombolytic agents were used in almost all the patients. Nevertheless, it occurred more frequently in baricitinib group than in placebo group and this cannot be overlooked as a serious harm.

WHO does not recommend remdesivir

Remdesivir is used as a basal agent for the treatment of COVID-19 in this study. However, ACTT-1 study, which is used as evidence to support the efficacy of remdesivir, is not reliable [8]. Moreover, a meta-analysis which included the largest study conducted by the World Health Organization (WHO) showed that remdesivir is ineffective, thus WHO does not recommend its use [9].

From these facts, it can be concluded that that baricitinib + remdesivir combination therapy is ineffective for severe pneumonia caused by COVID-19. Baricitinib should not be used.

In practice

Apparent efficacy, such as faster recovery by 1 day and tendency of improved clinical symptoms as compared with placebo group, were observed only in the subgroup of patients whose severity was score 6, and this is unnatural. Moreover, it is thought that the difference in baseline characteristics which exacerbates infection affected these outcomes favorably for baricitinib group.

Therefore, it is concluded that neither efficacy nor safety of baricitinib has been proven, and it should not be used for the treatment of COVID-19.

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COVID-19 vaccine:
Strong association with cardiovascular death, especially hemorrhagic stroke and venous thrombosis

Med Check Editorial Team

Abstract

● We analysed 196 death cases reported after inoculation of Pfizer-BioNTech COVID-19 vaccine (COMIRNATY) by June 9 in Japan. Japanese Ministry of Health, Labour, and Welfare (MHLW) virtually denied the causality of all cases without conducting appropriate epidemiological analysis.

● Mortality odds ratio (MOR) was calculated as the indicator of disproportionality in cause of death. We compared odds of cause of death after inoculation and death in Japanese vital statistics in 2019 as control non-vaccinated population. MOR was obtained by using the numbers of death from non-cardiovascular system as the reference causes for two age groups: vaccinated medical workers (20 to 74 year of age) and elderly (≧ 65years) separately.

●Of 31 deaths among vaccinated medical workers (both sexes), 26 (84%) died from cardiovascular diseases, such as stroke, myocardial infarction, venous thrombosis and pulmonary embolism (VT/PE) and heart failure, while 22% died in the general population. MOR is 19.4 ($p<0.0001$). MOR of hemorrhagic stroke (40.7) and VT/PE (114.0) were extremely high.

● Of the reported vaccinated elderly death cases, 69% died from cardiovascular causes, while 26% died in the general population. MOR is 5.9 ($p<0.0001$). MOR of hemorrhagic stroke (12.8) and VT/PE (24.9) were also very high.

● These suggest that COVID-19 vaccination is closely associated with the risk of death from cardiovascular causes, especially hemorrhagic stroke and VT/PE.

Keywords:

subarachnoid hemorrhage, intracerebral hemorrhage, hemorrhagic stroke, myocardial infarction, sudden cardiac death, reporting odds ratio, mortality odds ratio, MOR, COVID-19 vaccine

Introduction

On October 22, the Ministry of Health, Labor and Welfare (MHLW) announced that they had received 1312 reports of death after vaccination for COVID-19 by October 15, 2021 **[1]**.

Regarding 2 death case reports from hemorrhagic stroke, including subarachnoid hemorrhage, after COVID-19 vaccination of medical workers in Japan, we warned that "never twice without three times" in the Web MedCheck No193 (March 31, 2021) **[2]**. After the warning, the number of death case reports from hemorrhagic stroke became 4 in a short period of time (Web MedCheck No195 (April 26, 2021) **[3]**), and it has been increasing since then.

Since April 12, vaccination to the elderly (≧ 65) has begun, and a total of 196 death cases were reported by June 4, according to the data released by MHLW on June 9 **[4,5]**.

We restricted to analyze the death cases inoculated by May 30, because **(1)** vaccination to non-elderly/non-medical workers has begun on June 1. **(2)** Distribution of medical workers' age is not much different from that in the general population. However, **(3)** vaccinated non-

elderly/non-medical workers were much older than the general population.

Among them, the number of death cases of people who were assumed to be medical workers was 31 (17 women, 14 men) on June 4. Total 11 of them (10 females and 1 male) had hemorrhagic stroke, including 8 subarachnoid hemorrhages and 3 intracerebral hemorrhages.

In addition, it is noted that many deaths from cardiovascular causes such as ischemic stroke, myocardial infarction, mesenteric thrombosis, sudden cardiopulmonary arrest, heart failure and even venous thrombosis with pulmonary embolism were reported.

MHLW virtually denied the causality of all cases only by the information of case reports. They have not conducted appropriate epidemiological analysis and only say that vaccinees' mortality rate from hemorrhagic stroke is less than that in the general population and that therefore vaccination is not related to the increase of mortality risk from hemorrhagic stroke. However, they never take into account that vaccinees are far healthier and have lower mortality rate than in the general population. This is the "healthy user bias" or "healthy vaccinee effect", a typical example of confounding bias, which MedCheck has repeatedly emphasized **[6]**.

This article analyzes association between COVID-19 vaccination and death especially from cardiovascular diseases.

About mortality odds ratio (MOR)

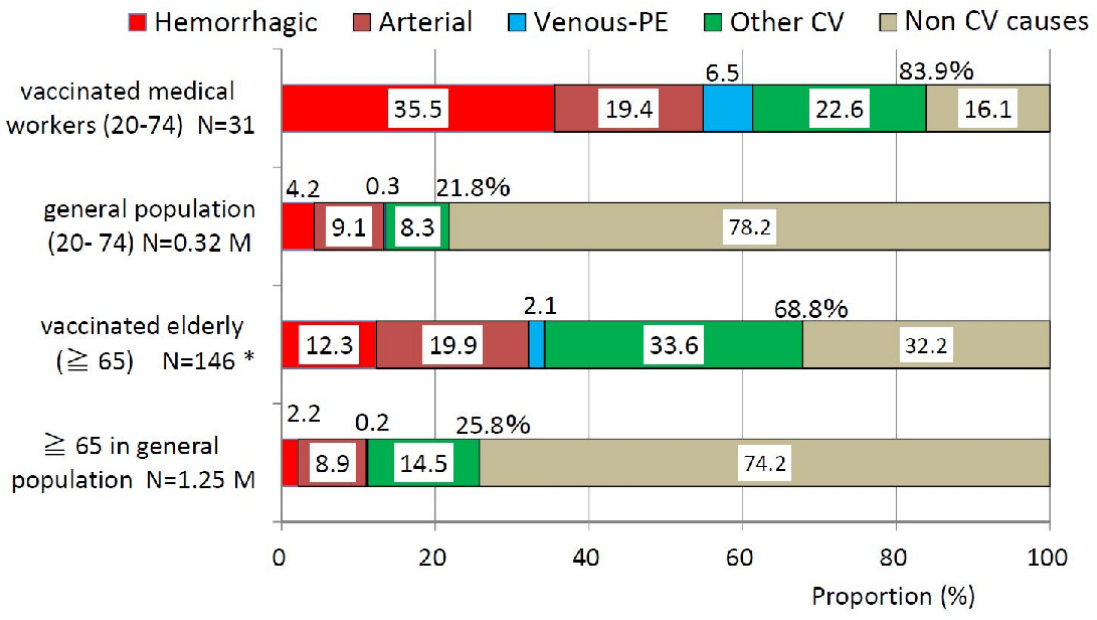
We used an epidemiological method "mortality odds ratio (MOR)" to detect disproportionality of cause of death **[7-9]**. This method is based on the following principle: if an exposure induces a specific disease leading to death, mortality odds of interest (cause of death of interest/other causes) in exposure group is significantly higher than that in non-exposed group.

In the case of COVID-19 vaccine, if the odds of a particular cause of death in vaccinated people is significantly higher than that in the general population, there may be causal link between the cause of death and COVID-19 vaccination.

In general, when there are 3 or more events, and proportional reporting ratio (PRR) is equal to higher than 2.0 with statistical significance, signals of disproportionate reporting is suggested **[10]**. In the case where reporting odds ratio (ROR), MOR or proportional mortality ratio (PMR) are applied, signals of disproportionate reporting may be the same.

We have not experienced such a vaccine that is targeted to almost all adult ages during the same period. It is not possible to compare adverse reactions to other pharmaceuticals other than vaccines either. Therefore, we used mortality data from the vital statistics in 2019 as control non-exposed mortality.

Figure 1: Comparison of cause of death: vaccinated and general population



As medical workers' ages are between 20 and 74, we used the mortality data with the same age group from the vital statistics in 2019 in Japan.

Cardiovascular cause of death were disproportionately high

We classified reported cause of deaths into the following categories:

(1) Hemorrhagic: hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage) and hemorrhage in any part of body,

(2) Arterial: arterial dissection, myocardial infarction, ischemic stroke or thrombosis of other arteries,

(3) Venous: venous thrombosis and/or pulmonary embolism (VT/PE),

(4) Other CV (cardiovascular): cardiac or cardiopulmonary arrest, heart failure, sudden death etc.

(5) Non-cardiovascular: include infection, senility, anaphylaxis etc., and

(6) Unknown cause.

The distributions of causes are shown in Figure 1 excluding unknown cause **(6)** among the elderly. Proportions of causes of death classified **(1)** to **(4)** among vaccinated (both medical workers and elderly) were all larger than those among corresponding general population. Proportions of all cardiovascular causes of death in vaccinated medical workers and corresponding control are 83.9 % and 21.8% respectively. Those in vaccinated elderly and corresponding control are 68.8% and 25.8 % respectively as shown in Figure 1.

Preferred MOR and the ordinary MOR

We calculated MOR by two age groups: vaccinated medical workers (20 to 74 year of age) and elderly (≧ 65years) separately.

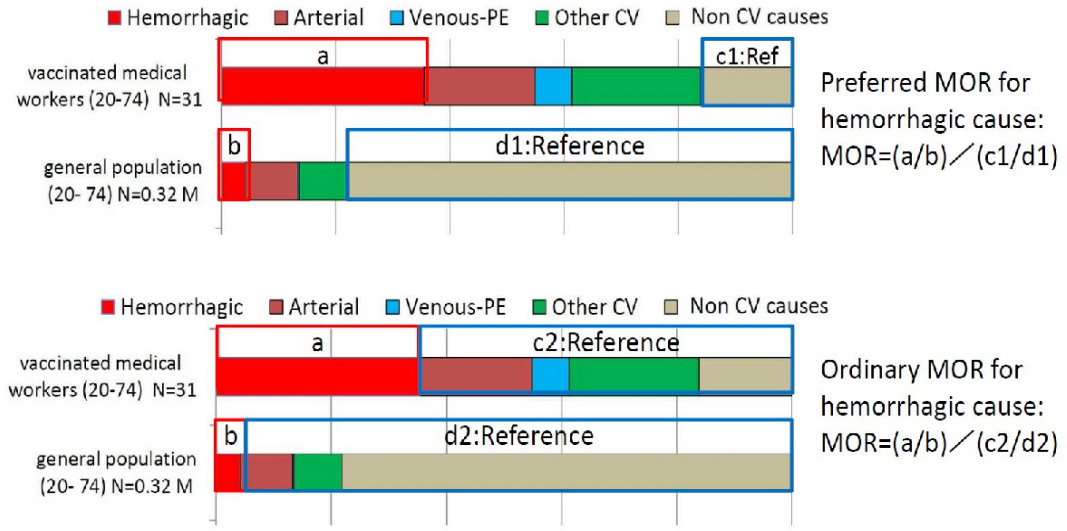
We preferred MOR which used the numbers of death from non-cardiovascular causes as the reference as shown in Figure 2, because the referent cause of death for ordinary MOR method includes other types of cardiovascular deaths which are also disproportionately higher than the general population as shown in Figure 3. Hence, preferred MOR reflects the disproportionality more accurately than the ordinary MOR.

Hemorrhagic stroke and VT/PE occurred especially disproportionately

Among 17 female medical workers who died after COVID-19 vaccination, 2 (12%) died from non-cardiovascular cause and 10 (59%) died from hemorrhagic stroke. In female general population (total 102,669), 83,651 (81.5%) died from non-cardiovascular causes and 4,583 (4.5%) died from hemorrhagic stroke. MOR from hemorrhagic stroke in female medical workers is 91.3 ($p<0.0001$).

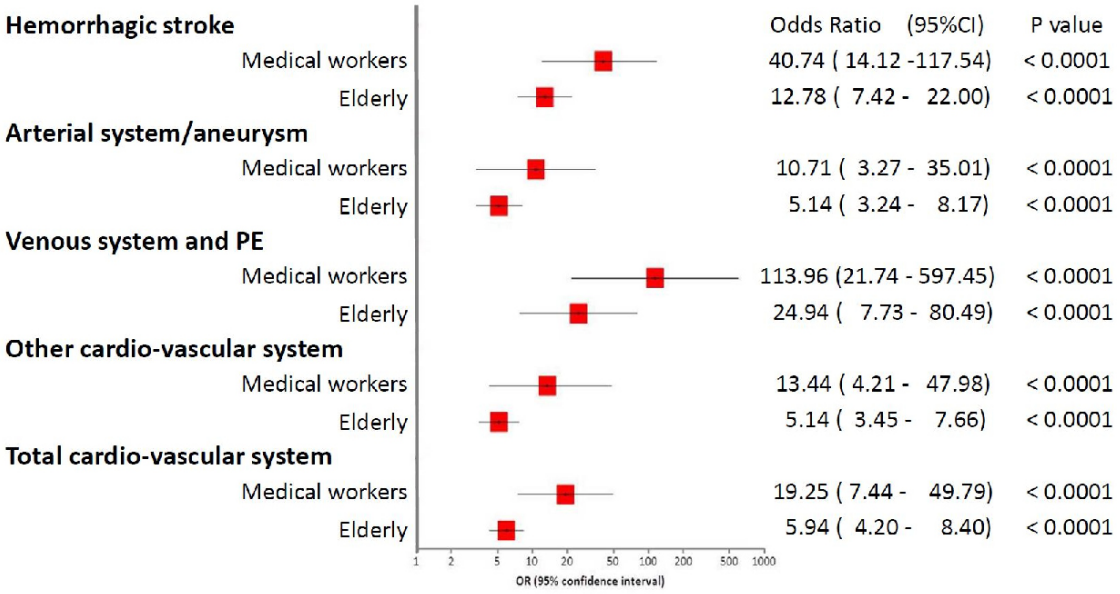
Sex adjusted MORs for death from hemorrhagic

Figure 2: Difference of two methods for calculation of MOR



The referent cause of death for ordinary MOR method includes other types of cardiovascular deaths which are also disproportionately higher than the general population.

Figure 3: Preferred MORs for various cardiovascular causes (sex adjusted)



stroke in medical workers and in elderly is 40.7 (95%CI:14.1-117.5, p<0.0001) and 12.8 (7.4-22.0, p<0.0001) respectively (Figure 3).

Sex adjusted MORs for death from venous causes are 114.0 (21.7-597, p<0.0001) and 24.9 (7.7-80.5, p<0.0001) respectively (Figure 3).

Men died from other cardiovascular diseases

In men, thrombosis and sudden death are more prominent than hemorrhagic stroke in both medical workers and the elderly.

For example, a 79-year-old man (Case 48, [5]) developed an acute myocardial infarction and was hospitalized. Four days later he also developed an ischemic stroke caused by a thrombosis of a large artery "left middle cerebral artery" followed by a cerebral herniation and cardiopulmonary arrest.

It is extremely rare that 2 serious events, myocardial infarction and ischemic stroke, occur one after another in a short period of time. However, MHLW experts assessed the causality and denied the causation for three cases, but all other cases were classified as "cannot be evaluated due to a lack of information" and no death cases was classified as even "cannot be denied". Hence, they practically denied causality in all death cases.

Sensitivity analyses were done by using ordinary methods for calculation of MOR. Figure 4 shows the comparison of results from preferred MOR methods and ordinary MOR method.

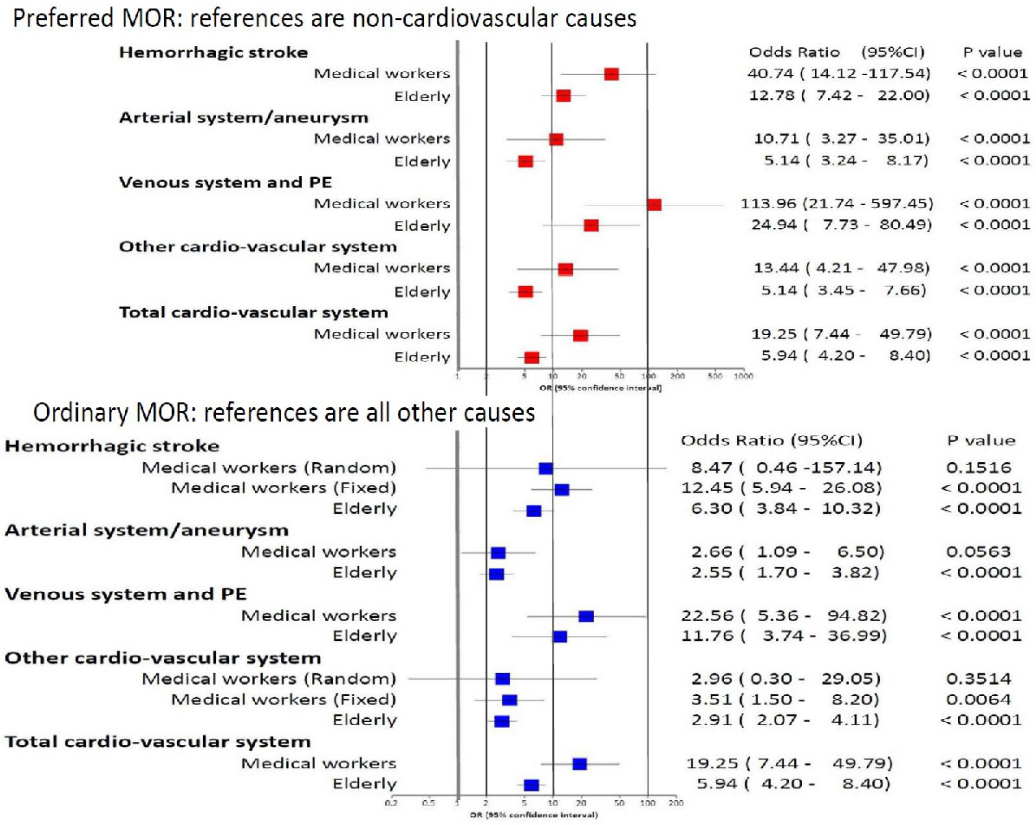
The dead after vaccination are previously healthy people on duty

With MOR, absolute mortality risk between those vaccinated and those in the general population cannot be compared. Hence we tried to estimate the mortality risk in those vaccinated considering that the medical workers are far healthier than the general population. In other words, we tried to estimate the mortality risk in those vaccinated by taking "healthy vaccinee effects" into account.

According to the data released by the MHLW, the number of inoculations by May 30 was 9.76 million for the first dose and 3.3 million for the second dose. The number of inoculations for medical workers can be calculated by subtracting the number of the elderly (5.31 million and 390,000 dose respectively) from the total number of doses respectively: The first dose was 4.45 million and the second dose was 2.91 million.

For the purpose of knowing how healthy the vaccinated people are compared to the general population, we calculated the age adjusted total mortality risk ratio of vaccinated medical workers (20-74 years old)

Figure 4: MORs by two different methods



Preferred MORs are much larger than the ordinary MORs (by 1.8 to 5.1 times) except of total cardiovascular system which are theoretically equal to each other.

compared with the general population. As a result, the total mortality risk ratio of vaccinated female medical workers to the general population was 0.065 (95%CI: 0.040-0.107, p <0.00001: Fixed effect) or 0.101 (0.062-0.165, p <0.00001: Random effect) .

There is no evidence from clinical trial results that the vaccine increased or reduced overall mortality. If increased, the above is underestimated and should not affect the judgment that vaccinated people are healthier than the general population. There is also no possibility that death from COVID-19 in vaccinated medical workers have decreased within 30 days after the second dose. Hence, in any case, the main reason of very low risk of death after vaccination in the medical workers is simply that they are healthy. Hence, vaccinated medical workers are about 10 to 15 times healthier than the general population.

Similarly, the risk ratio of hemorrhagic stroke of female medical workers was calculated: 0.80 (0.43-1.48, by Fixed effect) or 1.44 (0.70-2.97, by Random effect).

The risk ratio of hemorrhagic stroke of vaccinated female medical workers was divided by the risk of total mortality to adjust the health status. Adjusted risk ratio is 12.23 (5.55- 26.94, by Fixed effect) or 14.23 (5.95- 34.04 by Random effect).

These results also support the increased risk of death from hemorrhagic stroke among vaccinated people.

Causal inference and biological plausibility

We discussed causality including biological plausibility in the other article in this issue **[11]**.

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Causal link between vaccination and subsequent death

Translated and revised from Med Check (in Japanese) Sept. 2021 ; 21 (97):110-111

Med Check Editorial Team

Keywords:
COVID-19 vaccine, death after vaccination, incubation period, foreign cells, cell-mediated immunity, inflammation

"Causality cannot be denied" even by MHLW' s standard

The Ministry of Health, Labour and Welfare (MHLW) announced that among 919 death case reports by July 30, causality with vaccination were denied in 3 cases, and for the remaining 916 cases, the causality could not be evaluated due to a lack of information or other reasons [1].

However, the MHLW itself stated in a Q & A regarding the classification of adverse events that cases of "unknown causality" should be classified as "Causality cannot be denied" [2].

Moreover, as pointed out in another article in this issue [3], proportion of death from vascular diseases including hemorrhagic stroke after COVID-19 vaccination is disproportionately higher compared with the general population. Here we show some other important facts that indicate causality between vaccination and subsequent death.

Frequency should not change if there is no causality

If there is no causal relationship between COVID-19 vaccination and subsequently reported death, change in the number of reported deaths should not depend on the number of days after vaccination until death.

Days to death is similar to incubation period of COVID-19

However, as shown in Figure A, in medical workers or people under the age of 65, the number of reported death reaches a peak on 4 days after vaccination. The median was 5 days. For elderly people, the peak is on the next day of inoculation (median is 2 days). At any age, the number of death reports after 3 weeks post inoculation is only 2%.

When spontaneously infected with COVID-19, the peak of time from infection to symptom onset (incubation period) is 4 days, and the median is also 4 days [4] (Figure B).

The fact that the number of days from inoculation to death is concentrated in a short period of time and that it is similar to the incubation period of COVID-19 strongly suggests causality between vaccination and death.

Many cases could be omitted in the deaths of the elderly

One of the reasons why the number of days to death after vaccination is shorter for elderly people than those under 65 years old is that they often die suddenly from some symptoms such as aspiration associated with vomiting which may not cause death in younger people. In Norway, 1 in 1300 people aged 75 and over who received vaccination has died, and the relationship with the vaccine has been suspected [5].

In addition, some death cases which may be reported if occurred in younger people, may not be reported for elderly people. Particularly death cases except those occurred very shortly after inoculation may easily be omitted.

Mechanisms of SARS-CoV-2 infection and incubation period

If SARS-CoV-2 infects a person, it is trans-located to

the blood stream, and may be taken up into vascular endothelial cells from the site where the receptor ACE2 is abundant on the inner surface of blood vessels. Infected endothelial cells are recognized as foreign body by the host's immune system (cell-mediated immunity), and are attacked and eliminated. Children and people in their 20s have less ACE2 receptors and far safer than old people.

The cells on the inner surface of blood vessels are originally normal tissues and are essential parts for living organisms. If they are eliminated, the part of the vessels may be injured with wounds. The injured tissues must be repaired. An inflammatory reaction occurs to repair the tissue. This inflammatory response is a symptomatology of infection, such as fever, increased white blood cell count, increased heart rate, and increased respiratory rate. It usually takes 3 to 5 days to develop symptoms, with a median of 4 days **[4]**.

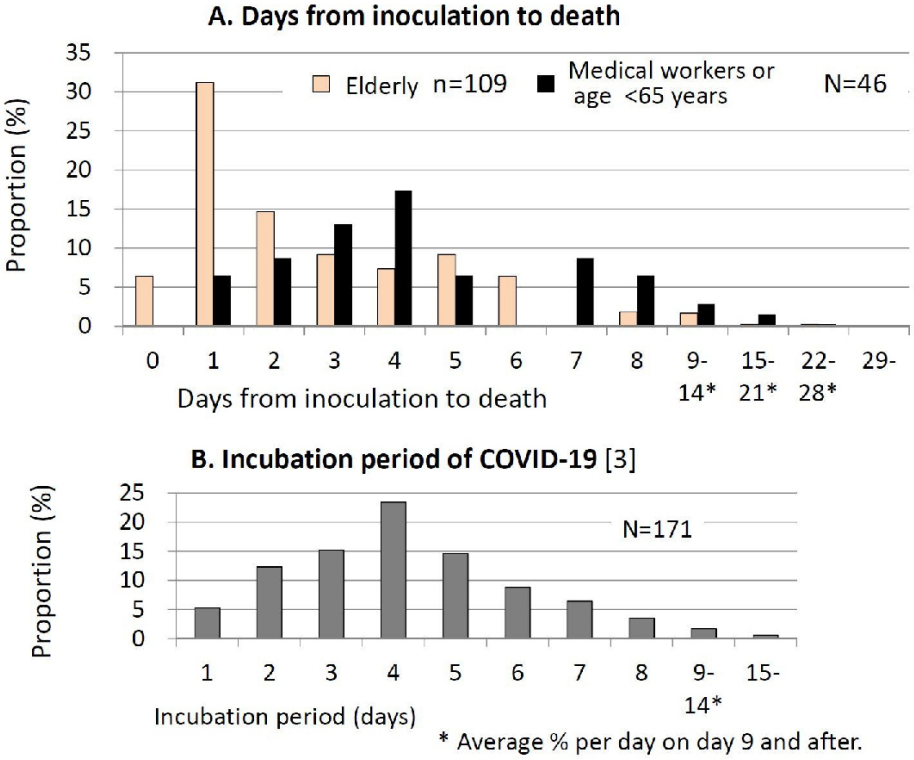
Biologically plausible: Days to deaths are similar to the incubation period

mRNA vaccine is encapsulated in lipid nanoparticles. After injection, through lymphatic vessels, it enters the blood stream and is taken up by immune cells (macrophages) where spike protein is made and is released into blood stream. Lipid nanoparticles containing mRNA may be taken into some endothelial cells by perhaps endocytosis in which spike protein may be made and released into blood stream. Released and circulating spike proteins in blood stream are taken up into vascular endothelial cells from the site where the receptor ACE2 is abundant on the inner surface of blood vessels.

Similar to infection, endothelial cells which are "as if infected" by spike protein and/or lipid nanoparticles containing mRNA are recognized as foreign bodies by the host's immune system, and are attacked and eliminated. Children and people in their 20s have less ACE2 receptors and far safer than old people.

Endothelial cells containing foreign substances are subject to "be eliminated" by the immune system. Around the damaged endothelium, blood coagulates and thrombus is made followed by myocardial infarction and/or ischemic stroke. If the damage of an inner surface of blood vessel is serious in a large artery, dissecting aneurysm or rupture of a small aneurysm may occur. If a small aneurysm ruptures in the subarachnoid space,

Figure: Distribution of days to death after vaccination and incubation period of COVID-19



For elderly people, data from table by May 30 are analyzed.
For medical workers and people under 65 years old, data by July 21 is analyzed.

subarachnoid bleeding occurs. If a very small artery ruptures inside the cerebrum, intra-cerebral bleeding occurs.

With regard to Pfizer vaccines, myocarditis **[6,7]** has been a problem in the United States. Hemorrhagic stroke, arterial thrombosis as well as dissecting aneurysm and venous thrombosis and/or pulmonary embolism may all be causally linked to vaccination of COVID-19.

Therefore, the fact that the number of **days to deaths after inoculation is similar to the incubation period** of COVID-19 in the medical workers or people under the age of 65 is biologically plausible and this also supports the causality.

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Mortality risk of vaccination is 7 times higher than that of COVID-19 in 20s

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Med Check Editorial Team

Keywords:
COVID-19 vaccine, death after vaccination, incubation period, foreign cells, cell-mediated immunity, inflammation

Introduction

Disproportionate increase of death from cardiovascular diseases was observed both among medical workers and elderly people who received COVID-19 vaccine compared with general population **[1]**. Distribution of the number of days to death from inoculation of COVID-19 vaccine is similar to that of incubation period of COVID-19 **[2]**. Based on such evidence and biological plausibility, causality between death from cardiovascular diseases and COVID-19 is substantially supported **[2]**.

Here we analyze the risk ratio of death from COVID-19 vaccination and that from COVID-19 by age especially people in their 20s, because some death cases with people in their 20s have been reported.

Reported death cases with people in their 20s [3]

A 25-year-old man: It was reported that he completed suicide due to psychosis. However, actually he accidentally died following abnormal behavior due to febrile delirium after vaccination.

A 26-year-old woman: She was found dead at home 4 days after vaccination. Postmortem CT scan revealed subarachnoid hemorrhage and cerebellar hemorrhage.

A 26-year-old man: He was found dead 5 days after vaccination by his family. Postmortem CT scan showed no lesions and he was diagnosed with cardiopulmonary arrest.

Mortality risk of vaccination in people in their 20s is 5 times higher than that of COVID-19

In the end of May 2021, the number of vaccinations inoculated for medical workers (age: 20 to 74) was 7.36 million doses (4.45 million persons) **[4]**. In the preliminary survey of 18,794 medical workers (men 34% and women 66%), age distribution was 21%, 24%, 25%, 21%, 8% and 1% for 20s, 30s, 40s, 50s 60s, and 70s, respectively **[5]**. Hence, it was estimated about 1.55 million doses (0.94 million persons) were for those in their 20s. Of these, 3 death cases above (2 men and 1 woman) were reported.

Mortality risk based on the number of inoculated persons is 3 out of 940,000 persons (3.2/million) in 20s.

On the other hand, mortality risk from COVID-19 is 7 out of 11.8 million persons in the same age group by June 2, 2021 (0.6/million) **[6]** or 10 out of the same population by August 11 (0.8/million) **[7]**.

Therefore, the mortality risk ratio after vaccination in 20s is 5.4 by June 2 (or 3.8 by August 11) compared with mortality risk from COVID-19.

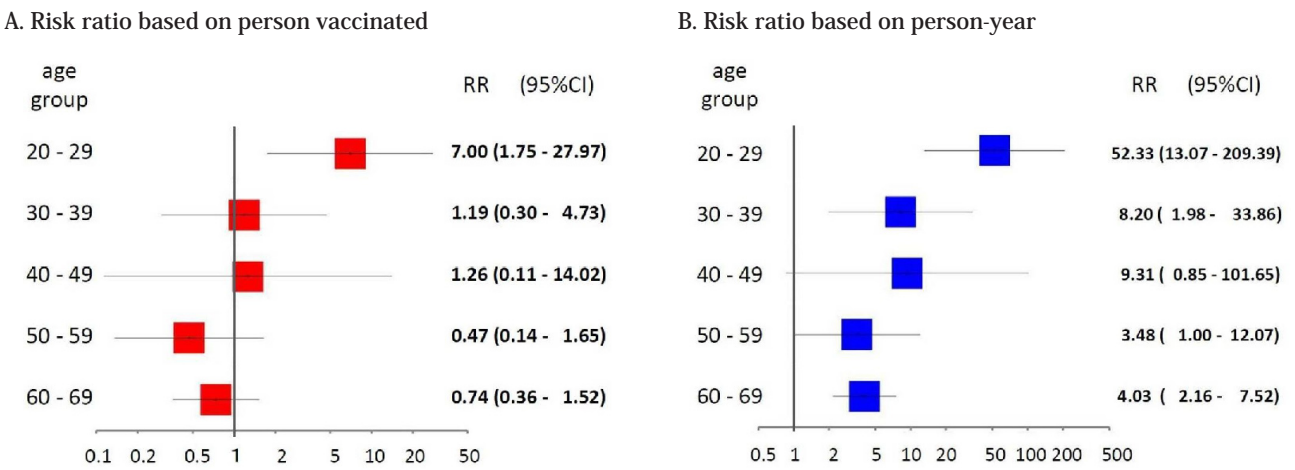
Sex adjusted risk ratio is 7.0 by June 2 (or 4.7 by August 11). Figure A shows sex adjusted risk ratio by age based on the COVID-19 death on June 2.

Risk ratio may be between 5 and 52 in 20s

Japanese Ministry of Health, Labour and Welfare (MHLW) requires reports of serious cases and deaths within 28 days after inoculation regardless of causal relationships, but they do not necessarily require reports of serious cases and deaths beyond 28 days post-inoculation. Hence, if all deaths, including those that occurred beyond 28 days after vaccination, were reported, risk may become higher.

By using person-year methods, mortality risk from vaccination in 20s is about 40 times higher than

Figure: Mortality Risk Ratio of vaccinated medical workers to death from COVID-19



RR: Risk ratio. All data are adjusted by sex for every age group. Death after vaccination is data released by MHLW [4]. The number of death from COVID-19 is based on the data from MHLW **[6]**

COVID-19 mortality risk (sex adjusted RR is 52.3).

However, the mortality rate beyond 28 days should be lower than that within 28 days, so the mortality risk ratio after vaccination in 20s may be between 5 to 40 times higher compared with death from COVID-19 (sex adjusted risk ratio may be between 7 and 52).

The estimated number of vaccinations inoculated for people in their 20s by July 23 is somewhat inaccurate because vaccination to people other than medical workers aged under 65 years started in June, but older people were recommended to be vaccinated earlier than younger people. Therefore, the age distribution of people vaccinated is totally unknown. If people aged under 65 years had COVID-19 vaccine proportionally as general population, number of vaccination in people in their 20s is estimated to be 3 million doses (about 2 million persons).

By July 30, 1 week later, 7 people had died after vaccination (Note 1). By using these data, mortality risk ratio of vaccinated people to COVID-19 mortality risk does not change significantly.

Harm of vaccination in children may be enormous

There were no deaths due to COVID-19 infection under the age of 20 until September 1, 2021. If children in this age group are vaccinated, it may cause death. Mortality risk from vaccination may be lower in children than people in their 20s. Even so, the mortality risk ratio cannot be calculated because the number of death from COVID-19 is "0" in Japan until September 1, 2021(Note 2).

The clinical trial of AstraZeneca's vaccine for children aged 6 to 17 years old was interrupted **[8]**. It was due to 79 cases of thrombosis with thrombocytopenia of which 19 have died were reported in adults, as the UK Medicines and Healthcare products Regulatory Agency (MHRA) announced on April 7, 2021 **[9]**.

According to a report on the outbreak in Massachusetts, more vaccinated people were diagnosed with COVID-19 than non-vaccinated people, most of which were delta strain infected: odds ratio= 1.26,p=0.025**[10,11]**.

Hospitalization rate was 1% in the outbreak in Massachusetts. No death was reported among 469 confirmed COVID-19 patients. Hence, the mortality risk from delta strain COVID-19 is not high. It is far lower than the case mortality rate (almost 6%) in May 2020 in the United States. Although delta strain is very infectious, it does not seem to be very toxic at least in the U.S. where 1 out of 9 people have already had confirmed COVID-19 overall case fatality rate is 1.68 % on August 19 **[12]**, and most people have been infected at least once with SARS-CoV-2.

In Japan, the fifth epidemic period began in early July, and on August 13, more than a month later, new infections were confirmed in more than 20,000 people a day. The number of deaths has gradually increased to over 20 per day, and it is estimated that the number will increase in the future.

However, the case mortality rate between August 17 and 31 (0.26%) is less than one-tenth of that around May

last year (more than 5%)(Note 3).

Even if children and adolescents and people in their 20s are infected, it is naturally mild or asymptomatic because they have less SARS-CoV-2 receptor ACE2 than adults especially old people.

It is a ridiculous to consider vaccination for school children.

Note1: According to the materials released by the MHLW [13] Case No 8716, a 27-year-old man seems to be Mr. Yusuke Kinoshita, a professional pitcher of Chunichi Dragons. He was given the first dose of the vaccine (Moderna) on June 28. Eight days later, on July 6 during training, he was found crouching and lost consciousness. Paramedics confirmed cardiac arrest. He resumed heartbeat after about 40 minutes at the hospital where he was transferred. He had no abnormalities on coronary angiography and no myocarditis on myocardial biopsy, but had mitral regurgitation. If acute necrosis of the papillary muscle to which the mitral valve chordae tendineae attach occurred, it might lead to massive regurgitation followed by acute pulmonary edema, shock, and cardiopulmonary arrest and loss of consciousness. It is one of the conditions with an extremely high case fatality rate. Papillary muscle ruptures that lead to cardiopulmonary arrest can occur after an acute myocardial infarction. If so, an association with vaccination is suspected. He died on August 3, 36 days after the inoculation.

Note2: Susequently 3 death from COVID-19 among people under the age of 20 were reported until November 2, 2021 (see p44-45)

Note3 : This case mortality rate is calculated as follows:
Numerator: number of death between August 17-31, 2021 (591)
Denominator: number of people with confirmed new infection between August 3-17. 2021(223,330)
However, age and sex adjusted case mortality rate during the fifth epidemic period (early July to October 2021) is not changed significantly compared with that during the first to the third epidemic period. Odds ratio is 1.10 (95% confidence interval: 0.995- 1.21, p=0.0629)

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COVID-19 vaccination: 3 teens died Causal link is suspected

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Med Check Editorial Team

The Ministry of Health, Labour and Welfare (MHLW) announced on October 22, 2021 that they received a total of 1308 reports of death after inoculation of COVID-19 vaccine by October 15, (1268 and 44 reports after Pfizer's and Moderna's, respectively) **[1]**. These death cases include 3 teens (all males) for whom brief case-reports are available **[1]**.

In addition, the approximate numbers of vaccinated people by age (every 10 years) until October 8 are available **[2]**. By using these data, causality between the deaths of the 3 teens and vaccination is discussed.

Case 1: Pfizer vaccine, death case number 1167 [3]

A 16-year-old male received the 1st inoculation on August 10, 2021. He had no underlying illness. On the 6th day after vaccination, he suddenly arrested. His spontaneous circulation was resumed from ventricular fibrillation after treatment by DC defibrillator. He was intubated and mechanically ventilated but died on September 1, 2021 (22nd day of vaccination).

Cause of death:

Reported: Non-obstructive intestinal ischemia

Corresponding MedDRA PT: Intestinal ischemia

Evidence basis for determining the cause: CT, blood test, electrocardiogram

Causality assessment:

Reported: cannot be assessed

Experts: γ (cannot be assessed) with the following comments: A 16-year-old male who suddenly arrested 6 days after the first vaccination and died. It is difficult to evaluate the cause with the current information.

Comments by MedCheck:

"Intestinal ischemia" that caused sudden cardiac arrest may be due to a blood clot in the fairly large mesenteric artery causing its obstruction. A healthy 16-year-old boy with no underlying disorder suffered from thrombosis of the intestinal (perhaps mesenteric) artery on the 6th day of vaccination, suffered from cardiac arrest and died 22 days after vaccination. It would be extremely rare for this to happen by chance.

In the vital statistics 2019, among those between the ages of 10 and 14, 2 males died of myocardial infarction, but death from cerebral infarction and other arterial embolisms or thrombosis was 0 among those between the ages of 10 and 19.

Therefore, it is almost certain that this boy died probably from intestinal thrombosis which was caused by the vaccine.

Case 2: Pfizer vaccine, death case number 961 [3]

A 16-year-old male received the 1st inoculation on July 15, 2021, died on July 23, 2021. Underlying disorder: attention deficit hyperactivity disorder. The psychiatrist had previously prescribed medication, but recently he had stopped taking it by himself and self-harm was observed.

Cause of death:

Reported: Suicide (falling from the top floor of the condominium)

Corresponding MedDRA PT: Suicide attempted

Evidence basis for determining the cause: Unknown

Causality assessment:

Reported: Not related (Possibility of other causes: Yes, attention deficit hyperactivity disorder)

Specialists: γ (cannot be assessed) without comments

Comments by MedCheck:

There is another case of "suicide" after COVID-19 vaccination. A 25-year-old male had a fever after

receiving the COVID-19 vaccine (Pfizer), which might have resulted in transient "febrile delirium". However, he was diagnosed with a psychosis and was recommended of consultation by psychiatrist. While he was being transported to a psychiatric hospital by car, he jumped out of the car and died accidentally. Then, the doctor determined the cause of death as "suicide" **[4]**.

Detailed information on the situation before falling from the top floor of the condominium in this 16-year-old male case is unknown. However, it is not so difficult to imagine that he had some feeling of illness after vaccination and he temporarily fell into a delirious state and could not take risk avoidance behavior at the top of the condominium and has fallen.

It might be similar to the cases of accidental deaths caused by delirium after taking Tamiflu. In these cases, transient abnormal behavior leading to death in an unavoidable state of danger was mistakenly judged as "suicide".

Case 3: Moderna vaccine, death case number 36 [5]

A 15-year-old male received the first inoculation on September 16, 2021. He lost consciousness 9 hours after the inoculation. He died on September 20, 2021.
Underlying disorder: He had cerebral arteriovenous malformation.

Approximately 9 hours after the inoculation on September 16, he suffered from headache, vomiting, and loss of consciousness, and was transported by ambulance. He was diagnosed with cerebral hemorrhage with ventricular perforation from cerebral arteriovenous malformation by CT.

Cause of death:

Reported: Cerebral hemorrhage with ventricular perforation from cerebral arteriovenous malformation

Corresponding MedDRA PT: cerebral hemorrhage, ventricular perforation, condition aggravated

Evidence basis for determining the cause: CT (cerebral hemorrhage/ventricular perforation from cerebral arteriovenous malformation)

Causality assessment:

Reported: cannot be assessed (Possibility of other causes: Yes, cerebral arteriovenous malformation)

Specialists: γ (cannot be assessed) without comments

Comments by MedCheck:

According to the vital statistics in 2019 **[6]**, the total number of deaths from hemorrhagic stroke in those aged 10 to 19 (total population: 15 million) was 26. Mortality rate is 1.7 per million person-years. Since this is the mortality rate in person-years, the rate in 9 hours after an action (in this case, vaccination to the event) should be divided by 365 and should be multiply by 9/24. Therefore, the probability that the hemorrhagic stroke happens in 9 hours in this age group is estimated as 0.0018 per million person-9 hours (1.7 x 9/24/365).

As of October 8, it is estimated that there are 4.4 million people aged 12 to 19 who have been vaccinated at least once **[2]**. Among these, one person died 9 hours after inoculation. Hence, 1/4.4 million died from hemorrhagic stroke during 9 hours. The estimated mortality rate is 0.23 per million person-9 hours. In simple terms, the mortality rate of 0.23 out of 1 million is about 130 times the mortality rate of spontaneous hemorrhagic stroke (0.0018 out of 1 million).

Hemorrhagic stroke is common after COVID-19 vaccine in adults

Among the vaccinated medical workers and the elderly, deaths from cardiovascular diseases, such as hemorrhagic stroke, arterial thrombosis, and venous thrombosis, were disproportionately reported. These deaths from cardiovascular causes and vaccination, and the effects of vaccination are strongly suspected **[7-9]**.

Hemorrhagic stroke and arterial cause is disproportionately high in teens

Among teens, 2 of the 3 deaths were sudden deaths due to cerebral hemorrhage and abdominal artery thrombosis. Mortality odds ratio for hemorrhagic stroke by comparing non-cardiovascular causes as the reference is 58.3 (95%CI: 3.5-957, p<0.0001) and for arterial cause MOR=252.5 (95%CI:14.1-4523, p<0.0001).

Mortality rate is higher in vaccinated than that in general population

Proportion of reported deaths among those who were vaccinated is 0.68 per million (3/4.4 million vaccinated). All 3 died or almost died within 8 days. In addition, some will die during the following one year after inoculation. If it is assumed that the vaccinated children and

adolescents will not die during the following one year, mortality rate is 0.68 per million person-years. On the other hand, among those between 10 to 19 year of age, 3 died due to COVID-19 during about one and a half years from the start of the COVID-19 epidemic. The mortality rate is 0.22 per million person-years.

Mortality rate of deaths after vaccination are about 3 times higher than that from COVID-19 (P=0.148). The association is not statistically significant, but it means that 80 to 90% can be considered correct, and if death occurs subsequently, association may become significant.

Therefore, it seems better to think that the risk of death from vaccines is about 3 times higher for children and adolescents than death from COVID-19.

The regulators will continue to endorse vaccination in children, but these data suggest that the risk of vaccinating children and adolescents outweighs the benefits.

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