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Editorial

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Harm of vaccine and Harm of data manipulation

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Recently, two cases of data manipulation by the Japanese Ministry of Health, Labor and Welfare (MHLW) have been revealed in relation to SARS-CoV-2 vaccines.

One is the case of misregistration of vaccine recipients. When comparing the proportion of newly reported COVID-19 patients by vaccination status, patients who were surely vaccinated but with unknown date of vaccination were treated as “non-vaccinated” by MHLW. Hence, the proportion was extremely low in the vaccinated and extremely high in the unvaccinated. As a result, the data gave the impression that the vaccine worked very well.

The data from April 11 onwards have been corrected as pointed out by a researcher. As a result, the proportion of new infections per 100,000 people no longer differs across most age groups. Considering the “healthy vaccinee effect”, the protective effect of vaccine is even lower.

The other is the manipulation to make the proportion of patients with myocarditis after vaccination appear low, as reported by a local TV. It is problematic because it is used in a promotion flyer of the MHLW, which local governments use for publicity, to show that the vaccine is safe. The flyer shows that the proportion of persons with myocarditis among vaccinated males in their 20s was 10 per million (Pfizer) and 26 per million (Moderna), while the proportion among COVID-19 male patients aged 15 to 39 was 834 per million. The head of the MHLW's Health Bureau told the Diet that the latter proportion was calculated from the following data: as of May 31, 2021, among 4,798 hospitalized COVID-19 patients of the same age in the hospitals nationwide, 4 had myocarditis. However, by this time, the cumulative number of male COVID-19 patients aged 15 to 39 was about 160,000. Four patients with myocarditis among 160,000 people means that proportion is as low as 25 per million.

The proportion among the vaccinated above is too low according to the data from the National Institute of Infectious Diseases. It is 102 per million in their teens and 47 in their 20s after two doses of Moderna’s vaccine. This proportion is much higher than that in patients with COVID-19. If you don't receive the vaccine nor have COVID-19, the incidence of myocarditis is even lower. Even after these were pointed out, the MHLW has no plan to change the description in the flyer.

The data manipulation of MHLW is nothing new. Therefore, MHLW cannot be expected to critically examine and review the data manipulation of mornupiravir, the manipulation of important baseline risk factors and the suspected masking failure of SGLT2 inhibitors’ trials. We recognize again that the role of this bulletin will become more and more important.

SARS-CoV-2 Vaccination Information
Increased myocarditis mortality especially in 20s to 30s adults

Translated and revised from Med Check (in Japanese) May 2022 ; 22 (101):70-72

Med Check Editorial Team

Abstract

- Japan's Ministry of Health, Labour and Welfare (MHLW) announced that cases of myocarditis after SARS-COV-2 vaccination had been confirmed and added warning to the package insert. In other countries, the association between myocarditis and SARS-COV-2 vaccination has been reported mainly in young males. In this article, we analyzed the association between myocarditis death and SARS-COV-2 vaccination based on the disclosed data.
- Myocarditis mortality after vaccination increased significantly as compared with that in the reference population (2019 population); particularly, it was about 21-fold and 14-fold in 20s and 30s adults, respectively. When suspected cases were included, it was 35-fold and 16-fold, respectively. In 40s adults, it was also significantly higher: 4.7-fold (5.9-fold when suspected cases were included).
- The post-vaccination myocarditis mortality rate may be higher, due to possible unreported deaths after vaccination, possible misclassification of cause of death and healthy vaccinee effect.

Conclusion: SARS-COV-2 vaccines are very harmful in 20s to 40s adults.

Keywords:

vital statistics, reporting omission, healthy vaccinee effect, frailty exclusion bias, misclassification, information bias, person-years

Introduction

SARS-COV-2 vaccines administration was launched on February 17th, 2021 in Japan, and as of February 2022, more that 80% of the population has reportedly been vaccinated [1].

Myocarditis is known as one of the adverse reactions to the SARS-COV-2 vaccines in young adults. For example, in Israel, many cases of myocarditis were reported in young males after the second dose [2]. In Korea, a 22-year-old male with no complication suddenly died 5 days after he had received Pfizer vaccine. The diagnosis of myocarditis was confirmed at autopsy [3].

In Japan, the Ministry of Health, Labour and Welfare (MHLW) announced that cases of myocarditis after SARS-COV-2 vaccination had been confirmed and added warnings to the package insert. The warnings, however only include that most myocarditis cases improve with rest during hospitalization, and do not mention death cases [4]. Therefore, the association between vaccination and myocarditis death has not been clarified.

Myocarditis mortality rate in the vaccinated population was compared with that in the general population in 2019 as reference. In order to examine the impact of under-reporting of post-vaccination deaths and other factors, total mortality in the post-vaccination population with those in the reference population was also compared. In addition, we calculated age adjusted total mortality in the vaccinated population in Japan and non-COVID-19 mortality rate by vaccination status in the United Kingdom (UK).

Table 1: Calculation methods of person-years for vaccinated population

Age	persons with only 1st dose		persons with full dose		Total person-years
	number	person-years	number	person-years	
	a	b=a×9.62/365	c	d= c×(11.58+21)/365	e=b+d
10-19	147,798	3,895	6,733,641	601,089	604,985
20-29	141,353	3,726	10,130,931	904,354	908,079
30-39	120,385	3,173	11,405,858	1,018,162	1,021,335
40-49	99,856	2,632	15,292,887	1,365,144	1,367,776
50-59	65,721	1,732	15,266,219	1,362,763	1,364,495
60-69	38,967	1,027	13,887,163	1,239,660	1,240,687
70-79	43,875	1,156	15,256,469	1,361,893	1,363,049
80-89	41,716	1,100	8,833,334	788,521	789,621
≧90	17,729	467	2,310,641	206,263	206,730

b: average days from dose 1 to death: 9.62 days
d: average days from dose 2 to death: 32.58 days

Risk of myocarditis death from SARS-COV-2 vaccines

Death cases after vaccination:

The risk of myocarditis death from SARS-COV-2 vaccines was calculated based on the death cases reported on "The summary of spontaneous cases reported as deaths after receiving SARS-COV-2 vaccine" disclosed by the panels of experts on vaccination and adverse reactions under MHLW (Feb. 18th, 2022) [5] Deceased vaccinees who had received first and/or second dose were analysed. By excluding duplicated cases or withdrawals, 1,384 deaths after Pfizer vaccine, 66 deaths after Moderna vaccine, and 1 death after AstraZeneca vaccine were examined (total 1,451 deaths).

Myocarditis death cases after vaccination:

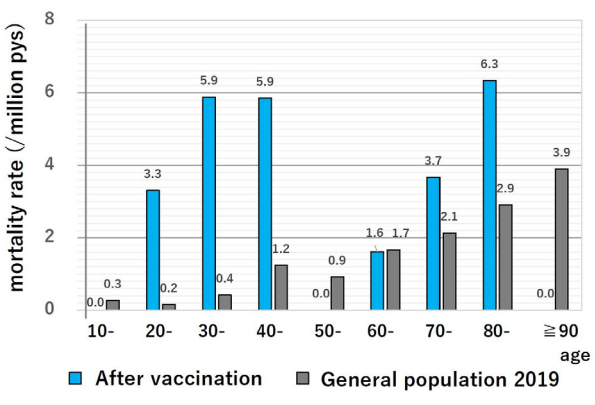
"Myocarditis death case" after vaccination was defined as the cases in which "myocarditis" was described in the column for cause of death on the above summary list. "Suspected myocarditis death case" was defined as the case in which it can be considered that the reporter suspected "myocarditis" from the description in the "other column" on the above summary list. They were classified as death from (or suspected from) I40 (acute myocarditis) under the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

Period of observation after vaccination:

In Japan, doctors are required to report serious reactions within 28 days vaccination if they suspected an association with vaccination, and reported cases were disclosed as in the summary list. However, not all serious reactions following vaccination were disclosed. In other words, only death cases in which doctors suspect the association were disclosed as in the summary list [5]. Some cases were reported beyond 28 days. After excluding cases in which the dates of vaccination, date of death and the number of doses were unknown, the average number of days to death was 9.6 after the first dose and 11.6 after the second dose. The second dose is usually given 21 days after the first dose. Therefore, the average number of days to death after the first dose were 32.6 days. The distribution of the number of days to death in all cases is shown in Supplementary **Figure 1** and Supplementary **Figure2**.

Figure: Myocarditis mortality after SARS-CoV-2 vaccination（comparison with general population in 2019 as reference）

A: Myocarditis mortality rate



pys: person-years

B: Relative risk of myocarditis mortality

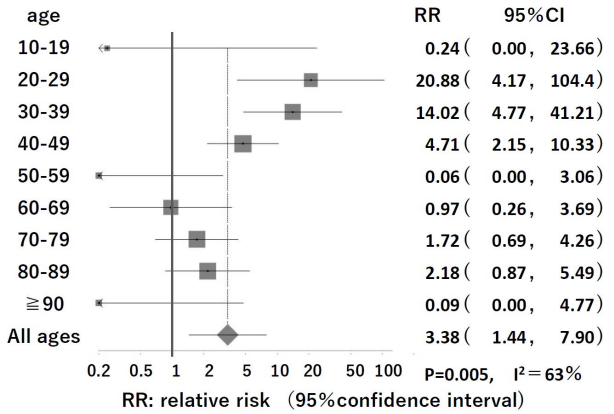


Table 2: Myocarditis death cases after vaccination and in the reference population

Age	After SARS-CoV-2 vaccine							Data from vital statistics 2019					mortality rate ratio *b after SARS-CoV-2 vaccine		
	person -years *a	Myocarditis death		including suspected		All-cause mortality		person -years	Myocarditis death		All-cause mortality				
		n	/m	n	/m	n	/m		n	/m	n	/m	Myocarditis death	including suspected	All-cause death
10-19	604,985	0	0.0	0	0.0	6	1.0	11,170,000	3	0.3	1,603	14	0.0	0.0	0.069
20-29	908,079	3	3.3	5	5.5	30	3.3	12,627,000	2	0.2	4,097	32	20.9	34.8	0.102
30-39	1,021,335	6	5.9	7	6.9	37	3.6	14,302,000	6	0.4	7,455	52	14.0	16.4	0.069
40-49	1,367,776	8	5.9	10	7.3	57	4.2	18,519,000	23	1.2	21,837	118	4.7	5.9	0.035
50-59	1,364,495	0	0.0	1	0.7	94	6.9	16,278,000	15	0.9	46,935	288	0.0	0.8	0.024
60-69	1,240,687	2	1.6	3	2.4	127	10.2	16,232,000	27	1.7	121,635	749	1.0	1.5	0.014
70-79	1,363,049	5	3.7	5	3.7	324	23.8	15,928,000	34	2.1	281,734	1,769	1.7	1.7	0.013
80-89	789,621	5	6.3	5	6.3	475	60.2	8,939,000	26	2.9	501,343	5,608	2.2	2.2	0.011
≧90	206,730	0	0.0	0	0.0	292	141.2	2,309,000	9	3.9	391,272	16,946	0.0	0.0	0.008

*a:Methods of calculation: See Table 1

*b: For 95% confidence interval of mortality rate ratio of myocarditis death, including suspected case, and all-cause death, see Figure B, supplementary Fig 3B and supplementary Fig 4B respectively.

Calculation of person-years after vaccination:

Person-years to death after vaccination among vaccinees were calculated, based on the number of SARS-COV-2 vaccinees by 10-year age classes as of February 14th, 2022, published by the cabinet office. The average number of days to death were also calculated (Table 1).

Myocarditis mortality in the reference population

Mortality rates of acute myocarditis (I40, ICD-10) in 2019 was computed from the number of I40 death in the vital statistics and estimated population by 10-year age classes [6,7], and were used as the reference mortality rates by age.

Myocarditis death cases by age (after vaccination and in the reference population)

Number of myocarditis death cases after vaccination and that of the reference population based on the 2019 vital statistics by 10-year age classes are shown in the Table 2 .

Markedly high risk of myocarditis death in 20s and 30s adults

Figure A shows the comparison of myocarditis mortality rates after vaccination and that in the reference population by 10-year age classes. It is very clear that myocarditis mortality rates were higher than in the reference population especially in 20s and 30s. Myocarditis mortality rate was 0.16 persons per 1 million person-years in 20s in the reference population. However, after SARS-CoV-2 vaccination, it was about 20-fold (3.3 persons per 1 million person-years) in 20s, about 14-fold in 30s, and about 5-fold in 40s. When suspected cases were included, it was 35-fold, 16-fold and 6-fold in 20s, 30s and 40s, respectively (See Supplementary Figure 3).

Figure B shows risk ratio (mortality rate ratio) and their 95% confidence interval. Myocarditis mortality in the post-vaccinated population were all statistically significantly higher compared to the reference population in the 20s, 30s and 40s.

Actual myocarditis mortality might be even higher

The following 3 points should be considered when interpreting these results.

1) Omission of reporting death cases (see Web Med Check No.195 [8])

Doctors are not obliged to report all post-vaccination deaths in Japan [9]. In fact, there was a case which was reported only after the doctor was pressured by the bereaved family [10]. There was a case of a 55-year-old woman who died from subarachnoid hemorrhage 5 days after vaccination. This case was once reported as a death case, but was withdrawn later. In other words, post-vaccination death cases had been disclosed only partially in Japan. According to the Centers for Disease Control and Prevention (CDC) of United States of America (US), by the end of February 2022, about 550 million doses had been administered, and about 13,000 deaths had been reported after vaccination [11]. On the other hand, the number of reported death cases were only about 1,500 cases while about 220 million doses had been administered in Japan. If death cases are reported as frequently as in the US, the

number of death cases would be about 3.5-times higher than those disclosed in Japan.

2) Healthy vaccinee effects (frailty exclusion bias) [12]:

The package inserts of SARS-COV-2 vaccines warn that administration to persons with a serious acute illness or a history of hypersensitivity was inappropriate [13, 14]. Furthermore, considering that myocarditis was listed as a "serious adverse reaction", administration to patients with a heart disease or other serious illnesses would be avoided, and thus both total mortality and myocarditis mortality due to vaccination could be underestimated.

The decisive evidence on healthy vaccinee effects (frailty exclusion bias) was revealed in the analysis of the data from the UK [15]. The age-adjusted mortality rate of non-COVID-19-related causes in 2021, which vaccination would not reduce, to the estimated age-adjusted mortality rate in 2021was 0.2-fold (one-fifth) in those who had received the second dose at the beginning. Age adjusted mortality rate was 1.8-fold in unvaccinated persons over the year 2021, and 0.83-fold at the beginning of vaccination and 2.6-fold over the year 2021 in those who had received first dose (those who could not have the second dose) [15].

The reason why the mortality rate of non-COVID-19-related causes, which vaccination would not reduce, was lower among those who had received second dose is because they had been healthier since before the vaccination and were able to receive second dose as they had no problem after first dose. Mortality rates over the year in the unvaccinated and those who received only first dose were high because the former originally more included those who had health problems which prevented them from vaccination (dying or critically ill persons would not be vaccinated), and the latter may have had experienced severe adverse reactions after the first vaccination (see Web-Med Check No. 203 [15] for details and p●-● of this issue).

In Japan, the total mortality rate after vaccination was one-tenth to one-hundredth of the total mortality of the reference population (one-fortieth in all age groups) (see Supplementary Fig.4,). This result suggests that there were many unreported death cases in addition to healthy vaccinee effects (frailty exclusion bias).

3) Information bias due to misclassification of causes of death [16]:

A Korean case report was the case which was first reported as sudden death, but later diagnosed as myocarditis at autopsy [3]. Considering that there are many cardiovascular deaths in the vaccinated [17], myocarditis might have been the cause of death after vaccination in cases which was reported as "cardiac arrest", "sudden death" or "arrhythmia". Israeli study reported that overreporting may not explain high rate ratio of myocarditis after SARS-CoV-2 vaccination [2].

Considering the above 3 points, namely omission of reporting, healthy vaccinee effects (frailty exclusion bias) and misclassification of causes of death, it can be inferred that mortality rate of myocarditis after vaccination would be even higher than the results shown here.

The harm and benefit of SARS-COV-2 vaccines are needed to consider

It has already been revealed that SARS-COV-2 vaccines contribute to increased hemorrhagic stroke mortality [8,17]. It has been also suggested that they are associated with deaths from arterial diseases, pulmonary venous thrombosis, and pulmonary embolism [17].

This article showed that myocarditis mortality rate increased especially in young adults after administration of SARS-COV-2 vaccines. The harm and benefit of the vaccines should be carefully considered in the light of these findings.

References

1) Japanese Cabinet Office: About COVID-19 vaccine in Japanese (accessed 2022.2.20) https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html
2) Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med. 2021; 385(23):2140-2149.
3) Choi S, Lee S, Seo JW, et al. Myocarditis-induced Sudden Death after BNT162b2 mRNA COVID-19 Vaccination in Korea: Case Report Focusing on Histopathological Findings. J Korean Med Sci. 2021; 36(40):e286. Published 2021 Oct 18.
4) MHLW COVID-19 vaccine Question and answers in Japanese (accessed 2022.2.20) https://www.cov19-vaccine.mhlw.go.jp/qa/0079.html
5) Japan's MHLW Database, in Japanese (accessed 2022.2.20) https://www.mhlw.go.jp/stf/shingi2/0000208910_00038.html
6) Vital statistics in 2019: Causes of death by age, in Japanese (accessed 2022.2.20) https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450011&tstat=000001028897&cycle=7&year=20190&month=0&tclass1=000001053058&tclass2=000001053061&tclass3=000001053065&result_back=1&tclass4val=0
7) Population estimates as at 1 October in each year in Japanese (accessed 2022.2.20) https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00200524&tstat=000000090001&cycle=7&year=20190&month=0&tclass1=000001011679
8) Med Check editorial team. Four women died of hemorrhagic stroke. Two times followed by a total of four times, with a strong causal relationship. Web Med Check No195 in Japanese (accessed 2022.2.20) https://npojip.org/sokuho/210426.html
9) MHLW: Call for spontaneous reports based on the vaccination law from medical doctors (accessed 2022.2.20) https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/index.html
10) News paper "Yomiuri shinbun" on May 9 2021(accessed 2022.2.20) https://www.yomiuri.co.jp/medical/20210508-OYT1T50380/
11) CDC. Selected Adverse Events Reported after COVID-19 Vaccination (accessed 2022.3.6) https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html
12) Med Check editorial team. Basic principles in Medical research Supplementary material to Med Check No92 in Japanese (accessed 2022.3.6) https://www.npojip.org/chk_tip/2020No92-furoku.pdf
13) Pckage insert of Pfizer vaccine "Cominarty" in Japanese (accessed 2022.2.20) https://www.kegg.jp/medicus-bin/japic_med?japic_code=00069248 This issue): ●-●.
14) Pckage insert of Moderna vaccine "Spikevax" in Japanese (accessed 2022.2.20) https://www.info.pmda.go.jp/go/pack/631341EA1038_1_02/
15) Med Check editorial team. Solid evidence for "healthy vaccinee effect" Web Med Check No203 in Japanese https://www.npojip.org/sokuho/220427.html Med Check in English. 2022: 8(24) (
16) Rothman KJ, Greenland S and Lash TL eds Modern Epidemiology 3rd ed. Wolters Kluwer/ Lippincott Williams & Wilkins, 2008
17) Med Check editorial team. Strong association with cardiovascular death especially hemorrhagic stroke and venous thrombosis. Med Check in English. 2022: 7(21/22): 32-37. www.npojip.org/english/MedCheck/Med%20Check%20Tip-21-2021-08&12.pdf

Non-COVID-19-related deaths were reduced in the vaccinated population

Robust evidence for healthy vaccinee effect

Translated from Web Med Check (in Japanese) No 203. 27 April 2022

Med Check Editorial Team

Abstract

Vaccinees are generally healthier than non-vaccinees. When study results are distorted (biased) because of this, it is generally called “healthy vaccinee effect” or “healthy user bias”. This article discusses this issue based on the data on mortality rates in the vaccinated and the non-vaccinated population in the UK.

The mortality rate of non-COVID-19-related deaths, which vaccination would not reduce, was 0.2-fold (one-fifth) of the 2021 estimated age-adjusted mortality rate in persons who had received 2 doses at the beginning of the COVID-19 immunization program in UK. On the other hand, it was 1.8-fold over the year (2021) in the non-vaccinated, and 2.6-fold over the year in those who had received only 1 dose (those who could not receive the second dose).

The reasons why the mortality rate, which vaccination would not reduce, was lower in those who had received the second dose is because they had been very healthy since before the vaccination and was able to receive the second dose as they had no problem with the first dose.

Mortality rates over the year in the non-vaccinated and those who had received only the first dose were high because the former originally had health problems, and the latter may have had experienced severe adverse reactions after the first vaccination, and this contributed to high mortality rate of non-COVID-19-related deaths.

Keywords:

healthy user bias, age-adjusted mortality rate, first dose, second dose, UK, COVID-19 related death, all-cause mortality

Introduction

Med Check No.101 [1] reported that mortality rate from myocarditis after COVID-19 vaccination was higher by 14 to 20 times in the vaccinees in their 20s to 30s as compared to the general population. This can be even higher, considering that there were unreported deaths, vaccinees were originally healthier than non-vaccinees, and some cases of myocarditis were reported as arrhythmia or sudden death (misclassification).

People who have severe illness especially who are about to die or fever on that day would avoid vaccination. Therefore, vaccinees are generally healthier than non-vaccinees. For this reason, if morbidity rates of illnesses they would have after vaccination in the vaccinated and non-vaccinated are directly compared, the result would not reflect the reality.

As explained above, the bias or distortion created by the tendency that vaccinees are originally healthier than non-vaccinees is called “healthy vaccinee effect” or “healthy user bias” in epidemiology. Especially in studies on harm and effect of vaccines, data must be carefully examined, considering the influence of this bias.

However, in most epidemiological studies on vaccines, it is ignored, although many baseline characteristics including age, sex, comorbidities or socioeconomic characteristics are adjusted. Vaccinees many of whom are healthy and non-vaccinees many of whom have illnesses are compared without adjustment of real health condition to conclude that vaccines are “effective” and “not harmful”.

While the issues of omission of reporting and misclassification are relatively easy to understand, “healthy vaccinee effect” is not well recognized even among experts despite its significance. One of the reasons why it is not

widely recognized as important, even though it is not so difficult to understand, is that it has not been theoretically examined well.

Moreover, one of the most important reasons is that if "healthy vaccinee effect" is rightly adjusted in epidemiological studies, evaluation of many vaccines would be overturned: those which have been considered "effective" and "not harmful" would be "ineffective" and "harmful".

Panels of experts of many countries as well as international organizations, such as World Health Organization (WHO), have been assessing vaccines as "effective" and "not harmful" based on the studies in which "healthy vaccinee effect" is not considered. However, if "healthy vaccinee effect" is rightly adjusted, the results would be overturned. Because of this, most epidemiological studies on harm and effectiveness of vaccines ignore this bias, and unscientific research results are published as academic peer-reviewed papers and adopted in policy making of national governments and WHO. As long as this would continue, adjusting "healthy vaccinee effect" in epidemiological studies would not be understood reightly and supported by the majority of people.

In reality, as Med Check has pointed out in its Web Med Check No. 198 "Harm and benefit of HPV vaccines" and No.199 "Resumption of HPV vaccines is very dangerous" [3], there is strong influence of "healthy vaccinee effect" on evaluation of seemingly effective and safe vaccines.

As regard to HPV vaccines, the study result was distorted. Because frail people avoid vaccination while healthy people receive vaccination (the vaccinated is healthier than the non-vaccinated), non-HPV-related cancers, which HPV vaccine would not prevent, are reduced in the vaccinated population. Furthermore, various other harms are reduced in the vaccinated population because of the influence of the bias.

This article explains this important issue, "healthy vaccinee effect" or "healthy user bias" or "frailty-exclusion bias" and shows that it is clearly at work in the studies on COVID-19 vaccines.

【1】Healthy vaccinee effect and frailty-exclusion bias

Frail people avoid vaccination and healthy people receive vaccination, resulting in overestimation of effect and underestimation of harm [2-5].

Distortion of results or yielding results different from the truth is called "bias" in epidemiology. Causes of such a bias are shown in details in another article in this issue.

Generally, this phenomenon is called "healthy vaccinee effect". When this concept is extended to include not only vaccines but also other medicines, a term "healthy user bias" is more appropriate.

On the other hand, focusing on the tendency that frail people avoid vaccination, a term "frailty selection bias" is also used. However, this term may cause misunderstanding that "frail people are selected to be vaccinated". Actually, there was a paper which misunderstood the term. Therefore, Med Check No.65 (May 2016) proposed to use the term "frailty exclusion bias" in its analysis on HPV vaccines [4].

However, as the term "healthy vaccinee effect" is more widely accepted even by doctors, Med Check has been using the term "healthy vaccinee effect (frailty-exclusion bias)" since then.

Therefore, "healthy vaccinee effect" and "frailty-exclusion bias" are two sides of the same coin, looking at the same phenomenon from the viewpoints of those who receive or avoid vaccination.

This article discusses that healthy vaccinee effect (frailty-exclusion bias) clearly has influence on the studies of COVID-19 vaccines, using the data on the mortality rates in the UK.

【2】Overview of the method

(1) Basic method

The basic method used to examine healthy vaccinee effect (frailty-exclusion bias) in studies on COVID-19 vaccines is as follows;

A. The 2021 age-adjusted mortality rate in the UK is estimated based on the national statistics data up to 2019 [6].

B. We noticed especially the non-COVID-19-related age-adjusted mortality rates by vaccination status (non-vaccinated, 1 dose or 2 doses or booster dose).

C. Ratio of the above two mortality rate (mortality rate ratio) is calculated and compared. [7,8].

(2) Mortality rates of non-COVID-19-related deaths are mainly compared.

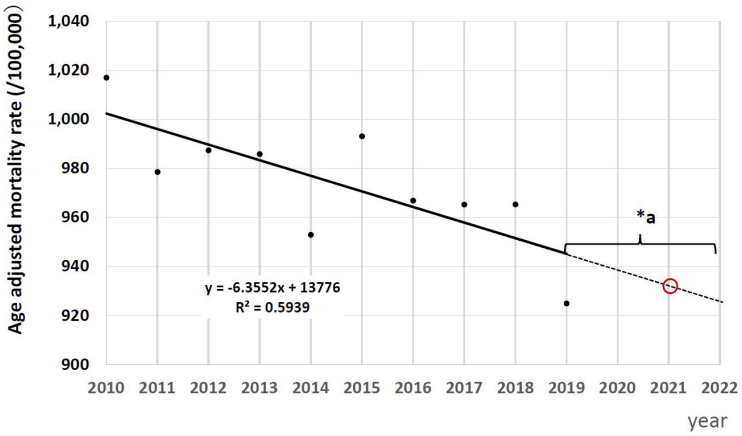
As of the age-adjusted mortality rates, not only total mortality rate, but also mortality rate of COVID-19 as well as that of non-COVID-19-related deaths were reported. [8] Among them, non-COVID-19-related death was the main focus of this analysis, Mortality rate of non-COVID-19-related deaths may increase if COVID-19 vaccines are

harmful. It may also increase when COVID-19 deaths are classified as non-COVID-19-related deaths. However, it would not be reduced by the vaccines. Therefore, this article focuses on the mortality rates of non-COVID-19-related deaths.

(3) Monthly age-adjusted mortality rate is used

Monthly age-adjusted mortality rates in the vaccinated and the non-vaccinated (by the number of doses) reported in the database [8] based on person-years and the number of deaths are used in our analysis.

Figure 1: Method for estimation of age-adjusted mortality rate in 2021



*a : The line is the extension of the regression line of 2010-2019 age-adjusted mortality rates. ○ : The Estimated rate in 2021 is 932/100,000 person-years.

(4) Mortality rates within and more than 20 days after vaccination are also compared

As regard to the vaccinated, age-adjusted mortality rates were reported for within 20 days of the first dose and for 21 days or later after the first dose, within 20 days of the second dose and for 21 days or later after the second dose, and within 20 days of booster (third) dose and for 21 days or later after the booster (third) dose.

The meaning behind these differences is explained below:

1) Most deaths within 20 days of the first dose occurred before the second dose.

2) Deaths which occurred 21 days or later after the first dose are the deaths of those who could not receive the second dose mainly for health reasons.

3) Deaths which occurred within 20 days of the second dose and 21 days or later after the second dose are the deaths of healthy people who were able to receive 2 doses as they had no problem with the first dose. However, they avoided booster dose for health reasons.

4) Those who received the third dose are healthy people who were able to have the second dose without problem.

【3】Results and Discussion

(1) Estimated age-adjusted mortality rate for 2021

The following data of the UK Office for National Statistics are used to calculate the estimated age-adjusted mortality rates, assuming that there was no pandemic of COVID-19 in 2021 Dataset: Deaths registered in England and Wales

The regression line of 2010-2019 age-adjusted mortality rates ($y = -6.3552x + 13776$) is extended to meet the year 2021 at 932/100,000 person-years. This is considered as the estimated age-adjusted mortality rate for the year 2021 (Figure 1).

(2) Daily number of COVID-19 deaths vaccinated and percent with full dose.

Figure 2 shows the trend of daily number of COVID-19 deaths, daily number of vaccinated and percent who received full dose of SARS-CoV-2 vaccine in the UK in 2021. The data source is Our World in Data (OWID), Coronavirus Pandemic (COVID-19) [7].

In the UK, daily number of COVID-19 deaths reached its peak on 20 January 2021 during the rhird wave of COVID-19 and it was reduced from April to June, 2021.

Apparently, it was reduced as the vaccination rate increased, but considering the situations in other countries, it cannot be the effect of vaccination (Note 1).

Note 1: For example, in Singapore, SARS-CoV-2 immunization was actively promoted, and the vaccination rate for the second dose was over 70% in August, 2021. However, especially around that time, a major pandemic began and the mortality rate was as high as 100/100 million persons in the end of September, and 400/100 million persons in November. Moreover, the vaccination rate of booster shots was over 50% in the mid-January, 2022 and reached 69% in the end of February. On the other hand, the numbers of infected people and deaths was 20 times higher in the end of February than those in the mid-January. The number of infected people reached its maximum of about 40,000 persons in one day. This is equivalent to 800,000 persons in the Japanese population. This shows that COVID-19 vaccines did not contribute much to prevent the pandemic and deaths unlike suggested by randomized controlled trials (RCTs) (see slide 18).

It is noteworthy that daily number of COVID-19 deaths in the UK was very low from April to June. As explained below in detail, this should be examined in contrast with the fact that during this period in the UK, mortality rates of non-COVID-

19-related deaths increased in the non-vaccinated and 21 days or later after the 1st dose.

(3) Age-adjusted mortality rate of non-COVID-19-related deaths

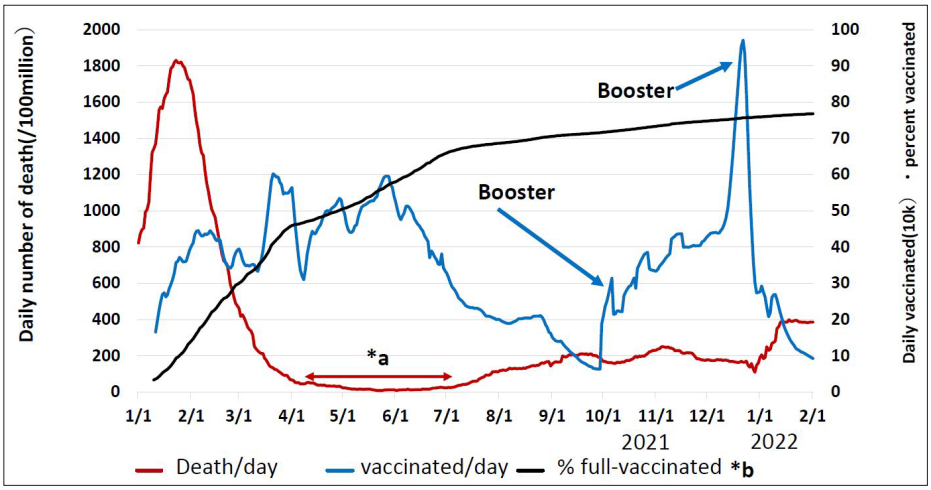
COVID-19 vaccines are believed to be effective in reducing onset and aggravation of COVID-19 (infection caused by SARS-CoV2), and thus reduce deaths. Its efficacy on reducing onset and aggravation is proven by RCTs.

However, they are not supposed to reduce non-COVID-19-related deaths, such as other infections, heart diseases and cancers, while they can increase these illnesses as adverse effects.

Therefore, if the mortality rate of non-COVID-19-related deaths in the non-vaccinated is higher than the 2021 estimated age-adjusted mortality rate, the increase can be attributed to the increase due to the effect of frailty-exclusion bias (healthy vaccinee effect).

In addition, if the mortality rate of non-COVID-19-related deaths in the vaccinated is lower than the 2021 estimated age-adjusted mortality rate, the reduction can be attributed to the reduction due to the healthy vaccinee effect (frailty-exclusion bias).

Figure 2: Trend of the daily COVID-19 deaths, daily number of vaccinated and percent who received full dose of SARS-CoV-2 vaccine.



Data source：Our world in Data(OWID)、Coronavirus Pandemic (COVID-19)
https://ourworldindata.org/coronavirus#explore-the-global-situation.
*a: Number of COVID death is very few.
*b: Full-vaccinated means 2 doses for the most SARS-CoV-2 vaccine except one product which require only one dose. The actual numbers of daily deaths and vaccination fluctuate greatly. Smoothed figures, which are calculated using figures before and after the original figures, are used in this analysis. The number of COVID-19 deaths was very small from April to June 2021.

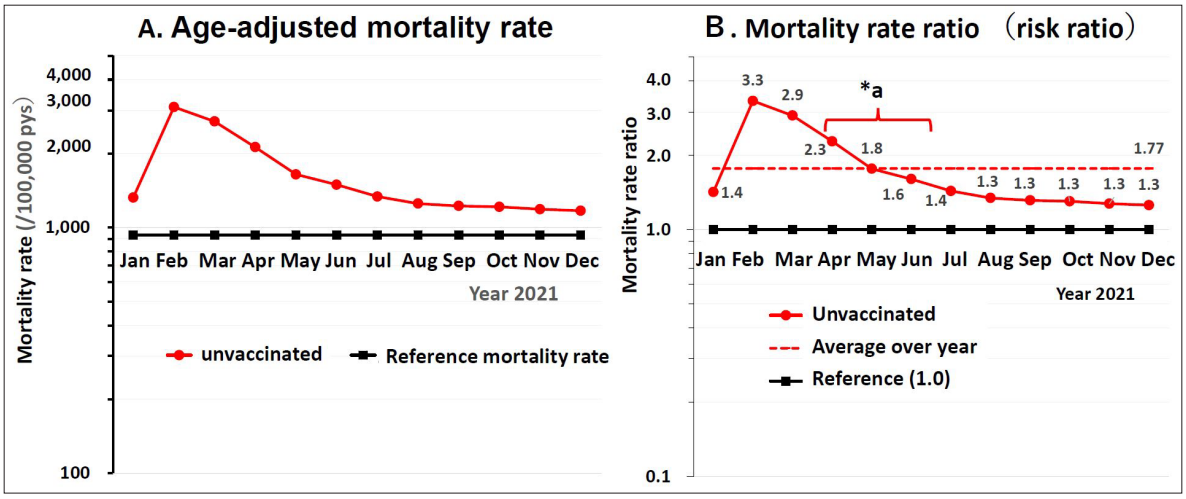
The source of data used for this analysis is Office for National Statistics Dataset [8].

1) The mortality rate of non-COVID-19-related deaths in the non-vaccinated (Figure 3)

Figure 3 shows the following:

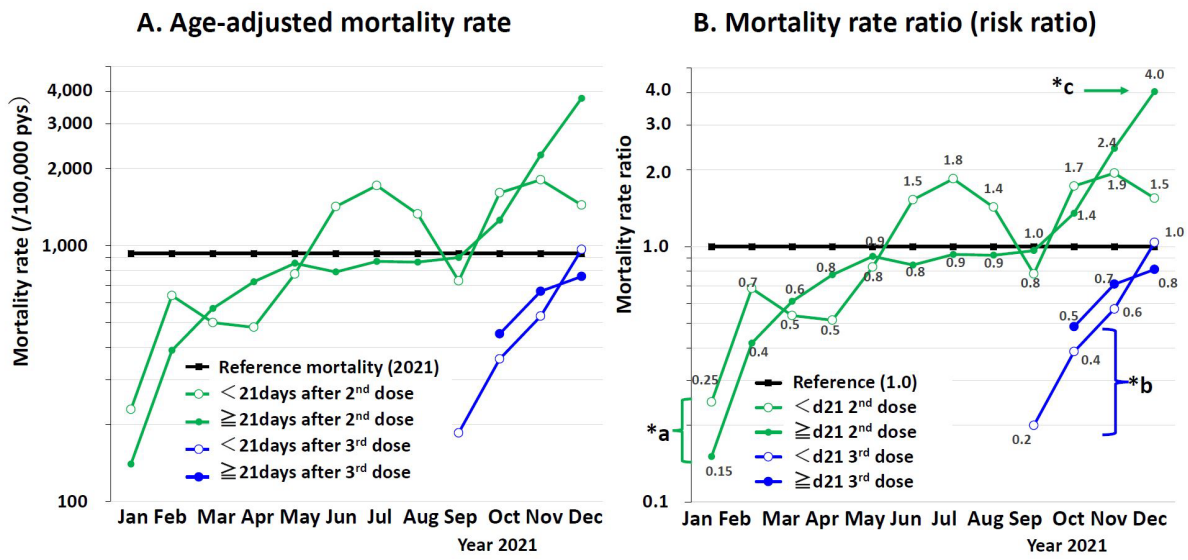
A. monthly age-adjusted mortality rates of non-COVID-19-related deaths and the 2021 estimated age-adjusted mortality rate as reference, and

Figure 3: Non-COVID-19-related deaths in unvaccinated population



From April to June, when there were very few COVID-19 deaths, the mortality rate ratio of non-COVID-19-related deaths to the estimated mortality rate in the non-vaccinated was average 1.9 (*a). This indicates that mortality rate in the non-vaccinated doubled due to frailty-exclusion bias.

Figure 4: non-COVID-19-related deaths after second and third doses



The mortality rates not only of COVID-19 (not shown in the figure 4, see Figure 8), but also of other illnesses (non-COVID-19 death) are markedly low in the vaccinated people, especially in those who could receive second (*a) or third doses (*b) (healthy vaccinee effects)
Mortality rate is high in those who could not have 3rd dose after 2nd dose (*c). This is because they avoided 3rd dose due to health problems. •frailty-exclusion bias.

B. mortality rate ratio (risk ratio) of non-vaccinated population to the 2021 estimated age-adjusted mortality rate as reference (1.0).

Mortality rates in the non-vaccinated people was constantly higher than the estimated mortality rates from January to December, 2021. The average mortality rate ratio was 1.77 annually, and 1.9 between April and June, when the mortality rate of COVID-19 was extremely low. During the period from mid-March to the end of June, excess mortality was almost minus according to OWID [9]. This means that higher mortality rate of unvaccinated in this period was not affected by the excess death due to potential SARS-CoV-2 infection.

This is because many frail people might have avoided vaccination. In other words, it was the result of frailty-exclusion bias.

2) Mortality rates of non-COVID-19-related deaths after the second and third doses

Fig.4 shows the following:

A. age-adjusted mortality rates of non-COVID-19-related deaths after the second and third doses and the 2021 estimated age-adjusted mortality rate as reference, and

B. mortality rate ratio (risk ratio) to the 2021 estimated age-adjusted mortality rate (1.0).

In the beginning of the immunization program, the mortality rate of non-COVID-19-related deaths in those who had received second dose was 0.2-fold (one-fifth) of the estimated mortality rate (Note 2). In other words, they were 5 times healthier than the general population.

Note 2: Rate ratio of the mortality is 0.2 which is the average of mortality rate ratio of non-COVID-19-related deaths within 20 days of the second dose (0.25) and that of 21 days or later after the second dose (0.15). Details of statistical testing is omitted here, but it is certain that they are statistically significant.

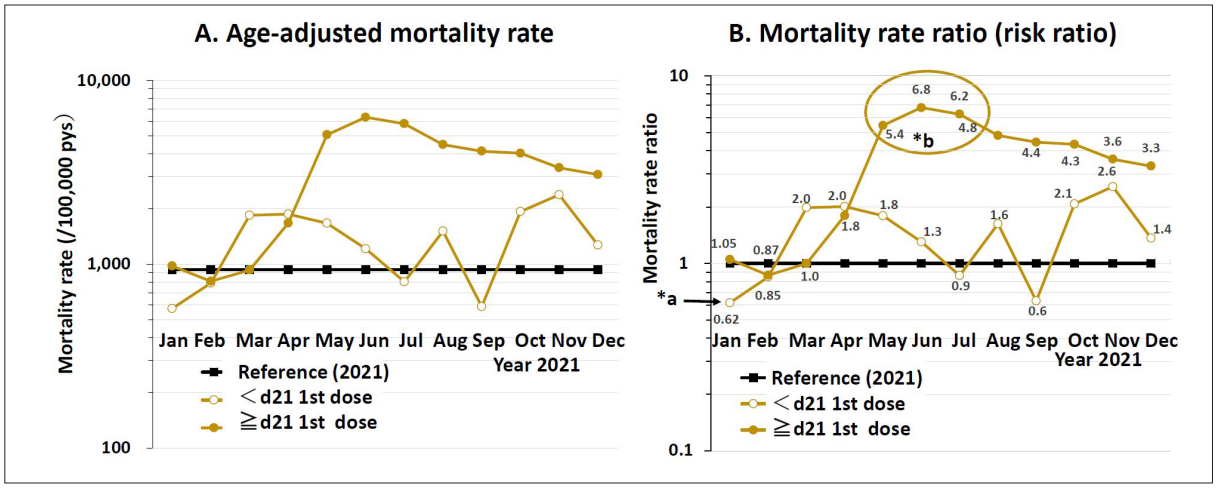
This tendency is consistent with the fact that the mortality rate ratio at the initial stage of introduction of booster shots which began in September 2021 was 0.2 (mortality rate was 0.2-fold).

It can be said that people who received the first vaccination early, and especially those who could receive second or booster vaccination were originally very healthy.

Mortality rates of non-COVID-19-related deaths are markedly low at the early stage after the second and third dose. This is exactly the effect of healthy vaccinee effect.

On the other hand, after the launch of booster shots began in September, mortality rates drastically increased especially in those who died 21 days or later after the second dose. This is because they had health problems and avoided the booster dose. This is a typical example of frailty-exclusion bias in which frail people avoid vaccination.

Figure 5: non-COVID-19-related deaths after the first dose



*a：At the initial stage of immunization program, the mortality rate within 20 days of the first vaccination was lower than the estimated mortality rate (mortality rate ratio: 0.62) due to the healthy vaccinee effect.

*b：However, the mortality rate was very high in people who could not receive the second dose when there was not so many COVID-19 deaths and vaccination was active (mortality ratio: 5.4-6.8). This is probably because they became sick after they had received the first dose. In other words, they were frail and excluded from vaccination (frailty-exclusion bias).

3) Mortality rate of non-COVID-19-related deaths after the first dose

Figure 5 shows the following:

A. age-adjusted mortality rates of non-COVID-19-related deaths after the first dose and the 2021 estimated age-adjusted mortality rate as reference, and

B. mortality rate ratio (risk ratio) to the 2021 estimated age-adjusted mortality rate (1.0).

At the initial stage of immunization program, the mortality rate after the first dose was lower than the estimated mortality rate. The mortality ratio within 20 days of the first vaccination was 0.62. This suggests that the vaccinees were healthy until this point.

However, the mortality rate ratio at 21 days or later after the first dose increased to 1.05. Usually the second dose is administered 21 days after the first dose. At this point, it is highly likely that those who could not receive the second dose had had health problems after the first dose.

Figure 6: Mortality rate of non-COVID-19-related deaths by number of doses (summary)

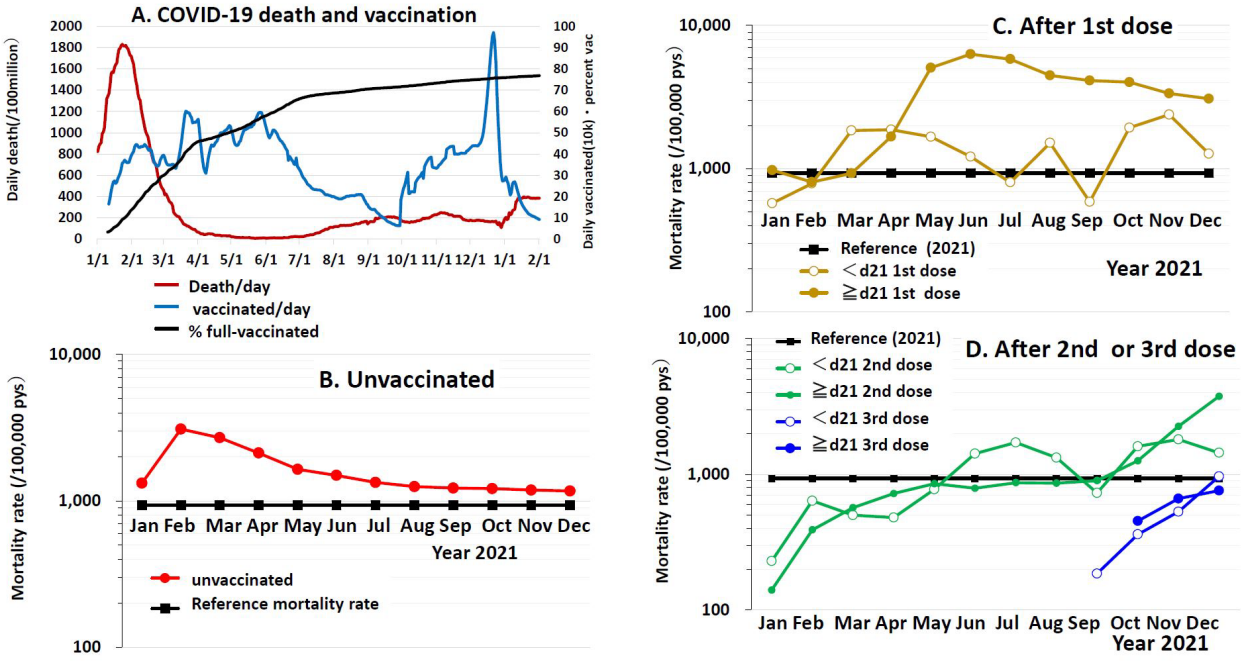
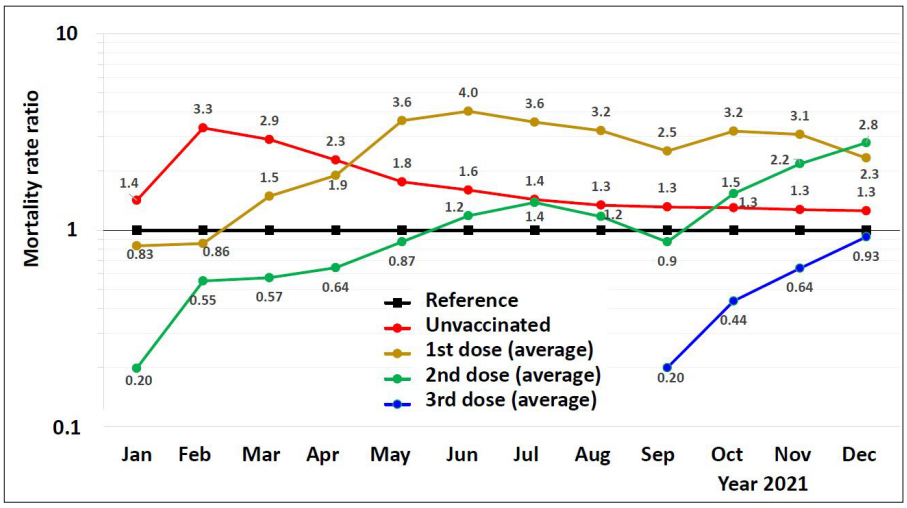


Figure 7: Mortality rate ratios of non-COVID-19-related deaths (summary)



This tendency became especially evident between May to July 2021, when there were very few COVID-19 deaths. The mortality rates increased to as high as 5.4-fold to 6.8-fold of the estimated mortality rates.

People who had received the first dose were relatively healthy. Among them, some died without receiving the second dose. It can be inferred that the additional deaths to the estimated mortality rate might be caused by the vaccines.

4) Mortality rate of non-COVID-19-related death comparing by number of doses

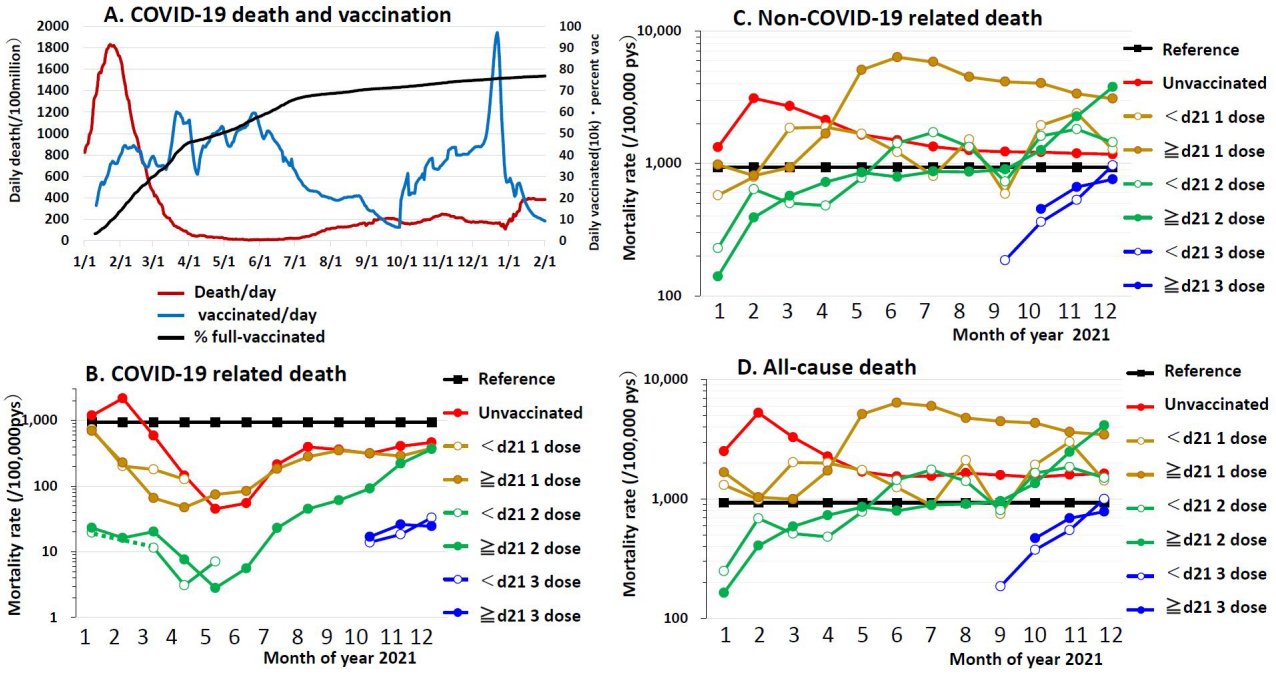
Figure 6 summarizes age-adjusted mortality rate of non-COVID-19-related deaths by the number of doses.

5) Mortality rate ratio of non-COVID-19-related deaths (by the number of doses)

Figure 7 shows mortality rate ratio of non-COVID-19-related deaths to the 2021 estimated age-adjusted mortality rate (1.0) by the number of doses. Mortality rate ratios of non-COVID-19-related deaths by the number of doses shown in the Figure 7 are the average of mortality ratios within 20 days and 21 days or later after vaccination.

People who were vaccinated with the first dose were supposed to be healthier than non-vaccinated people at the initial stage of the immunization program. However, as the vaccination was promoted, high-risk people began to receive vaccination. Among such people, there might have been many

Figure 8: Summary of trend in mortality rates of COVID-19, non-COVID-19-related deaths, and all-cause mortality rates



people who died within 20 days of the first dose, or died 21 days or later after the first dose, while they avoided the second dose because they had health problems after the first dose.

At least, the avoidance of the second vaccination is exactly the phenomenon of frailty-exclusion bias. Moreover, there is a possibility that substantial part of avoidance was due to health problems caused by adverse effects of the vaccines.

This has been clearly observed in deaths 21 days or later after the second vaccination since the administration of booster shots began.

6) Mortality rates of COVID-19 and non-COVID-19-related deaths, and all-cause mortality rate (by the number of doses)

Finally, trend in mortality rates of COVID-19, non-COVID-19-related deaths, and all-cause mortality rates are summarized by the number of doses in **Figure8**.

This article pointed out that healthy vaccinee effect (frailty-exclusion bias) has clearly influenced mortality rates of non-COVID-19-related deaths. Similar influence can be observed in mortality rates of COVID-19, and thus all-cause mortality rates, in which the former and the latter are combined.

Mortality rates of COVID-19 in the vaccinated seem to be markedly lower than that in the non-vaccinated. However, it should be noted that the mortality rates in the non-vaccinated are overestimated by about 2 times, and the mortality rates in those who received 2 doses are underestimated by one-fifth.

Conclusion

The mortality rate of non-COVID-19-related deaths, which vaccine does not reduce, was 0.2-fold of the expected age-adjusted mortality rate in full vaccinated. It was 1.8-fold in the non-vaccinated, and 2.6-fold in those who had received 1 dose.

The reasons why the mortality rate was lower in the former is because they had been very healthy and could receive 2 doses as they had no problem after the first dose. Mortality rates in the non-vaccinated and those who had received only one dose were high because the former originally had health problems, and the latter may have had experienced severe adverse reactions after the first dose, and this contributed to high mortality rate of non-COVID-19-related deaths. These indicate robust healthy vaccinee effect with SARS-CoV2 vaccine.

References

1) MedCheck Editorial Team. COVID-19 vaccine : Myocarditis mortality rate rises, especially among people in their 20s and 30s. Med Check 2022 : 22 (101) : 70-72.
2) Hama R. Web Med Check No198 (2021.12.28) Benefits and Harms of HPV Vaccines - Record of Hama's lecture at "Japanese foundation for Sexual Health Medicine" is released: https://www.npojip.org/sokuho/211228.html
3) MedCheck Editorial Team. Resuming HPV vaccination is very dangerous. Med Check in English 8(23): 3-10 https://www.npojip.org/english/MedCheck/Med%20Check%20TIp-23-2022-04.pdf
4) MedCheck Editorial Team. Symptoms after HPV vaccine: typical "frailty exclusion bias" in Nagoya City study. Med Check in English 2(5): 18-21
5) MedCheck Editorial Team. The core principle for "Medical Research Methods" : Supplement for MedCheck No92 (In Japanese): https://www.npojip.org/chk_tip/2020No92-furoku.pdf
6) Office for National statistics, Dataset : Deaths registered in England and Wales https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsregisteredinenglandandwalesseriesdrreferencetables
7) Our world in Data(OWID)、Coronavirus Pandemic (COVID-19) https://ourworldindata.org/coronavirus#explore-the-global-situation
8) Office for National Statistics, Dataset、Deaths by vaccination status, England https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsbyvaccinationstatusengland

Imbalance in baseline characteristics in molnupiravir trials

This is a letter [1] which summarize the article [2,3] criticizing the serious flaw of molnupiravir trials by MedCheck editorial team and was published as a letter to the editor of BMJ. It is a free access article and we introduce in this issue of MedCheck in English.

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MOLNUPIRAVIR'S PREMATURE AUTHORISATION

Imbalance in baseline characteristics in molnupiravir trials

Rokuro Hama *medical doctor*

Brophy emphasises the dangers of making decisions based on a single prematurely terminated trial.[1] The molnupiravir trials have several more problems[2,3]:

- The risk of hospital admission or death associated with molnupiravir was not significant in the all randomised population when adjusted for sex (hazard ratio 0.69, 95% confidence interval 0.48 to 1.01).
- Molnupiravir may worsen covid-19 outcomes after the interim analysis—simply calculating the rate of hospital admission or death in the population of participants who were included in the final analysis but not the interim analysis shows that the molnupiravir group had a non-significant higher risk (6.2%) than the placebo group (4.7%).
- The Move-Out trial has serious imbalances in baseline risk factors that favour molnupiravir. Patients with chronic obstructive pulmonary disease were assigned at a significantly lower rate to the molnupiravir group (odds ratio 0.31, P=0.0043).[4] The sum of the percentages of the participants with risk factors other than obesity was significantly lower in the molnupiravir group (43.4%) than in the placebo group (51.8%) (OR 0.71, P=0.019). With restriction to four risk factors (diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and active cancer), risk was almost 40% lower in the molnupiravir group (OR 0.61, P=0.0043).[4] These findings suggest that blinding might have been broken before the interim analysis.
- Significant imbalances (except obesity) were also observed in the all randomised population (OR=0.79, P=0.031[4]), which raises doubts about fair randomisation.
- Contradictory results were seen in moderate to severe covid-19. In subgroup analysis, molnupiravir seemed significantly effective in patients with moderate covid-19 and the effect size was greater than in those with mild covid-19.[5] But two randomised controlled trials targeting moderate covid-19 have been terminated because of futility.[6]
- The Move-In trial also has a serious imbalance in severity of covid-19 at baseline. Patients with score 6 covid-19 (admitted to hospital and given oxygen by non-invasive ventilation or high flow therapy) were significantly less common in the molnupiravir groups (2.3%) than in the placebo group (8.0%) (OR 0.27, P=0.025). But a non-significant higher risk of death (6.0%) was reported compared with placebo (2.7%) (OR 4.69, P=0.105). The ratio of mortality OR to OR of baseline score 6 was 17.38 (95% confidence interval 1.6 to 188.8) by Kolassa's method.[7]
- Molnupiravir has been associated with irreversible myelosuppression in dogs[5] and with DNA damage, bone marrow toxicity, and mutations in humans.[8] Were the deaths observed in the Move-In trial[3] associated with bone marrow toxicities?

Full clinical study reports of antivirals including molnupiravir and remdesivir[9] should be disclosed, and a reanalysis is needed as in the systematic reviews on neuraminidase inhibitors.[10]

Competing interests: None declared.

Full response at: https://www.bmj.com/content/376/bmj.o443/rr.

1 Brophy JM. Molnupiravir's authorisation was premature. *BMJ* 2022;376:o443. doi: 10.1136/bmj.o443 pmid: 35241455
2 Jayk Bernal A, Gomes da Silva MM, Musungaie DB, etalMOVe-OUT Study Group. Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. *N Engl J Med* 2022;386:509-20. doi: 10.1056/NEJMoa2116044 pmid: 34914868
3 Arribas JR, Bhagani S, Lobo SM, etalRandomized trial of molnupiravir or placebo in patients hospitalized with covid-19. *NEJM Evid* 2022;1:EVIDoa2100044. doi: 10.1056/EVIDoa2100044.
4 MedCheck Editorial Team. Antivirals for COVID-19: molnupiravir (Lagevrio). Doubt about efficacy due to serious baseline inbalance. Med Check in English 2022;8:11-16. https://www.npojip.org/english/MedCheck/Med%20Check%20Tip-23-2022-04.pdf
5 Medicines and Healthcare Products Regulatory Agency. Public assessment report national procedure Lagevrio 200mg hard capsules (molnupiravir). https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042560/Lagevrio_Public_Assessment_Report.pdf
6 Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: A systematic review of literature. *Diabetes Metab Syndr* 2021;15:102329. doi: 10.1016/j.dsx.2021.102329 pmid: 34742052
7 Kolassa S. Calculate 95% CI for ratio of odds ratio. https://stats.stackexchange.com/questions/471805/calculate-95-ci-for-ratio-of-odds-ratio
8 Kabinger F, Stiller C, Schmitzová J, etal. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. *Nat Struct Mol Biol* 2021;28:740-6. doi: 10.1038/s41594-021-00651-0 pmid: 34381216
9 MedCheck Editorial Team. Remdesivir (trade name: Veklury). Most likely ineffective for COVID-19. *MedCheck in English* 2020;6:39-45. https://www.npojip.org/english/MedCheck/Med%20Check%20Tip-18-2020-08-21.pdf.
10 Jefferson T, Jones MA, Doshi P, etal. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012;1:CD008965. doi: 10.1002/14651858.CD008965.pub4. pmid: 22258996

Review

Why do vaccine look effective?

Another evidence of healthy vaccinee effect

Translated from Web Med Check (in Japanese) No 205. 30 August 2022

Med Check Editorial Team

Abstract

- In spite of frequent inoculation of SARS-CoV-2 vaccine, the Omicron variant epidemic has progressed world widely, and monoclonal antibody products are all ineffective to this variant except one which is unavailable in Japan. These suggest that the vaccine is ineffective for prevention of COVID-19.
- However, vaccination is being promoted based on epidemiological studies in which authors claim that vaccine is effective to reduce COVID-19, especially severe cases by more than 90%.
- Analysis by MedCheck team using the data from the UK statistics revealed the presence of a healthy vaccinee effect (frailty exclusion bias) on non-COVID-19 death in SARS-CoV-2 vaccine users as compared to the unvaccinated (p24 in this issue).
- This article analyses the data of the epidemiological survey from Israel, and found that on the day of vaccination, the vaccinee had lower incidence of COVID-19: asymptomatic infection by 38%, symptomatic infection by 60%, hospitalised COVID-19 by 73%, severe COVID-19 by 83% and death due to COVID-19 by 87%. These are the results simply due to the fact that the vaccinees were healthier than the unvaccinated.
- Reduction of severity by 80% to 90% in epidemiological surveys may simply be the results of healthy vaccinee effect. We should not be fooled by experts' explanations.

Keywords:

SARS-CoV-2 vaccine, COVID-19, asymptomatic, symptomatic, hospitalisation, severe COVID-19, death, epidemiological study, frailty exclusion bias.

Introduction

The SARS-CoV-2 vaccine is almost ineffective against COVID-19 infected by the SARS-CoV-2 Omicron variant that has caused a global pandemic from the end of 2021 to the end of August 2022. In Singapore, the booster vaccination rate reached 70%, but at its peak of epidemic, 40,000 people (equivalent to 0.8 million for the Japanese population) were confirmed having COVID-19 in one day. In South Korea as well, 0.62 million people (1.5 million for Japanese population) had COVID-19 in one day at the peak, although 63% of the population had received booster dose [1]. Now one in 2.2 people had been confirmed having COVID-19 in Korea. These suggest that the vaccine is ineffective against the Omicron variant.

Ineffectiveness of almost all monoclonal antibody products on the Omicron variant [2-4] also suggest that the SARS-CoV-2 vaccine is ineffective against the Omicron variant, because antibody products were produced as the monoclonal antibody of original SARS-CoV-2 (Wuhan) strain and SARS-CoV-2 vaccines were also produced to induce antibody of original SARS-CoV-2 (Wuhan) strain.

However, epidemiological studies have reported high effectiveness even on the Omicron variant [5-7]. In Japan, it has been reported that vaccine effectiveness is nearly 90% against Delta variant infection, approximately 50% after the second dose, and 74% after the third dose against Omicron variant infection, showing high effectiveness [7].

In particular, vaccine effectiveness is reportedly 99% (Delta variant) and 95% (Omicron variant) in severe cases, including fatal cases. Based on such data, many countries still strongly recommend vaccination.

Although the situation of the epidemic suggests that the SARS-CoV-2 vaccine is not effective as described above, the epidemiological surveys show apparent effectiveness even on the Omicron variant. One of the most important reasons for this discrepancy may be because observational studies do not take "healthy vaccinee effect" (p 24 of this issue) into account.

This article presents the results of an analysis of epidemiological study from Israel: although the vaccine does not work on the day of vaccination, the results show that the vaccinee's incidences of asymptomatic infection, symptomatic infection, hospitalization, severe disease and death were reduced by 38%, 60%, 73%, 83%, and 87%, respectively. We will explain how these data were obtained from the original paper and will discuss what these mean.

Israel survey

A nation-wide cohort study to evaluate the effectiveness of the SARS-CoV-2 vaccine was conducted in Israel [8]. About 600,000 people each were selected from vaccinated and non-vaccinated population during the period from 20 December 2021 to 1 February 2021. The vaccine effectiveness was assessed by SARS-CoV-2 infection at day 7 or later after the second dose of vaccine, and it was 92% for documented infections, 94% for symptomatic COVID-19, 87% for hospitalised COVID-19, and 92% for severe COVID-19. Effectiveness for death was reportedly not assessed.

Fewer illnesses from the day of inoculation

In the supplementary material of the report, precise life tables are reported, including the number at risk, the number of events, the number censored by daily basis, by vaccination status (vaccinated and unvaccinated) and by event type (documented SARS-CoV-2 infection, symptomatic COVID-19, COVID-19 hospitalisation, severe COVID-19 and death due to COVID-19)from the day of vaccination (day 1) to day 44. The incidence rate of "asymptomatic SARS-CoV-2 infection" (/100,000 person-days (pd)) was calculated by the numbers of difference between all documented SARS-CoV-2 infection and symptomatic COVID-19.

The daily incidence rates of event (/100,000 pd) comparing the vaccinated and the unvaccinated for 1 week after the first inoculation are shown in the Figure 1 (asymptomatic SARS-CoV-2 infection: Figure 1 A and symptomatic Covid-19: **Figure 1 B**).

Incidence rates are lower in the vaccinated group than the unvaccinated group on day 1 especially of symptomatic Covid-19.

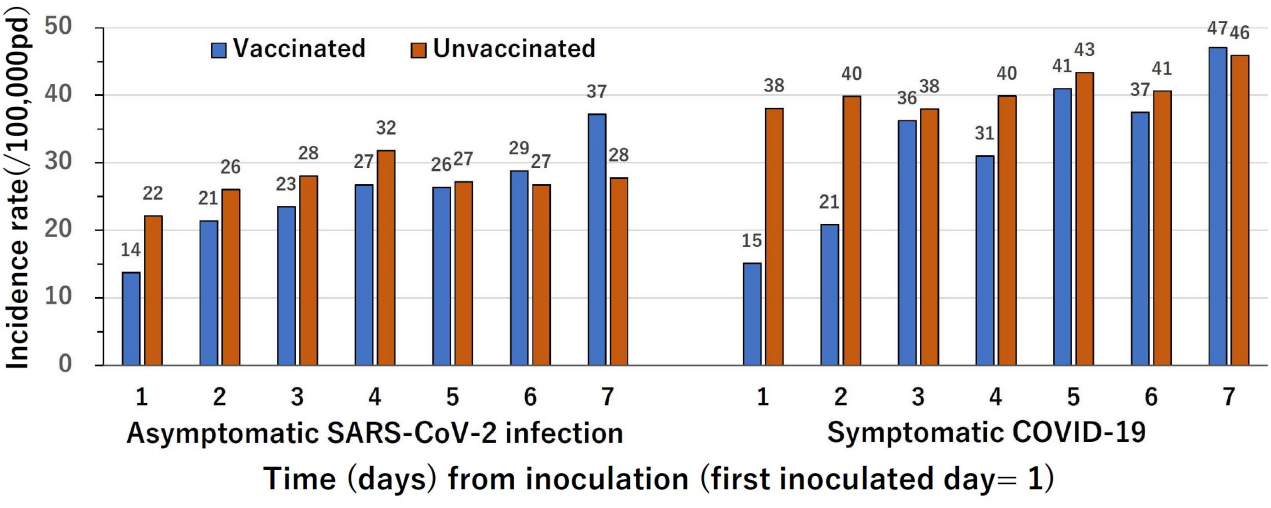
Incidence rates of asymptomatic infection (/100,000 pd) were 14 and 22 for the vaccinated and unvaccinated groups, respectively (difference is 8/100,000 pd), while those of symptomatic COVID-19 were 15 and 38, respectively (difference is 23/100,000 pd). These indicate that vaccinated group has lower risk of SARS-CoV-2 infection.

Risk increases until second week

In the unvaccinated population, incidence rate (/100,000 pd) is almost consistent at around 25 for asymptomatic infection and 40 for symptomatic COVID-19.

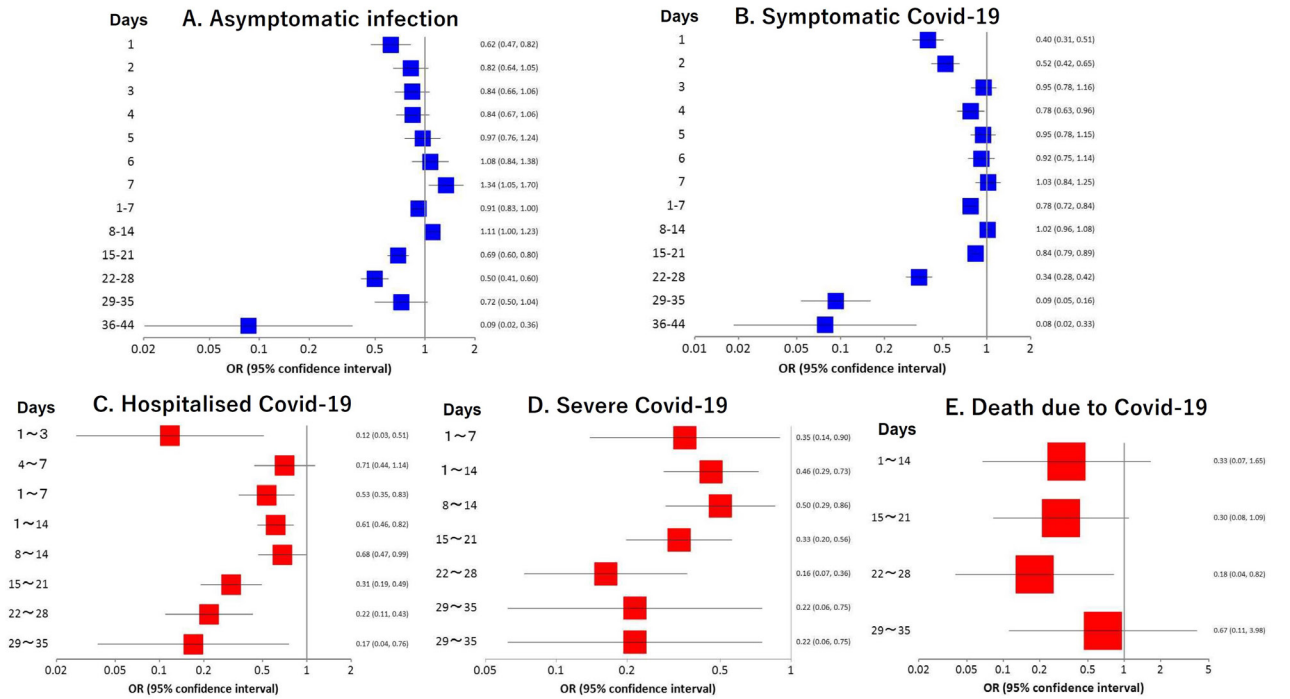
In the vaccinated population, incidence is the lowest on day

Figure 1: Daily incidence rates of COVID-19 by vaccination status up to day 7



Calculated by MedCheck team from the data in the supplementary Table S7 in ref [8].

Figure 2: Odds ratios of COVID-19 by time from first inoculation by severity



Calculated by MedCheck team from the data in the supplementary Table S7 in ref [8].

1 and the difference is the largest on day 1. It increased and almost reached the incidence of the unvaccinated on day 5 and day 6. On day 7, it exceeded that of the unvaccinated for asymptomatic infection (37 and 28, difference was – 9/100,000 pd) (Figure 1A). For symptomatic COVID-19, it slightly exceeded unvaccinated population on day 7 (47 and 46, difference was –1/100,000 pd) (Figure 1 B).

Odds ratios of COVID-19 by time from first inoculation by severity

Figure 2 shows odds ratios (ORs) of the vaccinated to the unvaccinated by time (days) from the first inoculation of vaccine, by severity of SARS-CoV-2 infection: **A. asymptomatic infection, B. symptomatic COVID-19, C. hospitalised COVID-19, D. Severe COVID-19 and E. Death due to COVID-19.**

On day 1, OR was 0.62 (95% CI: 0.47, 0.82) for asymptomatic infection and 0.40 (0.31, 0.51) for symptomatic COVID-19 (Figure 2A and 2B). Both ORs were statistically significant.

Odds ratio increased as the day passed and exceeded 1.0 and reached 1.34 (1.05,1.70) for asymptomatic infection and 1.03 (0.84, 1.25) for symptomatic COVID-19 on day 7.

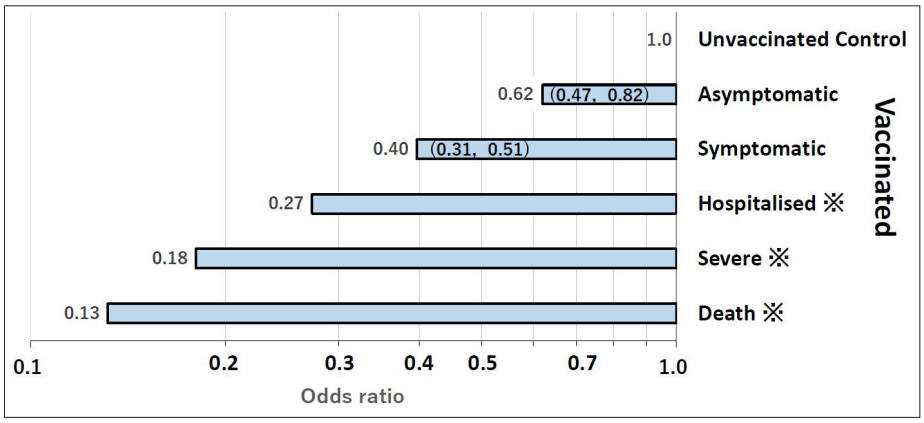
Average odds ratio of the first one week for asymptomatic infection was 0.91 (0.83, 1.00) and that of the second week was 1.11(1.00, 1.23) (Figure 2A). For symptomatic COVID-19 average odds ratio was 0.78 (0.72, 0.84) and 1.02 (0.96, 1.08), respectively (Figure 2B).

Estimation of odds ratio on day 1 for hospitalisation, severe case and death

Let's take a look at the odds ratios of hospitalised COVID-19 or other severer COVID-19 patients. In the unvaccinated population, hospitalisation occurred from day 1, but in the vaccinated population, hospitalisation did not occur until day 3. Severe COVID-19 occur from day 3 in the unvaccinated, while it did not occur until day 6 in the vaccinated. There was 1 death on day 7, and 6 deaths by day 14 in the unvaccinated, but 0 by day 10 and only 2 deaths in the vaccinated population by day 14 (1 each on day 11 and 14).

According to the raw data, the odds ratio for hospitalization is 0. Because the number of severe COVID-19 and death due to COVID-19 was 0 in both groups (vaccinated and unvaccinated), OR cannot be calculated. Therefore, OR for the hospitalised, severe cases and death due to COVID-19 on day 1 was estimated by the following formulas:

Figure 3: Odds ratio of COVID-19 on day 1 of vaccination



Calculated by MedCheck team from the data in the supplementary Table S7 in ref [8]. ※ : Since no event was recorded on day 1 of inoculation for the hospitalized, severe case or death due to Covid-19. Odds ratio of these events on day 1 was estimated from the data as described in the text. Since it is impossible for the vaccine to be effective from the day of vaccination, this apparent low risk does not mean that the vaccine is effective but that the vaccinated persons are at low risk of disease and death compared to the unvaccinated persons (or vaccinated persons are healthier than unvaccinated individuals), showing "healthy vaccinee effect (or frailty exclusion bias)".

OR (hosp. d1) = OR (hosp. d1-7) ×(OR(sympt.d1)/OR (sympt. d1-7)) (1)

OR (sever.d1) = OR (sever.d1-7) × (OR(sympt.d1)/OR (sympt. d1-7)) (2)

OR(death.d1) = OR(death.d1-14) × (OR(severe.d1)/OR(severe. d1-14)) (3)

(1) OR of hospitalisation on day 1 (OR(HPd1)) is estimated by multiplying the OR of hospitalisation during day 1-7 (OR(HPd1-7)) by the ratio of OR for symptomatic COVID-19 on day 1 (OR(SYd1)) to that of day 1-7 (OR(SYd1-7)).

(2) For severe COVID-19, odds ratios on day 1 was estimated by the similar method as (1).

(3) Odds ratio for death due to COVID-19 on day 1 (OR(D d1)) was estimated by multiplying the OR of death during day 1-14 (OR(D d1-14)), by the ratio of OR for severe COVID-19 on day 1 (OR(SVd1))(calculated by the formula (2)) to that of day 1-14(OR(SVd1-14)).

The severer the symptoms, the lower the odds ratio

Figure 3 shows the results. The ORs for asymptomatic infection and symptomatic COVID-19 on day 1 odds ratios and their 95% confidence intervals (95%CI) for asymptomatic infection, symptomatic COVID-19 that are accurately calculable by raw data are 0.62 (0.47, 0.82) and 0.40 (0.31, 0.51), respectively. However, 95%CI is not accurately calculated and it is not shown for hospitalisation, severe disease and death.

Vaccinees showed significantly lower OR of COVID-19 on the day of vaccination (on day 1) than the unvaccinated. Moreover, the OR decreased as the symptom became severer: OR for asymptomatic infection, symptomatic COVID-19, hospitalized COVID-19, severe COVID-19 and death due to COVID-19 are 0.62, 0.40, 0.27, 0.18 and 0.13, respectively (Figure 3).

These data do not indicate the effectiveness of vaccine, but if this is described in terms of "vaccine effectiveness", asymptomatic infections were reduced by 38%, symptomatic infections by 60%, hospitalization by 73%, sever COVID-19 by 82%, and death due to COVID-19 by 87%.

Since it is impossible to have such an effect at day 1 after vaccination, this apparent "effectiveness" simply indicates that the vaccinated persons were much healthier than unvaccinated persons. It clearly creates the illusion that the vaccine works very well especially on severe cases, unless "healthy vaccinee effect (frailty exclusion bias)" is taken into account.

Conclusion

Incidence rate of SARS-CoV-2 infection was lower in the vaccinated population on the day of inoculation: Asymptomatic infection by 38%, symptomatic infection by 60%, hospitalised COVID-19 by 73%, severe COVID-19 by 83% and death due to COVID-19 by 87%. These are the results simply due to the fact that vaccinees were healthier than the unvaccinated. Reduction of severity by 80% to 90% in epidemiological surveys may simply be the results of "healthy vaccinee effect". Hence, we should not be fooled by experts' explanations based on the epidemiological study which ignored "healthy vaccinee effect".

References

1) Med Check editorial team. Editorial "Vaccine cannot end the Covid-19 pandemic" MedCheck 2022: 22(101): 55 (in Japanese)
2) Bruel T, Hadjadj J, Maes P, et al. Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. Nat Med 2022. https://doi.org/10.1038/s41591-022-01792-5
3) Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. Nature 2022;604:553-6.
4) Takashita E et al. Efficacy of Antibodies and Antiviral Drugs against Omicron BA.2.12.1, BA.4, and BA.5 Subvariants. NEJM 2022; 387:468-470 DOI: 10.1056/NEJMc2207519
5) Buchan SA, Chung H, Brown KA, et al. Effectiveness of COVID-19 vaccines against omicron or delta infection. medRxiv. 2022. doi:10.1101/2021.12.30.21268565
6) Hansen CH, Schelde AB, Moustsen-Helm IR, et al. Vaccine effectiveness against SARS-CoV-2 infection with the omicron or delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study. medRxiv. 2022. doi:10.1101/2021.12.20.21267966 24
7) Arashiro T, Arima Y, Muraoka H. et al . COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection during Delta-dominant and Omicron-dominant periods in Japan: a multi-center prospective case-control study (FASCINATE study). Clin Infect Dis. 2022. PMID: 35918782
8) Dagan N, Barda N, Kepten E et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. NEJM. 2021 Apr 15;384(15):1412-1423. doi: 10.1056/NEJMoa2101765.PMID: 33626250
9)Med Check editorial team. Web MedCheck No 205 (Aug 30) Why vaccine looks like effective to prevent severe Covid-19 ? -Another evidence of Healthy vaccinee effect.

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