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Editorial

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Review

To be vaccinated, or Not ? Points You should Know

SARS-CoV-2 vaccines Doubles the Risk of COVID-19!

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Unacceptable Proposal: Experts ignored clinical trials

Translated from the Editorial in Med Check(in Japanese) Nov. 2022 ; 22 (104) : 127

Shionogi & Co., Ltd. has developed ensitrelvir (Zocova R), which is expected to be the first SARS-CoV-2 therapeutic agent developed in Japan, and applied for approval under the emergency approval system in July. As a result of the review, a reduction in SARS-CoV-2 viral load was observed compared to placebo, but there was no significant difference in alleviation of clinical symptoms such as fever, headache, sore throat, and cough. Therefore, it was determined that the efficacy could not be estimated, and the approval was postponed. We also think that it was a natural decision

In response to this postponement of approval, on September 2, 2022, the Japanese Association for Infectious Diseases and Japanese Society of Chemotherapy jointly announced "Emergency medical care is collapsing due to the seventh wave of the corona pandemic. Symptomatic medicines are also in short supply, and there is widespread public concern about accessibility to proper medical care. Japan's Ministry of Health, Labor and Welfare (MHLW) should seriously consider applying the emergency approval system to antiviral drugs that reduce viral load or expanding the indications of approved antiviral drugs as soon as possible. We urge the MHLW to make a decision."Ensitrelvir is a drug whose effectiveness has not even been confirmed. Nevertheless, they said that it should be approved because it can be expected to have an effect on clinical symptoms based only on the antiviral effect that is just a part of the results of clinical trials. Their statement is unscientific and ignores clinical trial results. Moreover, two executives of the Japanese Association for Infectious Diseases and one executive of both societies are doctors involved in the clinical trials, leading to an issue of conflicts of interest. In addition, it is not surprising that the general public thinks that the MHLW should approve it as soon as possible because the academic societies, which are groups of medical experts, said so. Their remarks may mislead public opinion. The role of academic societies, which are groups of experts, should be to disseminate correct information based on scientific and objective facts, but it seems that they are not fulfilling that role at all.

This issue evaluates vaccines against the Omicron BA.1 strain, which has been reported in the media to be administered after a shorter interval than originally approved. After reading this, you will be able to decide if you should also get a new BA.5 strain vaccine. We also would like our readers to spread the correct information obtained from this bulletin to their families and acquaintances.

Note : New approval system implemented from May 2022. Under this system, even before the completion of regular clinical trials, if the harm is not presumed to be too great to make the substance of no use, and if efficacy is presumed, manufacturing and marketing will be provisionally approved.

To Be Vaccinated or Not? Points You should Know

SARS-CoV-2 Vaccines Doubles the Risk of COVID-19!

Translated and revised from Med Check(in Japanese) Nov. 2022 ; 22 (104) : 128-139

Med Check Editorial Team

Four points you should know to assess safety and effectiveness of vaccines

Safety and effectiveness of "SARS-CoV-2 vaccines" are now at the forefront of public attention more than ever before. Our conclusion is that they are not effective at all, but may increase COVID-19 by two times and have only harm. SARS-CoV-2 vaccination should be avoided as the data suggest.

In this short series on vaccines, we will discuss safety and effectiveness of eachl vaccine. However, let us first think about important 4 points for evaluating safety and effectiveness of vaccines, which are often ignored or neglected by regulators and academic authorities, focusing on "SARS-COV-2 vaccines".

(1) Harm should be minimal, and benefit should outweigh harm: the balance depends on the situation

First of all, a vaccine is given to people who are not infected with the target infection, i.e., healthy people. Therefore, the harm should be minimal, and benefit should outweigh the harm. This is the major prerequisite. Moreover, the evaluation is not universal, but contextual: it changes as time and location (country, region) change, and thus it should be always reviewed and revised.

(2) Types of vaccines and whether they contain adjuvant or not

There are various types of vaccines. This article explains about adjuvants (immune enhancer). Adjuvants essentially have harms because they become effective only when they damage the tissues. When evaluating harms in clinical trials, it is important to determine whether or not adjuvants are used in the control.

(3) Beware of healthy vaccinee effect (bias)

People who have fever on the day of vaccination or those who are critically ill would avoid vaccination. Therefore, vaccinated people have better original health status than unvaccinated people. This bias is called **"healthy vaccinee effect"**. In almost all post-marketing observational studies, this bias is ignored, leading to the distorted evaluation of effectiveness and harm of vaccines. As a result, severer the cases, the more effective and less harmful, ineffective vaccines would appear to be.

(4) The doctrine of original antigenic sin

SARS-CoV-2 and influenza viruses are characterized by a high rate of mutation. When a human is infected with such a virus (hereafter X_0) for the first time, strong antibodies are developed against it (X_0). Later, if the body is exposed to the mutated virus (X_1), it would fight X_1 with the antibodies against X_0, and thus it would be infected with X_1. Even if vaccines for a mutant strain is inoculated, the body have already developed the antibodies against the original strain which it was exposed to by the first vaccination, and only weak antibodies would be produced against the mutant strain. Therefore, the vaccination would be ineffective. This phenomenon is called "the doctrine of original antigenic sin". It was clearly proven in the case of vaccines targeting the Omicron variants.

Conclusions: SARS-CoV-2 vaccines not only have no proof of efficacy against Omicron variants but also may increase risk of COVID-19 by two times, and have serious harms. The use of the SARS-CoV-2 vaccines should be immediately suspended.

Keywords: SARS-CoV-2 vaccine, adjuvant, healthy vaccinee effect, original antigenic sin, omicron variant, mutant strain

Introduction

Med Check No. 52 and No. 53 featured articles titled as "Let's learn more about vaccines" [1,2]. In addition, Med Check No.69 explained about vaccines, including the history, in another article titled as "To Vaccinate or Not?" [3]

The question many people may have now is whether or not to be vaccinated with vaccines for the Omicron variants. Is the vaccine effective and safe? This question is at the forefront of public attention more than ever before.

As mentioned in the beginning, Omicron adapted bivalent vaccines are not effective at all, but harmful, and there are solid data to prove this. This article explains about those data in the Q & A between a reader and an editor. "Reader" represents you who are reading this article now.

(1) "Harm-benefit balance" depends on the situation

Reader: You mentioned that whether benefit outweighs harm or not depends on "time and location (country/region)". What do you actually mean by this?

Editor: Let me explain with an example of COVID-19. The clinical trial which concluded that the preventive effect of the vaccine was 95% was conducted in the U.S. between the end of July and middle of November, 2020. This coincides with the end of the second wave and the beginning of the 3rd wave. During this period, 1 in 50 persons were infected with COVID-19, and 1 in 3000 died from the disease.

As it was the time of such an epidemic situation, SARS-CoV-2 vaccines prevented the symptomatic COVID-19 by 95% as well as aggravation during the most effective period (1.5 months after the second dose) [4-6]. One hundred ten persons had to be vaccinated to prevent 1 case of COVID-19.

Reader: During this period, there were not so many COVID-19 patients in Japan.

Editor: Yes, that's right. During this period, only 1 in 1500 persons was infected, one-thirtieth of that in the U.S., and 1 in about 150,000 persons died from COVID-19. In order to get the same number of COVID-19 as that in the U.S. clinical trial, 600,000 participants had to be enrolled each in vaccine and placebo groups. It is impossible to involve such a large number of participants. During this period, 3500 persons had to be vaccinated to reduce 1 case of COVID-19 in Japan.

Reader: Is there a post-marketing surveillance study?

Editor: Yes. **Fig. 1A** and **Fig. 1B** are both original analysis by Med Check based on the data from Israel on the risk of Pfizer's vaccine for having COVID-19 [7,8]. **Fig. 1A** is based on the survey for the first two doses of SARS-CoV-2 vaccine compared with unvaccinated [7]. **Fig. 1B** was based on that for the 4th dose compared with those with only 3 doses [8]. These figures showed the risk of COVID-19 by the number of days after vaccination.

Both **Fig. 1A** and **Fig. 1B** showed the result after adjusting for the original health status of vaccinated and unvaccinated individuals (healthy vaccinee effect). This adjustment is explained more in detail in the section **(3)** healthy-vaccinee effect. In other words, the risk of COVID-19 is shown as adjusted risk ratio (adRR) by the number of days after inoculation. Are you with us so far?

Reader: You mean that original health conditions of the vaccinated and the unvaccinated were adjusted and equalized to compare the risk?

Editor: Yes, that's right. **Fig. 1A** showed the risk after the first and second dose and Fig. 1B showed the risk after 4th dose compared with those with 3rd dose. In both **A** and **B**, ■ or ■ are on the right side of 1 until day 30 after vaccination. This means that the vaccinated were infected with SARSCoV-2 more frequently than the unvaccinated; vaccine did not reduce, but increased COVID-19 for a while after vaccination.

Reader: How did it happen?

Editor: We will address this issue in the section **(3)** healthy vaccinee effect (bias) later. In Fig. 1A, adjusted RR ■ (aRR) is on the left side of 1 finally after days 31-36 suggesting that the risk of COVID-19 infection declined after 31 days of vaccination. Risk ratio between day 34 and day 36 was 0.12. This means that the risk was 0.88 lower than 1.00: the risk was reduced by 88%. In other words, the vaccine effectiveness finally reached 88% 1 month after the vaccination.

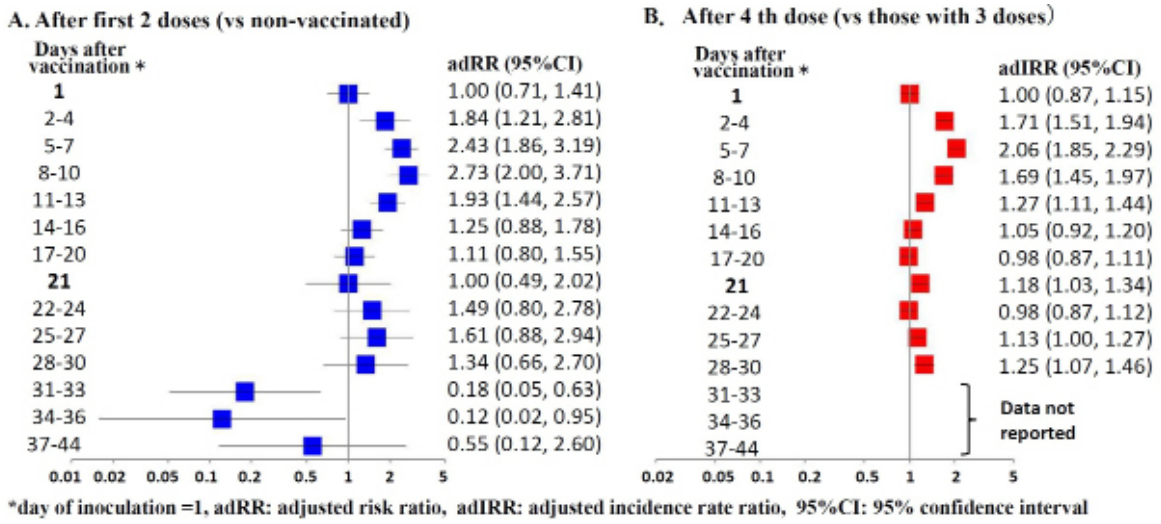
Reader: You mean that it doesn't work until 1 month after the vaccination?

Editor: That's right. This study was conducted between December 20, 2020 and February 1 2021, in the middle of the Alpha strain pandemic in Israel. If converted to the Japanese population, average 850,000 persons would have been infected with COVID-19 every day.

Reader: It was just like in the Omicron wave in Japan.

Editor: Yes, exactly. In February 2021, Israel had entered the pandemic where 7 in 100 persons had already been infected. Considering simply the state of infection, the benefit of the vaccine against the original strain (**Note 1**) also might have

Figure 1: Risk of asymptomatic infection/symptomatic COVID-19 by SARS-CoV-2 vaccines



(A) Risk of symptomatic COVID-19 after the first 2 doses is compared with the unvaccinated and shown by the number of days after vaccination. The risk at days 1-20 is adjusted by the risk at day 1 (risk ratio=0.40), and the risk at day 21 and thereafter by the risk at day 21 (risk ratio=0.22). The risk was reduced significantly at day 31 and thereafter as compared with the reference date (day 21). At days 34-36, the risk was 0.12. Based on this the vaccine effectiveness against symptomatic COVID-19 can be estimated as 88% (1-0.12). However, (B) the risk never became lower than that on the first day after the 4th dose. There is no data at day 31 and thereafter when the effectiveness was shown in (A). The significant increase at days 28-30 is probably due to harms of the vaccines. See Suppl. Fig 1B which shows significant increased risk after day 36 up to 6 months.

outweighed the harm in Israel.

Reader: At that time, how many people were infected with COVID-19 in Japan?

Editor: By the end of 2021, less than 1 in 100 persons had been infected. The "benefit" for the vaccine was touted as a preventive effect against COVID-19 infection. But in a country with low infection rates, such as Japan, harm of the vaccine was highly likely to outweigh the "benefit"; thus vaccination was not necessary the best remedy. This was discussed in detail in MedCheck in English No. 20 [6].

Note 1: SARS-CoV-2 first spread from Wuhan, China. Both Pfizer's and Moderna's vaccines are called "original vaccines" as they were designed to produce spike protein found in the original virus "SARS-CoV-2". Neutralizing antibodies against the original virus are called "original antibodies".

SARS-CoV-2 vaccines are not effective at all now

Reader: In Fig. 1B, the risk stays higher than 1 after 4th dose.

Editor: Yes, Fig. 1B is based on the study in Israel conducted during the Omicron pandemic from 3 January to 18 February 2022. The study compared the infection risk of those who received 4th dose of vaccine against the original strain with those who received their 3rd dose four months earlier. If the infection rate in Israel during this pandemic was converted to the Japanese population, it would have been infected about over 600,000 persons per day.

In this figure, healthy vaccinee effect (bias) was adjusted, the risk did not become lower than that on the first day of vaccination. In Fig. 1A, the risk started to decrease after day 31 from vaccination, but in Fig. 1B, no such a trend was observed. It can therefore be concluded that the 4th dose of vaccine was not effective. Furthermore, the increased risk between day 28 and day 30 was significant, suggesting that the 4th dose was only harmful [Note A].

Note A (added after publication of Issue No.104):

Suppl. Fig. 1A shows the risk of COVID-19 after 4th dose of Pfizer's vaccine compared with those who received the 3rd dose four months earlier based on the combined data (incidence rate ratio: IRR between day 1 to day 30 after inoculation) from the nation-wide survey in Israel [8] and the data (hazard ratio: HR between day 7 to day 181 after inoculation) from the prospective cohort study involving health care workers in Israel [25].

Suppl. Fig. 1B showed the risk of COVID-19 adjusted by the incidence rate ratio (IRR) at the day 1 of inoculation (IRR=0.45) in ref [8]. IRR (0.48) for day14 to 30 day (median 22) in ref [8] is just the same as HR (0.48) for d7 to d35 (median 21) in ref [25]. Hence after adjustment by 0.45(0.41 to 0.50), adHR reached 2.27 (95%CI: 1.79 to 2.87) during 103 to 181 days after 4th dose (median: day 142). This indicates that SARS-CoV-2 vaccine increased the risk having COVID-19

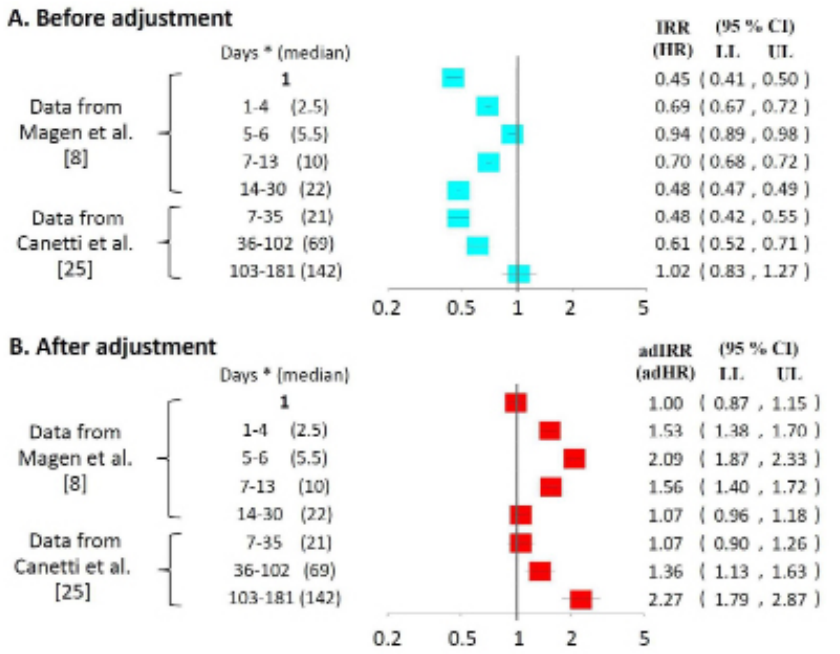
by more than double.

This phenomenon, increased risk of COVID-19 in vaccinees, especially after 4 weeks and thereafter of post-4th dose should be considered as a result of "antibody-dependent enhancement (ADE)" caused by the SARS-CoV-2 vaccine.

(2) Types of vaccines and adjuvants

Types of vaccines are explained in Med Check No.92 [9]. This issue shows **Fig. 6** to categorize various types of vaccines, including SARS-CoV-2 vaccines as well as other vaccines, and explains the categorization in the column. Here, it focuses on adjuvants.

Suppl. Figure 1: Risk of COVID-19 # after 4th dose of Pfizer vaccine compared with only 3 doses



*: day of inoculation =1, adRR: adjusted risk ratio, adIRR: adjusted incidence rate ratio, 95%CI: 95% confidence interval

#: asymptomatic infection or symptomatic COVID-19 for data of day 1 to day 30 [8] that are the same as those in the Fig 1B. COVID-19 data for day 7 to day 181 [25] are on the SARS-CoV-2 infection not particularly defined as asymptomatic or symptomatic.

Adjuvants are toxic and damage the tissue

Med Check No.53 [2] explains about adjuvants in detail. This article quickly reviews what adjuvant is.

Reader: First of all, what is an adjuvant?

Editor: In addition to antigens, an adjuvant is added to vaccines to enhance immune response. In other words, it is an immunostimulant.

Reader: It is added to any vaccines?

Editor: No, presence or absence of adjuvants in each vaccine will be discussed in the next issue.

Reader: Why do some vaccines contain adjuvants and some don't?

Editor: Depending on the types of vaccines, vaccination of antigens alone is not enough to create antibodies in the body. This is probably because in order to induce immune reaction, some degree of damage must be done to the body.

When viruses or bacteria enter the body, they release toxin so that they can easily penetrate into the body. In return the body tries to eliminate them by immune response. An adjuvant acts like the toxin, and damages the body to help antigens induce stronger immune response.

Reader: What substances are used as adjuvants?

Editor: The most common adjuvant is aluminum compounds called an "alum" adjuvant. An adjuvant contained in HPV vaccines (so-called cervical cancer vaccine) is a derivative of bacteria toxin (lipid A) of Salmonella. When this is injected with antigens, it injures the body, and leucocytes are attracted to treat it. However, when they treat the adjuvant, they are destroyed and release their genetic information, DNA. Then, DNA binds to protein in the body and acts as a foreign substance, inducing innate immunity to help build antibody.

In other words, substances that damage the body can work as adjuvants, but those that have no toxicity to damage the body cannot work as adjuvants.

Are vaccines with the same harm as adjuvants safe?

Reader: So, adjuvants alone can be harmful to the body?

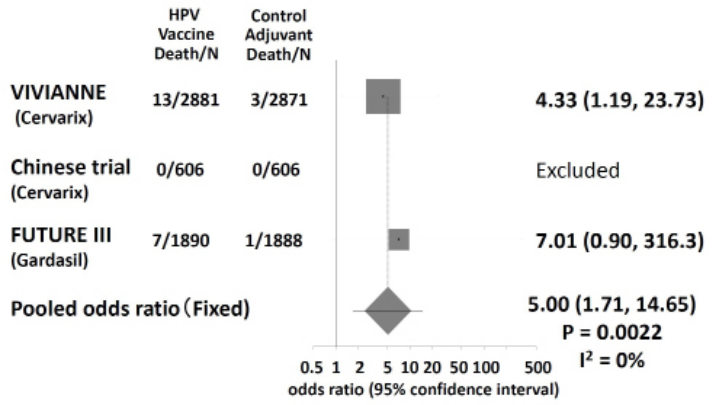
Editor: That's right. In clinical trials of HPV vaccines, Gardasil and Cervarix, an alum adjuvant or a Hepatitis A vaccine with an adjuvant was used as a control. Then, what do you think was the result?

Reader: HPV vaccines contain adjuvants. So, if they are compared with the control which contains only adjuvants….?

Editor: In young women aged 15-24, incidences of adverse events in HPV vaccine group and control group were almost the same. This result provided the basis for the HPV vaccine to be promoted as harmless

Reader: There was no difference in the incidences, but why can you say that the vaccine is safe? An adjuvant itself has

Figure 2:HPV vaccines increase mortality by 5 times in woman aged 25 or older



The figure is reproduced from the reference [10]. If the age is younger and mortality rate is one-fifth in both groups, (13+7) /5=4 persons in HPV vaccine group and (3+1) /5=0.8 persons in adjuvant group. As a result, the number of death is minimal, and there is no significant difference (P=0.32). If death in the control group happens to be 1 person, p value would be 0.69, suggesting no significant difference.

harms, right?

Editor: Yes, it does. However, they are considered to be "safe" because so-called experts have declared so. As mentioned above, even if there was no difference with a harmful adjuvant, it cannot be concluded that the vaccine is safe.

How can we be sure that it is harmful? I would like to explain some points. First of all, temporal change should be investigated. If a substance has no effect on the body, incidence (morbidity) of adverse events which occur newly, such as autoimmune diseases, is supposed to be constant over time. However, in both adjuvant and vaccine groups, the incidence of autoimmune diseases significantly increased within 6 months after vaccination, and decreased over time.

Another way to determine the harm is to compare the incidence rate (morbidity) with that of the same age group in the general population. Incidence rate (morbidity) of multiple sclerosis and ulcerative colitis in both adjuvant and vaccine groups were significantly higher than those of the same age group in the general population [10]. This can be evidence for the harm.

Reader: What were the differences in mortality?

Editor: There was no difference in mortality in women aged 15-24. However, in women aged 25-45, mortality increased by 5-fold over 4 years in the vaccine group as compared to the adjuvant group (Fig. 2) [10]. A substance that in.eases mortality by 5-fold in women aged 25 and above can never be safe for younger women. Because mortality rate is originally low in women aged 15-24, the difference was simply not so marked (See footnote of Fig. 2).

Through the efforts of victims of HPV vaccines and several organizations, including Med-Check, the governmental recommendation of HPV vaccine was once suspended. However, it is very disappointing that the recommendation was resumed.

Reader: By the way, do SARS-CoV-2 vaccines contain adjuvants?

Editor: Takeda Pharmaceutical's Nuvaxovid is a vaccine that contains "full-length spike protein" as an antigen, which is classified as E in Fig. 6 in page **14**. In this vaccine, surfactant is added as an adjuvant. Pfizer's and Moderna's vaccines, which have been used in Japan, contain no substance which is specifically claimed to be an adjuvant. However, lipid components which compose lipid nanoparticles are highly likely to be toxic and may act as an adjuvant. Considering the intensity of the harm of SARS-CoV-2 vaccines, it is reasonable to think that they contain substances which act like adjuvants.

(3) Healthy vaccinee effect (bias)

People who have fever on the day of vaccination or who are critically ill would not be vaccinated.

By appropriately interpreting the report from Israel [8, 25], it can be said that the 4th dose of the vaccine against the original strain was not effective as compared with the 3rd dose (Fig. 1B and Suppl. Fig. 1B). However, this study [8] reports that the vaccine reduced asymptomatic infection by 52%, symptomatic COVID-19 by 61%, hospitalization by 71%, severe cases by 64%, and death by 76% between day 14 and day 30 after vaccination.

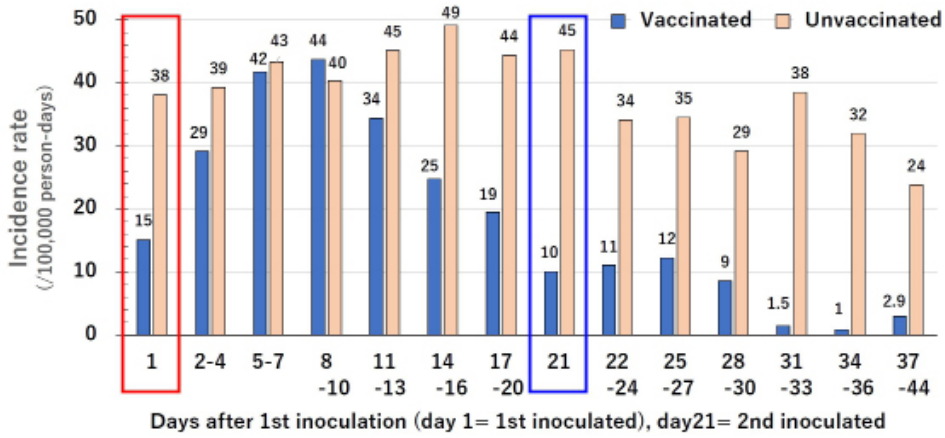
An ineffective vaccine would never prevent about three-fourths of the death. However, if healthy vaccinee effect was not adjusted before calculation, the result can be "cheated without actually lying".

The incidence of COVID-19 per 100,000 persons was only 15 persons in the vaccinated on the day of vaccination while it was 38 persons in the unvaccinated on the day which was equivalent to the day of vaccination (Fig. 3). Risk ratio of the vaccinated to the unvaccinated was 0.40.

Editor: What do you think about the data of the first day (Fig. 3 □)?

Reader: It looks as if the vaccine worked from the day of vaccination.

Figure 3: Trends of incidence rate (/100k) of COVID-19 since first day of inoculation:: comparison of vaccinated and unvaccinated (Nation-wide survey in Israel) [7]



(the incidence on the first day). However, on day 21 (Fig. 3 ☐), it was suddenly halved to **10.** This is statistically significant. On the same day, the incidence in the unvaccinated was **45** (persons per 100,000 person-days).

Trick to make ineffective vaccine appear to reduce death

Editor: Why did it halve?

Reader: Umm…. Why?

Editor: Yes, it really does. Why do you think the incidence in vaccinated people appears to be much lower than that in unvaccinated people?

Reader: Well…because the vaccinated people were healthier?

Editor: Exactly. What if the patient has a fever on the day of the scheduled vaccination?

Reader: They would avoid the vaccination.

Editor: How about those who are critically ill?

Reader: They would not be vaccinated, either. I think people who have some kind of illnesses would avoid vaccination.

Editor: Even if they have an illness, if their condition is stable, many of them would be vaccinated. So more precisely, "people who have had serious illness recently would avoid vaccination". After that, the incidence rate (persons per 100,000 person-days) in the unvaccinated stayed at around 40 (persons per 100,000 person-days), fluctuating along the increase/decrease in infection in Israel. However, in the vaccinated, the incidence rate gradually increased and between day 8 and day 10, it was higher than that in the unvaccinated.

Reader: That is due to a negative impact of the vaccine?

Editor: After vaccination, many people experience fever. When there is fever, it might not be just because of the vaccination, but of COVID-19. When they undergo a test, they might be actually found positive. This is not simply because the number of tests conducted have increased, but because they might have been weakened by fever, and they were infected and developed symptoms. After that, the incidence in the vaccinated gradually decreased. Then, as shown in Fig. 3, between day 17 and day 20, before vaccination of the second dose (☐), the incidence rate was **19**; higher than **15**

Editor: I'll give you a hint. What kind of people were able to receive the second dose?

Reader: Those who had no problem after the first dose. Oh, I see…Among the people who had high fever after the first dose, some would choose to avoid the second dose, right?

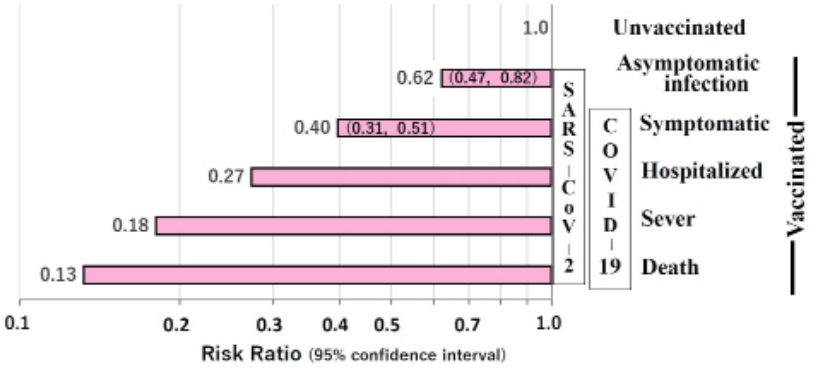
Editor: Exactly. People who received the second dose were even healthier than those who had the first dose. Risk (risk ratio) on the day of vaccination of the second dose is 0.22. It was much lower than the risk in those who had the first dose (0.40).

In Fig. 1A, the risk of COVID-19 on day21 and thereafter were adjusted by that on day 21 (explained below) in addition to the adjustment for day 1 to day 20 by that on day1.

Based on an Israeli study by Dangan et.al [7], the risk in the vaccinated group on the day of vaccination was estimated by severity. Since there was an adequate number of cases of asymptomatic infection and symptomatic COVID-19 from the first day, the risk and 95% confidence interval (95%CI) are directly estimated. However, the risk of hospitalization, aggravation and death was indirectly estimated, and 95%CI was not calculated. The rough estimate of risk was shown in Fig. 4.

If not adjusted by the risk on the first day, the vaccine seems to reduce asymptomatic infection by 38% ((1-0.62) ×100%, hereafter the same calculation method is used), symptomatic COVID-19 by 60%, hospitalization by 73%, severe disease by 82%, and death by 87%. However, vaccines would never be effective on the first day. Therefore, they must be divided by 0.62, 0.40, 0.27, 0.18 and 0.13, respectively, to equalize the risk (health condition) of the vaccinated and unvaccinated groups. Not only the risk ratio on the first day, but the risk

Figure 4: The apparent risk of asymptomatic infection or COVID-19 by severity on the day of inoculation



From the data of Dagan et al. [7], we estimated the risks of SARS-CoV-2 infection in SARS-CoV-2 vaccinees on the day of inoculation: The risk ratio and 95% confidence interval (95%CI) could be directly calculated for asymptomatic infection and symptomatic COVID-19, as events were enough to estimate. However, direct estimation of risk was difficult for COVID-19 hospitalization, severe COVID-19 and death due to COVID-19, because on the day of vaccination, no event was reported in the vaccination group for hospitalization and no event in both groups for severe case and death. Therefore, assuming that the increase in the risk of symptomatic COVID-19 from the date of vaccination to 1 to 2 weeks after vaccination also applied to severe and fatal cases, we estimated the risk ratio at the day of inoculation for hospitalization, severe case and death. Because it was impossible for the vaccine to be effective at the day of inoculation, these low risks in vaccinated people mean that the risk of infection (disease) in vaccinated people is low compared to unvaccinated people. This means that vaccinated people were healthier than unvaccinated people. It should be noted that the severer the disease, the stronger vaccine apparently works.

ratio thereafter should also be divided likewise.

Reader: Wait a minute. Why do you have to divide?

Editor: The health conditions on the day of vaccination are different in the vaccinated and unvaccinated groups, right? Suppose the risk (risk ratio) of becoming ill in the vaccinated is 0.5. In other words, the risk of COVID-19 in the vaccinated group is half (0.5) of that in the unvaccinated group. Therefore, in order to equalize the health conditions of the 2 groups (risk ratio: 1.0), 0.5 should be multiplied by 2. Among the numbers above (0.62, 0.40, 0.27, 0.18, 0.13), 0.40 is taken as an example here. The risk ratio of COVID-19 on the first day was 0.40 (1/2.5). Therefore, to equalize the risk of COVID-19 in the vaccinated and unvaccinated groups, 0.4 is divided by 0.4 or 0.4 is multiplied by 2.5.

Moreover, the health condition would continue to have influence thereafter as it does on the first day. Therefore, multiplying the risk ratio thereafter by 2.5 (or dividing it by 0.4) is needed for unbiased comparison.

Reader: But it is said that booster shots would especially reduce aggravation and death, isn't it?

Editor: The first Israeli study reported that the vaccine effectiveness after the second dose was 94% against symptomatic COVID-19 and 92% against severe diseases.

Reader: What would happen if this result is adjusted by the health condition?

Editor: The risk ratios were 0.06 (1-0.94) and 0.08 (1-0.92), respectively. If they were divided by 0.40 (the risk ratio of symptomatic COVID-19 on the first day) and 0.18 (the risk ratio of severe disease on the first day), the risk ratios are 0.15 and 0.44 and the vaccine effectiveness is as low as 85% and 56%, respectively.

Reader: How about the 4th dose in Israel?

Editor: It was reported that the vaccine effectiveness was 61% against symptomatic COVID-19, 64% against severe disease, 76% against COVID-19 death between day 14 and day 30. Can you calculate the risk ratio?

Reader: For symptomatic COVID-19, It is "1 - 0.61 = 0.39" and 0.36 (1-0.64) for severe disease and 0.24 (1-0.76) for death.

Editor: Correct. It had been confirmed that the degree of healthy vaccinee effect after the 4th dose was almost the same as that after the second dose (**Note 2**). Then, let's adjust it by the risk by severity on the first day after the second dose. For symptomatic COVID-19, 0.39 was divided by 0.4 and the adjusted risk ratio is 0.98. It meant that the vaccine was not effective at all. How about aggravation?

Reader: It is 0.36 divided by 0.18 and it becomes 2.0. Oh no, the risk is not reduced, but doubled?!

Editor: Yes, even the risk of death was nearly doubled: 0.24÷0.13 = 1.85. This suggests that the booster shots did not reduce aggravation and death, but they might rather increase those conditions.

This study reported only hospitalization and death from SARS-CoV-2, but not from thrombosis nor myocarditis after vaccination. The vaccine had no effect on prevention of

SARS-CoV-2 infection and symptomatic COVID-19, but has harms. It was estimated that the risk of hospitalization and death was even higher.

It is clear now that in order to assess the vaccine effectiveness by observation studies (**Note 3**), such as the Israeli study above; healthy vaccinee effect must be taken into consideration. Otherwise, ineffective vaccines would appear to be effective.

Reader: I understand it very well now.

Note 2: The only available data about the risk is that of asymptomatic infection/symptomatic COVID-19 on the day of the fourth vaccination (0.45) in the ref [8], which is almost the same as the risk of asymptomatic infection/symptomatic COVID-19 on the day of the second vaccination (0.48) in the ref [7].

Note 3: Observational studies are not conducted by intentional interventions like a randomized controlled study, but are based on observation of ongoing medical interventions. For example, conditions of infection and hospitalization or mortality rates in the vaccinated and unvaccinated are compared. In a cohort study, treated and untreated people (groups) are compared. On the other hand, a case-control study compares the proportion of people who were exposed to a particular substance before the onset in 2 groups of people: those with the disease and those without. Both are called observational studies. Recently, they are often called real world data (RWD), as well.

(4) The doctrine of original antigenic sin and vaccines against the Omicron variant

In the introduction, we have concluded that new vaccines against the Omicron variants have no effect, but only harms. The conclusion is based on the phenomenon called "the doctrine of original antigenic sin". To fully understand this phenomenon, complicated interpretation of data is necessary, but it might confuse our readers. So, we will avoid going into details with numbers and graphs, but will explain you in a simpler manner.

When a person (A) is infected with a virus (X_0) for the first time, he/she would develop strong immunity (antibodies) against this virus (X_0). In the case of COVID-19, the immunity is developed in the form of protective antibodies in the respiratory mucosa, such as in the nose, throat and bronchi, which is the entry point of the virus, as well as neutralizing antibodies in the blood.

Later, if infection with the mutant virus (X_1) of X_0 causes pandemic and A is exposed to X_1, the body would try to defend against X_1 with the immunity (antibodies) against X_0, which his/her body remembers. It would develop only little antibody against X_1, and thus it is not enough to eliminate X_1, leading to infection and onset of disease.

The same phenomenon would happen with vaccines. Coronavirus (SARS-CoV-2) which originates in Wuhan, China is called the "original virus" or "original wild type (WT) virus" (B_0). Vaccines which had been made so far are called the "original vaccines" or "original WT vaccines" as they were designed against the original (WT) virus (B_0). If a person A is vaccinated with B_0, he/she would develop antibodies against B_0 only in the blood, but almost no antibody in the nasal mucosa. Then, when the pandemic is driven by the Omicron BA1, BA2 or BA5 and A is exposed to those viruses, the body would try to counteract them only by the antibodies against B_0 in the blood, and thus the Omicron variant would easily enter the body, causing infection and symptomatic COVID-19.

This phenomenon is called the doctrine of original antigenic sin. It was first introduced by Thomas Francis, Jr. (1960) [12,13]. Through a series of his studies, he found that people of the same age have the same specific antibody against influenza virus, which corresponds to the first seasonal influenza virus that they were exposed to. He confirmed this by various methods, and introduced the concept of the doctrine of original antigenic sin [13].

The doctrine of original antigenic sin discussed in the MHLW meeting

The doctrine of original antigenic sin is well-known as Dr. Yoshimasa Takahashi, Director of Research Center for Drug and Vaccine Development, National Institute of Infectious Diseases, discussed it in the 31st Health Sciences Council Vaccine Taskforce (3-24-2022) as follows [14].

There is an immune phenomenon called "original antigenic sin" in English. I think this is the state of immunity given by vaccines etc. with conventional strains, and I think it is the current situation in Japan, but if you inoculate with a mutant strain type vaccine in such a situation, by definition, it is such an immune phenomenon that pre-existing immunity prevents new immunity from being induced against the mutant strain. However, this phenomenon called original antigenic sin is not a phenomenon that has been confirmed so far in the SARS-CoV-2, but it is a possible phenomenon as a general theory, and some reviews have proposed such a hypothesis. Such a situation is my current understanding. Above, I have supplemented the topic of original antigenic sin.

What happens when a person vaccinated with an original vaccine is infected with BA1

Dr. Takahashi implies that the doctrine of original antigenic sin is not confirmed with SARS-CoV-2. However, is it really so? SARS-CoV-2 vaccines used for the 3rd and 4th doses around the world are original vaccines. Many people who had been vaccinated were infected with BA1, BA2 or BA5 of the Omicron variants. Let us think about it through Q&A below.

Editor: Total 27 people were examined, who were vaccinated with the 3rd dose (so-called booster shot) of an original vaccine 6 months after the second dose of Pfizer's original vaccine. Which antibody titer do you think was the highest; those against ①original virus, ② BA1, or ③ BA5?

Reader: Because they were vaccinated with the original vaccine, the answer is ① antibody against the original virus.

Editor: Correct. Antibody titer against the original virus was 6.4 times higher than that against BA1 [15]. Next, another 27 persons who became ill after being infected with BA1 or BA2 of the Omicron variant were studied. About 80% of them had received 3rd doses of the original vaccine, and only 1 person had received no vaccination. One month (median 29 days) after infection, which antibody titer was the highest in their bodies? Please remember what was explained for the doctrine of original antigenic sin.

Reader: It's ①antibody for the original virus.

Editor: That's right. Do you guess how much more antibody against the original virus was produced after infection with BA1/BA2 of the Omicron variant as compared to the antibody against BA1; ① 1.5-2 times, ② 3-4 times, ③ 6-13 times?

Reader: Because it was after being infected with the Omicron variant, it must be less than when vaccinated with the original vaccine. So, it's ②3-4 times?

Editor: No, it was also 6.4-fold [15]. The report on the special approval for Pfizer's vaccine for BA1 [16] shows that it was 13.2-fold. So, it was from around 6-fold to 13-fold. By the way, antibody against BA5 strain (BA5 antibody), which caused the seventh wave of pandemic, was only about one-twentieth of the antibody against the original virus both after the 3rd dose and being infected with BA1/BA2 viruses [15].

Mouse tests with original vaccine proved the same

Reader: Which people had higher antibody titer; people who had received the 3rd dose or those who had symptoms of the Omicron BA1/BA2?

Editor: That's a good question. It is difficult to give you a definite answer as the antibody titer before symptoms of the Omicron BA1/BA2 began after the 3rd dose was not measured. However, antibody titer was 2-fold higher for any variants in those who had symptoms than in those who had received the 3rd dose [15]. In addition, in all studies, not only that the antibody titer was higher, but it was sustained longer in people who were infected than in those who had the 3rd dose.

In Israel, the 4th dose did not prevent the symptomatic COVID-19 by the Omicron BA1 (**Fig. 1B** and **Suppl.Fig 1B**). This means that the antibody titer increased after the 3rd or 4th dose was not high enough to prevent the symptomatic COVID-19 by the Omicron variant.

Mice pretreated with the original vaccine were given BA1 vaccine and the antibody titer was measured. The antibody titer for the original virus was 6-fold higher than that for the Omicron BA1, and was the highest, showing the similar result as in humans.

Reader: How about Takeda's vaccine? It is also an original vaccine, isn't it?

Editor: Yes, Takeda's Nuvaxovid is an original vaccine. Do you think it is effective?

Reader: I don't think so, as Pfizer's and Moderna's vaccines are not effective. How about the increased antibody titers after BA1 or BA5 vaccines are inoculated? Is it effective?

Editor: That's the most important point. We will take a look at the evidence which Japan's Ministry of Health, Labour and Welfare (MHLW) referred to for approval, especially how much increase was observed in the antibody titer. Before that, besides the increased antibody titer, what else is needed as the evidence for preventive efficacy?

Reader: Clinical trials?

Editor: Yes, that's right. To objectively prove the efficacy on reduction of the symptomatic COVID-19 and hospitalization due to COVID-19, it has to be confirmed by randomized controlled trials (RCTs).

Exceptional approval granted based only on antibody test

Reader: Vaccines for the Omicron BA1 and BA5 were approved very quickly. Were RCTs conducted?

Editor: No, RCTs to examine the prevention of symptomatic COVID-19 and hospitalization have not been conducted. Exceptional approval was urgently granted only based on the

antibody test [16]. Its legal basis is on the exceptional approval system in the revised Pharmaceuticals and Medical Devices Law issued on May 20, 2022.

Reader: Zocoba is now being examined in the emergency approval system, right?

Editor: Yes, for an anti-viral agent, Zocoba (see Editorials), an RCT was somehow conducted and its validity was being examined. However, vaccines for BA1 and BA5 were put not on the emergency approval but on the exceptional approval system [18]. "Exceptional approval system" had been established by law before May 20, 2022. However, it was revised that if the efficacy, a requirement for "emergency approval", is estimated, the substance is eligible for "exceptional emergency" approval by the revision of the Medicines and Pharmaceutical Devices Law on May 20, 2022 [18]. The sixth wave caused by BA1 and BA2 and the seventh wave by BA5 in 2022, an urgent response was given an importance, and the exceptional approval was granted based only on the increased antibody titer without confirming the preventive effect by clinical trials.

Please take a look at how much antibody titers increase in Fig. 5. What is the fraction of BA1 antibody (456) produced by the original vaccine to the original antibody (5998)?

Reader: One-thirteenth? It is smaller than one-sixth mentioned above.

Editor: Yes, I mentioned earlier 6-fold to 13-fold, and "13" came from this calculation. Then, is there any difference in the produced titer of original antibodies between the original vaccine and the BA1 vaccine?

Reader: No, not at all.

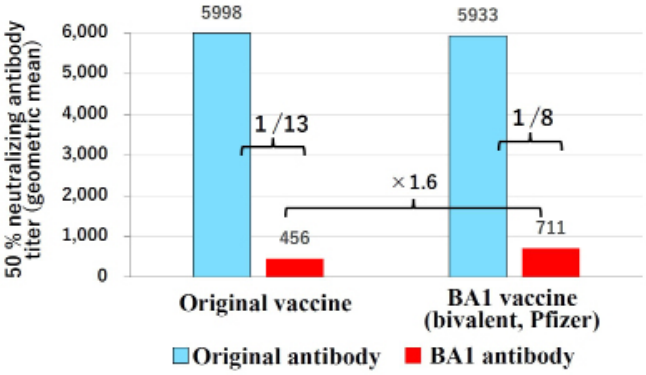
Editor: Right. What is the fraction of BA1 antibody (711) produced by BA1 vaccines to the original antibody?

Reader: One-eighth. It is only 1.6-fold of that produced by the original vaccine, and there is only little difference. Is such a vaccine really effective?

Editor: That's where the problem lies. MHLW granted the exceptional emergency approval to the BA1 bivalent vaccine, because it showed a statistically significant increase of BA1 antibody compared with original SARS-CoV-2 vaccine and satisfied the condition "efficacy is estimated". MHLW may have wanted to say that it should be approved without randomised clinical trials before the 8th wave would be prevailing in Japan.

Reader: Is the effect expected if the antibody titer reaches average 6000 just like the original antibody?

Figure 5: Slight increase of neutralizing antibody titer by BA1 vaccines (comparison with original vaccine)



Editor: Yes, but unfortunately, with the increased antibody titer (average 456) after 4th doses of the original vaccine, it showed almost no effect, and thus even if it increases to average 711, no effect is expected. The MHLW is supposed to be very much aware of this.

Reader: How about Moderna's BA1 vaccine or Pfizer's BA5 vaccine?

Editor: The antibody titer after Moderna's BA1 vaccine was 1.74-fold higher than that after the original vaccine (**Note 4**), but as for Pfizer's BA5 vaccine, no assessment report has been published, and no data were shown in the package insert [Note B].

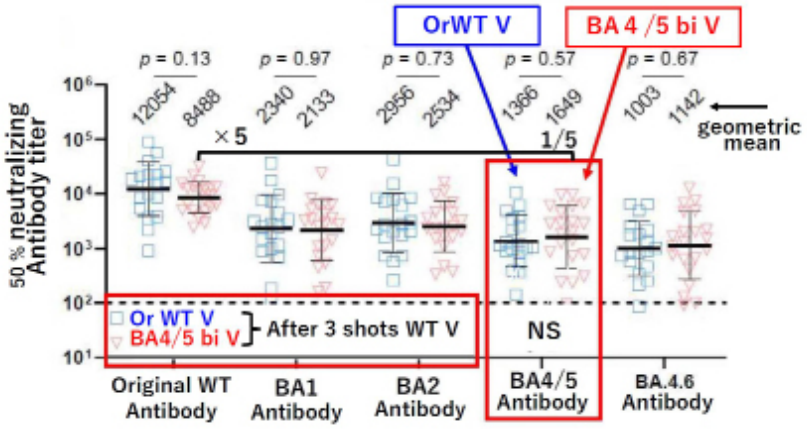
Note B: A bioRxiv preprint paper [26] reported "At 3-5 weeks post booster shot, individuals who received a 4th dose with a bivalent mRNA vaccine targeting BA.4/BA.5 had similar neutralizing antibody titers as those receiving a 4th monovalent mRNA vaccine against all SARS-CoV-2 variants tested, including BA.4/BA.5." (Suppl. Fig. 5)

Note 4: Some studies on preventive effectiveness on the symptomatic COVID-19 of Moderna's vaccines have been published, including those during the pandemic by the Omicron variant [20-24]. However, no study reported the risk ratio of symptomatic COVID-19 on the day of vaccination, and thus it was not possible to estimate healthy vaccine effect which could be estimated in the Israeli studies [7,8]. Healthy-vaccinee effect might occur with Moderna's vaccines as was the case in Israel. Therefore, the original vaccine is ineffective against symptomatic COVID-19 caused by the Omicron variant and so is Moderna's BA1 vaccines.

Reader: Why was the approval granted based on such data without conducting any clinical trial?

Editor: We don't know for sure, but if a large-scale RCT

Suppl. Figure 5: Antibody response by original WT vaccine vs BA4/5 bivalent vaccine after 3 doses of original WT vaccine



A part of the Figure 1B in the ref [26] is extracted showing "comparison of antibody responses induced by a fourth dose of the original wild type (WT) mRNA vaccine versus a BA.4/BA.5 bivalent mRNA vaccine as a fourth dose" especially on BA4/5 antibody. No difference on BA4/5 antibody responses was shown. BA4/5 antibody rise by a BA.4/BA.5 bivalent vaccine was only one fifth of original WT antibody titer.

was conducted, as was practice for existing vaccines, it would be confirmed that the vaccines were ineffective. Therefore, the MHLW probably wants to approve the vaccines if "the efficacy or effect is estimated" based solely on the antibody test, hoping that the effectiveness would be proven by studies conducted after the approval.

How to make ineffective substances look "effective"?

Reader: How can you make ineffective substances look "effective"?

Editor: Do you remember the methods mentioned in the section **(3)** ?

Reader: Ah ha, if the effect of an ineffective vaccine is compared between the vaccinated and unvaccinated without considering "healthy vaccinee effect", it would even appear to "reduce death".

Editor: Exactly. The MHLW probably intended to do this. Eventually, observational studies on the preventive effect of BA1 and BA5 vaccines on infection will be published like Israeli studies [8,25]. As a result, the effectiveness of vaccines on preventing symptomatic COVID-19, hospitalization, aggravation and even death might be not just "estimated", but "confirmed".

Effective for the 8th wave?

Reader: Is the 8th wave coming?

Editor: In France and Germany, as of October 24, 2022, the eighth wave has started, and what is worse, a new variant, a subtype of BA5, seems to be spreading. It might cause pandemic in Japan in winter, as well [Note C] .

Note C:

Around January 10, more than 200 thousand people are confirmed with SARS-CoV-2 infection every day and more than 400 people are dying every day in Japan, although many had the 4th dose of SARS-CoV-2 vaccines.

Reader: Will BA1 or BA5 vaccines be effective against the new variant?

Editor: No, not at all.

No effect, but harm

Editor: Do you think there is no harm if there is no effect?

Reader: No, I don't think so.

Editor: As for the effect, the body would acquire the immunity against the virus or the vaccine which it was first exposed to. When a similar virus enters the body, it tries to counteract with the immunity against the original virus or vaccine, so it is not effective against the similar one.

In addition, the body does not develop a defense system against harm even after many doses of vaccines. On the contrary, the harm might become severer each time.

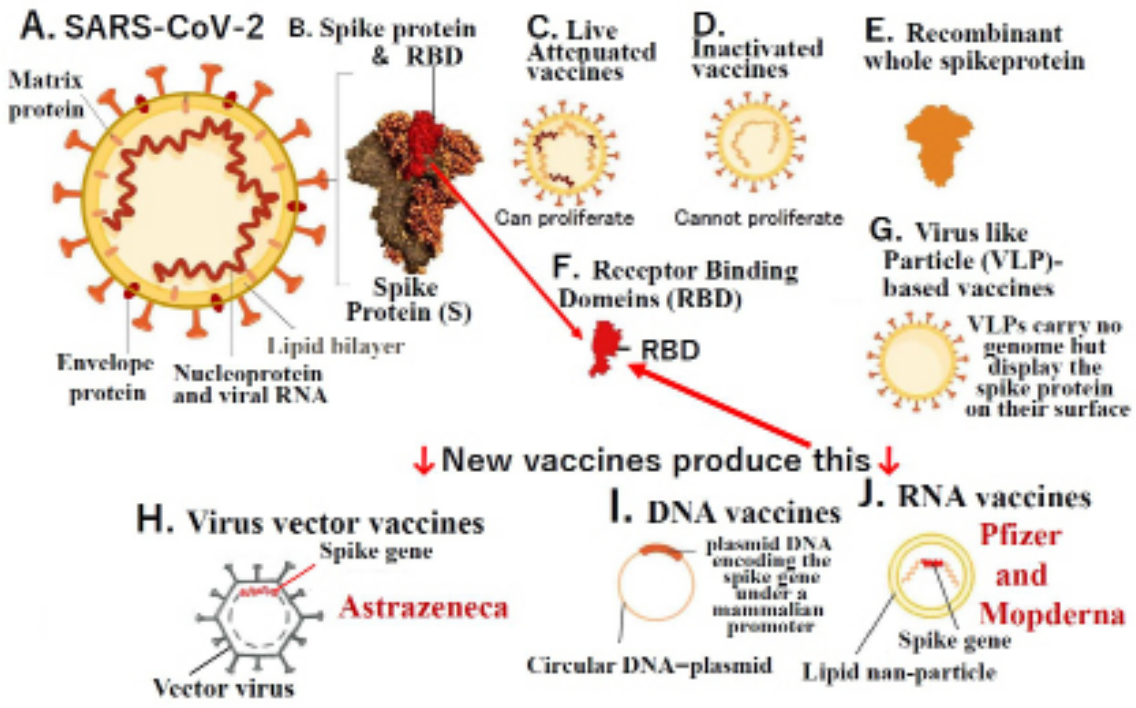
Reader: Is it an example of the point (1) for assessment of safety and effectiveness of vaccines: harm-benefit balance would change depending on timing?

Editor: Yes, now harm outweighs benefit all over the world, and the vaccination should be suspended immediately.

Conclusion

SARS-CoV-2 vaccines not only have no proof of efficacy against Omicron variants but also may increase risk of COVID-19 by two times and have serious harms. The use of SARS-CoV-2 vaccines should be immediately suspended.

Figure 6: Types of vaccines and their structures



Modified based on the figure 3 in ref [27]

Based on a figure in Krammer, F. Nature 2020:586, 516-527. https://doi.org/10.1038/s41586-020-2798-3, a part of the figure and explanation is revised.

Traditional methods of producing antigens (A-G in Fig. 6)

①Attenuated live virus/bacteria (C) :They are called "(attenuated) live vaccines". They include vaccines for measles and rubella, BCG for tuberculosis, rotavirus vaccine and former polio vaccines. Although it is rare, vaccine strains of the virus/bacteria may cause respective diseases.

② Inactivated virus/bacteria (D): Disease-producing capacity is destroyed. They include current polio vaccines and vaccines for whooping cough and Japanese encephalitis.

③ Virus-like particle (VLP)-based vaccines (G): They are produced by the recombinant methods, carrying no genome but have other component including spike protein on their surface or other antigen proteins: HPV vaccines (with adjuvants) belongs to this category.

④ Protein components (subunits) (E/F): that play an important role in infection and aggravation are refined from viruses which are cultured and proliferated in a chicken egg (influenza vaccine), or are genetically engineered (by the recombinant methods) and used as antigens (Nuvaxovid/Novavax = Takeda's SARS ― CoV-2 vaccine).

As SARS-CoV-2 infects human cells by binding its spikes to ACE2 receptors, the entire spikes or a part of them are used as antigens (See Fig. 6 for the structure of SARS-CoV-2 and types of antigens used for vaccines (candidates)).

New methods of producing antigens (H-J in Fig. 6)

There are mainly 3 new methods. All of them have genetic information to synthesize the whole protein or a part of protein like spike protein inside of the human body. When injected, they produce the target antigen proteins in the body. The differences are as follows.

① Using RNA itself (J)

In RNA vaccines, messenger RNA (mRNA, **Note 5**), which is genetic information of the SARS-CoV-2 virus, is used (the base sequence is partially changed). Bare mRNA is immediately decomposed by ribonuclease in the body. In order to prevent this, it is encapsulated in lipid nanoparticles. The lipid nanoparticles and RNA also plays the role of "adjuvants". Pfizer's and Moderna's vaccines are in this category.

② Using DNA (I)

Genetic information (RNA) of viral protein is once transcribed into DNA by reverse transcriptase (**Note 5**), and reverse-transcribed DNA fragments are embedded in a part of circular DNA (plasmid) and injected into the human body. This DNA is translated into mRNA and the protein of interest is synthesized in the human cells.

③ Using viral vectors (H)

Genetic information (RNA) of the protein of interest is embedded in a low-toxic virus, such as adenovirus, using as a vector, and they are injected to synthesize the protein inside of the human cells (AstraZeneca's vaccines).

Note 5: The human body usually translates genetic information in DNA and produces mRNA, a blueprint for protein, based on which protein is produced in the cell. However, as the genes of SARS-CoV-2 is RNA, in DNA vaccine candidates, single-stranded RNA is reverse-translated (reverse-transcribed) into double-stranded DNA to create DNA fragments.

How protein is produced in human: DNA → mRNA → protein

How protein is produced in SARS-CoV-2: (m) RNA → protein

RNA method: mRNA in lipid nanoparticles → protein production

DNA method: mRNA → DNA → mRNA → protein production

References

1)MedCheck editorial team. Let' s know more about vaccine! HPV-vaccine etc. MedCheck 2013 (Oct): 13(52): 4-49.(In Japanese)

2)ibid. Let' s know more about vaccine! Part 2: Hepatitis B, Japanese encephalitis, Rota virus, adjuvant etc MedCheck 2014 (Jan.): 14(53): 4-73. (In Japanese)

3)Tanida N. Vaccine; Inoculate or not inoculate? MedCheck 2017 : 17 (69): 4-7

4) Polack FP, Thomas SJ, Kitchin N et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 Dec 31;383(27):2603-2615. Epub 2020 Dec 10. PMID: 33301246

5) Baden LR, El Sahly HM, Essink B et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020 Dec 30 Online ahead of print. PMID: 33378609

6) MedCheck Editorial team. Vaccines for COVID-19: Is it useful in Japan? MedCheck in English 2021: 7(20): 3-11. Available at: https://www.npojip.org/english/MedCheck/Med%20Check%20Tip-20-2021-04-27.pdf 7) Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med 2021; 384(15):1412-23. doi: 10.1056/NEJMoa2101765

8) Magen O, Waxman JG, Makov-Assif M R et al. Fourth Dose of BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2022; 386(17):1603-1614. doi: 10.1056/NEJMoa2201688. Epub 2022 Apr 13

9) MedCheck editorial team. Vaccine candidates: Are they effective and safe ? MedCheck 2020: 20(92): 127-131(In Japanese)

10)Hama R. Benefit and harm of HPV vaccine: Latest evidence-based information: J Sexual Health 2021: 20 (4): 41-59. Available at: https://www.npojip.org/sokuho/211228.html (In Japanese)

11) MedCheck editorial team. Series, Critical Review on Guidelines (24): Guidelines for Management of COVID-19—It recommend use of molnupiravir with doubtful efficacy. MedCheck 2022 : 22 (103): 104-107 (In Japanese)

12) Monto AS, Malosh RE, Petrie JG, Martin ET.The Doctrine of Original Antigenic Sin: Separating Good From Evil. J Infect Dis. 2017 Jun 15;215(12):1782-1788. doi: 10.1093/infdis/jix173. PMID: 28398521

13) Francis T. On the doctrine of original antigenic sin. Proc Am Philos Soc 1960; 104:572–578. (Cited from ref. 12)

14) Takahashi Y. Remarks at the Health Science Council Immunization and Vaccine Subcommittee (2022-3-24) From the minute (in Japanese) available at: https://www.mhlw.go.jp/stf/newpage_25252.html

15) Hachmann NP, Miller J, Collier AY et al. Neutralization Escape by SARS-CoV-2 Omicron Subvariants BA.2.12.1, BA.4, and BA.5. Engl J Med. 2022 Jul 7;387(1):86-88. doi: 10.1056/NEJMc2206576. Epub 2022 Jun 22.PMID: 35731894

16)PMDA, Comirnaty RTU®, Report on Exceptional Approval (In Japanese). https://www.pmda.go.jp/drugs/2022/P20220912001/672212000_30400AMX00016_A100_1.pdf

17)Ying B, Scheaffer SM, Whitener B, et al. Boosting with variant-matched or historical mRNA vaccines protects against Omicron infection in mice. Cell. 2022 Apr 28;185(9):1572-1587.e11. doi: 10.1016/j.cell.2022.03.037. Epub 2022 Mar 28. PMID: 35452622

18) Ministry of Health, Labor and Welfare, Partial Revision of Law Concerning Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices (Pharmaceuticals and Medical Devices Law) in (in Japanese): https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000179749_00006.html

19) PMDA, Spikevax®, Report on Exceptional Approval (In Japanese). https://www.pmda.go.jp/drugs/2022/P20220912003/790314000_30300AMX00461_A100_1.pdf

20) Florea A, Sy LS, Qian L, Ackerson BK. et al. Effectiveness of mRNA-1273 vaccine booster against COVID-19 in immunocompetent adults. Clin Infect Dis. 2022 Sep 22:ciac785. doi: 10.1093/cid/ciac785. Online ahead of print. PMID: 36134518

21) Bruxvoort KJ, Sy LS, Qian L. et al. Real-world effectiveness of the mRNA-1273 vaccine against COVID-19: Interim results from a prospective observational cohort study. Lancet Reg Health Am. 2022 Feb;6:100134. doi: 10.1016/j.lana.2021.100134. Epub 2021 Nov 25. PMID: 34849505

22) Abu-Raddad LJ, Chemaitelly H, Ayoub HH. et al. Effect of mRNA Vaccine Boosters against SARS-CoV-2 Omicron Infection in Qatar. N Engl J Med. 2022 May 12;386(19):1804-1816. doi: 10.1056/NEJMoa2200797. Epub 2022 Mar 9. PMID: 35263534

23) Monge S, Rojas-Benedicto A, Olmedo C et al. Effectiveness of mRNA vaccine boosters against infection with the SARS-CoV-2 omicron (B.1.1.529) variant in Spain: a nationwide cohort study. Lancet Infect Dis. 2022 Sep;22(9):1313-1320. doi: 10.1016/S1473-3099(22)00292-4. Epub 2022 Jun 2. PMID: 35658998

24) Ioannou GN, Bohnert ASB, O'Hare AM et al (Observational Research Collaboratory;CORC). Effectiveness of mRNA COVID-19 Vaccine Boosters Against Infection, Hospitalization, and Death: A Target Trial Emulation in the Omicron (B.1.1.529) Variant Era. Ann Intern Med. 2022 Oct 11. doi: 10.7326/M22-1856. Online ahead of print.PMID: 36215715

25) Canetti M, Barda N, Gilboa M et al. Six-Month Follow-up after a Fourth BNT162b2 Vaccine Dose. N Engl J Med. 2022 Dec 1;387(22):2092-2094. doi: 10.1056/NEJMc2211283. Epub 2022 Nov 9. PMID: 36351266

26) Wang Q, Bowen A, Valdez R et al. Antibody responses to Omicron BA.4/BA.5 bivalent mRNA vaccine booster shot. https://www.biorxiv.org/content/10.1101/2022.10.22.513349v1

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