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Editorial

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Crisis of scientific assessment of pharmaceutical products

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Amidst all the media coverage of development, competitive procurement, and inoculation procedure of COVID-19 vaccines, scientific and critical media report for the efficacy and safety of the vaccines is very rare, although it is the most important issue.

What is worse, many countries, including France, which is known for mature democracy and high scientific standards, are now practically in the process of introducing compulsory vaccination. In Japan, policies in Europe and the United States are generally highly respected. Therefore, they often serve as an effective means to hold back Japanese policy makers whenever sloppy policies are about to be introduced in Japan. However, we cannot expect this to work in the case of COVID-19 vaccines.

While “disaster capitalism” expands due to the introduction of COVID-19 vaccines, the Ministry of Health, Labor and Welfare of Japan issued a notice on November 26, 2021 to resume active recommendation of the HPV vaccine (so-called cervical cancer vaccine), saying that there were no particular concerns about safety.

Regarding the HPV vaccine, Med Check has repeatedly questioned its efficacy and safety: HPV vaccine is harmful with no proof of efficacy for prevention of cervical cancer.

Globally, there is almost no critical appraisal of epidemiological studies that take healthy-vaccinee effects into account. For that reason, it is difficult to resist the trend of active recommendation of HPV vaccine in Japan where it is widely believed that the vaccine would prevent HPV infection.

However, if you calmly and scientifically look at the data analyzed in detail in this issue, you will understand how harmful and useless the HPV vaccine is.

The data from the clinical trial of molnupiravir, an antiviral agent for COVID-19, also had a bias in baseline characteristics that raise serious questions about randomisation and blinding in all pivotal RCTs of molnupiravir.

There is a reality that even peer-reviewed papers published in leading medical journals are not reliable.

It is necessary to reexamine the methods of drug evaluation once again, based on the discipline of science.

Review

Resuming HPV vaccination is very dangerous

Translated from Med Check (in Japanese) Jan. 2022 ; 22 (99):22-23

Med Check Editorial Team

Abstract

- Active recommendation of HPV vaccine will be resumed in April 2022 in Japan after 8-year suspension.
- Pooled odds ratio for all-cause mortality of 3 RCTs involving women aged 25 to 40 years was 5.00 (95% CI:1.71, 14.65, p=0.002). This clearly indicates that HPV vaccine is highly toxic.
- The data in a report of health science research group indicate serious healthy vaccinee effect and large risk ratio of "extensive pain and/or movement disorders" after HPV vaccination.
- A large-scale questionnaire survey (Nagoya study) indicates that those who became dependent on a walking stick or wheel chair after vaccination was about 47-fold as compared with the unvaccinated, by adjusting the risk before vaccination.
- In the three epidemiological studies reporting that HPV vaccine reduced cervical cancer, healthy vaccinee bias was not adjusted. If the bias is adjusted, all these studies cannot conclude that HPV vaccine reduced HPV associated cancer including cervical cancer.

Conclusion: **It is dangerous to resume the active recommendation based on the results of observational studies which ignore healthy vaccinee effect.**

Keywords:

HPV vaccine, Healthy vaccinee effect, disability, bias adjustment, active recommendation, mortality

Introduction

On November 26th, 2021, Japan's Ministry of Health, Labour and Welfare (MHLW) decided to resume active recommendation of HPV (human papillomavirus) vaccine, or so-called "cervical cancer vaccine" in April 2022 after the council had approved the resumption on November 12th [1].

As the main basis for this decision, the MHLW refers to the following two findings obtained during the 8-year suspension of the active recommendation. One is the results of a health science research group led by Sofue, which has concluded that various symptoms were found also in the non-vaccinated [2]. Another is the UK study, which has reported that the vaccination has contributed to the reduction in cervical cancer incidence [3].

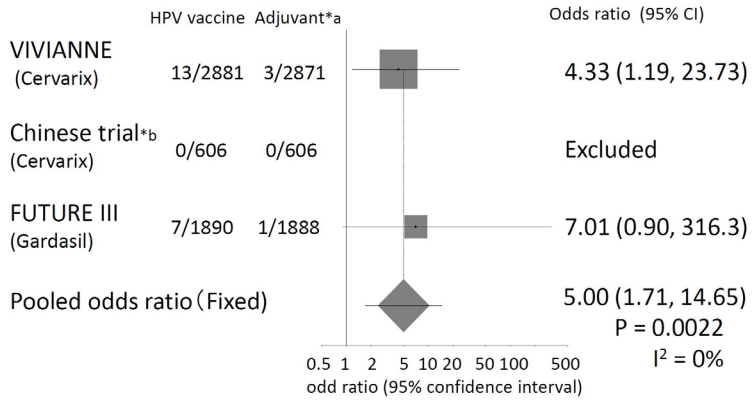
However, as have been examined in Med Check [4-19], The Informed Prescriber (TIP) [20,21] and others [22,23] in detail, HPV vaccine is very harmful while there is no robust evidence indicating that it reduces cervical cancer. This paper explains evidence for harm and critically reviews the data which the MHLW referred to [2,3]. The overview was also published in Med Check No.99 in Japanese (Jan. 2022) [24].

Five-fold increase in mortality in women aged 25 and over

In randomized controlled trials (RCTs) for HPV vaccine, involving women under 25 years old, there was no difference in the incidence of adverse events nor mortality, as compared with the control [4a,5a,5b]. This result is largely associated with the young age of the participants as well as the adjuvants used in these trials as comparator: an alum adjuvant was used as a comparator for "placebo group" in an RCT for Gardasil (FUTURE II study) [25] and a hepatitis A vaccine containing alum adjuvant as a comparator in an RCT for Cervarix (PATRICIA trial) [26-28].

However, according to the meta-analysis using the data from 3 RCTs (4 reports) for HPV vaccine, involving women aged 25

Figure1: Mortality risk within 4 years after the first injection (Meta-analysis of 3 RCTs targeted mid-adult women)



HPV vaccine increases mortality by 5-times in mid-adult women (aged 24 or 25 years and oldert). This clearly indicates no benefit, but harm.
*a: Alum adjuvant was used in the control in VIVIANE study (Cervarix) [29,30] and FUTURE III study (Gardasil) [31], and hepatitis B vaccine that contained alum adjuvant was used in the control in Chinese study (Cervarix) [32].
*b: The follow-up time was 1 year in Chinese study [32] and 4 years in the other 2 studies [29-31].

to 40 years [29-32], pooled odds ratio for the risk of all-cause mortality was 5.00 (95% CI:1.71, 14.65, p=0.002) [22] (Figure 1). This clearly indicates that HPV vaccine is highly toxic.

The results of the health science research group led by Sofue

This paper examines the results of the health science research group led by Sofue [2], which the MHLW considers as one of the crucial pieces of evidence for the resumption of active recommendation.

The results were published in March 2017 in the health science research of the fiscal year 2016 titled "Epidemiological study on the evaluation of efficacy and safety of cervical cancer vaccine", of which Tomotaka Sofue was a chief researcher.

This study concluded "in those aged 12 to 18 years, the complaining proportion (proportion of those reporting symptoms) of 'various symptoms which are similar to those assumed to have occurred after HPV vaccination' was …40.3/100,000 persons in women and 20.4/100,000 in unvaccinated women. In other words, even among the young unvaccinated, 'various symptoms' were experienced by the certain number of them."

"Various symptoms which are similar to those assumed to have occurred after HPV vaccination" refer to "extensive pain and/or movement disorders". Based on this report, the MHLW announced that "various symptoms are also found in the unvaccinated population."

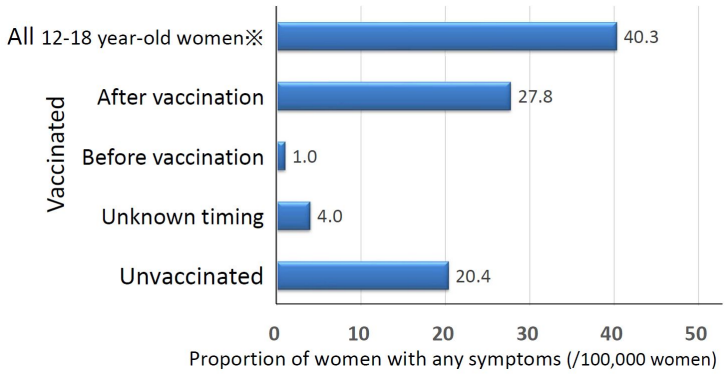
Among 1590 women who reportedly had various symptoms, vaccination status was unknown in 604 women (nearly 40%), and the proportion of those reporting symptoms was 27.8/100,000 persons in women with clear history of vaccination. Very important data, which the research group and the MHLW did not mention, should be introduced here.

Among women who received HPV vaccine, only 1.0/100,000 women had had symptoms before vaccination (Figure 2). This is merely one-twentieth of the proportion of those with symptoms in the unvaccinated (20.4/100,000 persons). As the duration of observation before/after vaccination and duration of observation of the unvaccinated are unknown, the proportion cannot be accurately compared. However, the proportion of those with symptoms drastically increased from 1.0/100,000 persons before vaccination to 27.8/100,000 persons after vaccination.

Contrarily, in women with no history of vaccination, the proportion of those with symptoms should be constant for a few years when they are young. Unlike in the vaccinated women, it is quite unlikely that the proportion would change markedly (although it might show slight increases by aging). Suppose the proportion of those with symptoms remains the same throughout the half of the time when they are 12 to 18 years old, in the first half (equivalent of "before vaccination" in the vaccinated), it would be 10.2/100,000 persons. Based on this, the proportion of those with symptoms before vaccination is only one-tenth in the vaccinated women.

There were 4.0/100,000 persons in whom it was unknown whether the time of symptom onset was before or after vaccination. Even if they all had symptoms before vaccination, the proportion of those with symptoms would be only 5/100,000 persons, which is only one-fourth of that in the unvaccinated women (20.4/100,000 persons). When 4/100,000 persons is proportionally distributed to 27.8 persons and 1 person, the proportion of the vaccinated women with symptoms before vaccination would be 1.14/100,000 persons. This is about one-ninth of 10.2 persons, the proportion of the unvaccinated women with symptoms in the first half of the time.

Figure2: HPV vaccination status and the proportion of women with any symptoms



Note that the proportion of women with any symptoms is 20-fold in the unvaccinated women and 27.8-fold in the vaccinated women after vaccination as compared with that the vaccinated before vaccination.

※ Among 1590 women who had any symptoms, vaccination status was unknown in 604 women (38%), which is more than the unvaccinated (477 women) and the vaccinated (525 women). Therefore, the proportion of those with any symptoms in all 12-18 year-old women is higher than that in the vaccinated women after vaccination.

These suggest how much healthier the vaccinated women were as compared with the unvaccinated. They also show how frequently symptoms occurred in women who avoided vaccination and were classified as the unvaccinated.

Hence, the apparent or crude risk with one or more symptoms after HPV vaccination (1.36) should be multiplied by 9.0 to adjust health condition before vaccination. Adjusted risk with any symptom after HPV vaccination become 12-fold which is extremely high.

Moreover, the proportion above is that in women with at least one symptom. The risk ratio of HPV vaccine for at least one symptom is 27.8/20.4 = 1.36. However, this risk ratio increases as the number of symptoms increases. The proportion of those with 10 or more symptoms was 15.6/100,000 persons in the vaccinated while it was 5.3/100,000 persons in the unvaccinated. The risk ratio was about 3-fold (15.6/5.3). These results are similar to that of the Nagoya study, which is discussed below.

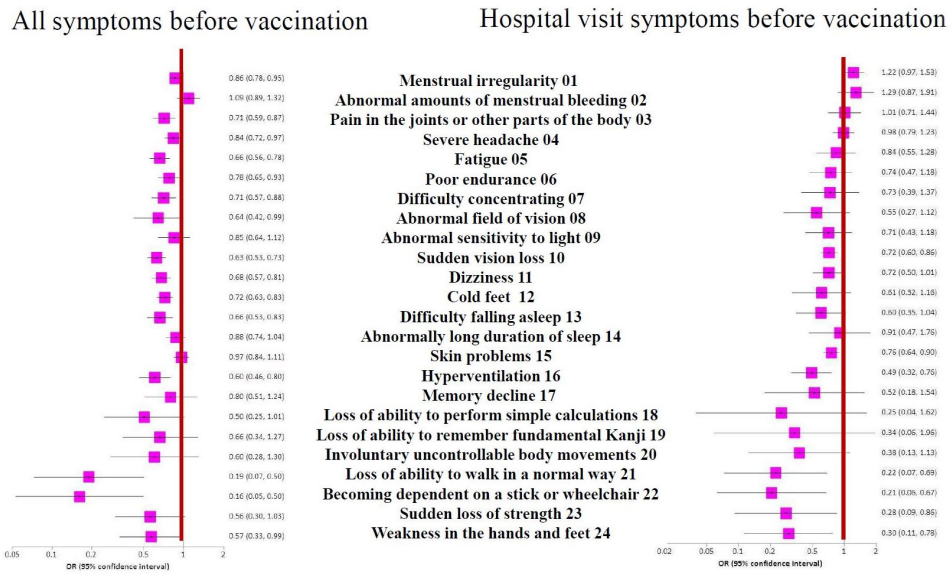
Healthy vaccinee effect is evident in the Nagoya study

The Nagoya study is a large-scale questionnaire study, involving about 70,000 women aged 15 to 21 years to investigate symptoms before and after receiving HPV vaccines. The results of this study have already been reported in back numbers of MedCheck [18,19].

In this article, the risk after vaccination is adjusted by the risk of symptoms before vaccination, and adjusted odds ratio and 95% confidence interval are calculated.

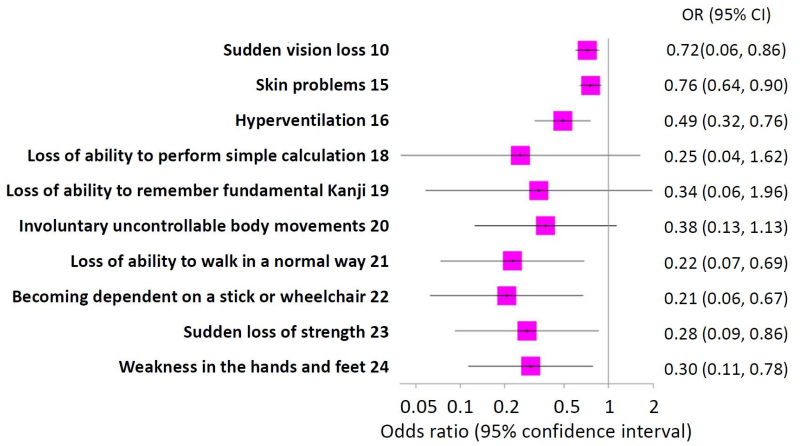
Figure 3 shows the risk (odds ratio) computed by comparing the frequency of symptoms before vaccination in the

Figure3: Health condition of the HPV vaccinated women before vaccination (Nagoya study, odds ratio against the unvaccinated)



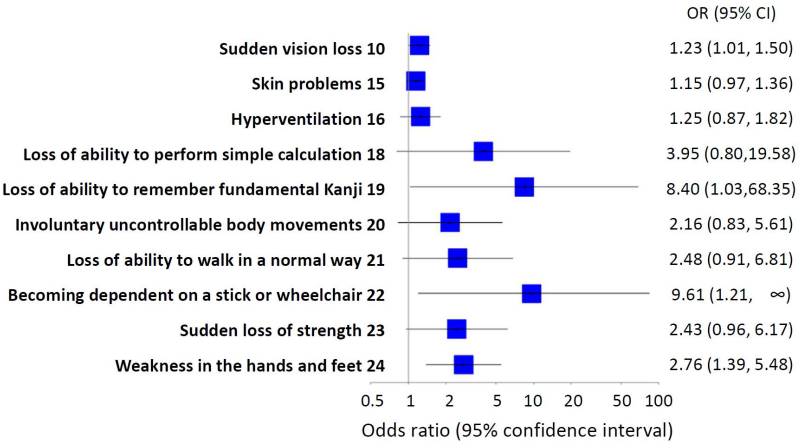
Almost all symptoms occurred less frequently in the vaccinated group than in the unvaccinated group. This implies that there were more healthy women in the vaccinated group while there were more sickly women in the unvaccinated group.

Figure4: Odds ratio of main symptoms that led to hospital visit before vaccination (HPV vaccinated v.s. unvaccinated)



Logistic regression analysis was used to calculate age-adjusted odds ratios (ORs) and 95% CIs. Many symptoms, especially severe symptoms, led to hospital visit significantly less frequently in the vaccinated group than in the unvaccinated group before vaccination.

Figure5: Symptoms leading to hospital visit after vaccination (vaccinated v.s. unvaccinated):



Some severe disorders that led to hospital visit were significantly higher after vaccination without adjustment by the odds ratio before vaccination.

vaccinated group and that in the unvaccinated during the same period, using logistic regression analysis. When odds ratio (■) is smaller than 1 (vertical line), it indicates that there were less women with symptoms in the vaccinated group than in the unvaccinated group. When the right or left tip of the horizontal line does not reach 1, the difference is considered statistically significant.

In almost all symptoms, ■ is on the left side of 1 (smaller than 1), suggesting that less women in the vaccinated group had symptoms before vaccination as compared with the unvaccinated women. In other words, vaccinated women were otherwise very healthy before receiving HPV vaccine. Therefore, without adjusting by health condition at baseline, the new onset of harmful events after vaccination would not be significant unless they occur at extreme frequency. This is why adjustment by the risk of symptoms before vaccination is necessary.

Figure 4 shows the odds ratios of the main symptoms which led to hospital visit before vaccination in vaccinated to the unvaccinated and 95% CI. Significantly less women had hospital visit for the following symptoms before vaccination in the vaccinated group than in the unvaccinated group: sudden vision loss (OR 0.72), skin problems (OR 0.75), hyperventilation (OR 0.49), loss of ability to walk in a normal way (OR 0.22), becoming dependent on a walking stick or wheelchair (OR 0.21), sudden loss of strength (OR 0.28), and weakness in the hands and feet (OR 0.30). It should be noted that those who had hospital visit for severe symptoms, such as loss of ability to walk in a normal way, becoming dependent on a walking stick or wheelchair, sudden loss of strength and weakness in the hands and feet, were found less in the vaccinated group and extremely more in the unvaccinated group; the difference was 3 to 5 fold.

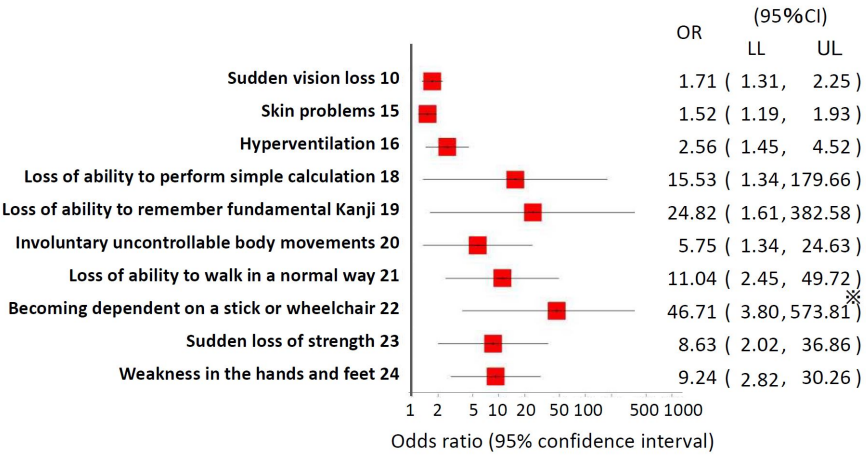
"Symptoms leading to hospital visit" occurred significantly more after vaccination without adjustment

After vaccination, symptoms which led to hospital visit were observed more frequently in the vaccinated group than in the unvaccinated group. Figure 5 shows the odds ratio of the vaccinated to the unvaccinated of the main symptoms and 95%CI after receiving HPV vaccine without adjustment by the odds ratio before vaccination.

In particular, those who had hospital visit because they become dependent on a walking stick or wheelchair, and because they experienced weakness in the hands and feet was 9.6-fold and 2.8-fold, respectively, as compared with the unvaccinated group. For these severe symptoms, the difference was statistically significant. It is noteworthy that it was statistically significant even without adjusting by the odds ratio of symptoms before vaccination.

Figure 6 shows odds ratios of the vaccinated against the unvaccinated of the main symptoms which led to hospital visit after vaccination and 95%CI adjusted by the odds ratio of

Figure6: Symptoms that led to hospital visit after vaccination (HPV vaccinated v.s. unvaccinated) Age-adjusted logistic regression analysis adjusted by symptoms before vaccination.



When adjusted by the odds ratio of symptoms before vaccination [33], OR becomes extremely high. ※ : 95% CI marked with ※ is calculated, assuming that the upper limit of 95% CI for OR is 100.

symptoms before vaccination.

When the risk after vaccination was adjusted by the risk before vaccination, those who became dependent on a walking stick or wheel chair after vaccination was about 47-fold as compared with the unvaccinated.

It was also statistically significant in other symptoms, such as loss of ability to remember fundamental Kanji (25-fold), loss of ability to perform simple calculations (16-fold), loss of ability to walk in a normal way (11-fold), weakness in the hands and feet (9.2-fold), sudden loss of strength (8.6-fold), and involuntary uncontrollable body movements (5.8-fold) [23].

Apparent reduction of cervical cancer may be due to "healthy vacicnee effect"

Next, this article examines the results of epidemiological studies which concluded that HPV vaccine reduced cervical cancer, namely the UK study [3], which the MHLW considered was important, the Finnish study [34], and the Swedish study [35].

First of all, we show the examination results of the Finnish study [34], because it provides us a level of "healthy vaccinee effect" in HPV vaccination.

It reported that incidence rate of HPV associated invasive cancer was significantly lower in HPV vaccinated women than in the unvaccinated, while incidence rates of other, non-HPV associated common cancers, such as breast cancer or thyroid cancer did not differ between the two groups by comparing separately.

However, these numbers of non-HPV associated cancers were too small for separate comparison. When incidences rate of non-HPV associated cancers as a whole are compared, it was 0.43-fold, showing a significant difference (OR 0.43, 95%CI:0.20-0.93, p=0.028).

HPV vaccine does not reduce the incidence of non-HPV associated cancers, such as breast cancer and thyroid cancer. Hence this reduction implies that the unvaccinated women were originally "sickly" or had some kind of health problems, which prevented them from receiving vaccination, and which were related to the increased risk of cancer.

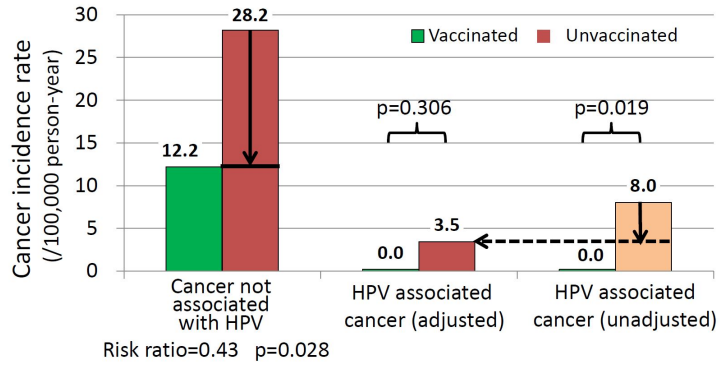
These health problems may also affect the incidence rate of cervical cancer. If health condition in the unvaccinated women was the same as in the vaccinated groups, the incidence rate of cervical cancer in the unvaccinated group (10/124,245py) should be multiplied by 0.43 and would be 4.3/124,245py. When this incidence rate is compared with that in the HPV vaccinated group (0/65,656), no significant difference is found (OR=0.13, 95%CI: 0.004, 4.13, p=0.3665) (Figure 7).

Since vaccination coverage was as low as 35% in the Finnish cohort and incidence rate of non-HPV associated cancers was 0.43-fold in the vaccinated women as compared with the unvaccinated, it can be theoretically inferred that about a half of those who were prone to cancer avoided HPV vaccination [12].

The Swedish study [35] reported that the incidence rate ratio for the comparison of the vaccinated population with the unvaccinated population was 0.37 at all ages.

Figure 8 is based on the cumulative incidence curve of cervical cancer among women who had been "vaccinated before the age of 17, at the age of 17 to 30 years, and

Figure7: Reality of Finnish study, which concluded the vaccination significantly reduced HPV associated cancer



All HPV associated invasive cancers: 0/65,656=0/100,000 vs 10/124,245=8.0/100,000 (p=0.019)
All other cancers 8/65,656=**12.2**/100,000py vs 35/124,245=**28.2**/100,000 py
Risk ratio=0.43（95%CI: 0.20-0.93） (p=0.028)

HPV vaccine does not reduce the incidence of other cancers, thus this reduction implies that the unvaccinated women were originally "sickly". If health condition in the unvaccinated women was the same as in the vaccinated groups, the number of patients with HPV associated cancers in the unvaccinated group would be 10×0.43=4.3. When 0/65,656 and 4.3/124,245 are compared, the difference is not significant (p=0.3665).

unvaccinated women" which was shown in the study [35]. We added the adjusted cumulative incidence curve of the unvaccinated group calculated by the methods below.

Based on the data of this study [35], the HPV vaccination coverage is estimated as 35%, similar to that in Finland.

Therefore, just like in the Finnish study, the incidence rate of cervical cancer in the unvaccinated group should be multiplied by 0.43 for fair comparison to adjust the healthy vaccinee bias. Based on this, the risk in the vaccinated group is 0.86-fold as compared with that in the unvaccinated group, and the risk for cervical cancer in the vaccinated is not significantly different.

The red bold line in Figure 8 is the curve calculated by multiplying the curve for the unvaccinated group by 0.43. The cumulative incidence rate in women who were vaccinated at the age of 17 to 30 years tended to be higher than this.

There were only two cases of cervical cancer reported in women who were vaccinated before the age of 17. The adjusted risk ratio is 0.12 and the upper limit of 95% CI is 0.34. This does not differ much from the risk ratio of non-HPV associated cancers in Finland (0.43, 95%CI: 0.20-0.93), and is still poor as evidence to support the preventive effect of HPV vaccine against cervical cancer for this age group.

The UK study: the cause of reduction in women aged 12-13 years may be bias

In England, where the HPV vaccination coverage is very high, a comparison was made between women of generations before and after the introduction of the HPV immunisation program. The incidence rate ratio of cervical cancer is 0.66 (95%CI: 0.59-0.75) in women vaccinated at the age of 16 to 17, 0.38 (95%CI: 0.29-0.48) in those vaccinated at the age of 14 to 15, and 0.13 (95%CI: 0.06-0.28) in those vaccinated at the age of 12 to 13, as compared with the women at the same age of the older generation: they all showed significant difference. In other words, in women who had been vaccinated at the age of 16 to 17 years, 14 to 15 years and 12 to 13 years, the incidence rate of cervical cancer was reduced by 66% (about two-thirds), 38%, and 13%, respectively.

Although details are not explained here, based on the result of the Finnish study, it can be inferred that about a half of women who were sickly have avoided HPV vaccination.

Figure8: Results of Swedish study and adjusting healthy vaccinee bias

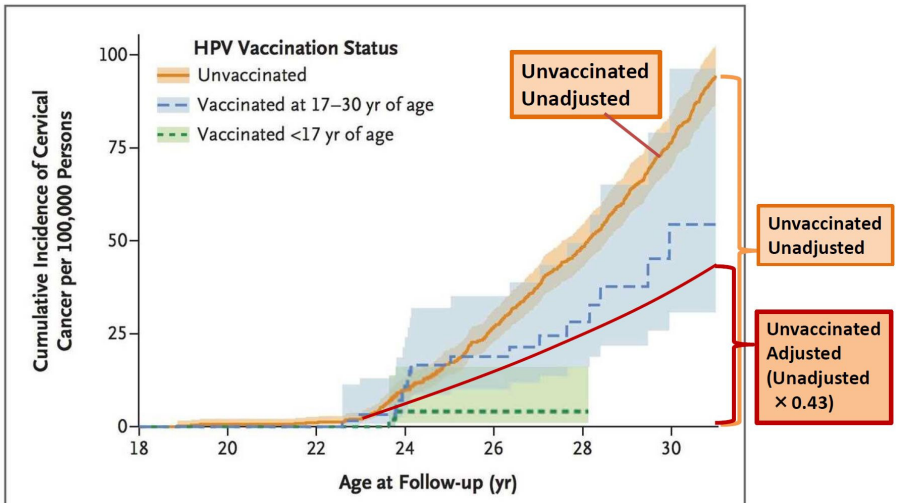


Figure 2. Cumulative Incidence of Invasive Cervical Cancer According to HPV Vaccination Status.
Age at follow-up is truncated in the graph because no cases of cervical cancer were observed in girls younger than 18 years of age.

Avoidance of vaccination by a half of sickly women affects the proportion of sick persons in the unvaccinated population compared with simultaneously vaccinated population, but it does not affect those of women of the previous generation who did not receive vaccination.

However, the proportion of sickly women who were vaccinated may be reduced, since certain proportion of women may avoid vaccination due to health problems. Therefore, even if female population of the previous generation was chosen as a control, this bias "healthy vaccinee effect" would remain and could also be applied to the UK study.

Then, the incidence rates ratio (0.66) of those who were vaccinated at the age of 16 to 17 is higher than 0.5, showing no difference with that of the unvaccinated group (previous generation). Moreover, in women who were vaccinated at the age of 14 to 15, the upper limit of 95% CI of incidence rate ratio is 0.48. It is close to 0.5 and suggests no difference with that of the unvaccinated (previous generation).

In women who were vaccinated at the age of 12 to 13, the upper limit of 95% CI of incidence rate ratio is 0.28. Suppose 70% of them, which is the upper limit of proportion of women who were excluded from vaccination, have avoided vaccination, the risk in the vaccinated group is 0.3-fold of that in the unvaccinated. This is not very different from 0.28, the upper limit of 95% CI of the incidence rate ratio in women who were vaccinated at the age of 12-13. Therefore, if adjustment is made accurately with health condition before vaccination, it is uncertain whether there would be significant difference as compared with the unvaccinated (previous generation).

The authors of this study [3] wrote that vaccination at the age of 12 to 13 is markedly effective because 12 to 13 year-old girls have not yet been exposed to HPV. If so, by the time they reach the age of 14, many of them have already experienced sexual intercourse and have been exposed to HPV. However, this is questionable.

It is rather suspected that apparent preventive effect against cervical cancer is simply because healthy vaccinee effect also has strong impact on this age group. Furthermore, women in this age group might have stronger tendency to avoid vaccination when they have any health problems. It should be carefully examined whether such a tendency is also related.

Conclusion

It is dangerous to resume the active recommendation based on the results of observational studies which ignore healthy vaccinee effect.

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Antivirals for COVID-19:molnupiravir (Lagevrio®)

Doubt about efficacy due to serious baseline imbalance

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Med Check Editorial Team

Abstract

- Molnupiravir (Lagevrio®), an oral antiviral agent for COVID-19 is used in many countries by emergency use authorisation including Japan. It is based on a interim analysis of clinical trial (MOVe-Out trial) which showed that it halved hospitalisation or death (hospitalisation/death) in mild to moderate COVID-19 patients.
- However, sex adjusted hazard ratio in all-randomised population was not significant and the baseline imbalance of the risk factors makes the results doubtful. In the interim analysis population, patients with COPD was assigned less than one third in the molnupiravir group. The sum of the proportion of important four risk factors was significantly lower in the molnupiravir group (19.4%) than in the placebo group (28.4%) (odds ratio 0.61, p=0.003).
- In the MOVe-IN trial which targeted hospitalised COVID-19 patients, score 6 COVID-19 patiens who needed non-invasive ventilation or high flow oxygen were significantly 0.27 fold less assigned in molnupiravir group than the placebo group, but mortality rate increased in the molnupiravir group non-significantly. If the baseline imbalance was adjusted, mortality rate might increase significantly.
- Molnupiravir mutates viral genes and prevents them from replication, but at the same time it suppresses cell division in mammals. Irreversible myelosuppression (whole blood cell damage) was observed in dogs given 0.4 times the human equivalent dose for 22 days. Was it really safe in humans?,
- There are too many inconsistencies in clinical trials of antiviral agents. It is necessary to re-analyse the disclosed clinical trial reports and re-examine whether it is really effective or safe.

Conclusion: The efficacy of molnupiravir on COVId-19 has not been proven. There is also a risk of mutation of virus and of toxicity to the bone marrow (blood cells) in humans. Don't use molnupiravir.

Keywords:
molnupiravir, baseline imbalance, hospitalisation, death, MOVe-Out, MOVe-IN, randomisation, myelotoxicity

Did regulators examine the full clinical study reports?

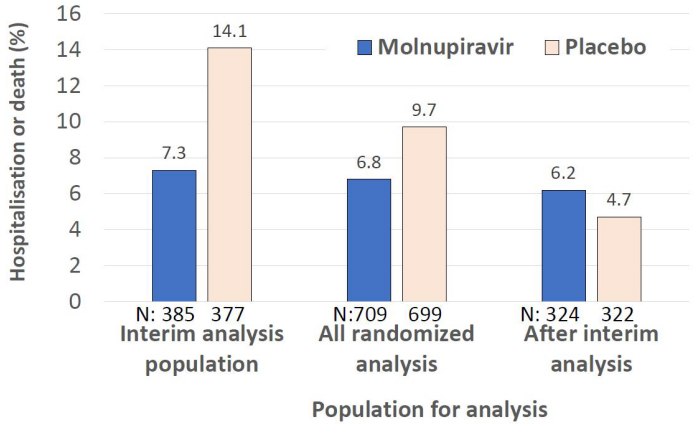
On November 4, 2021, the UK's medicines regulator has issued temporary authorisation of the antiviral drug molnupiravir (Lagevrio® MSD) for the treatment of mild to moderate COVID-19 in adults with at least one risk factor for severe illness [1,2]. At that moment, scarce evidence for efficacy and safety of the agent was open to the public: only the press released data by MSD were available saying that molnupiravir reduced the risk of hospitalisation or deaths by approximately 50 percent compared to placebo for patients with mild or moderate COVID-19 at risk in interim analysis of phase 3 study [3,4].

On November 21, 2021 the European Medicines Agency (EMA) has also issued emergency use advice (EUA) supporting a decision by national authorities for the possible early use of molnupiravir based on the interim analysis results [5].

On December 23, 2021 US Food and Drug Agency (FDA) gave an emergency use authorisation (EUA) [6] and on the next day, Japanese regulatory authorities [7,8] gave a "provisional authorisation" to the molnupiravir. Authorisation was issued in the US and Japan after the publication (December 16, 2021) of peer reviewed paper (MOVe-Out trial) on the phase 3 randomised controlled trial (RCT) including not only the interim analysis (N=775), but also the full analysis of all randomised sample (N=1433) [9].

France canceled the order of molnupiravir [10] and EMA did not give formal authorisation to molnupiravir by the end of January 2020 [11], because it was significantly less

Figure1: Proportion of Hospitalisation or death by time of analysis



Interim analysis (IA): OR (odds ratio) is 0.48 (95%CI: 0.30-0.78, p=0.0023) according to the calculation by MedCheck [17]. All randomised analysis: Hazard ratio was 0.69 (0.48-1.01) reported by Jayk Bernal et al. [3]. After interim analysis (AIA) : OR is 1.35 (0.68-2.68, p=0.395) comparing both groups and 3.35 (1.85-6.06, p<0.0001) comparing IA and AIA populations of placebo groups according to the calculation by MedCheck.

effective than previously thought [10,11]. This is considered to indicate the followings: the risk reduction of hospitalisation/death by day 29 of molnupiravir group fell from about 50 % in the interim analysis to about 30 % in the full analysis of all randomised samples [9]. The editorials of British Medical Journal entitled "Molnupiravir's authorisation was premature" [12] emphasised the dangers of making decisions based on a single prematurely terminated trial.

This paper discusses the other serious problems which reduce the value of molnupiravir especially the imbalance of important risk factors not found in the approval documents for molnupiravir by regulators of UK [1,13], US [14] and Japan [15,16].

Sex-adjusted hazard ratio was not significant

In the interim analysis of MOVe-Out trial, participants receiving molnupiravir had a lower risk of hospitalisation/death through day 29: 7.3% (28 of 385 participants) in the molnupiravir group as compared with 14.1% (53 of 377 participants) in the placebo group and. Risk difference was reported as -6.8% (one-sided p = 0.0012). Odds ratio was 0.48 (two-sided p = 0.0024) according to the calculation by Med Check [17].

In the all-randomised modified intention-to-treat population, risk difference was narrowed to -3.0 % (95%CI, -5.9 to -0.1): 6.8% (48 of 709 participants) in the molnupiravir group as compared with 9.7% (68 of 699 participants) in the placebo group [9]. (Figure 1).

By a time-to-event analysis, the rate of hospitalisation/death through day 29 was approximately 31% lower with molnupiravir than with placebo (hazard ratio, 0.69; 95% CI, 0.48 to 1.01). The risk of hospitalisation/death was reduced about 31 % and was not halved. The risk difference was barely significant, and was not significant by the time-to-event analysis [9].

Molnupiravir may worsen COVID-19 after interim analysis

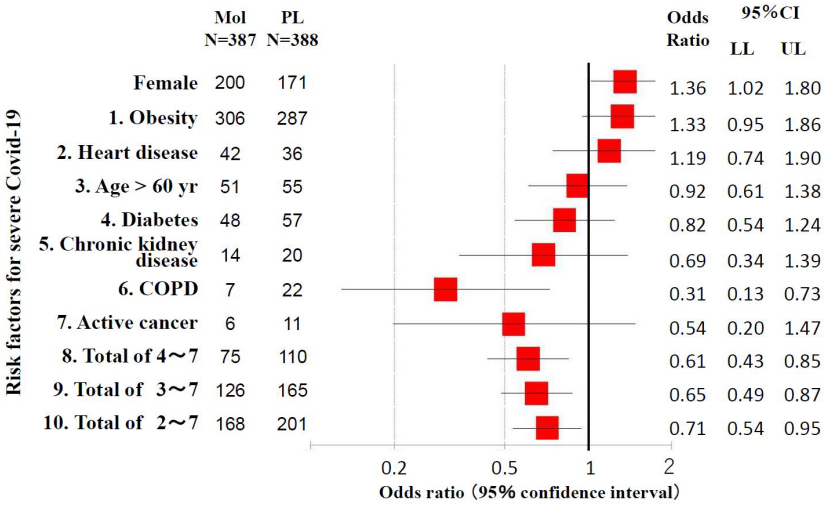
When calculating simply the proportion of hospitalisation/death among population who were not included in the interim analysis but included in the final analysis, the molnupiravir group had a higher risk (6.2 % or 20 of 324 participants) than the placebo group (4.7% or 15 of 322 participants), although the difference was not significant.

Significant imbalance in proportion of risk factors

In the phase 3 RCT [9], participants were selected as eligible if they had one of the seven risk factors for severe illness from COVID-19: obesity (BMI ≧ 30), age > 60 year (old age), diabetes mellitus (DM), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), serious heart disease, and active cancer.

Jayk Bernal et al [9] describe that with the exception of an imbalance in sex, baseline characteristics were similar in the two groups including the above risk factors. However, in the interim analysis population, proportion of participants with

Figure2: Comparison of baseline characteristics (interim analysis population)



COPD was significantly less assigned in the molnupiravir group: odds ratio is 0.31 (95% CI: 0.13 to 0.73, p=0.0043) and those with obesity was marginally significantly more assigned in the molnupiravir group (odds ratio 1.33, 95% CI: 0.95 to1.86, p=0.094) by MedCheck's analysis [17].

Among the 7 risk factors, more patients with 2 risk factors (obesity and serious heart diseases) were assigned to molnupiravir group, while less patients with the other 5 risk factors (old age, DM, CKD, COPD and active cancer) were less assigned to the molnupiravir group.

The sum of the percentages of the participants who have risk factors other than obesity (group 10 in the Figure 2) was significantly lower in the molnupiravir group (43.4%) than in the placebo group (51.8 %). Odds ratio is 0.71 (95%CI: 0.54 to 0.95, p=0.019). If the sum of the percentages of risk factors was restricted to the 4 risk factors (DM, CKD, COPD and active cancer), odds of participants with important risk factors was almost 40 % lower in the molnupiravir group: Odds ratio is 0.61, 95%CI: 0.43 to 0.85 p = 0.0043 (Figure 2) [17].

Significant imbalances also in all-randomized population

Similarly, the sum of the percentages of the patients who have risk factors other than obesity in the all-randomised population was also significantly lower in the molnupiravir group (53.8%) than in the placebo group (59.4%). Odds ratio is 0.79 (95%CI: 0.64 - 0.98, p=0.031). If the sum of the percentages of risk factors were restricted to the 4 risk factors (DM, CKD, COPD and active cancer), odds ratio was 0.77 (95%CI: 0.61 - 0.97, p = 0.026) which shows the significant imbalance of risk factors in the both groups (Figure 3) [17].

If the hazard ratio of hospitalisation/death by a time-to-event analysis were adjusted by the baseline characteristics, it may become non-significant at all. For example, the ratio of hazard ratio for hospitalisation/death (0.69) to odds ratio of sum of baseline risk factors except obesity (0.79) was 0.87 (95%CI: 0.57-1.33) according the methods described by Kalossa [18].

Doubt about the randomisation

Significantly lower sum of proportion of participants with risk factors in the analysis of all-randomised population raises doubt as to whether the randomisation has been fairly conducted in the trial.

A further significant imbalance in the above risk factors in the interim analysis, and a great difference in the proportion of participants with COPD alone (odds ratio 0.31, p=0.0043) suggests the possibility that before the interim analysis, blinding might have been broken. Is there any possibility of selections of patients for interim analysis?

Subgroup analysis may not support the efficacy

In a subgroup analysis, it was reported that molnupiravir showed no efficacy for those with diabetes nor with severe heart disease, although it showed apparent efficacy for obese participants [9] (Figure 4A). No data for efficacy have been reported for those with CKD, COPD nor active cancer. In addition, it cannot be denied that the result of apparent effect on obese people and females may be affected by the bias of other risk factors. Hence, it may be hard to say that it is effective for these subgroups.

Two RCTs for moderate COVID-19 were terminated due to futility

According to the document submitted to the UK regulator by Merck Sharp & Dohme (UK) Ltd [13], hospitalisation/death was significantly reduced in the subgroup of moderate COVID-19 and the effect size was greater in the moderate patients (Risk difference=-8.0, 95%CI: -15.5, -0.5) than in the mild patients (-4.9, 95%CI:-10.5, 0.2) [13] (Figure 4B).

However, two RCTs for moderate COVID-19 have been terminated due to futility by the interim analysis **[19]**.

MOVe-IN trial also has serious imbalance in baseline severity

In the MOVe-IN trial [3], participants with

Figure3: Comparison of baseline characteristics (all-randomised population)

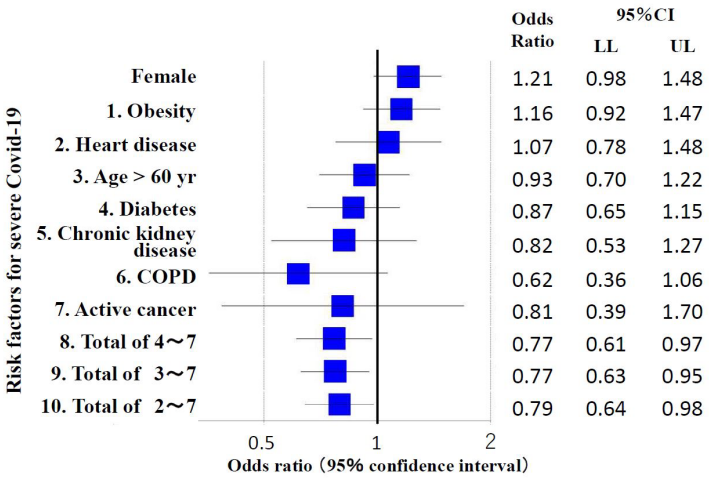
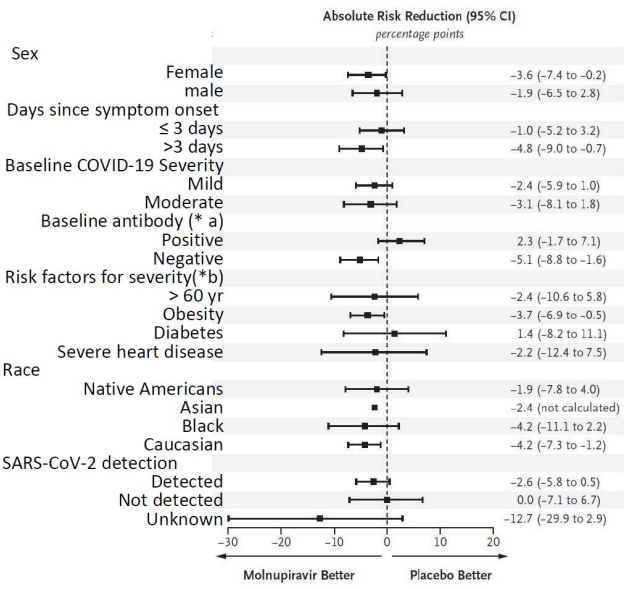


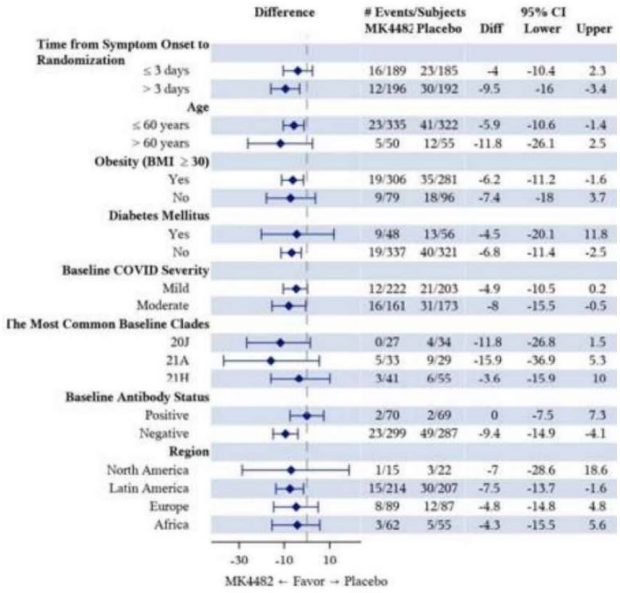
Figure4: Absolute risk reduction by Subgroups

A) all randomised population



Excerpt from Figure 3 of reference [9]

B) Interim Analysis population



Excerpt from Figure in p30 of reference [13]

a: Positive antibody against SARS-CoV-2 nucleocapsid. In other words, it is not an "antibody against spike protein" that is produced by a vaccine. It means that positive person has a history of COVID-19.

* b: Subgroup analysis results for chronic kidney disease, COPD, and active cancer have not been reported in the text and Supplementary appendix.

score 6 COVID-19 (hospitalized and administered oxygen by non-invasive ventilation or high flow) were significantly less assigned in molnupiravir groups (5/218=2.3%) than the placebo group (6/75=8.0%): OR=0.27 (95%CI:0.08-0.91, p=0.025). Despite this serious bias favouring molnupiravir group, non-significant increase of death was reported in molnupiravir group (13/218=6.0%) compared with placebo group (2/75=2.7%): OR=4.69 (95%CI: 0.60-36.50, p=0.105). If the baseline imbalance favouring molnupiravir group is adjusted, OR for all-cause mortality may be statistically significant. For example, the ratio of mortality odds ratio to odds ratio of baseline score 6 was 17.38 (95%CI:1.60-188.84) according the methods described by Kalossa [18].

Reanalysis is needed and the reasons of serious imbalance should be verified.

It is necessary to reanalyse acurate incidence of hospitalisation or death (MOVe-Out trial) and mortality rate (MOVe-IN trial) by adjusting baseline risk factors (MOVe-Out trial) and baseline severity especially of score 6 (MOVe-IN trial).

It is necessary to verify why the completely opposite or highly contradictory results were observed among RCTs targeted at moderate COVID-19.

Beware of DNA damage, bone marrow toxicity and mutations

Molnupiravir is a substance similar to some antivirals including favipiravir or ribavirin, which causes mutations not only in viral genes to prevent proliferation but also which may suppress human cell division [20-23]. Especially, bone marrow toxicity is the most serious concern, because irreversible myelosuppression (total blood cell damage) was observed in dogs that were treated with 0.4-fold the human equivalent dose according to the area under the curve (AUC) level of active form of molnupiravir at the 800 mg q 12 h human dose for 22 days and no observable adverse effect level (NOAEL) is only 0.13-fold the human dose [13].

Full clinical study reports should be disclosed and reanalysis is needed

As was warned by Sidebottom et al in the editorial of BMJ, in the absence of sufficient evidence of safety and efficacy raises serious concerns about further mistakes being made [24]. It seems that the warning has come true. The RCTs of antiviral agents for SARS-CoV-2, such as remdesivir [25,26] and baricitinib [27], which are authorized for emergency use in various countries also have contradictions.

In order to resolve these situations, as was conducted in the systematic reviews on neuraminidase inhibitors [28] including oseltamivir (Tamiflu) [29,30], clinical study reports should be disclosed and should be examined.

Conclusion

The efficacy of molnupiravir on COVId-19 has not been proven. There is also a risk of mutation of virus and of toxicity to the bone marrow (blood cells) in humans. Don't use molnupiravir.

Competing interests: None

Summary of this article is available as "Concern about baseline imbalance in mulnupiravir trials": a rapid response by Hama R. to an Editorials of British Medical Journal entitled ""*Molnupiravir's authorisation was premature" at:*
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