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Threat of a New Drug Disaster: What Can We Do?

Petition

Petition to Stop Plans for Routine Vaccination with Abrysvo®

MED CHECK

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Threat of a New Drug Disaster: What Can We Do?

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Last autumn,the Ministry of Health, Labour and Welfare(MHLW) decided to include Ablisvo,a matermal vaccie to prevent RS virus infection in their children, in the routine vaccinetion schedule starting in April 2026.

In the 32nd issue (April 2025),we concluded that Abrysvo was not recommended, as its harms outweigh its benefits. Deeply concerned by the scale of harm anticipated from its routine use, we have re-evaluated the data in exhaustive detail. Following rigorous internal deliberation, the editorial board determined to first present our arguments in international English-language medical journals. Subsequently, we have addressed this through a series of online "Extra edition". Furthermore, we have formally submitted a petition rquesting the MHLW to halt the inclusion of Abrysvo in the routine immunization program.

This action mirrors our historical precedent regarding the pediatric ointment for atopic dermatitis (Tacrolimus 0.03%). At that time, we submitted a petition requesting no-approval due to concerns over carcinogenicity. Approximately one week prior to the meeting of the relevant conuchi meeting—then the highest deliberative body for new drug approvals—we dispatched a formal petition to all committee members. Moved by the data we provided, the members engaged in nearly an hour of debate on the carcinogenic risk, resulting in the unprecedented measure of ordering a "re-execution of carcinogenicity studies." The drug was eventually approved in June 2003, but under exceptionally stringent conditions: patients had to be informed of the cancer risk and provide consent, and prescription records had to be handed directly to the patient.

In the United States, roughly two years after these strict Japanese regulations were implemented, the FDA issued a document highlighting the ointment's carcinogenicity. This was followed the next year by the mandate of a Black Box Warning and letters to parents. By late 2009, multiple large-scale epidemiological studies suggested a link to malignancies such as lymphoma. Our detailed analysis incorporating a 2021 systematic review confirmed a strong association with malignant lymphoma, particularly in children, validating our original warnings. Paradoxically, however, Japan saw a relaxation of these regulations in 2021. For a detailed discussion of these issues, please refer to MedCheck in English No.26(April 2023).http://medcheckjp.org/wp-content/uploads/2023/05/Eng-no-26.pdf

The current situation surrounding Abrysvo is hauntingly reminiscent of those events. As the Japan Institute of Pharmacovigilance (MedCheck), we remain committed to taking every possible measure, one step at a time, to safeguard public health.

Petition to Stop Plans for Routine Vaccination with Abrysvo®

In Japan, the Pfizer vaccine “Abrysvo®,” which is administered to pregnant women for the purpose of preventing respiratory infections caused by respiratory syncytial virus (RSV) in infants, became a publicly funded routine vaccination from April 2026.

As a result of a detailed review of clinical trials that were the basis for approval in issue No. 118 of MedCheck, it became clear that the harms outweigh the benefits. Subsequent further examination of clinical trials has made it even clearer that the harms exceed the benefits.

Therefore, on March 11, we submitted a petition to the government requesting the suspension of its routine vaccination program.

In the Editorial, under the title “Threat of a New Drug Disaster: What Can We Do?”, we considered the significance of submitting this request to the government, based on our past experience of appealing to the authorities and helping to prevent drug disasters.

We publish the petition submitted to the government. After the submission to the government, we held a press conference at the Ministry of Health, Labour and Welfare. In brief, please see the press release that summarized the key points presented on that occasion.

In addition, regarding this issue, we published three BMJ rapid responses showing the serious flaws in the phase 3 trial of Abrysvo, and also that although RSV test-positive infections decreased, test-negative infections increased, meaning that there was no benefit even for the children who were born. Please read them as well (ref. [13-15]).

March 11, 2026

To: Mr. Kenichiro Ueno

Minister of Health, Labour and Welfare

Petition to Stop Plans for Routine Vaccination with Abrysvo®

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Executive Summary

[1] Routine vaccination with Abrysvo should not be initiated until its efficacy and safety have been adequately confirmed.

The routine use, beginning in April 2026, of the vaccine Abrysvo® (hereinafter “Abrysvo”), administered to pregnant women for the prevention of RSV infection in infants, has been scheduled.

However, following a detailed review by MedCheck, numerous concerns have been identified regarding both the efficacy and safety of Abrysvo. The government should disclose the information necessary to resolve these concerns and, together with independent third parties, conduct a renewed evaluation of the vaccine’s efficacy and safety. Until such re-evaluation confirms that Abrysvo is both effective and safe, we request that routine vaccination with Abrysvo not be initiated.

We respectfully submit the following five requests:

1. To disclose of maternal medication and substance-use histories, which are strongly suspected to have contributed the apparent bias in favour of Abrysvo in the reported rates of congenital anomalies and neonatal deaths.
2. To conduct adjusted analyses using these data and to re-evaluate both efficacy outcomes (including hospitalised respiratory tract infections and hospitalised RSV infections) and adverse-event outcomes.
3. For efficacy outcomes, to include all lower respiratory tract infections, including both RSV-positive and RSV-negative cases, rather than RSV-positive cases alone, and to place particular emphasis on one-year hospitalisation data for respiratory tract infections.
4. To prioritise absolute risk reduction (ARR) over relative risk reduction (RRR: or vaccine efficacy [VE]), in benefit assessments, and to compare ARR with the risk difference (RD; absolute risk increase [ARI]) for serious adverse events in order to reassess whether the benefits outweigh harms.
5. To refrain from initiating routine vaccination until re-evaluation confirms that the benefits outweigh the harms.

[2] The principal concerns regarding efficacy and safety are as follows.

1. **Questionable safety of Abrysvo considering failure of similar GSK's product**

   A similar vaccine developed by GSK was halted during clinical development because of increased rates of preterm birth and neonatal death. It is therefore questionable whether Pfizer's closely related product, Abrysvo, should be considered safe.

2. **Suspected allocation imbalance favoring Abrysvo**

   The significantly lower combined rate of congenital anomalies and non-RSV-related infant deaths in the Abrysvo group strongly suggests that maternal medication/substance-use history may have been unevenly distributed in favor of Abrysvo. These data have not been disclosed, and potential confounding due to such history has not been adjusted for in outcome assessments, including both efficacy and safety evaluations.

3. **Unusually favourable outcomes for Abrysvo**

   The evaluation of outcomes appears unnatural. "Severe" RSV-positive medically attended lower respiratory tract infection (RSV-MA-LRTI), used as a prioritized primary endpoint, occurred implausibly less often in the Abrysvo group than medically attended or hospitalised cases, raising concern about possible unmasking and rendering this endpoint inappropriate.

4. **Overlooked rise in RSV-negative LRTIs (lower respiratory tract infections)**

   No adequate consideration has been given to the possibility that reductions in RSV-positive lower respiratory infections may be offset by increases in RSV-negative lower respiratory infections. When RSV-positive and RSV-negative medically attended LRTIs are assessed together, no net benefit of Abrysvo is observed.

5. **Absolute risk reduction (ARR) for benefit-harm comparison**

   The benefits of Abrysvo are presented almost exclusively in terms of relative risk reduction (RRR) for lower respiratory tract infections, i.e. vaccine efficacy (VE), while ARR has not been considered at all. For an appropriate comparison of benefits and harms, ARR for lower respiratory tract infections should be compared with the absolute risk increase (ARI) for harms, namely the risk difference (RD).

6. **Statistical interpretation should be applied appropriately**

   In the safety evaluation of Abrysvo, the government uses relative risks (risk ratios) for individual serious adverse events and interprets p-values>0.05 as indicating "no difference" and therefore "safety," whereas they should properly be interpreted as "insufficient evidence to claim a difference." This approach is inappropriate.

   Furthermore, even in cases where p-values are close to 0.1–0.2, situations in which the risk difference is as large as twice the ARR are still being interpreted as showing "no difference" or "safe," which is also incorrect. Beta error

(type II error) should be taken into account, confounding due to imbalance in allocation should be adjusted for, and the magnitudes of both benefits (efficacy) and harms should be re-evaluated.

7. Comparison using harmonised severity of efficacy and harm indicators

1) Appropriate indicator for efficacy and harm

Hospitalised RSV respiratory tract infection (efficacy indicator) was compared with serious adverse events (harm indicator).

2) The absolute risk reduction (ARR) was 0.5% in terms of hospitalised RSV-RTI

According to our analysis, even when assessed in RSV-positive cases, the 1-year ARR for hospitalised RTI was also approximately 0.5%. The number needed to treat for an additional beneficial effect (NNTB) was approximately 200.

3) Induced preterm delivery risk due to pregnancy complications exceeds infant benefit

The above-mentioned benefit (ARR 0.5%) is offset by the significant risk difference of 0.49% for induced preterm deliveries associated with serious hypertensive disorders of pregnancy (formerly known as "pregnancy toxemia"), and the risk difference of 0.65% for total induced preterm delivery due to pregnancy complications exceeded infant benefit. The number needed to treat to harm (NNTH) was 205 and 154, respectively.

In addition, the risk difference for all serious adverse events (requiring hospital-level care or higher) in mothers up to six months postpartum was 1.06% (p = 0.2127), with an NNTH of 95.

4) Infant harms exceed benefit by more than twofold

Among all serious adverse events in infants, excluding "congenital anomalies and deaths not attributable to RSV infection," which are suspected to reflect allocation bias, analysis of other serious adverse events showed a risk difference of 1.20% (p = 0.1249) over the first one or two years of life, with an NNTH of 83.

When these findings are interpreted under the assumption of p>0.05 as "no difference" or "safe," the probability of overlooking serious harm is considered high. Furthermore, after adjusting for confounding due to allocation imbalance, the results may also become statistically significant.

8. Routine vaccination may benefit about 2,500 people but harm more than 10,000 annually.

Although the results do not show statistical significance at the 0.05 level for type I error ("false-positive error"), we estimate the potential scale of harm that could arise from routine immunisation by avoiding overlooking true effects and taking into account possible allocation imbalance.

If 80% of pregnant women are vaccinated under a routine immunisation programme, approximately 500,000 women would be vaccinated in the initial period, resulting in a similar number of births. As a result, approximately 2,500 infants per year would avoid hospitalisation due to RSV infection within the first year of life. However, approximately 5,000 mothers would experience hospitalisalion-level adverse reactions within six months postpartum, of whom more than half would undergo induced preterm delivery, and half would experience preterm delivery indicated due to hypertensive disorders of pregnancy (previously-called "pregnancy toxemia"). In addition, it is estimated that approximately 6,000 infants would experience hospitalisation-level adverse reactions within the first one to two years of life.

Detailed Reasons for This Opinion

Because infection of infants with respiratory syncytial virus (hereinafter, RSV) may become severe and may result in death, the following have been approved in Japan for its prevention: the RSV vaccine administered to pregnant women (Abrysvo®) [1,2], and the monoclonal antibodies palivizumab (Synagis®) [3,4] and nirsevimab (Beyfortus®) [5,6], intended for high-risk newborns and infants.

Among these, it was decided in November 2025 that Abrysvo, administered to pregnant women, would be

introduced as a publicly funded routine vaccination beginning in April 2026 [7]. MedCheck analyzed mainly the results of the Phase III clinical trial of Abrysvo [8–10], which formed the basis for approval, and already pointed out in Issue No.118 [2] that the harms outweighed the benefits. Thereafter, routine vaccination was decided upon; however, articles in the British Medical Journal (BMJ) have raised debate regarding why two products developed by different companies, which are otherwise very similar, have been associated with divergent safety findings-one was considered harmful while Abrysvo was not. Concerns have also been raised regarding the need to verify preterm birth with Abrysvo [11], and the conduct of informed consent [12].

Therefore, we have newly examined in detail the scale of harms that may occur if vaccination is implemented on a wide scale [13–19].

1. Questionable safety of Abrysvo considering failure of similar GSK's product

Pfizer's RSV vaccine is a non-adjuvanted vaccine using as its antigen the F-protein utilized by RSV when infecting cells (RSVpreF derived from RSV-A and RSV-B subgroups). On the other hand, for the same purpose, GSK similarly developed a non-adjuvanted vaccine candidate using an antigen common to RSV subtypes A and B (RSVpreF3), and conducted a Phase III trial in pregnant women. However, because preterm birth increased by 38% compared with the placebo group (Relative Risk = 1.38; 95% Confidence Interval [95% CI]: 1.08, 1.75), and neonatal mortality doubled (Relative Risk = 2.16; 95% CI: 0.62, 7.55), development was suspended at that stage [20].

2. Suspected allocation imbalance favoring Abrysvo

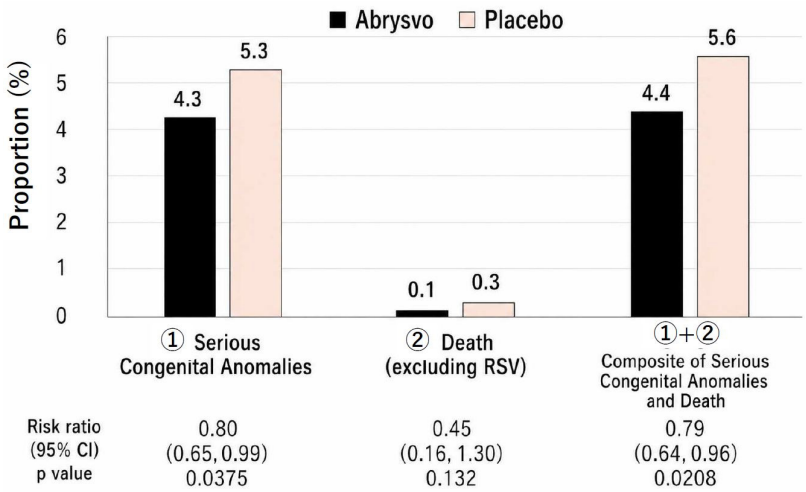
All Abrysvo trials [8–10] were placebo-controlled randomized controlled trials (RCTs). This presupposes that allocation between the vaccine group and placebo group was balanced. However, in the Phase III trial [8–10], there may have been imbalance in random allocation.

If pregnant women ingested (used) substances that do not cause congenital anomalies, congenital anomalies would neither increase nor decrease. Rather, they should occur at approximately the same rate in both groups. On the other hand, if substances that interfere with fetal development were ingested (used), congenital anomalies would be expected to increase.

However, in the Phase III trial of Abrysvo, serious congenital anomalies were fewer in the Abrysvo group than in the placebo group, and this difference was statistically significant. That is, in the principal report [8], the vaccine group was 4.3% (152/3568) and the placebo group was 5.3% (189/3558), with a risk ratio of 0.80 (95% CI: 0.65, 0.99), p = 0.0375 [2,13,16] (Figure 1).

Such an imbalance could occur if mothers in

Figure 1: Imbalances in congenital anomalies and deaths raise suspicion of allocation bias.



The total of ① and ② takes into account one overlapping case of death due to congenital anomaly.

the placebo group had been exposed at a high rate to external risk factors that increase congenital anomalies, such as anticonvulsants, sleeping pills, anxiolytics, antidepressants, alcohol, illegal drugs, radiation, smoking, or certain infections (for example rubella, excluding RSV infection).

The protocol [8] stated "current substance use, and obstetric history・・・ will be generated for each group based on the maternal safety population." However, in the published Phase III trial papers [8–10], in the summary technical documentation, and in the review report [1], only maternal age, gestational week at vaccination, and race were reported as baseline characteristics, while medication (substance) use history was not described.

Further, in the Phase II trial [1], the proportion of congenital anomalies was higher, though not statistically significant, in the Abrysvo group (21.5% = 17/79) than in the placebo group(11.5% = 9/78): Risk Ratio = 1.86 (95% CI: 0.89, 3.93), p = 0.093. Such a marked difference between the results of the Phase II and Phase III trials raises further doubts regarding the appropriateness of randomization in the Phase III trial.

The proportion of congenital anomalies among newborns is generally 3–4%. However, the proportions in the clinical trials considerably exceeded this: Phase III placebo group: 5.7% [8] , Phase II Abrysvo group: 21.5% , Phase II placebo group: 11.5%. Maternal medication (substance) use history—particularly use of sleeping pills, anxiolytics, antidepressants, anticonvulsants, illegal drugs, and similar agents—should be disclosed as important background factors that may cause congenital anomalies.

Next, we discuss mortality imbalance. Short gestational age at delivery, namely preterm birth, is an important factor affecting increased neonatal mortality and complication morbidity [21]. In the clinical trial of the similar GSK vaccine, as mentioned in section **1**, the risks of both preterm birth and neonatal death were increased [20]. On the other hand, in the Abrysvo trial, although preterm birth increased to a level approaching statistical significance, the total number of deaths unrelated to RSV was approximately half that in the placebo group(5 vs 11 in the principal report [8] and 8 vs 13 in the final report [9]), although these differences were not statistically significant at the alpha-error level of 0.05.

The combined risk ratio for congenital anomalies and deaths unrelated to RSV was 0.79 (95% CI: 0.64, 0.96), p= 0.0208, which was statistically significant (after taking into account one overlapping death due to congenital anomalies).

If imbalance existed between groups in maternal medication (substance) use history, it could affect not only congenital anomalies in newborns but also mortality, and could greatly influence the incidence of various other adverse events.

For the above reasons, medication (substance) use history in the Phase III Abrysvo trial should be disclosed, and if imbalance existed, the primary outcomes and adverse events should be reanalysed with adjustment for medication use history.

3. Unusually favourable outcomes for Abrysvo

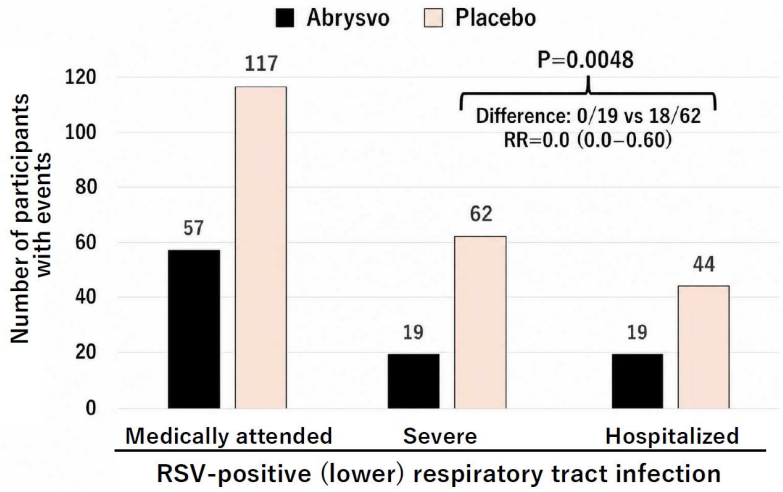
Severe RSV-positive medically attended lower respiratory tract infection (severe RSV-MA-LRTI; hereinafter abbreviated as severe RSV cases) is defined as medically attended respiratory tract infection (MA-RTI) with a positive RSV test and accompanied by at least one of the following signs [8]: Fast breathing (respiratory rate[RR] ≥70 bpm for <2 months of age [60 days of age], ≥60 bpm for ≥ 2 months to <12 months of age, or ≥50 bpm for ≥12 months to 24 months of age), SpO_2 <93%; or other more severe clinical signs.

According to the results of the principal report [8], severe cases appear to have included cases milder than hospitalised RSV-RTI (hereinafter abbreviated as hospitalised cases). This is because, during the first 180 days after birth, combining both groups, there were 81 cases classified as severe cases (S), whereas there were 63 hospitalised cases (H).

If allocation in the Phase III RCT of Abrysvo (MATISSE trial [8–10]) had been fair and masking complete, the ratio of "hospitalised cases (H)" to "severe cases (S)" should have been similar in the Abrysvo group (Ha/Sa) and placebo group (Hp/Sp). Accordingly, 1 − H/S, namely (S−H)/S, should also have been similar in both groups.

Up to 90 days after birth, the numbers of "severe" and "hospitalised" cases were similar in both groups (the number of "hospitalised" cases was slightly higher in

Figure 2: The extreme difference in severe cases suggests possible unmasking



For medically attended cases and hospitalised cases, Placebo : Abrysvo ≈ 10 : 5. For severe cases alone, it was 10 : 3, with fewer in the Abrysvo group. The risk ratio (RR) of severe cases without hospitalisation among sever cases in Abrysvo group compared with placebo group was 0.0 (95% CI: 0.0, 0.60), P = 0.0048. These data suggest the possibility of failure of blinding.

the Abrysvo group, but the difference between groups was extremely small).

However, among children classified as severe cases by 180 days after birth, which was treated as a prioritized primary outcome, the number of cases not resulting in hospitalization (S−H) was 18 cases (62 - 44) in the placebo group and 0 cases (19 - 19) in the Abrysvo group.

Comparing the proportion 0/19 in the Abrysvo group with 18/62 in the placebo group, the risk ratio was 0 (95%CI:0-0.60, p= 0.0048 by Fisher's exact test (two-sided)). Thus, the difference in proportions was statistically significant (Figure 2).

Therefore, in the Phase III RCT, the proportion of severe cases reported by 180 days after birth in the Abrysvo group relative to the placebo group was too low compared with medically attended cases and hospitalised cases. This strongly suggests that masking was incomplete, and that evaluators may have known whether participants had received Abrysvo or placebo. In other words, it strongly suggests the possibility of failure of masking, making it highly likely that severe cases were not evaluated fairly, and that the efficacy of Abrysvo was overestimated.

Accordingly, severe cases (severe RSV-MA-LRTI) are of low reliability as a primary endpoint, and it is inappropriate to prioritize them as the primary outcome.

Together with the preceding section suggesting imbalance in allocation, these data, which suggest a failure of masking, seriously impair the reliability of the Phase III trial of Abrysvo. Verification using the original data from the clinical study report is therefore necessary.

4. Overlooked rise in RSV-negative LRTIs (lower respiratory tract infections)

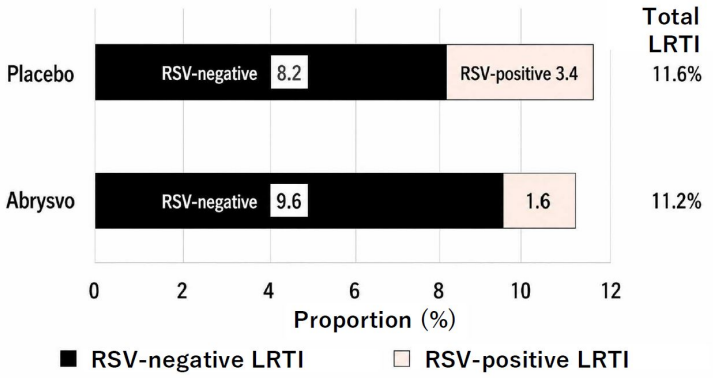
As examined in detail in Issue No. 118 (May 2025) of MedCheck [2], when severe RSV test-positive cases or medically attended cases within 90 days and within six months after birth are used, vaccine efficacy (VE) appears to exist; however, for medically attended infant lower respiratory tract infection cases due to all causes, there was no benefit at any time point [2] (Figures 3-A and 3-B).

Figure 3 shows a comparison of the proportions of RSV-positive, RSV-negative, and total medically attended lower respiratory tract infection cases. Figure 3-A shows, in enlarged form, only the results through 180 days after birth. RSV-positive cases decreased by 1.8%, from 3.4% to 1.6%; however, RSV-negative cases increased by 1.4%, from 8.2% to 9.6%, and the total changed from 11.6% to 11.2%, thus in substance not decreasing at all.

Figure 3-B shows the transition of cumulative proportions at each time point through 360 days after birth. It is clear that there was no difference in the proportion of total medically attended lower respiratory tract infection cases at any time point.

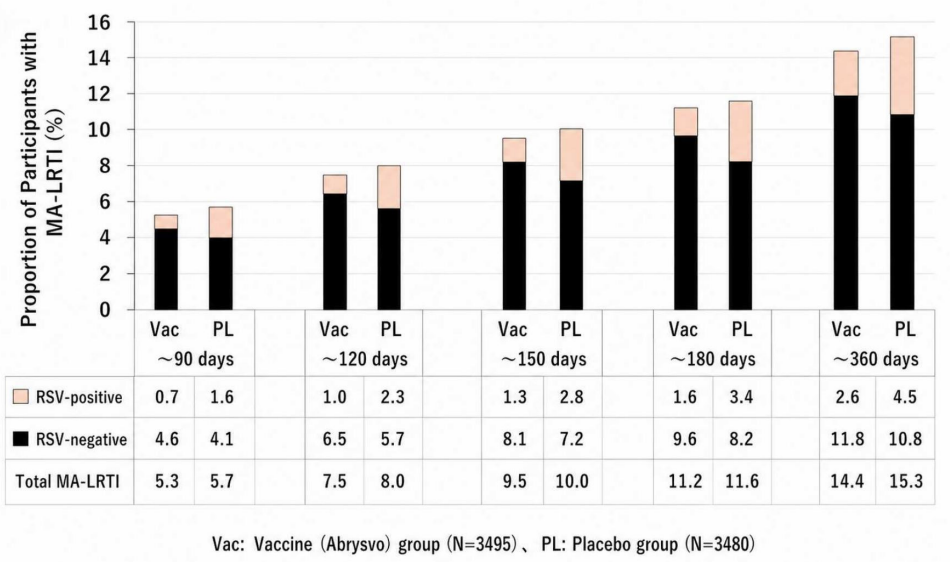
Figure 3: Comparison of RSV-positive, RSV-negative, and total medically attended LRTI cases

A: Comparison through 180 days



RSV-positive cases decreased by 1.8%, from 3.4% to 1.6%; however, RSV-negative cases increased by 1.4%, from 8.2% to 9.6%, and the total changed only from 11.6% to 11.2%, indicating virtually no overall reduction. LRTI: lower respiratory tract infection.

B. Trends of cumulative proportions



Vac: Vaccine (Abrysvo) group (N=3495), PL: Placebo group (N=3480)

RSV-negative lower respiratory tract disease should originally show no difference; however, overall, RSV-negative lower respiratory tract disease was more frequent in the Abrysvo group, and RSV-negative cases increased in the vaccine group by a proportion corresponding to the proportion by which RSV-positive cases decreased. This suggests an effect involving a combination of false-negative conversion among RSV-infected persons and a phenomenon related to viral interference. If test-positive medically attended lower respiratory tract infections (the □ portion in Figure 3) are subtracted from all medically attended lower respiratory tract infections (the total of the □ and ■ portions in the bar graph of Figure 3), what remains is the proportion of test-negative medically attended lower respiratory tract infections (the ■ portion in Figure 3). Looking at this, test-negative lower respiratory tract infections increased by a proportion approximately corresponding to the reduction in test-positive lower respiratory tract infections, and therefore the total medically attended lower respiratory tract infections became almost unchanged. It should be noted that all "severe cases" and all "hospitalised cases" were not reported, and therefore RSV-negative "severe cases" and "hospitalised cases" cannot be calculated.

The fact that there was no difference at any time point in medically attended infant lower respiratory tract infection cases due to all causes is also acknowledged in the Fact Sheet [7,22].

In addition, the web materials for MedCheck Issue No.118 [2] show the cumulative total number of lower respiratory tract infection cases expressed as numbers of persons, together with the transition of the breakdown into RSV-positive and RSV-negative cases: https://medcheckjp.org/wp-content/uploads/2025/03/118f05.pdf (in Japanese).

Moreover, as stated in the MedCheck [2], severe or life-threatening adverse events from birth to one month of age were more frequent in the vaccine

group, and by this fact alone, harms exceeded the benefit (reduction of RSV-positive lower respiratory tract infections). For pregnant women as well, severe or life-threatening maternal adverse events within one month after vaccination were significantly more frequent, and in particular severe pre-eclampsia (hypertension during pregnancy accompanied by proteinuria), which is an important pregnancy complication, and severe preterm delivery related events (preterm delivery, premature labour, or preterm premature rupture of membranes) were significantly more frequent [2].

5. Absolute risk reduction (ARR) for benefit-harm comparison

The government's claimed "evidence base" for the decision to introduce Abrysvo into the publicly funded routine vaccination program is described in the Fact Sheet [7,22]. The Fact Sheet states that, based on the results of the Phase III trial [8–10], "severe" lower respiratory tract infection due to RSV within 90 days after birth or within 180 days after birth was prevented by 82% and 69%, respectively, and that although adverse events showed a tendency for preterm birth and hypertensive disorders of pregnancy to be more frequent, there was no significant difference between the vaccine group and the placebo group, and therefore the vaccine was safe. The Japan Pediatric Society has also recommended vaccination on the same grounds [23].

The Fact Sheet presents figures such as vaccine efficacy of 82% and 69%, numbers that give the impression that the vaccine works very well. However, these are results of analyses using "severe RSV" cases, for which, as pointed out in section **2**, masking may have been broken. When hospitalised RSV cases are used, efficacy is 56.8%, and when hospitalised RSV cases after one year are used, efficacy is 33.3%.

A further important point is that the percentages expressing efficacy are the relative rate of reduction of disease (RRR, Relative Risk Reduction: **Note 1a**). For comparison with harms, what is important is by how many percentage points disease was actually reduced (ARR, Absolute Risk Reduction: **Note 1b**), and by how much harms increased (Absolute Risk Increase, or RD, Risk Difference: **Note 1c**).

The absolute risk reduction (ARR%) was only 0.78% at 90 days and 1.24% at 180 days even for severe RSV cases, and for hospitalised RSV respiratory tract infection cases it was only 0.72% at 180 days and 0.55% at 360 days (p.11, **Figure 4** in section **7**: p = 0.0473). According to the final report [10], for hospitalised RSV respiratory tract infection cases it was only 0.73% at 180 days and 0.46% at 360 days (**Figure 4**). Moreover, when calculating how many vaccinated persons are required for one person to receive benefit (NNTB: **Note 1d**), the result is one in 182 persons or one in 218 persons, although the p-value was 0.1257, and not statistically significant.

Note 1：**(a)** Vaccine efficacy is usually expressed as the relative reduction rate (RRR, relative risk reduction). If the number of events (disease cases) is E, the denominator is N, risk is R, the placebo group is p, and the vaccine group is v, then from the placebo-group risk Rp = Ep/Np and the vaccine-group risk Rv = Ev/Nv, the relative risk (or risk ratio RR) = Rv/Rp. Relative risk reduction = (Rp − Rv)/Rp = 1 − Rv/Rp = (1 − RR) × 100(%) This expresses vaccine efficacy (VE: vaccine efficacy).

(b) The index expressing this is absolute risk reduction (ARR: absolute risk reduction). ARR = Rp − Rv

(c) The index expressing this is absolute risk increase, or risk difference (risk reduction: RD). RD = Rv − Rp = −ARR

(d) Number needed to treat for an additional beneficial effect (NNTB) NNTB = 1/ARR

6. Statistical interpretation should be applied appropriately

In the Fact Sheet [7,22], under the section on infant safety, it is stated that "Small for gestational age (SGA) was 6.9% in the vaccine group and 6.4% in the placebo group; low birth weight (2,500g or less) was 5.1% in the vaccine group and 4.3% in the placebo group; congenital anomalies were 5.6% in the vaccine group and 6.7% in the placebo group; developmental delay was 0.7% in the vaccine group and 0.5% in the placebo group; and no differences were observed between the two groups." Thus, the incidence proportions of individual adverse events were compared between the two groups, and because "no differences were observed," the vaccine was regarded as safe.

In addition, regarding preterm birth, it is stated that: "In the MATISSE trial, although the incidence of preterm birth was not statistically significant, a numerical imbalance was observed, with 5.7% in the vaccine group and 4.7% in the placebo group

Table 1: Proportion with preterm birth in the Phase III Clinical Trial (MATISSE) of Abrysvo (From Table 4 of the Fact Sheet)

Populations	Proportion with preterm birth Vaccine group(%)	Placebo group (%)	Risk ratio (RR)	95% confidence interval
Overall population	5.7	4.7	■ 1.20	0.98-1.46
By vaccination timing				
Gestational age: 24 to<28 w	6.8	6.6	1.03	0.73-1.46
Gestational age: 28 to <32 w	6.8	4.8	1.43	1.02-2.02
Gestational age: 32 w or more	4.3	3.7	1.16	0.83-1.63
By income level				
High-income countries	5.0	5.0	▼ 1.00	0.79-1.28 ▲
Non-high-income	7.0	4.0	1.73	1.22-2.47
Upper-middle-income	7.5	4.2	1.80	1.25-2.60
Lower-middle-income	2.6	5.1	0.51	0.05-5.43
Low-income	3.1	2.1	1.48	0.25-8.69

Quoted from Table 4 of the Fact Sheet [7,22]. Symbols such as ■, ▲, and ▼ were added by our Center.

(RR: 1.20 [95% CI: 0.98, 1.46])…. On the other hand, in the Japanese subgroup, the incidence was lower in the vaccine group (vaccine group: 3.0%, placebo group: 5.6%, RR: 0.54 [95% CI: 0.22, 1.33]). … The European Medicines Agency (EMA) states that, although preterm birth increased slightly among pregnant women in the high- and middle-income country group, this difference was not statistically significant, the absolute increase in the number of preterm births was small, and as a result did not lead to an increase in adverse neonatal outcomes."

However, as seen in Table 1 above (Table 4 of the Fact Sheet [7,22]), the upper limits of the 95% confidence intervals of the subgroup risk ratios for preterm birth are 1.28 for high-income countries (▲), and 1.33 for Japan (described above). These values are larger than the point estimate of the risk ratio for the overall population, which is 1.20 (■). In other words, this indicates that the value of 1.20, the point estimate for the overall population, is compatible with both the high-income-country subgroup and the Japanese subgroup. Moreover, the upper limits of the 95% confidence intervals of the risk ratios for these high-income countries and Japan are greater than the lower limit of the 95% confidence interval of the risk ratio for non-high-income countries, which is 1.22 (▼). Furthermore, it is difficult to discern from the data in Table 4 above (1.00, 1.80, 0.51, and 1.48 in order from high-income countries onward) any tendency for the risk of preterm birth to become higher as national income becomes lower.

Therefore, merely because the point estimates for the subgroups of high-income countries and Japan are 1.00 (high-income countries) or 0.54 (Japan), and do not exceed 1 as in the overall population, it is extremely dangerous to regard them as completely heterogeneous from the risk ratios of the overall population or of non-high-income countries, to conclude that "Abrysvo is considered safe in Japan and other high-income countries," and to ignore the numerically imbalanced result in the overall population, which had a p-value of 0.070 and was close to statistical significance, thereby concluding "safe." Accordingly, it is necessary to consider the overall population risk ratio of 1.20 (p=0.070). Moreover, the risk difference is 1.0%, which is almost twice the ARR of approximately 0.5% for hospitalised RSV respiratory tract infection cases at 360 days after birth.

In considering this important issue, it is also essential to consider how benefits and harms are compared. If comparison is made using relative benefit, for example, if in 1,000 persons, 15 persons (1.5%) in the placebo group are reduced to 5 persons (0.5%) in the vaccine group, this becomes one-third. In other words, it would mean a statistically significant 67% reduction. However, in terms of absolute risk reduction, this means only a reduction of merely 1%.

On the other hand, for example, suppose harms increase from 170 persons out of 1,000 (17%) in the placebo group to 200 persons (20%). At the commonly

used p-value threshold of 5% (0.05), this is not statistically significant (p=0.08), but the absolute risk increase (risk difference) is 3.0%. However, because it cannot be said that there is a statistically significant difference in harms, if this is recognized as "no difference," it comes to be regarded as safe. We believe that, in such a case, harms would be overlooked.

In statistics, it is common to use a probability of 0.05 as the significance testing level for the error of concluding that there is a difference when in truth there is none (Type I error, also called alpha error, or a rash error). However, in statistics, the beta error—the error of saying "there is no difference" when in truth there is a difference (also called a careless error, or an oversight error)—is also important.

In evaluating efficacy, emphasis must be placed on alpha error, that is, incorrectly concluding that something ineffective is effective. However, if alpha error is made too strict in evaluating harms, this may lead to overlooking harms that truly exist, thereby allowing damage to expand; therefore beta error must also be taken into consideration.

Furthermore, with regard to this Phase III trial of Abrysvo, the results concerning congenital anomalies and neonatal death strongly raise suspicion of serious imbalance in allocation. Taking this into account, the numerical imbalance of a 1.0% risk difference with a p-value of 0.070 should be considered statistically meaningful, and this harm should not be overlooked.

7. Comparison Using Harmonised Severity between Efficacy and Harm Indicators

1) Appropriate indicator for efficacy and harm

The principal concern of MedCheck is to conduct an integrated analysis of the benefits and harms of Abrysvo. As stated in section **4**, RSV-positive medically attended lower respiratory tract infection (RSV-MA-LRTI) is itself offset by RSV-negative medically attended lower respiratory tract infection (MA-LRTI), and on that basis alone it can be said that Abrysvo offers no benefit. However, here we examine whether benefit outweighs harm when the reduction in RSV-positive cases, which served as the basis for approval, is regarded as the benefit.

To do so, it is necessary to compare outcomes of similar severity: the severity of the vaccine efficacy outcome (RSV infection) and that of adverse events. As pointed out in section **3**, "severe" cases are inappropriate as an efficacy outcome because there is a possibility of data manipulation; therefore, "hospitalised cases" (serious cases requiring hospitalisation or more severe outcomes) are used.

The term "serious" in serious adverse events (SAEs) refers to cases requiring hospitalisation, prolonged hospitalisation, persistent disability, death, and similar outcomes [24]. Therefore, these correspond in severity to "hospitalised RSV infection cases" as the benefit outcome, and "serious adverse events" should be used as the harm outcome for comparison.

2) The absolute risk reduction (ARR) was 0.5% in terms of hospitalised RSV-RTI

According to MedCheck's analysis, when evaluated using RSV-positive cases, as shown in section **5**, the one-year ARR for hospitalised RTI was approximately 0.5% (though this was not statistically significant in the final report). The NNTB was approximately 200.

Figure 4 shows the proportion of RSV-positive hospitalised respiratory tract infections up to one year of age, from the primary report [8] and the final report [9]. The risk difference was 0.55% in the primary report [8] (p=0.0473) and 0.46% in the final report [9] (p=0.1257) (for details, see section **5**).

3) Induced preterm delivery risk due to pregnancy complications exceeds infant benefit

Figure 5 shows the proportion of induced preterm deliveries due to pregnancy complications including serious hypertensive disorders of pregnancy (HDP), formerly known as pregnancy toxemia. The following data appear in the main text of the final report [9] as adverse events related to pregnancy and childbirth.

More than one-third of pregnant participants with preterm deliveries reported additional adverse events other than preterm delivery (RSVpreF 42.2%, placebo 33.1%), which were most commonly preeclampsia (RSVpreF 11.7%, placebo 5.8%), any premature rupture of membranes (RSVpreF 6.8%, placebo 8.1%), and gestational hypertension (RSVpreF 3.9%, placebo 2.9%).

Quoted from reference [9]. RSVpreF is an abbreviation for Abrysvo. Preeclampsia is another term for hypertensive nephropathy of pregnancy.

Figure 4: Proportion of RSV-positive hospitalised respiratory tract infection cases (up to one year of age)

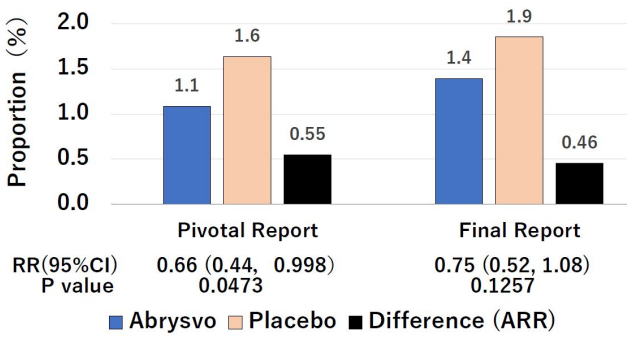
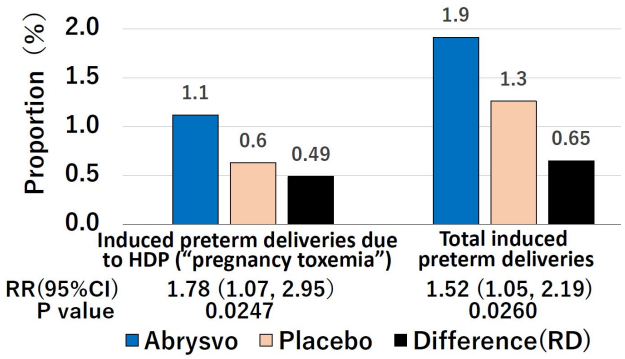


Figure 5: Proportion of induced preterm deliveries due to complications (final report)



The risk difference for induced preterm delivery in Figure 5 is larger than the ARR for RSV-positive hospitalised respiratory tract infection in Figure 4. Moreover, in the final report the ARR for hospitalised respiratory tract infection was not statistically significant (Figure 4, right), whereas the risk difference for induced preterm delivery was statistically significant (Figure 5, both). "Pregnancy toxemia" is now referred to as serious hypertensive disorders of pregnancy (HDP). HDP includes gestational hypertension without proteinuria, preeclampsia (gestational hypertension with proteinuria), and eclampsia when seizures occur.

Multiplying these percentages by the number of pregnant women with preterm delivery (206 in the Abrysvo group and 172 in the placebo group), there were 24 versus 10 cases complicated by preeclampsia, and 8 versus 5 cases complicated by gestational hypertension, for totals of 32 versus 15 hypertensive disorders of pregnancy. Using the numbers of vaccinated mothers (3682 in the Abrysvo group and 3675 in the placebo group), the risk ratio for 32 (0.9%) versus 15 (0.4%) was 2.14 (95% CI: 1.15, 3.95), p=0.0133, meaning more than double the risk in the vaccine group and statistically significant. The risk difference was 0.46% (these data are omitted from Figure 5).

Meanwhile, Appendix 10 of the final report [9] ("Adverse Events that are Potential Indications for Preterm Delivery Among Pregnant Participants With Preterm Delivery") showed that hypertensive-disorder-related events qualifying as complications leading to induced preterm delivery were: eclampsia 2 vs 1, preeclampsia 32 vs 18, gestational hypertension 9 vs 5, for totals of 41 vs 23 in the Abrysvo and placebo groups, respectively. The risk ratio was 1.79 (1.07, 2.98), p=0.0247, and the risk difference was 0.49% (Figure 5 left).

Pregnancy complications other than hypertensive disorders of pregnancy(HDP) that became indications for induced preterm delivery included amniotic cavity infection (1 vs 2), fetal growth restriction (7 vs 4), gestational diabetes (4 vs 3), hemorrhage in pregnancy (2 vs 1), premature separation of placenta (8 vs 7), placental insufficiency (1 vs 0), threatened uterine rupture (0 vs 2), and others, totaling 70 vs 46. The risk ratio was 1.53 (95% CI: 1.05, 2.22), p=0.0260, and the risk difference was 0.65% (Figure 5 right).

It is clear that the above totals of 41 vs 23, and 70 vs 46, represent conditions serious enough to justify induced preterm delivery because leaving them untreated would affect maternal and fetal prognosis, and therefore correspond to serious adverse events.

The risk difference of 0.46–0.49% for induced preterm delivery due to hypertensive disorders of pregnancy is roughly the same level as the absolute reduction in one-year infant RSV hospitalisations (0.46–0.55%), and the risk difference of 0.65% for total induced preterm delivery including other causes exceeds it. On this basis alone, it can no longer be said that benefits outweigh harms.

The number of mothers experiencing serious adverse events from vaccination to six months postpartum was, according to FDA materials [20], 598 in the Abrysvo group (16.2% of 3682) and 558 in the placebo group (15.2% of 3675). The p-value was 0.2127, and therefore not statistically significant by the alpha-error threshold of 0.05. However, the risk difference was 1.06%. This corresponds to almost twice the absolute reduction in one-year infant RSV hospitalisations (0.46–0.55%).

These results should statistically be interpreted

as data for which "a difference cannot be said to exist," when considering the possibility of overstating significance (alpha error). However, given the strong suspicion of allocation bias in the trial, we considered that, had randomisation been fair, a difference would likely have been demonstrable, and therefore we calculated NNTH (number needed to treat for an additional harmful effect) here.

What is especially noteworthy is that preterm deliveries requiring medical intervention due to hypertensive disorders of pregnancy, which were considered to occur at approximately the same frequency as RSV-positive hospitalised cases, and preterm deliveries requiring medical intervention due to pregnancy complications, which were estimated to occur at the same or higher frequency, showed statistically significant differences even without such assumptions, more than offsetting the benefit to infants.

Further, as noted above, considering beta error (missed detection error) and the strong suspicion of allocation bias in the trial, the point that harm to mothers reached twice the level of benefit to infants cannot be ignored. Taking these points into account, and assuming statistical significance for the sake of argument, our calculation of NNTH indicates that if 95 pregnant women receive Abrysvo, one pregnant woman will experience serious harm.

If 200 pregnant women receive Abrysvo, one infant RSV respiratory tract infection hospitalisation can be prevented, but in exchange two mothers will suffer harm equivalent to hospitalisation or worse: one induced preterm delivery due to any hypertensive disorders of pregnancy, and one or more total induced preterm deliveries due to pregnancy complications including hypertensive disorders of pregnancy and others.

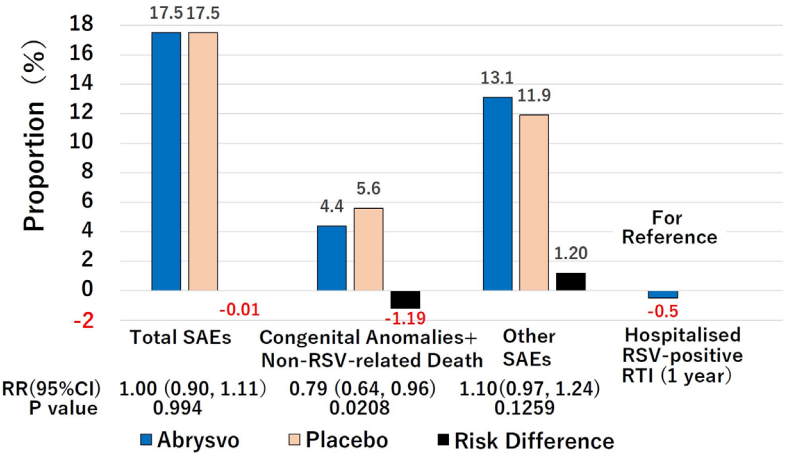
4) Infant harms exceed benefit by more than twofold

The actual number of infants experiencing at least one serious adverse event (SAE) from birth until study completion (one or two years depending on the follow-up period) was not reported either in the primary report [8] or the final reports [9,10]. According to FDA materials [20], there were 625 infants in the Abrysvo group (17.52% of 3568) and 623 in the placebo group (17.51% of 3558), showing no difference at all (Figure 6).

However, as shown in section **2**, the combined total of congenital abnormalities and non-RSV-related deaths, which should not decrease, was significantly lower with Abrysvo, raising suspicion of allocation bias [2,13,16].

Even in randomised controlled trials, adjustment for imbalanced background factors is commonly performed when allocation bias is suspected. However, in the Abrysvo trial, histories of drug/substance use—likely to have been imbalanced—were not disclosed,

Figure 6: Comparison by category of serious adverse events occurring in infants (up to age 1–2 years: primary report)



The width of harm after excluding congenital abnormalities and non-RSV-related deaths, which should not decrease, namely the risk difference for other serious adverse events of 1.20%, exceeds by more than double the width of benefit in Figure 4 (absolute risk reduction for hospitalised respiratory tract infection of 0.46–0.55%).

Table 2: Comprehensive evaluation of serious events in mothers and infants from maternal Abrysvo vaccination (summary of Phase III trial)

Outcomes [Reference]	Abrysvo (a)			Placebo (p)			RD (%) (−ARR:%)	NNTB (H)*a	Risk Ratio (RR)		P value
	Na	Ea	a%	Np	Ep	p%			RR	95%CI	
①a RSV-confirmed hospitalised LRTI (1 year) [8]	3,495	38	1.1	3,480	57	1.6	−0.55	182	0.66	(0.44,1.00)*b	0.0473
①b RSV-confirmed hospitalised LRTI (1 year) [9]	3,585	50	1.4	3,563	66	1.9	−0.46	218	0.75	(0.52, 1.08)	0.1257
②a Maternal: Induced preterm deliveries due to HDP*c [9]	3,659	41	1.1	3,646	23	0.6	0.49	204	1.78	(1.07, 2.95)	0.0247
②b Maternal: All induced preterm deliveries [9]	3,659	70	1.9	3,646	46	1.3	0.65	154	1.52	(1.05、2.19)	0.0260
②c Maternal: All SAEs (～ postpartum 6M) [20]	3,682	598	16.2	3,675	558	15.2	1.06	−95	1.08	(0.96, 1.23)	0.2127
③ Infant: All SAEs (full study period; 1 or 2 years) [20]	3,568	625	17.5	3,558	623	17.5	0.01	—	1.00	(0.89, 1.13)	0.9938
④ Infant: Serious congenital anomalies *d [8]	3,568	152	4.3	3,558	189	5.3	−1.05	—	0.80	(0.65, 0.99)	0.0375
⑤ Infant: Non-RSV-related deaths *e [8]	3,568	5	0.1	3,558	11	0.3	−0.17	—	0.45	(0.16, 1.30)	0.1317
⑥ Infant: ④ + ⑤ *f	3,568	157	4.4	3,558	199	5.6	−1.19	—	0.79	(0.64, 0.96)	0.0208
⑦ Infant: Other SAEs (③ excluding ⑥) *g	3,568	468	13.1	3,558	424	11.9	1.20	−83	1.10	(0.97, 1.24)	0.1259

N: denominator; E: number of events; a: Abrysvo group; p: placebo group; ARR (absolute risk reduction) = p-a (%); risk difference = a-p (%). NNTB = 100/ARR = -100/risk difference (RD) = -100/(a-p). RR: risk ratio (adverse events are also shown as RR for consistency with lower respiratory tract infection outcomes). 95% CI: 95% confidence interval.

*a: NNTB = number needing vaccination for one person to benefit (also called NNVB). If negative, it is the number needing vaccination for one person to be harmed. For items ③–⑥, NNTB(H) is not shown for the reasons in *c and *d.

*b: The 99.17% confidence interval for vaccine efficacy (%) adjusted for multiplicity with other endpoints was reported as 33.3 (-17.6 to 62.9), which is not statistically significant. Calculated from this, the risk ratio is 0.67 (0.37, 1.18).

*c: HDP: hypertensive disorders of pregnancy, including gestational hypertension without proteinuria, preeclampsia (hypertension with proteinuria), and eclampsia in which seizures occur.. Serious HDP is formerly known as pregnancy toxemia.

*d: Congenital abnormalities may increase if some external factor is added, but should not decrease. Since they significantly decreased in the Abrysvo group, this is likely due to bias at random allocation.

*e: Likewise, if preterm birth increases, neonatal death would generally increase, but in this trial it instead fell to less than half, also close to significance and likely due to allocation bias. However, histories of exposure to drugs, alcohol, smoking, illegal drugs, and other substances affecting congenital abnormalities or neonatal death were recorded but not disclosed. Therefore, for valid serious adverse events (⑦), data excluding ⑥ (serious congenital abnormalities ④ + non-RSV-related death ⑤) from ③ total serious adverse events are appropriate.

*f: In the placebo group, one death due to hypoplastic ventricle overlapped with serious congenital abnormality and death, so one person was subtracted from the total of 200.

*g: Although items ②c and ⑦ have p>0.05, their risk differences exceed in absolute value the ARR of RSV-positive hospitalised lower respiratory tract infection in item ① (0.46, 0.55). Because of reasons *c and *d, significance may emerge after correcting allocation bias, and in order to prevent beta error (missed detection), NNTB(H) is shown.

and no adjustment of outcomes based on them was performed.

Using the post hoc risk ratio for congenital abnormalities and non-RSV-related deaths as a prior risk ratio, and applying the Prior Event Rate Ratio (PERR) adjustment method [25], with 95% confidence intervals estimated by the Kolassa method [26], congenital abnormalities and non-RSV-related deaths naturally become 1.0 (95% CI: 0.74, 1.35), statistical significance is eliminated. However, this cannot be applied to other adverse events. Also, without individual raw data, adjustment of hazard ratios using a Cox proportional hazards model is impossible.

Therefore, a subgroup analysis was conducted of serious adverse events excluding congenital abnormalities and non-RSV-related deaths from all serious adverse events. The result was 13.1% in the Abrysvo group versus 11.9% in the placebo group, p=0.1259. The risk difference was 1.20% (Figure 6).

This risk difference is more than twice the absolute reduction in one-year infant RSV hospitalisations (0.46–0.55%). As noted regarding maternal effects, although not statistically significant under alpha-error standards, considering the strong possibility that allocation favoured the Abrysvo group [13,16], this is by no means a negligible difference if beta error (missed detection error) is to be avoided. Therefore, assuming significance for the sake of argument, calculation of NNTH shows that one in 83 infants would experience serious harm.

The data examined in this section **7** are summarised in Table 2.

If 200 pregnant women receive Abrysvo, one infant RSV infection hospitalisation can be prevented, but in exchange there is concern that two or more infants may experience harm equivalent to hospitalisation or worse over one to two years. Harms must not be missed.

8. Routine vaccination may benefit about 2,500 people but harm more than 10,000 annually.

There were just over 680,000 births in Japan in

2024 (January 1 to December 31) [27]. Although the declining birth rate is expected to continue, if 80% of pregnant women receive vaccination under routine immunisation, approximately 500,000 mothers would be vaccinated for the time being, and nearly the same number of newborns would be born.

Although these figures are not statistically significant except significant increase of induced preterm delivery due to pregnancy complications at the alpha-error 0.05 level, we estimated the potential scale of harm under routine vaccination in order to avoid overlooking harms and to take potential imbalance in baseline characteristics into account.

As a result, approximately 2,500 infants would avoid RSV infection severe enough to require hospitalisation during the first year after birth. On the other hand, approximately 5,000 mothers would suffer harms severe enough to require hospitalisation within six months postpartum, of whom more than half would suffer induced preterm deliveries due to any pregnancy complications, including mostly due to serious hypertensive disorders of pregnancy (formerly known as pregnancy toxemia). In addition, approximately 6,000 infants would be estimated to suffer harm severe enough to require hospitalisation during the first or second year after birth.

[3] Requested actions to resolve concerns regarding efficacy and safety (restated)

For the reasons above, we respectfully submit the following five requests:

1. To disclose of maternal medication and substance-use histories, which are strongly suspected to have contributed the apparent bias in favour of Abrysvo in the reported rates of congenital anomalies and neonatal deaths.
2. To conduct adjusted analyses using these data and to re-evaluate both efficacy outcomes (including hospitalised respiratory tract infections and hospitalised RSV infections) and adverse-event outcomes.
3. For efficacy outcomes, to include all lower respiratory tract infections, including both RSV-positive and RSV-negative cases, rather than RSV-positive cases alone, and to place particular emphasis on one-year hospitalisation data for respiratory tract infections.
4. To prioritise absolute risk reduction (ARR) over relative risk reduction (RRR: or vaccine efficacy [VE]), in benefit assessments, and to compare ARR with the risk difference (RD; absolute risk increase [ARI]) for serious adverse events in order to reassess whether the benefits outweigh harms.
5. To refrain from initiating routine vaccination until re-evaluation confirms that the benefits outweigh the harms.

Conclusion：We request suspension of plans for routine vaccination with Abrysvo®

At the 72nd Health Sciences Council Vaccination and Vaccine Subcommittee Basic Policy Committee on 19 November 2025, routine use of Abrysvo was approved. At that meeting, regarding the harm of preterm birth with Abrysvo, one committee member stated, referring to this class of vaccines including the GSK product, “I think it is probably true that this class of vaccine induces preterm birth,” expressing a view similar to that of MedCheck. However, routine vaccination was subsequently approved without discussion reaching the detailed points raised in this MedCheck’s petition letter.

We conclude that routine maternal vaccination with Abrysvo may cause substantial harms to both mothers and infants and may result in new large-scale drug-induced sufferings.

We request that the government review the possibility of imbalance in baseline characteristics at allocation and re-evaluate harms, and that, until such a review is completed—and unless the review still concludes that benefits outweigh harms—routine maternal vaccination with Abrysvo should be suspended, and routine vaccination plans not be initiated.

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