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Self-amplifying mRNA vaccine

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What the Government Should Do Before Introducing the Replicon Vaccine

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A self-amplifying mRNA vaccine “Kostaive®”, which is called shortly “a replicon vaccine” in Japan and also known as the next-generation mRNA vaccine against SARS-CoV-2 (the novel coronavirus), was approved in Japan in November 2023, making it the first country in the world to do so. This vaccine is designed to prevent SARS-CoV-2 infection. The term “replicon” comes from the word “replication,” indicating that this is a self-replicating mRNA vaccine, meaning the mRNA in the vaccine can replicate itself once administered.

It has been approved because Japanese regulators considered that the clinical trials demonstrated effectiveness in preventing both the onset and worsening of COVID-19, with similar safety to the current Pfizer vaccine, while producing more antibodies and having longer-lasting effects, despite requiring a smaller dose. The Japanese government has provided a subsidy of 3 billion yen (about 20 million dollars) to Meiji Seika Pharma, the manufacturer of Kostaive®, and is supporting emergency development projects such as vaccine production systems.

Med Check has not conducted a detailed evaluation of the replicon vaccine but has concluded that existing SARS-CoV-2 vaccines should not be used. This conclusion is based on the assertion that these vaccines are not only ineffective but may actually increase the number of infections. Additionally, since the vaccine’s mRNA is absorbed by all cells in the body to produce spike proteins, it triggers immune reactions and causes a range of serious harms in various parts of the body.

As of July 31, 7835 people have been certified for relief under the Vaccine Health Damage Relief System, with 747 of these cases resulting in death. The most common causes of death reported are cardiovascular diseases such as myocardial infarction and stroke. These numbers—7835 cases of relief and 747 deaths—are 2.2 times and 4.9 times higher, respectively, than the total number of cases (3522) and deaths (151) certified for all vaccines other than the SARS-CoV-2 vaccine over the past 45 years. It is no exaggeration to say that this represents a significant drug disaster.

The basic mechanism of the replicon vaccine is the same as that of existing mRNA vaccines. Because it is self-replicating, even a small amount of the vaccine can produce a large number of antibodies and have a sustained effect. However, this also means that more spike protein is synthesized, which raises concerns about more severe and prolonged adverse reactions.

Despite the numerous reports of harm, the government continues to administer vaccinations and plans to introduce the replicon vaccine, which could potentially cause even more harm, as a routine vaccination starting this autumn. Before recommending a new vaccine, the government should first assess the damage caused by existing vaccinations and halt their use as soon as possible.

Palivizumab (Synagis®): in High-Risk Children

Is it useful for Preventing RS Virus Infection ?

Translated and revised from Med Check (in Japanese) Sep. 2024; 24 (115)：111-113

MedCheck Editorial team

Abstract

●Palivizumab is a monoclonal antibody that targets respiratory syncytial virus (RSV) like nirsevimab (see page 23). It was approved in 2002 for its preventive efficacy on severe RSV infections in high-risk children, including preterm infants and those with congenital heart disease (CHD).

●Two large-scale randomized controlled trials (RCTs) evaluated palivizumab's efficacy and safety. The results suggested that it may reduce both the rate and duration of hospitalization due to RSV infection.

●However, according to our critical review, both RCTs revealed a high likelihood of allocation imbalance favoring palivizumab, which casts doubt on the reliability of the reported efficacy. For example, in one RCT, the placebo group showed significantly more non-RSV-related deaths than in the palivizumab group.

●In addition, more patients in the palivizumab group required mechanical ventilation after hospitalization for RSV infection. The reduction in RSV-related hospitalizations conflicts with the increase in severe cases requiring ventilation. A similar trend emerged in another RCT.

●The RSV antigen test used in these trials can produce false negatives, even in infected patients. This issue may explain the observed apparent reduction in RSV-related hospitalizations.

Conclusion: There is no conclusive evidence that palivizumab effectively prevents severe RSV infections in high-risk children. Therefore, its use is not recommended.

Keywords:

thrombosis, pulmonary hypertension, congenital heart disease, allocation bias, false negatives, antibody-dependent enhancement

Introduction

Palivizumab (Synagis®) is a monoclonal antibody that binds to the F protein of RSV, blocking the virus from entering human cells, much like nirsevimab (Beyfortus®), which is also discussed in this issue (p23). We reviewed palivizumab to better understand nirsevimab.

One major difference between the two drugs lies in their dosing schedules: palivizumab requires monthly administration, while nirsevimab, due to its longer serum half-life, needs only a single injection per season.

Allocation Imbalance in RCTs

Two phase III placebo-controlled RCTs supported palivizumab's approval [1, 2].

The first study, published in 1998 [1], involved 1,502 infants (1,002 in the palivizumab group and 500 in the placebo group). The participants included preterm infants (gestational age ≤ 35 weeks) up to 6 months old or children with bronchopulmonary dysplasia up to 2 years old. The study examined the efficacy of monthly injections over five doses. The abstract highlighted palivizumab's "efficacy and safety," noting a 55% reduction in RSV-related hospitalizations, fewer hospitalization days, and less oxygen use during hospitalization, compared with the placebo group. However, these results were all calculated per 100 participants (total hospitalization days/100 participants etc Supplementary Appendix 1, 2: Table).

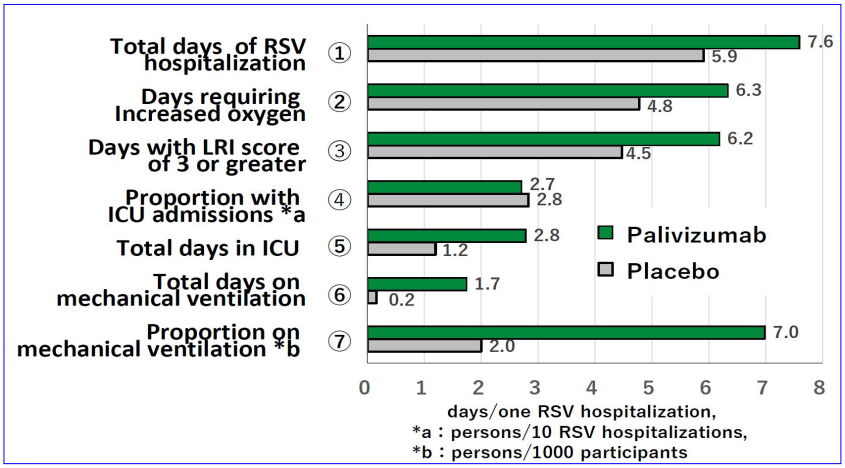
When expressed per RSV-related hospitalized child,

Table : Data suggesting allocation bias of the Study 1

			Placebo N=500	Palivizumab N=1002	P value
RSV-related hospitalization	Hospitalization	Number	53 (10.6%)	48 (4.8%)	<0.001
		Days/100 participants	62.6	36.4	<0.001
	Requiring Increased O_2	Days/100 participants	50.6	30.3	<0.001
	LRI score ≧3	Days/100 participants	47.4	29.6	<0.001
	ICU admission	Yes	15 (3.0%)	13 (1.3%)	0.026
		Days/100 participants	12.7	13.3	?
	Mechanical ventilation	Patients who needed	1 (0.2%)	7 (0.7%)	0.282
		Days/100 participants	1.7	8.4	0.211
		death	0	2 (0.2%)	0.445
Data suggestimg allocation imbalance of the study		All cause death	5 (1.0%)	4 (0.4%)	0.169
		Non-RSV-related death	5 (1.0%)	2 (0.2%)	0.045

Based on the Japanese summay basis of approval of palivizumab [4], the non-RSV-related causes of death in the palivizumab group were:
1) sudden death after the worsening of the pulmonary hypertension and
2) sudden infant death syndrome after onset of mild congestion on the next day of the second dose.
Both deaths are likely to be adverse reactions to palivizumab, although the investigators denied the causality.

Figure 1: Reality of the RSV hospitalized patients



When various indicators were calculated per patient with RSV hospitalized, ④ Proportion of ICU admission was only similar in both groups, but the others (①-③, ⑤-⑦) were all increased in the palivizumab group than in the placebo group. Why these happened ?
1) **False-negative testing** due to the antigen detection-based assays for the diagnosis of RSV infection and
2) the antibody dependent enhancement **(ADE)** may be the two major cause for these phenomena.

all indices were higher in the palivizumab group than in the placebo group (**Figure 1**). More patients required mechanical ventilation in the palivizumab group (7 vs. 1), and RSV-related deaths occurred only in the palivizumab group (2 vs. 0), contradicting the supposed reduction in RSV-related hospitalizations (**Table**).

Additionally, non-RSV-related deaths were significantly higher in the placebo group at 1.0% (5/500) compared with 0.2% (2/1,000) in the palivizumab group (P = 0.0446) (**Table**). Since palivizumab does not affect non-RSV-related deaths, these findings suggest an allocation imbalance favoring the palivizumab group.

Palivizumab and False-Negative RSV Tests

The apparent reduction in RSV-related hospitalizations could result from palivizumab causing false-negative RSV tests.

The U.S. package insert for palivizumab states, "Palivizumab may interfere with immunological-based RSV diagnostic tests such as some antigen detection-based assays," which could lead to false-negative results [5]. Since the two pivotal RCTs relied on antigen tests to diagnose RSV, palivizumab likely caused some RSV-infected patients to test negative, skewing the hospitalization data.

We can support this with robust evidence. **Figure 2** shows no significant difference in bronchiolitis and pneumonia between the placebo and palivizumab groups (17.5% vs. 18.6%, P = 0.59). However, when excluding RSV-related hospitalizations, bronchiolitis and pneumonia were significantly more common in the palivizumab group (12.7%) compared with the placebo group (8.0%) (P = 0.007). This suggests that the reduction in RSV-related hospitalizations might be an artifact caused by palivizumab-induced false-negative test results (**See also Supplementary Appendix 3**).

Antibody-Dependent Enhancement (ADE)

Even when RSV antibodies bind to the virus, they do not always alleviate respiratory symptoms. In fact, artificial antibodies can sometimes worsen infections, a phenomenon known as antibody-dependent

enhancement (ADE) [6]. In three pooled phase II placebo-controlled RCTs, 22% of the palivizumab group experienced more severe respiratory disorders compared with 11% of the placebo group [4] (**Figure 3** or **Supplementary Appendix 4**). Additionally, two RSV-related deaths occurred in the palivizumab group, while none occurred in the placebo group in Study 1. These deaths might have resulted from ADE.

Gimenez et al [7]. found that RSV-specific monoclonal antibodies and human sera with low titers of RSV-specific antibodies could enhance RSV infection in human monocyte cells in vitro. Their findings also suggested a potential correlation between ADE and RSV infection severity in infants, highlighting a possible link between antibody-dependent enhancement and increased infection severity (**Supplementary Appendix 5**).

ADE occurs when antibodies bind to non-target viral sites, allowing the virus to enter immune cells or other body tissues more easily, thus worsening infection. This phenomenon halted early RSV vaccine development.

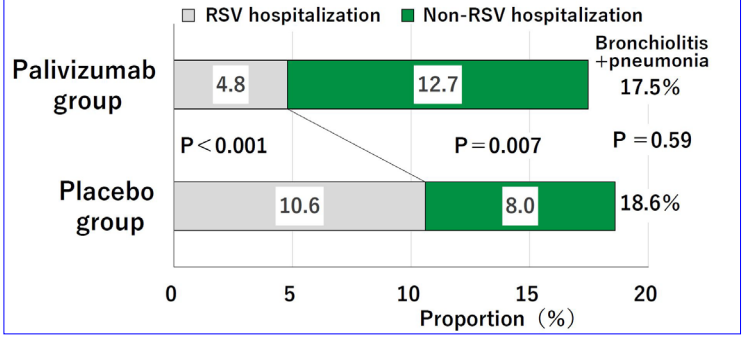
Allocation imbalance in RCT on children with CHD?

The second pivotal RCT published in 2003 compared palivizumab with placebo in 1,287 children phenomenon with hemodynamically significant congenital heart disease (CHD) (2nd study) [2]. Its abstract also describe that palivizumab recipients had a 45% relative reduction in RSV hospitalizations, a 56% reduction in total days of RSV hospitalization per 100 children and a 73% reduction in total RSV hospital days with increased supplemental oxygen per 100 children showing significantly lower serious adverse events in palivizumab group..

However, non-RSV-related hospitalizations, which palivizumab could not reduce, were nearly significantly lower in the palivizumab group (53.5%) than in the placebo group (59.0%) (p=0.056), raising suspicions of allocation imbalance (**Supplementary Appendix 6.1**).

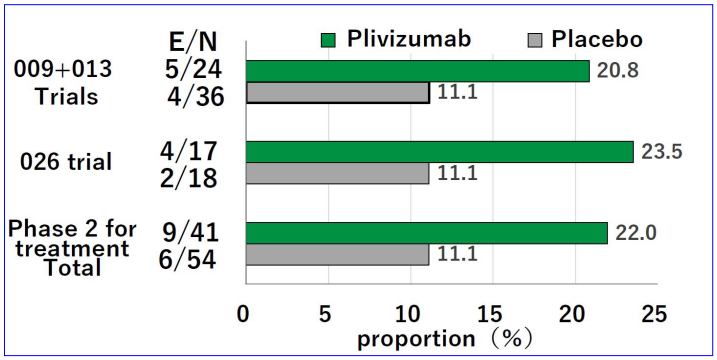
This is likely the result of the fact that, as shown in **Supplementary Appendix 6.2**, all four indices (hypercyanotic episode, increased pulmonary blood flow, pulmonary hypertension, and congestive heart failure) tended to be lower in the palivizumab group. In other words, as in the first study, there may be any imbalance of the random assignment favouring the palivizumab group. In addition, false negative RSV-antigen testing might have affected.

Figure 2: Bronchiolitis and pneumonia as adverse events and RSV hospitalization



The combined proportion with bronchiolitis + pneumonia as adverse events was 17.5% in the palivizumab group and 18.6% in the placebo group, which was not significantly different. However, hospitalization due to RSV was significantly (p<0.0001) lower in the palivizumab group. On the other hand, those residual hospitalization was significantly (p=0.0066) higher in the palivizumab group, at 12.7% vs. 8.0%. **These results suggests that palivizumab have induced many false negatives for RSV infection by using antigen detecting based testing.**

Figure 3: Proportions with serious respiratory adverse events in some phase 2 treatment trials of palivizumab: Possible relation to antibody-dependent enhancement (ADE)



E: serious respiratory adverse events, N: number of subjects. The meta-analysis results showed that the pooled odds ratio was 2.20 (95% CI: 0.63, 8.25), P = 0.1713 (Exact Fisher, two sided), I^2 = 0%. In the RSV infection, pnenomena involving ADE have been reported and confirmed [7].

RSV Antibodies and Worsening Heart Disease

In Study 1 [1], which focused on preterm infants, one of the two deaths unrelated to RSV infection involved pulmonary hypertension. Another patient developed congestion the day after receiving the palivizumab injection and died suddenly four days later.

In Study 2 [2], which involved children with congenital heart disease, the researchers did not report causes of death, making evaluation impossible.

Before palivizumab's development, an RCT using serum-derived immune globulin with a high titer of RSV antibodies (RSV-IGIV) in high-risk infants with CHD and other conditions [8,9] found more harm in the antibody group. As a result, researchers advised against using the antibody in infants with CHD [9]. The study reported six deaths out of 160 in the antibody group, compared with none in the placebo group ($p = 0.091$) [8] (**Supplementary Appendix 8**).

In another study [9], 28% of the antibody group underwent cardiac surgery due to serious adverse events, compared to 8.5% in the placebo group ($P = 0.009$). None of the 83 children in the placebo group needed surgery due to unexpected worsening of cyanosis, stroke, or death, while 10 out of 111 children in the antibody group experienced such events (**Supplementary Appendix 9**).

Children with CHD are prone to venous thrombosis, and surgery further increases this risk [10]. RSV antibody injections likely exacerbate thrombosis tendencies, worsening cyanosis, even with slight increases in pulmonary artery thrombosis. Considering the reported causes of death from nirsevimab (page 23), such as pulmonary hypertension, pulmonary artery stenosis, and pulmonary vein stenosis, thrombosis appears to be the most serious adverse reaction to monoclonal antibody treatments for RSV.

Uncritical Recommendations in Japanese Guidelines

The "Consensus Guidelines for the Use of Palivizumab in Japan" [11], published by the Japan Pediatric Society, recommends palivizumab for preterm infants and those with bronchopulmonary dysplasia to prevent severe RSV symptoms. However, these guidelines fail to address the concerns raised in this review.

In Practice

The two large-scale RCTs that evaluated palivizumab's efficacy and safety both showed allocation imbalances favoring the palivizumab group. Additionally, the reduction in RSV-related hospitalizations likely resulted from false-negative RSV test results, casting further doubt on the findings. Thus, neither efficacy nor safety has been conclusively proven.

While palivizumab is indicated for preventing severe RSV infection in high-risk infants, we do not recommend its use, even in the case with these indications.

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Nirsevimab (Beyfortus®): for RSV infection prevention

RSV-related hospitalizations decrease, but deaths increase

Translated and revised from Med Check (in Japanese) Sept. 2024; 24(115):108-110

MedCheck Editorial team

Abstract

●Respiratory syncytial virus (RSV) causes respiratory tract infections, but severe cases are rare in infants. A monoclonal antibody against RSV, palivizumab, has been administered monthly to high-risk children.

●Nirsevimab (Beyfortus®), available since May 2024, maintains effective blood concentrations for several months after a single injection. It was approved for use in both high-risk children and full-term healthy infants.

●Approval for full-term healthy infants is based on a randomized controlled trial (RCT), which showed reduced RSV-related hospitalizations compared with the placebo group. However, while no deaths occurred in the placebo group, five deaths were reported in the nirsevimab group, indicating a higher mortality rate.

●In an RCT comparing nirsevimab with placebo in preterm infants, and in another RCT comparing it with palivizumab in high-risk infants having congenital heart disease (CHD), RSV related hospitalizations were reduced. However, the mortality rate tended to increase.

●A combined analysis of three major RCTs by us revealed a significantly higher mortality rate, likely due to an increase in non-RSV related conditions, particularly thrombosis.

Conclusion: Nirsevimab should not be used in any infants including for universal immunization

Keywords: congenital heart disease, monoclonal antibody, mortality, thrombosis, cyanosis, healthy user bias, confirmation bias, false negative, unknown bias, life table, palivizumab

Med Check's Evaluation:

Not recommended in any infants

Generic name: Nirsevimab

Brand Name: Beyfortus® intramuscular injection 50 mg, 100 mg

Indications: Suppression of serious lower respiratory tract disease caused by RSV infection in newborns and infants

Dosage and Administration: During the first RSV infection season after birth, newborns and infants weighing less than 5 kg are usually given a single intramuscular injection of 50 mg, and those weighing 5 kg or more are usually given a single intramuscular injection of 100 mg. During the second RSV season after birth, a 200 mg single intramuscular injection is typically administered.

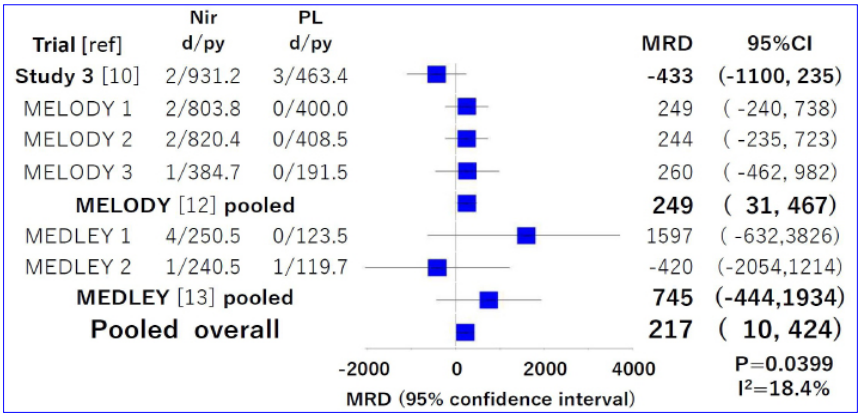
Marketing Authorization Holder: AstraZeneca K.K.

Introduction

Nirsevimab is a monoclonal antibody developed to prevent the worsening of respiratory tract infections caused by RSV. Nirsevimab inhibits viral infection by binding to a F-protein essential for RSV to enter human cells. Its antibody molecule has been slightly modified to remain in the serum longer than the conventional anti-RSV monoclonal antibody preparation, palivizumab (Synagis®), requiring only one injection per RSV season [1,2].

While palivizumab is recommended only for infants at risk of developing severe symptoms [3,4], nirsevimab has also been approved for healthy children not at risk of developing severe symptoms [1,2]. In Japan, the cost of the injection (900,000 yen) for healthy children is not covered by the health insurance [5], but in Spain and France, national universal immunization campaign with

Figure 1: All-cause mortality rate differences in three pivotal RCTs of nirsevimab: meta-analysis



Nir: nirsevimab, PL: placebo, d: number died, py: person-years, MRD: mortality rate difference, 95%CI: 95% confidence interval, All pooled MRD were calculated as Fixed effects by StatsDirect 3.3.6.
P value for pooled MELODY trial was 0.0254 (I^2=0%), P value for pooled MEDLEY trial was 0.2197 (I^2=62.9%).
Created by MedCheck using data from 3 pivotal RCTs of nirsevimab [10-13].

nirsevimab has already started in 2023 [6] (**Supplementary Appendix 1**). This article examines whether nirsevimab reduces RSV-related hospitalizations and deaths in high-risk children and healthy infants compared with palivizumab or with placebo and discuss its potential harms.

RSV infection and prevention before nirsevimab

RSV spreads through droplets, is ubiquitous, and highly contagious. Almost 100% of infants are infected by age three, and most recovery without treatment. However, 1-2% of infected infants under one year of age may require hospitalization due to bronchiolitis or pneumonia [7,8].

High-risk infants, those born preterm before 35 weeks of gestation and those with chronic lung disease or congenital heart disease, are more likely to develop severe RSV infection, leading to high hospitalization rates. Monthly intramuscular palivizumab injections has been recommended for these high-risk infants during epidemics before nirsevimab[8,9] .

Please refer to page 19 of this issue for our critical review on the efficacy and safety of palivizumab [5].

Hospitalization reduced in healthy infants, but...

A randomized controlled trial (RCT) of nirsevimab comparing with placebo on healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days of gestation included 1453 infants (Study 3) [10] (Note 1). Among the 969 infants who received nirsevimab, 2.6% developed medically attended RSV-associated lower respiratory tract infection within five months after injection, compared with 9.5% in the placebo group (p<0.001). The hospitalizations rate was 0.8% in the nirsevimab group and 4.1% in the placebo group (p<0.001) [10].

Another placebo-controlled RCT (the MELODY trial) included 3,012 full-term (or born after 35 weeks of gestationinfants) healthy infants [11, 12]. The proportion of patients with medically attended RSV-associated lower respiratory tract infections within five months after injection was 1.2% in the nirsevimab group compared with 5.4% in the placebo group, and that with hospitalizations were 0.4% and 2.0%, both significantly lower in the nirsevimab group (Note 2).

Note 1: The subjects in the three pivotal nirsevimab trials [10-13] were all assigned in a 2:1 ratio to the nirsevimab group and the placebo or palivizumab group.

Note 2: The RSV infection diagnosis used in the RCT of palivizumab was an antigen-detecting based method, so even if patients were infected with RSV, the test could return a false negative result. However, the diagnosis used in the RCTs of nirsevimab utilized RT-PCR, so this does not seem to affect the results.

Nirsevimab increased total mortality (Figure 1)

According to the protocol of the MELODY trial [12], participants were followed up for 511 days after injection (**Supplementary Appendix 2 and 3**). No deaths occurred in the placebo group (n=996), while five deaths (0.25%) were reported in the nirsevimab group (n=1998).

We created a life table **(Supplementary Appendix 4)** dividing the study period up to 511 days by three period (0 to 151days, 151 to 361 days and 361 to 511 days) according to the protocol and the data from the supplementary materials[12] **(Supplementary Appendix 2 and 3)**.

After the mortality rate difference was calculated for three periods, pooled mortality rate difference for three periods was calculated. The result showed that nirsevimab increased the mortality rate, with an

mortality rate difference of 249 deaths per 100,000 person-years (95% confidence interval: 30.7-467), which was statistically significant (p = 0.0254) (**Figure 1: MELODY** [12] **Pooled or Supplementary Appendix 5**).

The cumulative mortality rate in the nirsevimab group over the three periods is estimated to be 751 deaths (95%CI: 53.14, 1448.2) per 100,000 person-years(**Supplementary Appendix 6 and 7**)., considerably higher than the infant mortality rate in the general population in each country that participated in the clinical trial. For example, in Japan, the mortality rate for infants of the same age as the study subjects is approximately 78.2 deaths per 100,000 person-years. Even in countries with the highest infant mortality rates in Europe, it is 409 deaths per 100,000 pearson-years (**Supplementary Appendix 8**).

According to the protocol of MELODY trial, only healthy infants were included in the trial, excluding those with fevers or receiving treatment for chronic illnesses. Therefore, the mortality rate should be lower than that in vital statistics surveys that include sickly children. Hence, it is highly probable that that the mortality rate increaed due to nirsevimab administration.

Mortality increased including high-risk infants

In an RCT (MEDLEY trial) [13] comparing nirsevimab with palivizumab in 925 high-risk infants (preterm birth before 36 weeks of gestation, chronic lung disease or congenital heart disease) the number of medically attended RSV infection was 3 (1%) in the palivizumab (control) group and 4 (0.7%) in the nirsevimab group, showing no difference. However, the number of deaths up to 151 days post-vaccination was 0 in the palivizumab group and 4 (0.7%) in the nirsevimab group (with one additional death in each group after 151 days).

A meta-analysis was conducted to determine the extent of the increased mortality rate in the nirsevimab group compared with the control group (placebo or palivizumab) across the three major RCTs of nirsevimab [10-13]. The results showed that the mortality rate in the nirsevimab group was significantly higher than in the control group, with a mortality rate difference of 217 deaths per 100,000 person-years (p = 0.0399) (**Figure 1**).

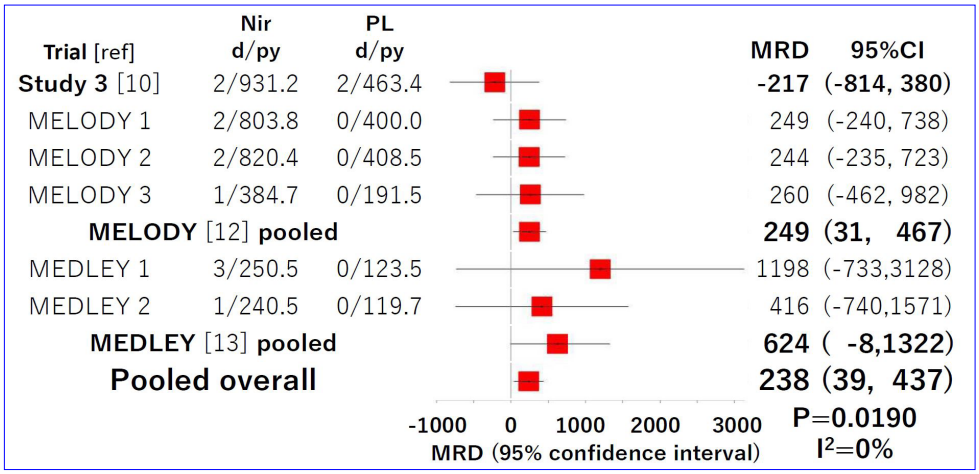
The harm of nirsevimab: death probably due to thrombosis

Nirsevimab appear to increase the risk of mortality, possibly due to thrombosis. We examined the cause of deaths separately due to RSV infection and deaths unrelated to RSV (**Table: next page**). There were two deaths possibly due to RSV infection in the control group (oee from RSV pneumonia in the placebo group and one from bronchiolitis in the palivizumab group) and one death from acute bronchiolitis in the nirsevimab group, with no statistical difference (P = 0.5381 when meta-analyzed by time period).

On the other hand, deaths unrelated to RSV were significantly more common in the nirsevimab group (P = 0.0190) (**Figure 2**).

In the control group, only one patient in the placebo group had pericardial effusion. In the nirsevimab group,

Figure 2: Non-RSV related mortality rate differences in three pivotal RCTs of nirsevimab: meta-analysis



Nir: nirsevimab, PL: placebo, d: number died, py: person-years, MRD: mortality rate difference, 95%CI: 95% confidence interval, All pooled MRD were calculated as Fixed effects by StatsDirect 3.3.6. P value for pooled MELODY trial was 0.0254 (I^2=0%), P value for pooled MEDLEY trial was 0.0802 (I^2=0%). Created by MedCheck using data from 3 pivotal RCTs of nirsevimab [10-13].

Table: Causes of death in three randomized controlled trials of nirsevimab

Trial name Subjects	Nirsevimab group: Number of participants	Control group: Number of participants
Study 3 Preterm	Nirsevimab : 968	Placebo : 479
	Death	Pericarditis
	Pulmonary vein stenosis	Bacterial pneumonia
		RSV-pneumonia
MELODY Term, healthy	Nirsevimab : 1998	Placebo : 996
	cause unknown *	None
	acute gastroenteritis (could be ischemic gastroenteritis)	
	acute gastroenteritis (could be ischemic gastroenteritis)	
	Skul fracture (automobile accident)	
	cause unknown	
MEDLEY Preterm or high-risk (CHD or CLD)	Nirsevimab : 614	Palivizumab : 304
	SUD with CHD (VSD+ASD etc)	*Bronchiolitis*
	SUD in pumonary atresia with VSD	
	Cardiogenic shock with heart failure due to VSD+ASD	
	Cardiopulmonary failure, secondary to acute bronchiolitis	
	SARS-CoV-2 pneumonia	

*: The investigator suspected undiagnosed metabolic disease but the infant died of an unknown cause.
The cause of death for ***black (italic)*** could be due to RSV infection even if RSV testing was not performed.
Red (Bold) indicates the cause **unknown or sudden unexpected death (SUD) or cardiovascular death.**
Blue (Bold) indicates the other **non-RSV-related death**, but "acute gastroenteritis" could be **ischemic gastroenteritis**

however, one patient each experienced pulmonary artery stenosis, pulmonary vein stenosis, cardiogenic shock, and unexpected sudden death; three deaths were of unknown origin, two patients died of acute gastroenteritis, one of skull fracture (in a traffic accident), and one from SARS-CoV-2 infection, totaling 11 patients. Notably, in the three patients who died in MELODY trial [13] due to pulmonary artery stenosis, cardiogenic shock, and unexpected sudden death, in addition to ventricular septal defects, all three had one to three cardiac anomalies or central nervous system abnormalities (**Table**). As for two death from acute gastroenteritis, the possibility of death from ischemic gastroenteritis due to mesenteric thromboembolism cannot be denied.

Hgh titer immune globulin against RSV harmed CHD

In one RCT using a serum-derived antibody preparation against RSV for congenital heart disease, there were no deaths in the placebo group, but six infants in the antibody group died [14], and in another RCT, the proportion with worsening cyanosis was significantly higher in the antibody group [15] (see also p19 on palivizumab). Furthermore, children with congenital heart disease are inherently prone to venous thrombosis, and surgery further increases this risk [16]. It is therefore hypothesized that injecting RSV antibodies, including nirsevimab, may promote thrombosis formation and increase the incidence of pulmonary artery thrombi, potentially worsening cyanosis.

The Japanese package insert for nirsevimab lists thrombocytopenia as an adverse reaction [2]. Thrombocytopenia is probably a result of thrombosis. Looking at the causes of death, there are some cases of pulmonary artery stenosis, cardiogenic shock, sudden death, and death of unknown cause, suggesting that thrombosis could occur, leading to sudden death from cardiovascular disease.

Pitfalls in the results of observational studies

Nirsevimab has been extensively used in Europe and the United States since 2022, and many observational studies have been published. A systematic review with meta-analysis of nirsevimab on the effectiveness against RSV hospitalization was reported analysing five RCTs and eight observational studies with 45,238 infants from 19 series [17]. The results of each of the 19 series are presented as the percent preventive effectiveness of hospitalization which is (1 – RR) × 100, where "RR" is the risk ratio. The calculated pooled risk ratio (95% confidence interval) on RSV hospitalization was 0.19 (0.13-0.29) for the five RCTs and 0.10 (0.07-0.13) for the 14 series of observational studies. Looking at these figures alone, it appears that the effectiveness on prevention of RSV hospitalizations was significantly greater (less risk

ratio) by the observational studies than by the RCTs.

However, this is probably due to "healthy user bias" and "misclassification due to false negative testing results" as well as possibly due to "confirmation bias." The subjects in the MELODY trial at the screening were healthy without fever and chronic diseases and were randomly allocated, ensuring that the health conditions of the infants in the nirsevimab group and the placebo control group were essentially the same. In addition, both the carer and the investigator basically didn't know which were administered.

However, in the real-world clinical practice, which the observational studies targeted, infants who did not receive nirsevimab include more those who could not receive nirsevimab due to febrile infectious diseases. The Japanese package insert [2] recommends avoiding its use in children with moderate to severe acute infections or febrile illnesses. These induce "healthy user bias". In addition, in the real-world clinical practice, doctors who see infants know whether the infant received nirsevimab or not. It may affect the decision of the doctor "to test RSV or not" and "to hospitalize infant or not" (confirmation bias). Moreover, if antigen-detection-based testing were used (as it may be still common in the real-world practice) instead of RT-PCR method, substantial proportion of RSV infected infants may miss to be diagnosed as RSV infection due to the presence of nirsevimab in the infant's plasma (misclassification).

Therefore, the results of the RCTs, which are based on random assignment, should only be trusted and the results from the observational study should be ignored or they should only be used as the indicator of the extent of "overall unknown bias" including "healthy user bias", "confirmation bias" and "misclassification due to false-negative". Overall unknown bias is calculated as 0.10/0.19 which yielded 0.50 (95%CI: 0.30, 0.83).

In addition, this systematic review and meta-analysis report did not mention death at all.

In Practice

Nirsevimab reduces RSV-associated lower respiratory tract infection and hospitalizations in both high-risk and healthy infants. It also appears to be convenient as requiring a single injection. However, when used in healthy infants, nirsevimab has higher risk inducing death, particularly from non-RSV-related causes such as thrombosis. Due to the increased mortality, nirsevimab should not be used in any infants.

Do not use nirsevimab for universal immunization.

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#602, Katsuyama 2-14-8, Tennouji-ku,
Osaka JAPAN 543-0043