New Products related

Palivizumab (Synagis®): in High-Risk Children

Is it useful for Preventing RS Virus Infection ?

Supplementary Appendix

MedCheck Editorial Team

September 15, 2024

Appendix 1

Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants

The IMpact-RSV Study Group. Pediatrics. 1998 Sep;102(3 Pt 1):531-7.PMID: 9738173

Abstract

Objective. To determine the safety and efficacy of prophylaxis with palivizumab in reducing the incidence of hospitalization because of respiratory syncytial virus (RSV) infection in high-risk infants. Methods. A randomized, double-blind, placebo-controlled trial was conducted at 139 centers in the United States, the United Kingdom, and Canada. During the 1996 to 1997 RSV season, 1502 children with prematurity (</=35 weeks) or bronchopulmonary dysplasia (BPD) were randomized to receive 5 injections of either palivizumab (15 mg/kg) or an equivalent volume of placebo by intramuscular injection every 30 days. The primary endpoint was hospitalization with confirmed RSV infection. Children were followed for 150 days (30 days from the last injection). Those with hospitalization as a result of RSV infection were evaluated for total number of days in the hospital, total days with increased supplemental oxygen, total days with moderate or severe lower respiratory tract illness, and **incidence and total days of** intensive care and **mechanical ventilation.** The incidence of hospitalization for respiratory illness not caused by RSV and the incidence of otitis media were also evaluated.

The placebo and palivizumab groups were balanced at entry for demographics and RSV risk factors. **→Is it true？**

Ninety-nine percent of children in both groups completed the protocol and ~93% received all five scheduled injections.

Results. Palivizumab prophylaxis resulted in a 55% reduction in hospitalization as a result of RSV (10.6% placebo vs 4.8% palivizumab).

Children with prematurity but without BPD had a 78% reduction in RSV hospitalization (8.1% vs 1.8%); children with BPD had a 39% reduction (12.8% vs 7.9%). When gender, entry age, entry weight, BPD, and gestational age were included in a logistic regression model, the effect of prophylaxis with palivizumab remained statistically significant. The palivizumab group had proportionally fewer total RSV hospital days, fewer RSV hospital days with increased oxygen, fewer RSV hospital days with a moderate/severe lower respiratory tract illness, and a lower incidence of intensive care unit admission. Palivizumab was safe and well tolerated. No significant differences were observed in reported adverse events between the two groups. Few children discontinued injections for related adverse events (0.3%). Reactions at the site of injection were uncommon (1.8% placebo vs 2.7% palivizumab); the most frequent reaction was mild and transient erythema. Mild or moderate elevations of aspartate aminotransferase occurred in 1.6% of placebo recipients and 3.6% of palivizumab recipients; for alanine aminotransferase these percentages were 2.0% and 2.3%, respectively. Hepatic and renal adverse events related to the study drug were similar in the two groups. Conclusions. Monthly intramuscular administration of palivizumab is safe and effective for prevention of serious RSV illness in premature children and those with BPD.

This is not described in the abstract but・・・・

How false negative testing affected these data？

How did they treated severe respiratory infection with false negative testing?

Appendix 2-1 : Secondary Endpoints of the IMpact-RSV Study

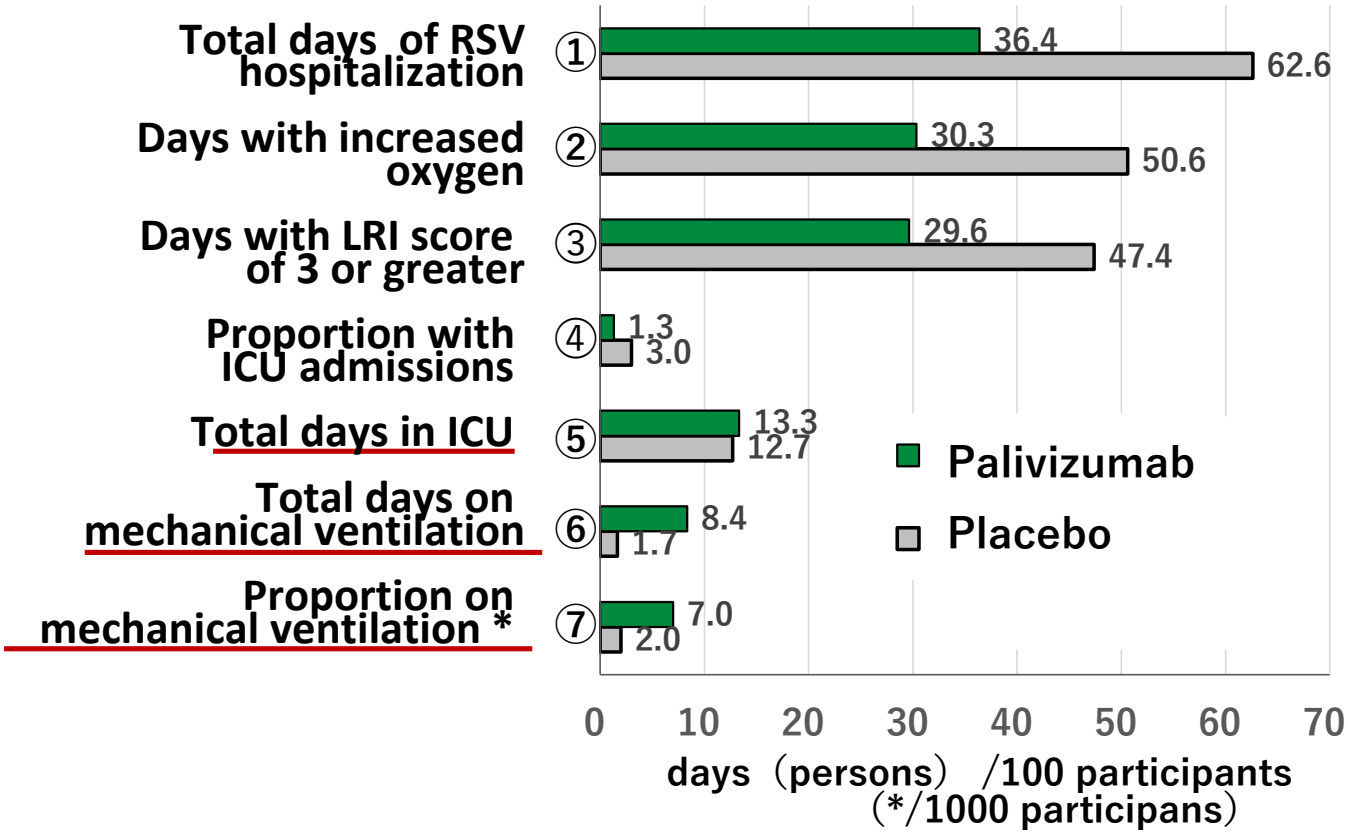
			Placebo group	Palivizumab group	P value
RSV	Total days of RSV hospitalization	Total days	313.1	364.6	＜0.001 注1
		Days/100 patients	62.6	36.4	
	Days Requiring increased oxygen	Total days	253.0	304.0	＜0.001 注1
		Days/100 patients	50.6	30.3	
	Days with LRI score ≧3	Total days	237.0	297.0	＜0.001 注1
		Days/100 patients	47.4	29.6	
	ICU admissions (Patients)	No	485 (97.0%)	989 (98.7%)	0.026 注2
		Yes	15 (3.0%)	13 (1.3%)	
	Total days in ICU	Total days	63.5	133.6	0.023 注1
		Days/100 patients	12.7	13.3	
	mechanical ventilation (Patients)	No	499 (99.8%)	995 (99.3%)	0.282 注2
		Yes	1 (0.2%)	7 (0.7%)	
	Days on mechanical ventilation	Total days	8.3	83.7	0.211 注1
		Days/100 patients	1.7	8.4	

From the “clinical documents” among the summary basis of approval dossier (p290～)　file:///C:/Users/gec00/Downloads/10015900_21400AMY00008_270_1.pdf

Appendix 2.2： Figure for the original data of IMpact-RSV study

Abstract says

① Fewer total RSV hospital days,
② Fewer RSV hospital days with increased oxygen,
③ Fewer RSV hospital days with LRI score of≧ 3
④ Lower incidence of ICU admission.
What is the reality?



Total days in ICU per 100 participants were not different. On the other hand, total days on mechanical ventilation were longer in the palivizumab group.

RSV hospitalized patients
palivizumab 48/1002
Placebo 53/ 500

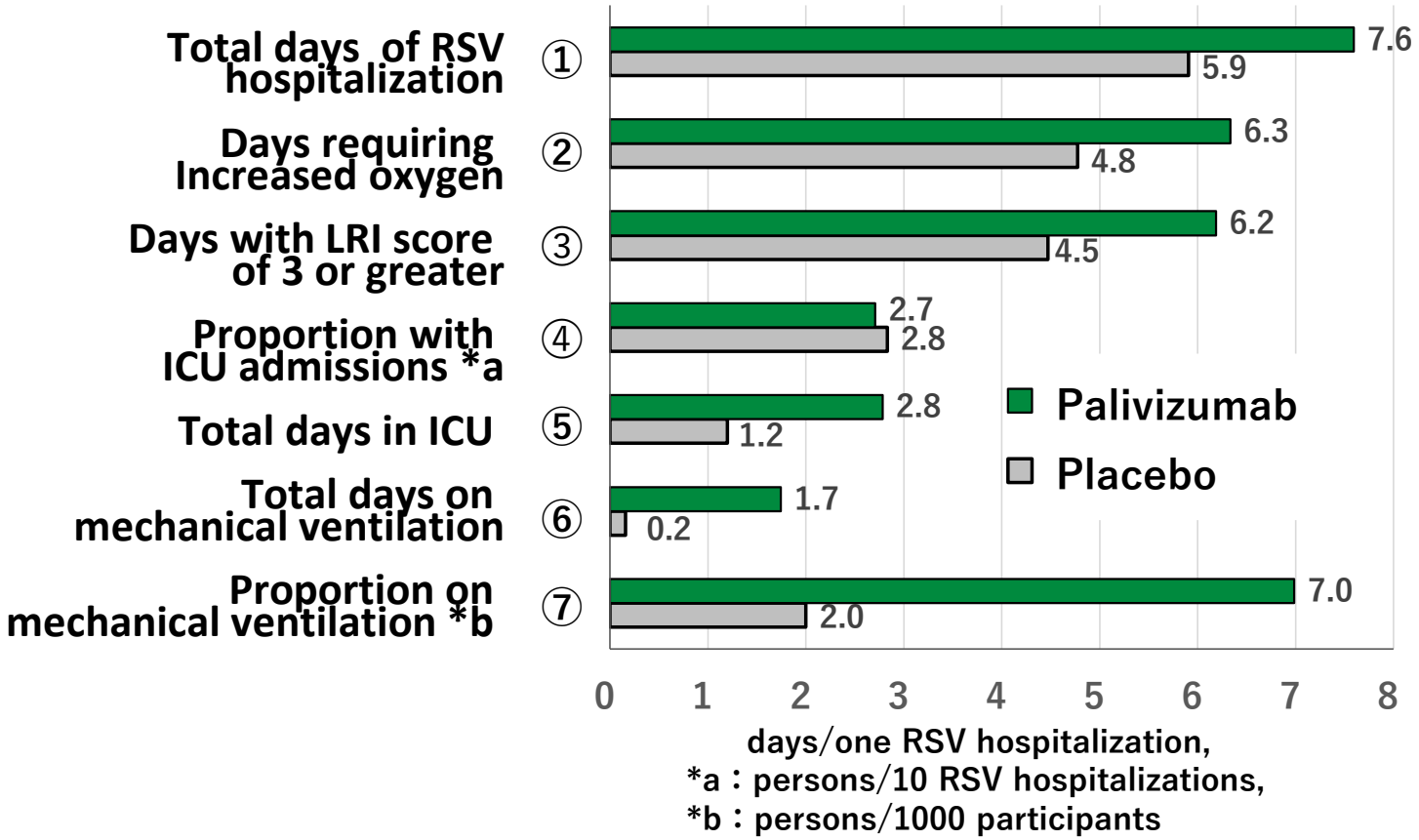
How will be these indexes per RSV-hospitalized children ??

Appendix 2.3 (same as Figure 1) :

Reality of the IMpact-RSV study

Abstract says

① Fewer total RSV hospital days,
② Fewer RSV hospital days with increased oxygen,
③ Fewer RSV hospital days with LRI score of≧ 3
④ Lower incidence of ICU admission.
What is the reality?



Per patient with RSV hospitalized:
④Proportion of ICU admission was only similar in both groups
But
① Total RSV hospital days
② Days with increased oxygen
③ Days with LRI score of≧ 3
⑤Total days in ICU
⑥Total days on mechanical ventilation
per patient with RSV hospitalized:
⑦Proportion on mechanical ventilation per 1000 participants
were all increased in plivizumab group than placebo group.

Why these happened ?
1) False-negative testing due to the antigen detection-based assays for the diagnosis of RSV infection and
2) Due to the antibody dependent enhancement (ADE)

Appendix 3.1 ：

Respiratory Adverse Events reported in the IMpact-RSV Study(1)

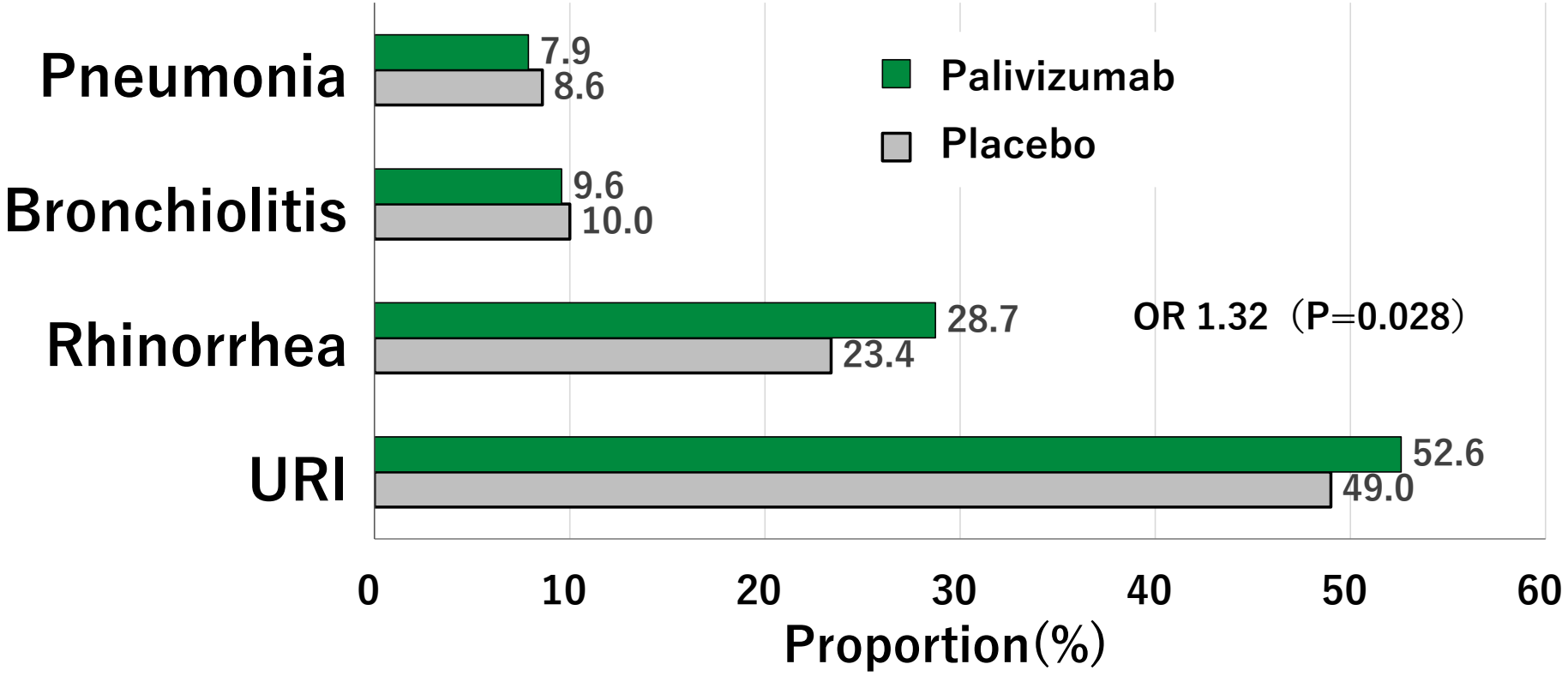
Summary of the adverse events by organ system

		Placebo group	Palivizumab group	P value
安全性評価例数	N for safety analysis	500	1002	
有害事象発現例数	Cases with any AE	482 (96.4%)	961 (95.9%)	0.778
有害事象発現件数	Number of any AE	2737	5417	
Adverse Events				
一般的全身障害	General system	247 (49.4%)	497 (49.6%)	0.956
発熱	Fever	134 (26.8%)	272 (27.1%)	
疼痛	Pain	34 (6.8%)	85 (8.5%)	
呼吸器系障害	Respiratory disorders	411 (82.2%)	835 (83.3%)	0.610
細気管支炎	Bronchiolitis	50 (10.0%)	96 (9.6%)	
咳き		90 (18.0%)	186 (18.6%)	
肺炎	Pneumonia	43 (8.6%)	79 (7.9%)	
鼻炎	Rhinorrhea	117 (23.4%)	288 (28.7%)	
上気道炎	URI	245 (49.0%)	527 (52.6%)	
喘鳴		67 (13.4%)	138 (13.8%)	

From the “clinical documents” among the summary basis of approval dossier (p290～) file:///C:/Users/gec00/Downloads/10015900_21400AMY00008_270_1.pdf

Appendix 3.2：

Respiratory Adverse Events reported in the IMpact-RSV Study (2)

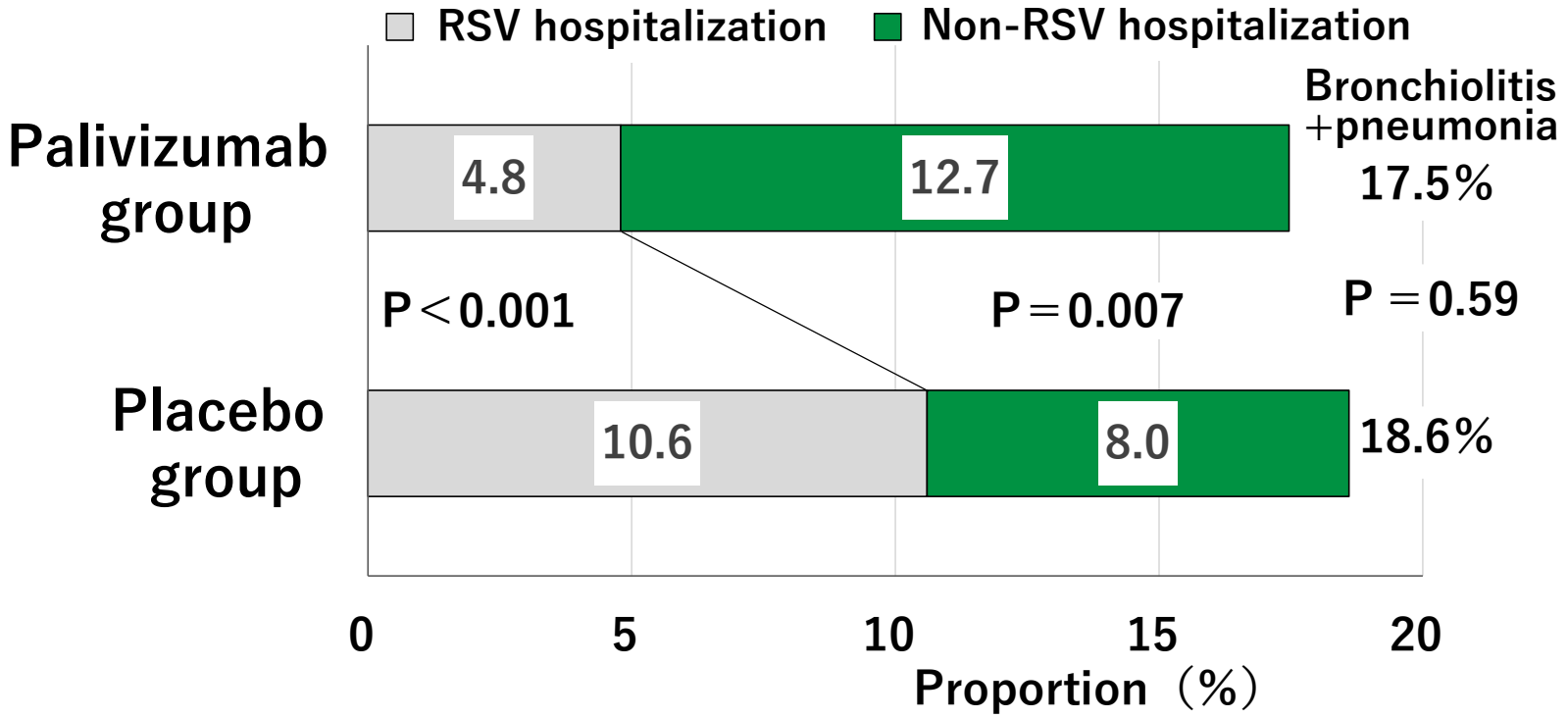


The sum of pneumonia and bronchiolitis as adverse events were slightly less frequent in the palivizumab group, but rhinitis was significantly more frequent by about 32% (p = 0.028), and upper respiratory tract infections (URI) were rather more frequent in palivizumab group. So it cannot be said that palivizumab reduces respiratory tract infections.

From the “clinical documents” among the summary basis of approval dossier (p290～)　file:///C:/Users/gec00/Downloads/10015900_21400AMY00008_270_1.pdf

Appendix 3.3 (same as Figure 2)：

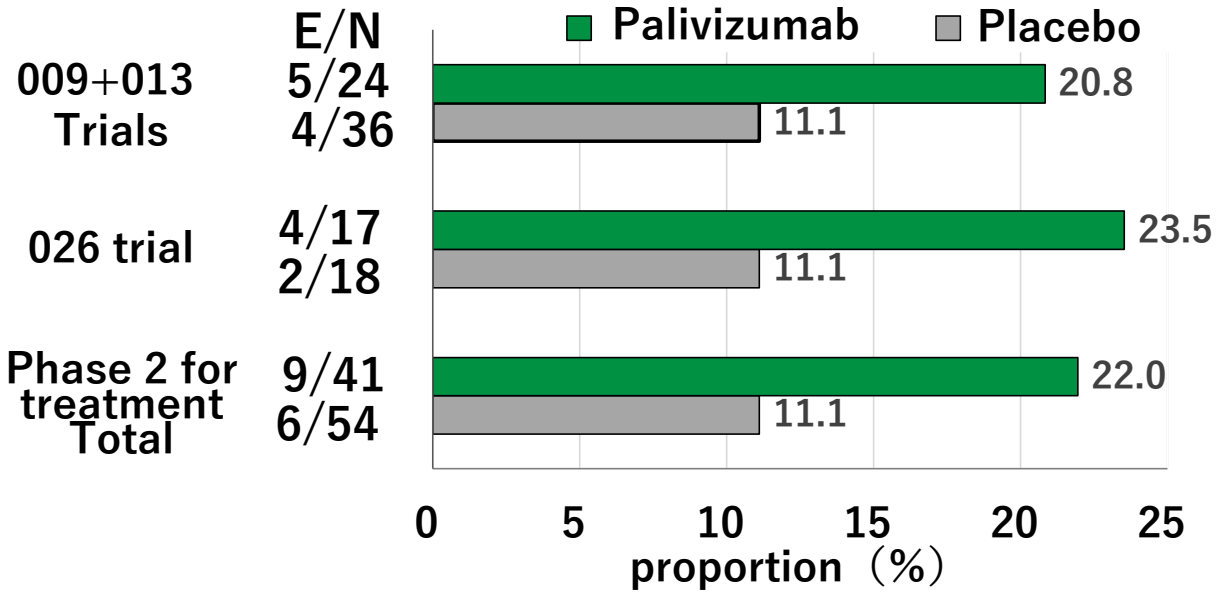
Bronchiolitis and pneumonia as AE and RSV hospitalization



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.**

From the “clinical documents” among the summary basis of approval dossier (p290～) file:///C:/Users/gec00/Downloads/10015900_21400AMY00008_270_1.pdf

Web Appendix 4 ： Proportion with serious respiratory adverse events in treatment trials: 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, phenomena involving ADE have been reported and confirmed. See next slide.

Appendix 5.1: Neutralizing and Enhancing Activities of Human Respiratory Syncytial Virus-Specific Antibodies

7) Gimenez HB et al. Clin Diagn Lab Immunol. 1996;3(3):280-6. doi: 10.1128/cdli.3.3.280-286.1996

Abstract

- The neutralizing and enhancing activities of respiratory syncytial virus (RSV)-specific antibodies were examined.
- These two biological activities were measured for a panel of six monoclonal antibodies (MAbs) specific to the RSV surface F and G glycoproteins.
- Four MAbs specific for the F protein possessed both neutralizing and enhancing activities.
- One MAb (11-2-D2), specific to the G protein, enhanced RSV infection of U937 cells, a human macrophage cell line, but did not neutralize virus infectivity.
- One MAb (11-3-A3), specific to the F protein, efficiently neutralized virus infectivity but did not enhance RSV infection of U937 cells.
- MAb 11-3-A3 neutralized representative strains of the two antigenic subtypes of RSV. Assays performed with mixtures of MAbs showed that high concentrations of MAb 11-3-A3 masked the enhancing activity of MAb 11-2-D2.
- The assay of mixtures of two MAbs possessing only enhancing activities demonstrated that this response was synergistic. The role of neutralizing and enhancing antibodies in determining the outcome of RSV infection was examined for infants from whom cord blood serum samples were collected at birth.
- There was no significant difference in the magnitude of the serum-enhancing activities between infants who were hospitalized with RSV infections and a group of age- and sex-matched control infants with no reported respiratory illness requiring hospitalization.

By our examination, there were significant to nearly significant differences.

- However, the results indicated a possible correlation between RSV infection of the infants and the occurrence of in vitro antibody-dependent enhancement of the cord blood sera at a serum dilution of 10(-2).
- A significant inverse correlation was found between the plaque-neutralizing and enhancing activities of the cord blood sera from infants, irrespective of subsequent RSV infection.
- These data are discussed in relation to the possible contribution of antibody-dependent enhancement to the normal course of RSV pathology in vivo.

Appendix 5.2: Neutralizing and Enhancing Activities of Human Respiratory Syncytial Virus-Specific Antibodies

7)Gimenez HB et al. **Clin Diagn Lab Immunol. 1996;3(3):280**-6. doi: 10.1128/cdli.3.3.280-286.1996

Introduction

Human respiratory syncytial virus (RSV) is a major cause of severe respiratory infections in infants, with **a peak incidence among 2-month-old babies**.

Epithelial cells of the respiratory tract are the primary target of virus infection. In addition, Human alveolar macrophages are susceptible to RSV infection.

In general, high levels of RSV-specific neutralizing antibodies in serum reduce the risk of severe virus infection but do not provide complete protection against reinfection (15). This report discusses the involvement of antibody-dependent enhancement (ADE) in the normal pathogenesis of RSV. In vitro ADE has been described for several viruses, including human immunodeficiency virus type 1 and influenza A virus. A role for ADE has been proposed for both dengue virus and rabies virus infections in vivo.

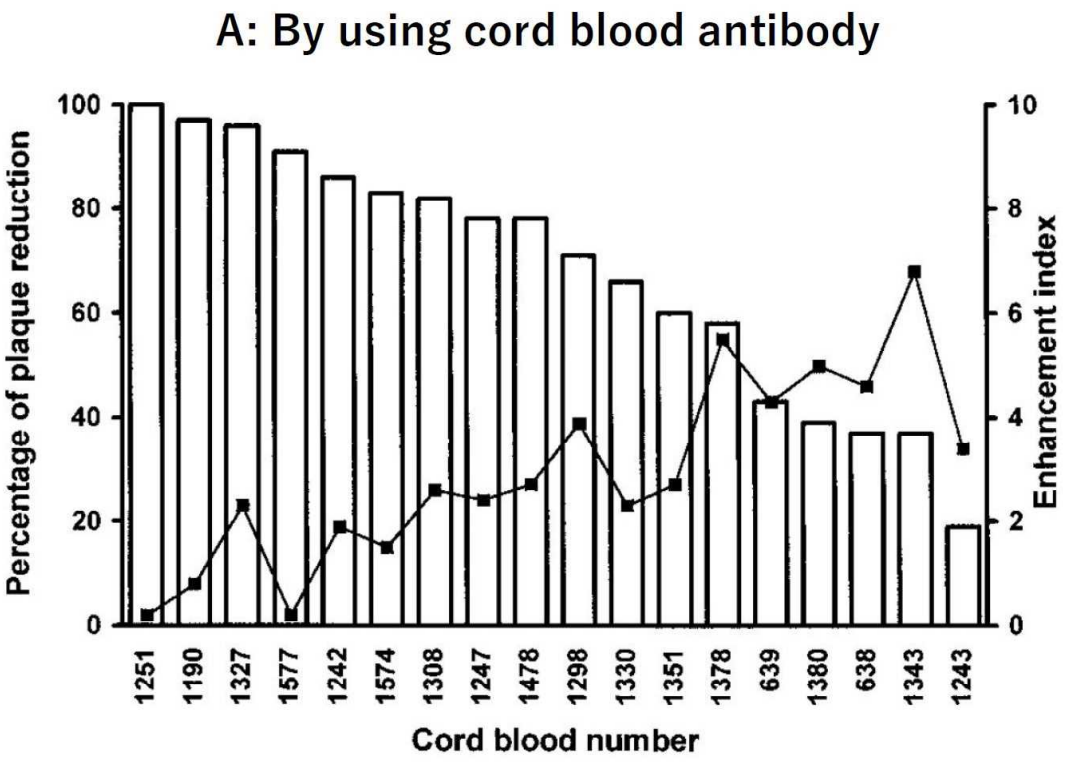
Presence of maternally acquired dengue virus-specific antibodies either protects infants from or increases their risk of severe dengue virus infection, depending on the ADE activity of the serum. RSV-specific monoclonal antibodies and human sera from children and adults with low titers of RSV-specific antibodies can enhance RSV infection of human monocyte cells in vitro.

- Osiowy et al have also demonstrated ADE for convalescent-phase sera collected from young infants (<6 months) and adults who had had recent RSV infections.
- Recently, it was reported that BALB/c mice inoculated with high doses of RSV produced high levels of inflammatory cytokines (tumor necrosis factor alpha and interleukin 6) known to be expressed by macrophages (17).
- A reduction in the microbicidal activity of RSV-infected murine alveolar macrophages was also reported by Frankeullmann et al. (10). Moreover, RSV infection of U937 cells, a monocyte cell line, causes a stimulation of leukotriene C4, a mediator of bronchial inflammation (1).
- We propose that the infection of monocyte cells by RSV in the presence of antibody during in vivo RSV infection could contribute towards the normal virus pathology either by increasing virus infection (i.e., ADE) or by modifying the role of the monocyte as a control point in the host's immune response; these effects may not be exclusive.

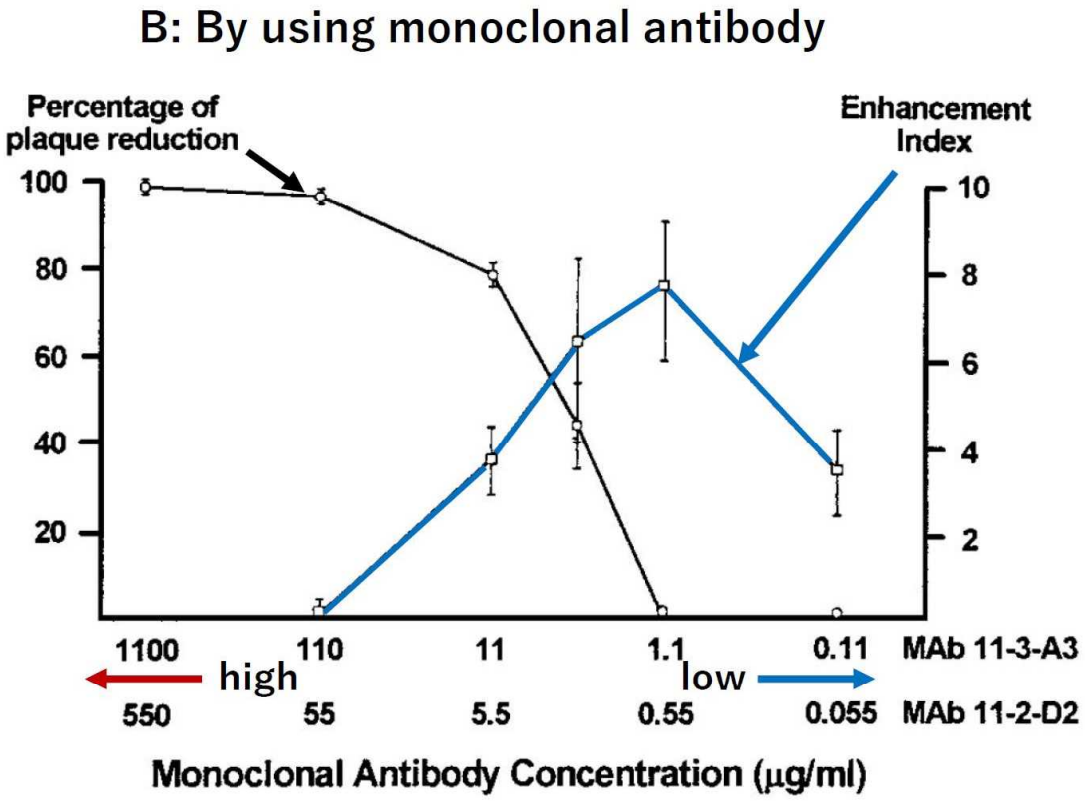
Appendix 5,3:

Neutralizing and Enhancing Activities of Human Respiratory Syncytial Virus-Specific Antibodies

7) Gimenez HB et al. Clin Diagn Lab Immunol. 1996;3(3):280-6. doi: 10.1128/cdli.3.3.280-286.1996



From Gimenez et al [7], Figure 3



From Gimenez et al [7], Figure 2

Appendix 5.4：

Neutralizing and Enhancing Activities of Human Respiratory Syncytial Virus-Specific Antibodies

Although the main case-control study results were not significant due to the small sample size and possibly due to the non-optimal dilution, odds ratio was large at 4.42, the p-value was close to significance at 0.0847, and I2 was 0%, showing no heterogeneity due to dilution. Considering this, together with the fact that a significant inverse correlation was observed between the plaque neutralizing activity and enhancing activity of infant umbilical cord blood, it is indicated that the magnitude of the serum-enhancing activities of infants umbilical cord blood is related to the severity of infant RSV infection.

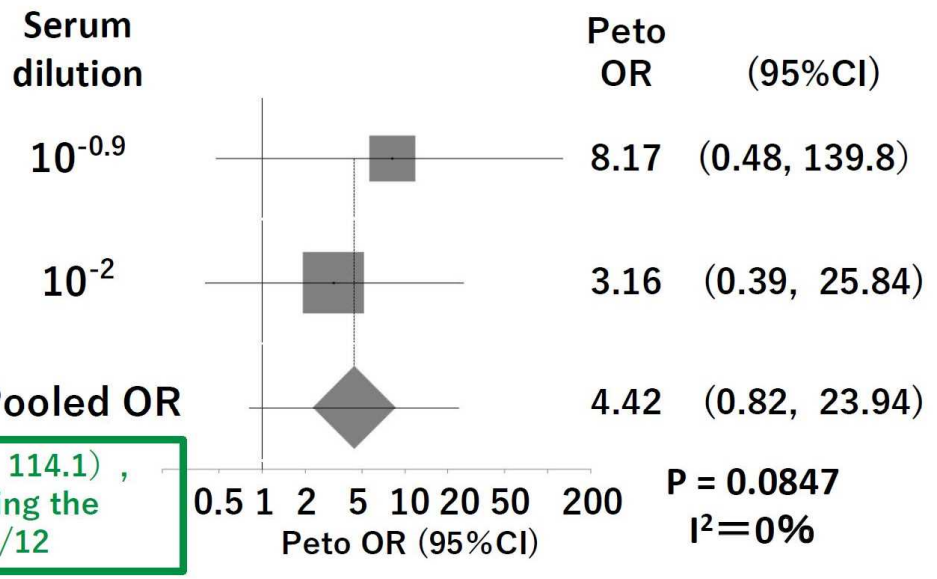
TABLE 3. Classification of cord blood sera according to enhancing activity at various serum dilutions

Cord blood serum dilution	Infant group	No. of serum samples: With an EI of <2.0	With an EI of ≥2.0	With peak EI	Total tested
$10^{-0.9}$	Case(RSV hsp)	9	2	0	11
	Control	11	0	0	11
	Total	20	2	0	22
10^{-2}	Case(RSV hsp)	1	11	11	12
	Control	3	9	6	12
	Total	4	20	17	24
10^{-3}	I	5	7	1	12
	II	1	11	6	12
	Total	6	18	7	24
10^{-4}	I	9	2	0	11
	II	8	4	0	12
	Total	17	6	0	23

2/11
0/11
11/12
9/12

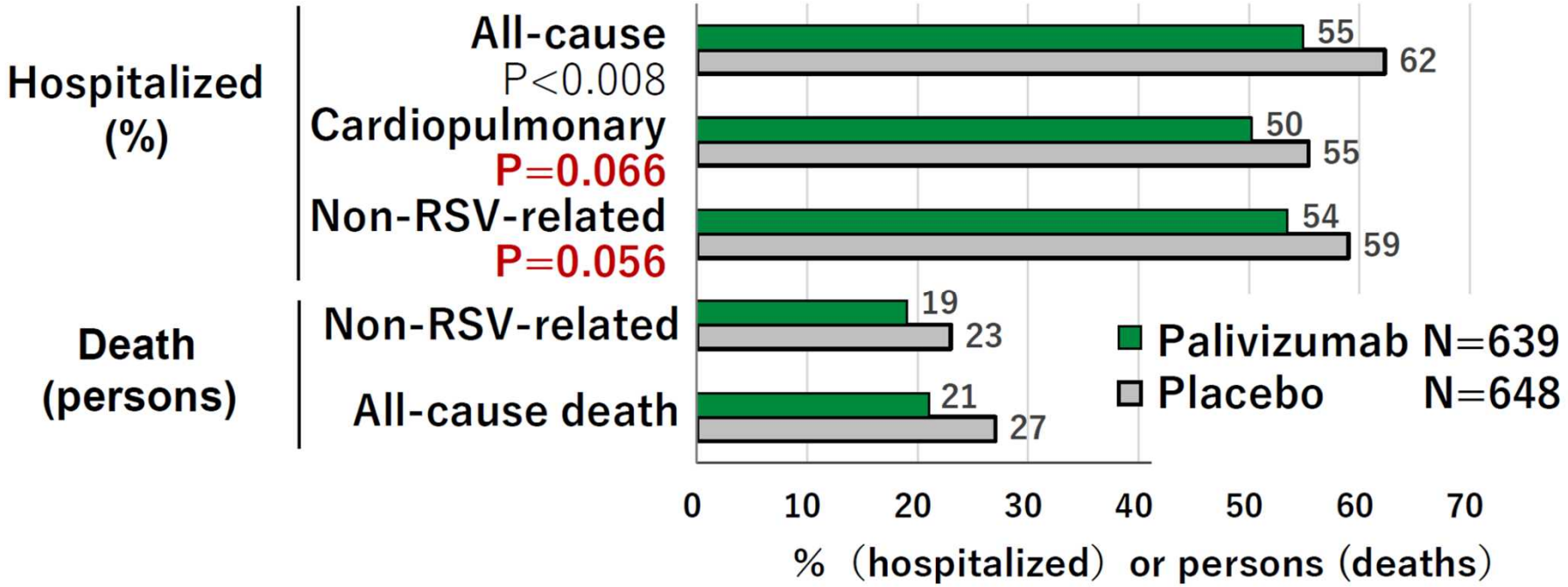
Meta-analyzed

OR is 11.0（1.06，114.1），p=0.0247： by using the data: 11/12 and 6/12



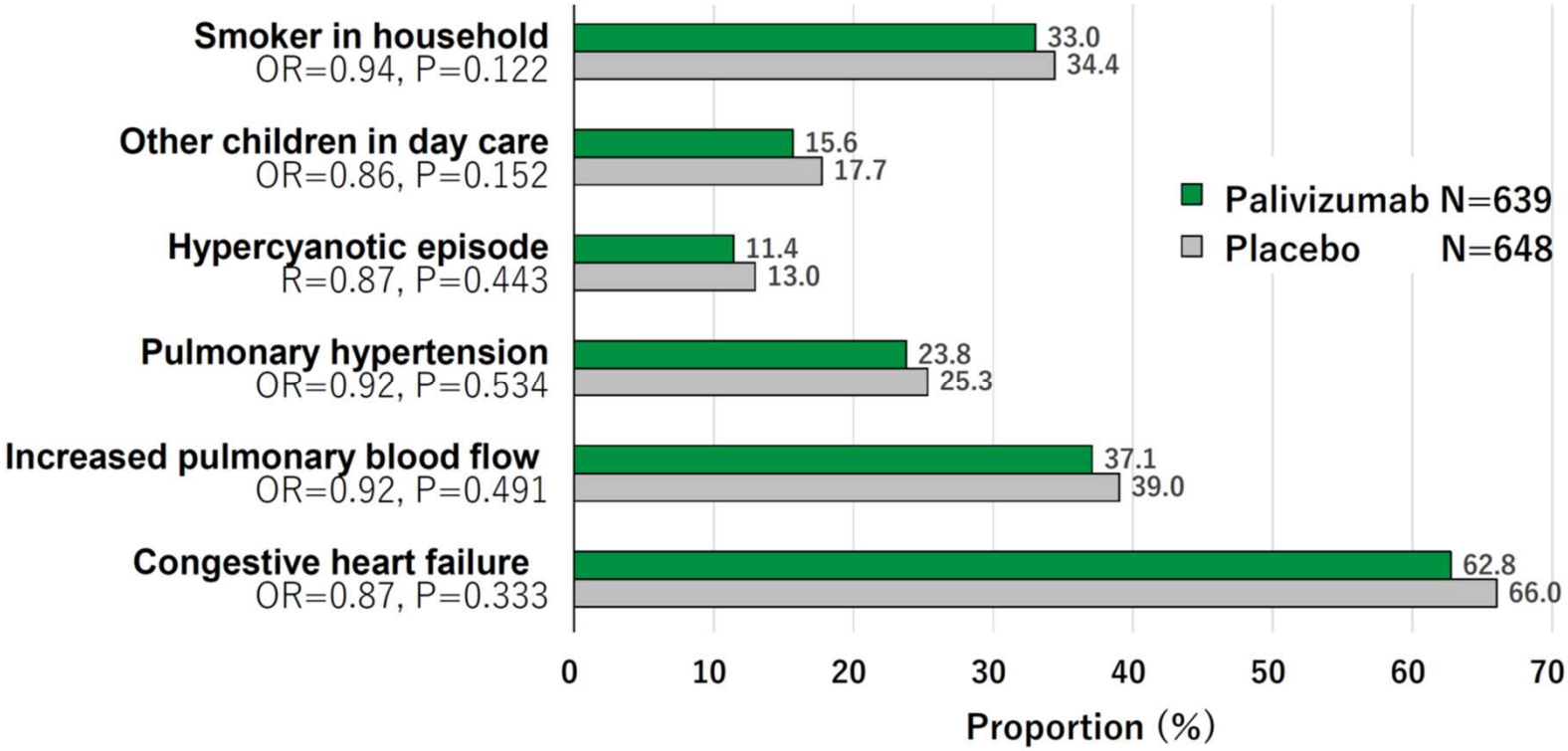
7) Gimenez HB et al. Clin Diagn Lab Immunol. 1996;3(3):280-6.
doi: 10.1128/cdli.3.3.280-286.1996

Appendix 6.1 : Non-RSV hospitalizations in the second study [2]



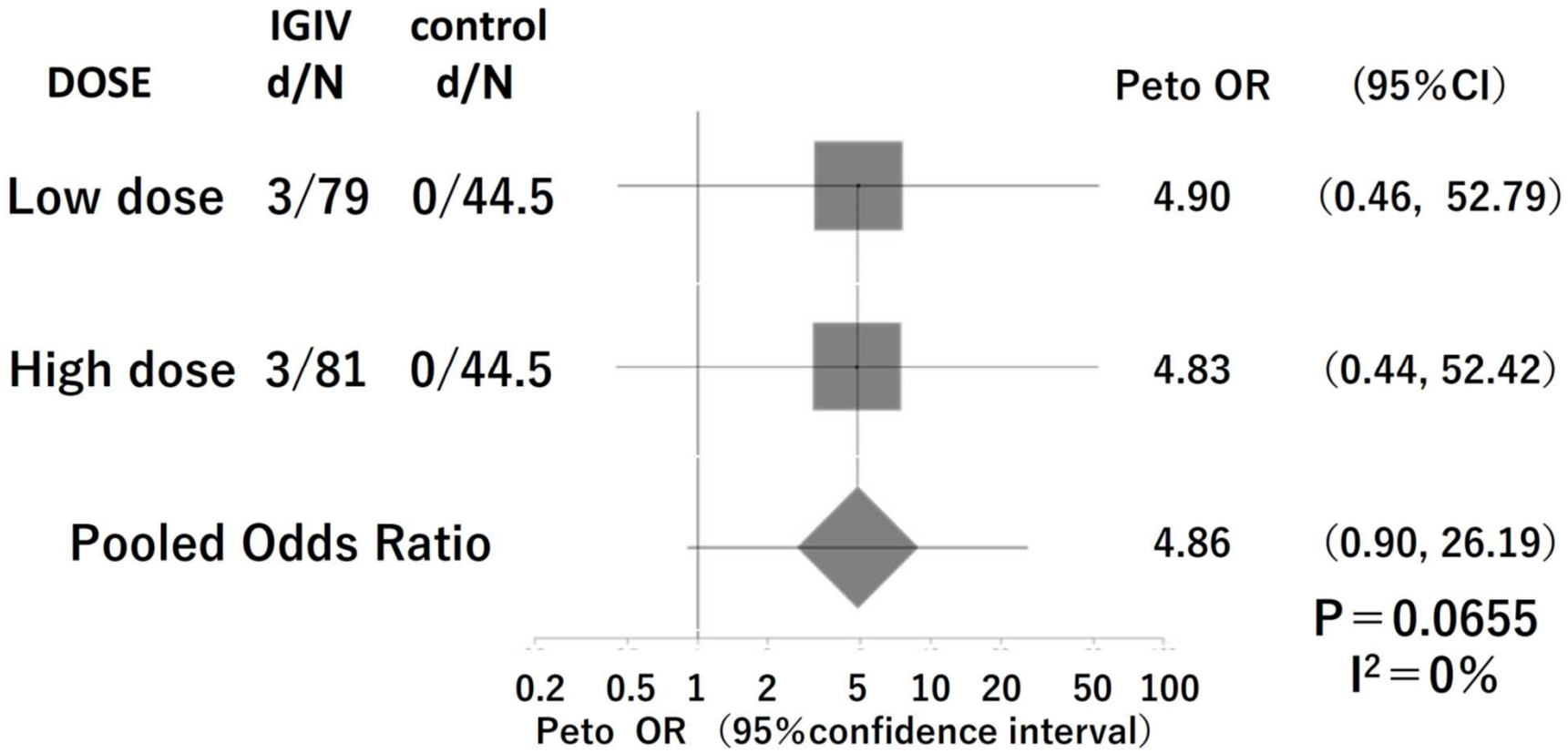
In the second study, hospitalizations due to non-RSV infection or due to cardiopulmonary disease were nearly significantly lower in the palivizumab group, although palivizumab could not reduce non-RSV-related hospitalizations. This is likely the result of the fact that, as shown in Web Appendix 6-2 (next slide), all four indices of (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 allocation that favored the palivizumab group. In addition, false negative RSV-antigen testing might have affected.

Appendix 6.2 : Baseline Characteristics in the second study [2]



ORs (odds ratios) were calculated by MedCheck editorial team based on the reported numbers. P values are based on the reported data on the Table 1 of the second study [2]. There were no significant differences in individual baseline characteristics, but the four indices of hemodynamics (hypercyanotic episode, increased pulmonary blood flow, pulmonary hypertension, and congestive heart failure) all tended to be lower in the palivizumab group. These might have affected the results of non-RSV hospitalizations in Web Appendix 6-1, in addition to the false-negative RSV testing by using antigen-detecting based test.

Appendix 7 : Mortality risk in Anti-RSV immunoglobulin (RSV-IGIV)

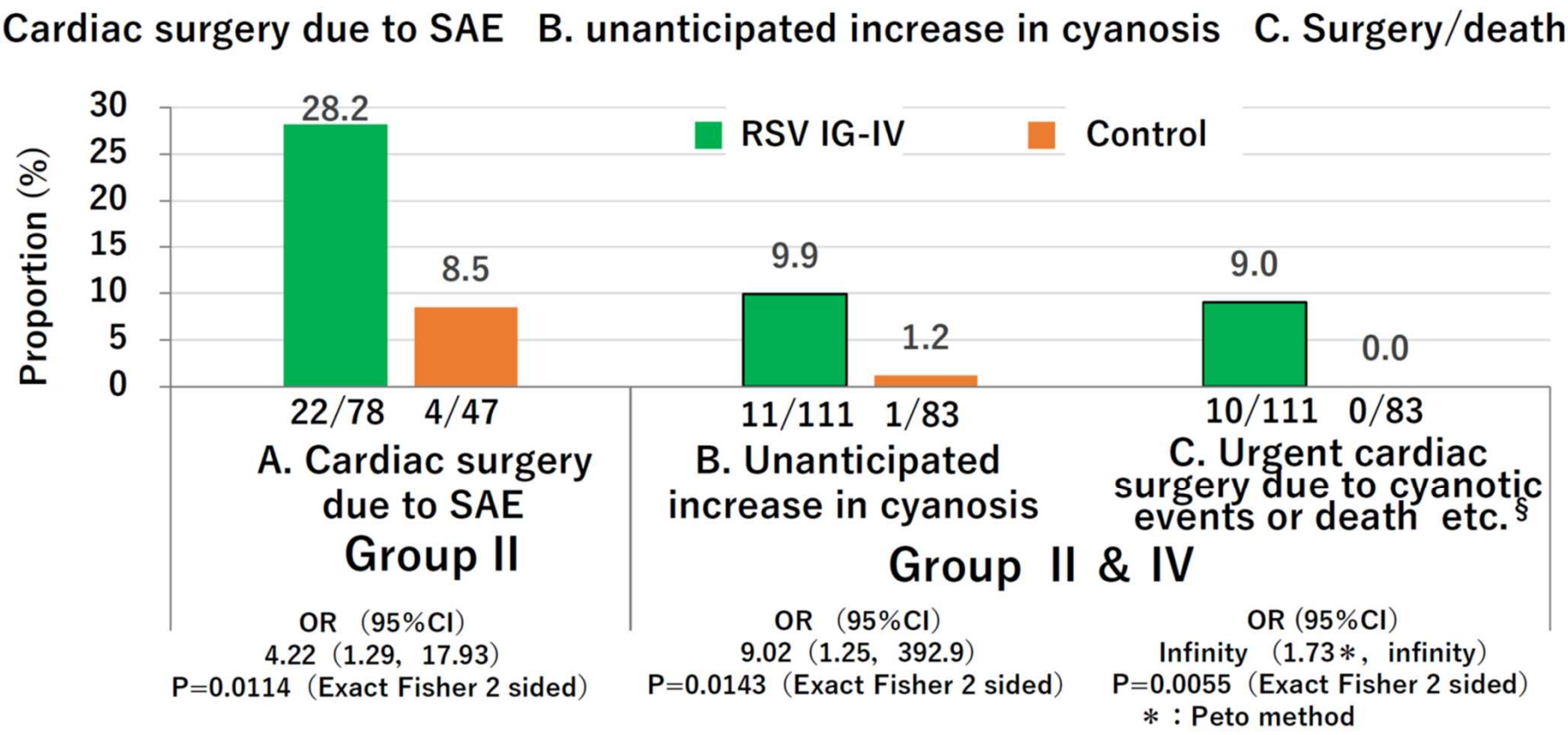


Since there was only one control group, the subjects were divided equally and were assigned to the both groups for meta-analysis. Meta-analysis results indicate marginally significant increase of odds of death.

Appendix 8：

More unanticipated increase in cyanosis in the RCT with RSV IG-IV on CHD children

9)The Cardiac Study Group: Simoes EA et al. J Pediatr. 1998 Oct;133(4): 492-9. doi: 10.1016/s0022-3476(98)70056-3.PMID: 9787686



Group II：Biventricular heart with right-to left shunt (ie, teratology of Fallot etc.)
Group IV：single ventricle or hypoplastic left heart. §:including one death and one cerebrovascular event