Alternative Explanation of the Results

In infants born at 29 to 32 weeks' gestation, Farber et al[1] conclude that palivizumab dispensing reduces respiratory syncytial virus (RSV)-diagnosed hospitalizations but increases hospitalizations due to bronchiolitis without RSV diagnosis. I disagree with the interpretation of study results provided by the authors. By using data reported in Table 2 and Table 5 of the article, I prepared a new table (Table 1). In Table 1, I have collapsed "no palivizumab" and "1–25% eligible doses dispensed" groups into a single category because they did not substantially differ in the frequency of RSV-diagnosed and RSV-undiagnosed admissions. The total, observed admissions (with and without RSV diagnosis) according to palivizumab dispensing are reported in the second column. If no or low (1%–25%) palivizumab eligible dosages were adopted in all infants, we would observe the same frequency of RSV-diagnosed hospitalizations (ie, 5.14%) throughout all infant groups. As a consequence, the total admitted infants (with and without RSV-diagnosed admissions) would be 8.37% (instead of 7.6%) in the group "30%–50%," 7.51% (instead of 4.7%) in the group "60%–75%," and 9.66% (instead of 5.9%) in the group "80%–100%." Thus, increasing palivizumab doses dispensed is associated with a dose–response reduction in observed total admissions as compared with those expected in the case of no or low (1%–25%) palivizumab eligible doses. This result overturns the interpretation of study findings provided by the authors. Therefore, the increase in admissions without RSV diagnosis does not seem to be an adverse effect of palivizumab, but it could be the expression of "confounding by indication" (patients with more severe disease are more likely to be treated with higher dosages and then more likely to experience hospitalizations for causes other than RSV).

Furthermore, for data in Table 4 of the article (infants born at 29–32 weeks' gestation), there is a mistake in the *P* value calculation when RSV-undiagnosed hospitalizations are compared between 0 and >1 doses dispensed. The correct *P* value is not .05 (as the authors reported) but .061. Thus, there is "no significant increase in non-RSV hospitalization" in infants with palivizumab dispensing >1 as compared with remaining infants. Finally, to see whether a given protective drug effect is counterbalanced by a negative one, the likelihood of being helped or harmed[2] should be appropriately calculated (Table 2) as the ratio between the number needed to harm and the number needed to treat.

As reported in the last column (Table 2), the analysis in terms of likelihood of being helped or harmed shows that palivizumab treatment is 36% more likely to help (in terms of reduction in RSV-related hospitalizations) than to harm.

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Conflict of Interest: Dr Tripepi has received honoraria from Abbvie and Biotest.

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Author's Response

On Careful Reanalysis of Our Findings I Stand by Our Results and Interpretation

In the comment by Dr Tripepi, "Alternative Explanation of the Results," I respectfully disagree with assertions that we misinterpreted our findings.

Our specific aim was to determine the different effects of palivizumab on hospitalizations with an RSV diagnosis and hospitalizations without an RSV diagnosis. We clearly showed differences and a dose–response effect.[1] It appears Dr Tripepi would like an analysis of pooled hospitalization rates (hospitalization with RSV diagnosis plus hospitalization for bronchiolitis without an RSV diagnosis) for infants born at 29 to 32 weeks' gestation to determine whether there is a net benefit or harm.

When we sum RSV and non-RSV hospitalizations (Tables 3 and 4 of the article) by receipt of any palivizumab, we find a 6.4% hospitalization rate for those who were dispensed ≥1 palivizumab doses compared with 6.9% for those who were not dispensed any palivizumab. This small

TABLE 1

Palivizumab Dispensing	Observed % of Admitted Infants			Expected % of Admitted Infants if "No Prophylaxis' or Low (1%–25%) Eligible Doses Would be Adopted		Observed – Expected
Eligible doses dispensed	*With and without RSV diagnosis*	*With RSV diagnosis*	*Without RSV diagnosis*	With RSV diagnosis	*With and without RSV diagnosis*	Difference in Admission rate (with and without RSV diagnosis)
No Palivizumab/1%–25%	7.0%	5.14%	1.89%	5.14%	...	...
30%–50%	7.6%	4.30%	3.23%	5.14%	8.37%	–0.77%
60%–75%	4.7%	2.37%	2.37%	5.14%	7.51%	–2.81%
80%–100%	5.9%	1.41%	4.52%	5.14%	9.66%	–3.76%

TABLE 2

Number Needed to Treat	Number Needed to Harm	Likelihood of Being Helped or Harmed
1/(0.0497–0.0308) = 53	1/(0.0332–0.0194) = 72	72/53 = 1.36

TABLE 3 Hospitalization With RSV Diagnosis or Bronchiolitis Without an RSV Diagnosis by Receipt of ≥1 Palivizumab Doses, 29- to 32-wk Gestational Age Infants

	Hospitalization for RSV or Bronchiolitis Without RSV Diagnosis	No Hospitalization for RSV and No Hospitalization for Bronchiolitis Without RSV Diagnosis
Palivizumab dispensing ≥ 1	54 (6.41%)	789
Palivizumab dispensing = 0	82 (6.90%)	1106

$P = .66$.

TABLE 4 Hospitalization With RSV Diagnosis or Bronchiolitis Without an RSV Diagnosis by Receipt of ≥80% of Eligible Palivizumab Doses Versus No Palivizumab Dispensed, 29- to 32-wk Gestational Age Infants

	Hospitalization for RSV or Bronchiolitis Without RSV Diagnosis	No Hospitalization for RSV and No Hospitalization for Bronchiolitis Without RSV Diagnosis
≥ 80% of eligible palivizumab doses dispensed	21 (5.93%)	333
Palivizumab dispensing = 0	82 (6.90%)	1106

$P = .52$.

difference is not statistically significant ($P = .7$). This analysis would be appropriate because the real-world intervention is prescription of palivizumab (Table 3).

For his analysis, Dr Tripepi combined the "no palivizumab" and the "1%––25% of eligible doses dispensed," claiming that the groups did not differ substantially. This claim is incorrect. The RSV hospitalization rate differed by 74% (4.97% vs 6.72%) between these 2 groups, hardly a trivial difference. The relevant clinical question is how a palivizumab prescription to which the patient is adherent compares with no palivizumab. It appears that in pooling the data, Dr Tripepi simply summed the percentages. This is not a correct strategy because the "RSV hospitalization: no" group included the patients who had a hospitalization for bronchiolitis without an RSV diagnosis, and the "non-RSV bronchiolitis hospitalization: no" group included those who had a hospitalization with an RSV diagnosis.

To address the concerns raised by Dr Tripepi, I compared the best-case scenario: ≥80% of eligible palivizumab doses dispensed versus no palivizumab dispensed. We found a 5.93% hospitalization (RSV + bronchiolitis without RSV diagnosis) rate for those who received ≥80% of palivizumab doses compared with a 6.90% hospitalization rate for those without palivizumab. The small difference is not statistically significant ($P = .5$) (Table 4).

Dr Tripepi claims that the P value for Table 4 of the article is not correct, stating it should be .06 instead of .05. Although results may differ by statistical test used, we chose to use the χ^2 test for these analyses. I reanalyzed these data and confirmed that the P value is .049 by χ^2 test. The more conservative Fisher test yields a slightly higher P value at .06.

In conclusion, I stand by our results and conclusions. Pooling data on hospitalization with RSV and bronchiolitis without an RSV diagnosis revealed only small differences by palivizumab administration status that were neither statistically significant nor clinically important.

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