Confounding by Indication Limits Conclusions of Study of Palivizumab Effectiveness

The study by Farber et al[1] on the retrospective effectiveness of palivizumab for late preterm infants contains critical design flaws that call into question many of its conclusions.

The study is a retrospective cohort study of infants born at 29 to 36 weeks' gestation from 9 Texas Medicaid managed care programs. The study was funded by managed care organizations with a financial interest in justifying cost reductions associated with palivizumab approvals. Among infants born at 29 to 32 weeks' gestation, those with ≥1 insurance claim for palivizumab had a 38% lower rate of hospitalization for respiratory syncytial virus (RSV) (5.0% vs 3.1%, $P = .04$). For the infants born at 33 to 36 weeks' gestational age, RSV hospitalization was not different between the 2 groups.

However, because of the nature of the claims data, the authors were not able to adequately control for confounding by indication, which occurs when the clinical indication for selecting a particular intervention also affects the outcome.[2] It is a common fallacy that performing an observational study of effectiveness results in a real-world estimate of the true benefit of an intervention. This is true only if confounding can be controlled for in the design or analysis of the study,[2] neither of which was done here.

Multiple known risk factors for RSV hospitalization were neither matched for in the study design nor controlled for in the analysis. These factors include low birth weight, male sex, length and complications of neonatal hospital stay, child care attendance, family size, maternal smoking, formula feeding, and young age. The authors' own data demonstrate that such confounding was indeed present, because palivizumab recipients were significantly younger than non–palivizumab recipients ($P < .001$). In addition, among children born at 29 to 32 weeks' gestation, palivizumab dispensing was associated with a statistically significant increased risk in non-RSV bronchiolitis hospitalization. The most plausible reason for this finding is that children who were prescribed palivizumab constituted a higher-risk group for hospitalization from respiratory infection.

Two randomized controlled trials of palivizumab have been performed in the patient population under discussion. The first study demonstrated a 78% relative reduction in RSV hospitalization (8.1% vs 1.8%, $P < .001$).[3] The second study found an 82% relative reduction (5.1% vs 0.9%, $P = .01$).[4] There is no reason to believe that the efficacy of this drug has waned over time. However, it is important for it be administered as it was studied. In the study by Farber et al,[1] 38% of infants born at 29 to 32 weeks' gestation had ≤50% of the recommended doses dispensed; similar data for the infants born at 33 to 36 weeks' gestation are not reported. Palivizumab is approved by the US Food and Drug Administration only for monthly administration throughout the entire RSV season.[5] Inadequate dosing regimens are not expected to be as effective.

Our vulnerable patients deserve the best data-driven individualized care. Studies that are retrospective, are nonrandomized, and show internally confirmed major evidence of confounding should not be used to override the data from carefully designed randomized trials.

Thomas G. Boyce, MD
Pediatric Infectious Diseases, Mayo Clinic
E-mail: boyce.thomas@mayo.edu

Ram Yogev, MD
Pediatric Infectious Diseases

John P. DeVincenzo, MD
Pediatric Infectious Diseases

Leonard R. Krilov, MD
Pediatric Infectious Diseases

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Author's Response One Should Not Dismiss Our Findings as "Just Statistics"

Dr Boyce's group criticizes our study as biased on "confounding by indication" and states that therefore results should be dismissed. Because 41.5% of the otherwise healthy infants born at 29- to 32-weeks' gestation in our population received ≥1 doses of palivizumab, a very large proportion of this population is represented. To decrease risk of confounding by indication, we carefully excluded infants who had claims suggesting a significant chronic illness that could affect risk for severe RSV disease. The full list of exclusion criteria was

published in the Supplemental Materials. To reduce variation by socioeconomic status, our data set was restricted to a Medicaid-insured population. Variation by age group at start of RSV season was accounted for in our multivariate analyses. Furthermore, in the 29- to 32-week age group this variation was small, with only a 17-day difference in mean age between those who received ≥1 palivizumab doses and those who did not receive any.[1] Variation in physician practice is the likely explanation for the most of the variation in rates of palivizumab prescribing that we observed.

Boyce et al claim that our results conflict with the results of the randomized controlled clinical trials on palivizumab. This assertion is incorrect. As stated in our discussion, our results are consistent with those of IMPACT-RSV trial.[2] Among the subgroup of infants born at 29- to 32-weeks' gestation who received ≥80% of recommended doses of palivizumab, we saw a statistically significant decrease in hospitalizations with an RSV diagnosis. The absolute magnitude of the difference was small because of the low rate of RSV hospitalization in this population. Those data are reported in Table 2 of our manuscript. Boyce et al cite a study performed in the Netherlands (the MAKI trial) to support the efficacy of palivizumab for infants born at 33- to 35-weeks' gestation. However, the randomization procedures for that trial did not adequately balance the treatment groups for important variables known to influence outcomes; specifically, their control group had greater rates of maternal smoking, lower rates of breast feeding, and greater day care attendance.[3]

What raises substantial concern from our study results, and was ignored by Boyce et al, is the increase in hospitalizations for bronchiolitis without an RSV diagnosis associated with palivizumab administration. Dismissing that finding as "confounding by indication" is irresponsible. The most likely explanations are respiratory viral infections picked up in the pediatrician's office (because palivizumab administration requires multiple trips to the pediatrician's office) or false negative RSV tests (because viral load would probably be decreased by the palivizumab), both of which have evidence supporting them, as cited in the manuscript. Why was this finding not reported in the randomized controlled clinical trials? There are 2 plausible explanations. Perhaps it was not looked for, because the specific aim of the trials was to examine the impact on hospitalizations for RSV disease. The other plausible (and most likely) explanation is that infection control procedures were much better in the clinical trial than in many physicians' offices, leading to more respiratory viral infections associated with visits to receive palivizumab in the real world than in the clinical trial setting.

As our data were used to validate the 2014 American Academy of Pediatrics (AAP) Guidance to not administer palivizumab to otherwise healthy infants born at ≥29 weeks' gestation, the main criteria used by the AAP (that RSV hospitalization rates in the population of otherwise healthy infants born at 29 to 36 weeks' gestation are low and that rates in infants born at 29 to 32 weeks' gestation are not substantially different from those of infants born at 33 to 36 weeks' gestation)[4] are validated by our results. The finding of increased hospitalizations for bronchiolitis without an RSV diagnosis associated with palivizumab administration is concerning and lends support to the 2014 AAP guidance statement.

Dr Boyce's group asserts that support from managed care organizations represents a conflict of interest to "justify cost reductions associated with palivizumab approvals." It should be noted that 7 of the 9 participating managed care organizations are provider-sponsored, not-for-profit organizations. Managed care organizations are interested in delivering value to members. Cost–benefit analysis is very different from cost reduction, because cost–benefit analysis focuses on value delivered. Determining cost–benefit ratios is a legitimate and important interest of managed care organizations and provides important benefits to society.

Harold J. Farber
Associate Professor of Pediatrics, Pulmonary Section Baylor College of Medicine, Texas Children's Hospital, and Texas Children's Health Plan
E-mail: hjfarber@texaschildrens.org

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Author's Response: One Should Not Dismiss Our Findings as "Just Statistics"

Harold J. Farber

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Harold J. Farber

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