## 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.

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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

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