Clarifying Costs and Benefits of Respiratory Syncytial Virus Immunoprophylaxis

In response to recent studies demonstrating that palivizumab use in moderate preterm infants may decrease subsequent wheezing, Meissner and Kimberlin1 discuss costs associated with palivizumab but make multiple statements that may not be consistent with the best available evidence.

The stated hospitalization cost of $8530 (2009$) is not representative of respiratory syncytial virus (RSV) hospitalizations among palivizumab-eligible infants; it is the average cost of bronchiolitis hospitalizations among US children <2 years.2 Using the same source, the Kids’ Inpatient Database, the average RSV hospitalization (International Classification of Diseases, Ninth Revision, Clinical Modification 079.6; 466.11, 480.1) cost for all infants was $14832 (2009$).3 Among high-risk infants, costs of RSV hospitalization and associated care through 12 months of age range from $20 160 to $39 399 (2010$).3 The authors also state the number needed to treat (NNT) with palivizumab to prevent 1 RSV hospitalization for most infants ranges from 19 to 170. In the Canadian Pediatric Society’s RSV prevention position statement, high-quality NNT estimates range from 12 to 23 depending on the population. Lower quality estimates from studies of health care utilization databases, such as those referenced by the authors, often yield higher NNTs due to underdiagnosis of RSV and limited use of RSV-specific codes.

Meissner and Kimberlin1 state that RSV hospitalizations are becoming less common among children eligible for palivizumab, citing a 17% decrease in bronchiolitis hospitalization rates from 2000 to 2009 among US children <2 years.2 However, Hasegawa et al2 also found a 34% increase in children with high-risk conditions from 2000 to 2009. According to a personal communication with Dr Hasegawa, the hospitalization rate among children at high risk rose by 29%. This increase despite palivizumab use is not surprising given that most children at high risk do not receive palivizumab and use has declined since 2006.

Concerning the cost of palivizumab, the authors state that rebates may modify the cost, but the cost presented does not incorporate rebates. Federally mandated rebates for Medicaid recipients and discounts for 340B-eligible organizations have resulted in ~40% reduction in palivizumab cost for ~60% of palivizumab recipients, as described in a recent publication3 and a Centers for Disease Control and Prevention analysis at the June 23, 2010, Advisory Committee on Immunization Practices.

Finally, the authors state that mortality reduction cannot be included in palivizumab analyses because it has not been demonstrated in randomized trials. However, mortality reductions are commonly included in cost-effectiveness studies even without statistically significant differences in randomized trials. Two examples include an economic evaluation of pediatric influenza vaccination conducted by the Centers for Disease Control and Prevention and investigators from Harvard University, as well as the UK Health Technology Assessment of palivizumab.4 There is no evidence to support the authors’ statement that “adverse long-term outcomes such as death are not prevented by passive immunotherapy.” Cost-effectiveness analyses of palivizumab should consider all downstream costs and savings and use the best available evidence. As the authors state, quality of life and other factors must be considered. Calculating cost per quality-adjusted life-year gained is the recommended approach to understand the benefits of an intervention relative to costs and enables comparison with other health interventions.5

Conflict of Interest:
Kimmie McLaurin is an employee of AstraZeneca. Christopher Ambrose is an employee of MedImmune.

References

Authors’ Response Re: Clarifying Costs and Benefits of Respiratory Syncytial Virus Immunoprophylaxis

We appreciate the interest expressed by employees from MedImmune and
McLaurin and Ambrose suggest a mean hospital charge of $8530 for 1 RSV hospitalization is not accurate and cite a charge for RSV hospitalization for children at high risk <13 months of age as $20,160 to $39,599. The reference for their figures is an article authored by MedImmune employees, and they exceed charges reported in other studies.1 A higher mean charge for an RSV hospitalization will drive a cost analysis in favor of immunoprophylaxis. As noted in our commentary, cost figures proposed by the manufacturer consistently are higher and more favorable to use of prophylaxis than figures used in analyses conducted by independent researchers.2 Also, as noted in our commentary, even with variation in assumptions such as a doubling or tripling of hospital charges, sensitivity analyses continue to demonstrate high cost relative to minimal benefit.2

McLaurin and Ambrose suggest that the number needed to treat (NNT) came from “lower quality estimates from studies of health care utilization.” The authors may be surprised to learn the NNT of 20:1 came directly from the IMPaCT-RSV trial, a study sponsored and conducted by MedImmune.3 By most accounts, the IMPaCT-RSV trial is regarded as well designed and carefully conducted. Apart from infants who required ~28 days of oxygen in the NICU, results from the IMPaCT-RSV study produced figures for NNT of 17:1 to 152:1.4 Thus, the NNT used in our calculation of 20:1 is conservative. Surprisingly, McLaurin and Ambrose refer to an NNT of 12:1 to 23:1 as “high quality” data from the Canadian Pediatric Society. Canadian guidelines do not recommend immunoprophylaxis for children with a gestational age >32 weeks (unlike American Academy of Pediatrics guidelines for the United States, which recommend prophylaxis up to 35 weeks’ gestation).5 Thus, the Canadian numbers have little relevance to the United States, which has more liberal guidelines.

McLaurin and Ambrose suggest that rates of RSV hospitalization are increasing among children at high risk because “most high-risk children do not receive prophylaxis.” We are unaware of published data suggesting an increase in the number of infants who are not receiving prophylaxis as recommended in the most recent American Academy of Pediatrics guidelines.6 A more likely explanation for increasing rates of RSV hospitalization among children at high risk is that immunoprophylaxis offers minimal and perhaps less protection than noted in the initial IMPaCT-RSV trial against RSV hospitalization.

We laud McLaurin and Ambrose and their company for offering rebates. The figures cited regarding rebates (“40% reduction in palivizumab cost for 60% of palivizumab recipients”) are considered proprietary by the company and cannot be confirmed by independent sources. If these figures accurately reflect the price structure, we encourage strongly an extension of these rebates. The consistent yearly increase in the price of palivizumab stands in stark contrast to the cited rebates. The average wholesale cost of a 100-mg vial of palivizumab in 2004 was $1416. In 2013, the average wholesale cost of an identical vial has more than doubled to $2962.

Mortality reduction cannot be included in a cost analysis of RSV prophylaxis. No randomized, placebo controlled clinical trial with palivizumab has demonstrated a statistically significant reduction in mortality rate due to RSV among hospitalized children. Earlier estimates of RSV mortality among hospitalized children do reflect more recent data. A report utilizing 2 national databases (the Pediatric Health Information System and the Kids’ Inpatient Database) demonstrate that ~84 deaths per year occur during the RSV season, that these deaths occur in children with complex medical conditions, and that the deaths are generally unrelated to RSV infection.7 This reduction in mortality likely reflects the fact that ICU care is more effective now than in earlier years.

We agree that cost per quality adjusted life year saved is recommended by the Centers for Disease Control and Prevention as an optimal approach for relative evaluation of interventional therapies. However, the inability of palivizumab prophylaxis to produce a measurable reduction in mortality and the minimal reduction on subsequent episodes of wheezing determine that the cost/quality adjusted life year is highly likely to far exceed a reasonable figure.

We concur with the rapidly growing consensus among pediatricians, other health care providers, and policy makers that RSV immunoprophylaxis has become so costly and the impact is so minimal that it is difficult to justify its use for the vast majority of infants and children who now receive palivizumab prophylaxis.

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Conflicts of Interest:
None declared.

REFERENCES
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