

Cost-effectiveness of respiratory syncytial virus prophylaxis in premature infants less than 32 weeks gestational age in Turkey

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To the Editor,

We read with interest the recent publication by Oncel et al.¹ on the cost-effectiveness of respiratory syncytial virus (RSV) prophylaxis in preterm infants and their intriguing conclusions. In our opinion, several methodological issues and the case-control study design merit careful deliberation prior to adoption of the results into clinical practice.

The main aim of this study was to evaluate the cost-effectiveness of RSV prophylaxis with palivizumab in Turkey, by comparing hospitalization rates and costs as well as results of risk analyses in preterm infants who were treated either with palivizumab or conservatively. The retrospective nature of the study significantly limits the authors' ability to gauge the magnitude of the baseline risk of RSV-related hospitalization and the true impact of prophylaxis with palivizumab. Several biases were transparent at the inception of the study: the fundamental lack of a precise definition for an RSV-related hospitalization based on specific diagnostic tests, failure to establish parental contact in order to assess if patients were admitted to other institutions during the study period, lack of a description of the hospital network, which may pose a referral-filter bias, absence of a defined strategy to ensure all hospitalizations were captured, and failure to cite reasons for refusal of prophylaxis, which could profoundly influence the outcome relative to an infant's demographic and environmental risk for acquiring RSV infection inclusive of the parents' socioeconomic status. The control group in the study comprised infants whose parents refused prophylaxis, and this may include poor-risk or non-compliant patients or infants with extraneous characteristics that may adversely influence the outcome of interest. The overall convenient sample size

was relatively small with few controls (n=71) compared to the treated group (n=201), and no sample size justification was provided, with the authors' claiming that it was deemed sufficient. Therefore, the incurred, large random variability, combined with the difficulty of controlling for potential unknown confounders using historical controls, makes it impossible to establish a cause and effect relationship and severely jeopardizes the applicability of the results.

In addition, the authors' selection of ICD-10 codes to answer the addressed RSV-related research question may be contentious. While an expanded definition for all lower respiratory tract infections (LRTI), irrespective of viral etiology, was appropriately chosen, none of the utilized codes except J12.1 and J21.0 were specific enough to nucleate RSV-related hospitalization, which was the primary outcome, and this may have significantly reduced the numbers in the assembled cohorts²⁻⁴.

More importantly, the authors' primary objective was to evaluate the cost-effectiveness of palivizumab in the preterm population. The analysis was done from a purely payer's perspective and was based on the total medical costs incurred for the hospitalized patient without due consideration of both the direct and indirect medical costs from the societal viewpoint. Therefore, there was no attempt to establish the short- and possible long-term benefits of prophylaxis in this group of infants, which are important for the calculation of downstream costs⁵⁻⁸. A decision analytic model should be employed to estimate the cost-effectiveness of palivizumab relative to no prophylaxis. The more commonly utilized cost-effectiveness measure is the incremental cost-effectiveness ratio (ICER), which is expressed

as the cost per quality-adjusted life year (QALY) gained with palivizumab relative to no prophylaxis with lifetime follow-up^{4, 9-11}. It is also essential to conduct sensitivity analyses on important point estimates such as health utilities, discounting applied to both costs and outcomes, sharing of vials, and mortality⁴. The authors could have employed an existing decision tree model^{4,9,10} designed using data from a large international clinical trial of palivizumab versus placebo¹² and meshed more solidly assembled prospective hospitalization data from the Turkish population to derive more robust, country-specific cost-effectiveness data. The number needed to treat (NNT) must be based on a consistent, compliant time frame for treatment and non-treatment, and the authors do not document whether the hospitalizations were limited to children aged <2 years or if patients experienced one or more hospitalizations for the same event. Of major concern is that the patients were not tested for RSV, which leads to a fallacious interpretation of the results. This unfortunately also completely invalidates the NNTs and the estimates of both the benefit (RSV-related hospitalization avoided) and possible harm of therapy (side effects). Therefore, the overall efficacy of palivizumab in the reported study cannot be derived since the authors' only report hospitalizations for non-specific LRTI, and the documented rates cannot be compared to other similar studies in the scientific literature¹³⁻¹⁵.

In the discussion, the authors state that there is a chasm between the American Academy of Pediatrics' recommendations and current clinical practice due to non-compliance with the proposed number of palivizumab doses during the RSV season. However, they do not address the issue of compliance in their study, which may impact the rate of RSV-related hospitalization. The authors do provide good examples of studies conducted in Netherlands¹⁶ and Germany¹⁷ where the investigators concluded that palivizumab prophylaxis should be targeted at high-risk infants based on risk factors such as male gender, bronchopulmonary dysplasia (BPD), birth during the early part of the RSV season, and daycare attendance. As far as we are aware, despite the findings by Rietveld et al.¹⁶, the Dutch RSV prophylaxis guidelines¹⁸ have not changed, and encompass all preterm babies <32 weeks gestational age and infants

with BPD, with additional consideration for prophylaxis in infants with pulmonary disorders such as cystic fibrosis, certain congenital heart defects, Down syndrome, and those with immunodeficiency. The German RSV prophylaxis recommendations¹⁹ do not reference Roeckl-Wiedmann et al.¹⁷, but have incorporated their findings such that palivizumab is provided for all infants <2 years who are dependent on medical therapy for their disease and for preterms <29 weeks gestational age who are <12 months old at the start of the season, while infants between 29-32 weeks receive prophylaxis if they are moderate risk with ≥ 2 risk factors, namely neurological disorders, discharge early in the RSV season, and siblings who are school-age or in daycare.

Oncel et al.¹ reported that the reductions in non-specific LRTI hospitalizations were statistically insignificant in infants ≤ 28 completed weeks gestational age with and without BPD and make a huge leap extrapolating their results to the efficacy of palivizumab, implying equivalence of LRTI hospitalizations with their estimated reduction of RSV-related hospitalization, which was not assessed. The grade and quality of the evidence from the large-scale randomized, double-blind, placebo-controlled Impact trial¹² has led international pediatric advisory bodies to recommend prophylaxis for all infants ≤ 32 weeks gestational age who are <6 months of age at the start of the RSV season and those with BPD who are <2 years of age who receive medical therapy within 6 months before the start of the RSV season²⁰⁻²². Real-world experience also justifies usage in these populations as do the Turkish guidelines in 2007^{23,24}. It seems surprising therefore that the authors now choose to use incorrectly calculated NNTs to gauge costs for RSV prophylaxis in the two groups of palivizumab and non-palivizumab recipients and to inappropriately deem that palivizumab was not cost-effective. This contravenes their already clearly delineated guidelines established by their local neonatal society. Furthermore, a discussion of nosocomially acquired RSV infection and support for prophylaxis in this unique scenario seems misplaced in the context of a flawed economic evaluation of RSV prophylaxis.

Quality of Health Economic Studies (QHES) scores can be employed to appraise cost-

minimization, cost-effectiveness and cost-utility analyses conducted in everyday practice. The overall score of the authors' article can be guardedly rated as only 12 out of 100, based on the instrument that involves 16 criteria with weighted point values²⁵. Unfortunately, the extremely low score reduces the credibility of the authors' conclusions and the article does not offer any scientific evidence to either support or nullify the use of RSV prophylaxis in premature infants. Moreover, the study should not be employed to establish any firm guidelines or recommendations for the use of palivizumab for potential at-risk infants in Turkey. Efficiently designed, cost-effective studies should be urgently conducted after the epidemiology and impact of RSV-related illness is established, in order to more accurately evaluate the benefit of prophylaxis locally. Clear thresholds of ICERs/QALY need to be defined for the adoption of palivizumab prophylaxis in specific sub-groups of high-risk infants based on local Turkish Health Care System benchmarks. The authors should be encouraged to pursue more robust prospective studies before dismissing their existing, prudent RSV prophylaxis recommendations²⁴, which are evidence-based and in keeping with current international position statements. Many of the pharmacoeconomic issues highlighted by the QHES must be thoroughly addressed in future research in order to provide rigorous, well-defined, objective measurements of the results. This will lend strength to the findings and will streamline both the generalizability and applicability of RSV prophylaxis in the premature population.

Key words: respiratory syncytial virus, prematurity, palivizumab, prophylaxis.

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