Supplementary Online Content


eAppendix. Additional Details of Statistical Methods
eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix. Additional Details of Statistical Methods

The main goal of our statistical analysis was to estimate the age at which the risk of RSV-hospitalization (RSV-ha) in late-preterm infants no longer exceeded the level of RSV-ha risk in 1-month old term infants.

We started with the development of an age trend model that we could use to characterize the effect of age on RSV-ha risk in term and late-preterm infants. After fitting this regression model and identifying functions of the estimated regression parameters that efficiently described the shapes of the term and preterm age curves, we equated the preterm age curve function (with age left as an unknown) to the level of RSV-ha risk predicted by the term age curve function evaluated at 1 month of age. After algebraic rearrangement of this new equation, we used a root-finding optimization routine to solve this highly non-linear function of the regression parameters for the unknown age at which preterm RSV-ha risk fell to the level of term RSV-ha risk at 1 month of age. Because of the difficulty in directly estimating the standard error of this age estimate, we bootstrap-sampled the original dataset 1000 times and refitted the original age trend regression model to each of these datasets to obtain a sample of 1000 age estimates. We then used the 2.5 and 97.5 percentiles from this sample to define an empirical 95% confidence interval (CI) for the age estimate.

Age trend model for RSV-ha risk in term and preterm infants

Because of the size of our Florida and Texas analysis datasets and our need to use bootstrap methods to estimate 95% CIs for our preterm age estimates, we developed our age trend model for RSV-ha risk as a proportional odds model within a discrete time survival analysis framework. This class of models is analogous to the Cox proportional hazards model, with the probability of an RSV-ha occurring within discrete time intervals modeled as a function of (possibly time-dependent) covariates. To handle time-dependent covariates, we partitioned patient follow-up into 15-day periods (biweeks) and characterized each biweek with regard to age (defined as age at the beginning of each biweek), calendar month (defined as the month associated with the majority of days within each biweek), and palivizumab exposure (defined as at least 7 days of exposure within a biweek). We explicitly modeled the baseline hazard function as a categorical sequence of the 8 biweeks that could be observed within a complete patient follow-up period (i.e. a 4-month RSV season core).

We used restricted cubic splines (RCS) in the proportional odds model to characterize the shape of age trends in RSV-ha risk. Knot locations for the RCS regression terms were chosen using established guidelines. We fitted models with different numbers of knots and used the Akaike Information Criterion (AIC) to select the number of knots which most efficiently characterized age trend shapes. We considered both "parallel trend" models, where the shape of the age trend was assumed to be the same in both term and preterm infants and only the intercepts of the age curves could differ, and "independent trend" models in which RCS regression terms interacted with term status, allowing both shape and intercept to differ between term and preterm age curves.
To explore the effect of possible misclassification of RSV-ha as LRT-ha, we extended our final Florida and Texas models to include a RSV-ha false negative rate misclassification parameter and then generated age estimates assuming various levels of misclassification.

Age trend models were fitted using PROC LOGISTIC in SAS V9.2 (SAS Institute, Cary NC). We used PROC NLMIXED to fit the age trend model that included a misclassification rate parameter. We used the "uniroot" function in R V2.15.0 (R Development Core team, Vienna Austria) to solve our function of the regression parameters for the unknown preterm age. To calculate RSV-ha incidence rates from our proportional odds models, we assumed that the predicted probability of an RSV-ha occurring within a biweek could be viewed as the expected fraction of an event expected to occur within 15 patient-days of follow-up, and rescaled this rate appropriately. For purposes of graphic display, we averaged these rates over the 4 core RSV season-months and the 5 RSV seasons used in our study.

eReferences