

A NEUTRAL BAYESIAN REFERENCE ANALYSIS OF INCIDENCE RATES OF RARE CLINICAL EVENTS

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Bayesian modeling of the incidence rate parameter provides a convenient method to estimate the location of the true incidence rate and to quantify its associated uncertainty. Often we use complex models to derive the posterior distribution of the parameters of interest, but tend to ignore comparisons to inferences from a simple reference analysis. In the pharmaceutical industry, there seems to be no universally accepted reference Bayesian analysis that would act as a baseline for comparison for all parties involved, including the regulatory agencies. Comparisons of posterior intervals with classical confidence intervals are often made but are not helpful, since their definitions are completely different. Without a reference model, it is impossible to judge whether the posterior resulting from a given Bayesian model is reasonable or not. There is a definite need for such 'gold standard' analyses.

However, the choice of a Bayesian reference model for incidence rates is not trivial. Under binomial and Poisson sampling distributions, shrinkage is practically unavoidable, but also desirable. This is especially prominent in the case of rare events, even for the simplest models and also for positive observed rates. There are no fully 'uninformative' models, and it will be necessary to inject some prior information into the model, but it is not necessarily clear how much prior information is acceptable for a reference model. Rather than considering the shape or quantiles of the reference prior distribution itself, the resulting posterior distributions for all possible cases should be acceptable also a priori. In practice, this means that the results from a reference Bayesian analysis should not deviate much from the observed point estimate, which is, arguably, a 'gold standard' for comparison in the mind of the clinical investigator.

I propose the well-known binomial-beta and Poisson-gamma conjugate models as reference Bayesian models, with the provision that the prior hyperparameters been chosen specifically to yield posteriors that are centered almost exactly at the point estimate. These models can be characterized as 'neutral' as they do not appear to favor excessively large nor small values when compared to the point estimate. These models should be suitable as potential consensus priors for a reference Bayesian clinical safety data analysis. From the posterior distributions of the independent rate parameters one can also derive reference posterior distributions for the risk differences and (log) odds ratios, as well as fully stratified and pooled analyses. I illustrate the usage of these models in the context of a drug safety data analysis, contrasting the inferences with those obtained from common meta-analytic models.