

# Further considerations on rotavirus vaccination and seizure-related hospitalization rates

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## Dear editor

We have read with interest the comments from Orrico-Sánchez et al<sup>1</sup> regarding our recent paper on extraintestinal features of rotavirus (RV) infection.<sup>2</sup> Their main concerns relate to the section dealing with the potential of RV vaccines to decrease hospitalizations due to seizures, and more specifically, the issues we raised in regards to their non-significant findings that might have been caused by the use of an overfitted statistical model.<sup>3</sup> As our article was a general review beyond the relationship between RV and seizures, we did not have room for detailed explanations. We now take the opportunity to address Orrico-Sánchez et al's concerns.<sup>3</sup>

Contrary to what we stated in our recent paper,<sup>2</sup> Orrico-Sánchez et al<sup>1</sup> indicated that their original publication<sup>3</sup> did not include primary care cases but only convulsion-related hospitalizations (ICD-9CM code 780.3). We apologize for this confusion which was caused by our misunderstanding of the authors' description in their paper: "All primary care visits and hospitalizations are recorded in clinical databases".<sup>3</sup>

We take issue, however, with the other comments by Orrico-Sánchez et al<sup>1</sup> which are at least imprecise, if not incorrect. First, in our review<sup>2</sup> we simply mentioned the different methodology employed by Orrico-Sánchez et al<sup>3</sup> based on using absolute frequencies as a possible reason that might help explain their contrasting findings when compared to those in other studies. This does not qualify as a criticism.<sup>1</sup> In fact, in our recently submitted study on seizures and RV vaccine we also considered absolute frequencies and took into account population size as covariate. Having said this, a remarkable difference between our analyses (in our previous paper<sup>4</sup> and in the one submitted) and those carried out by Orrico-Sánchez et al,<sup>3</sup> is that we showed detailed information on hospitalization rates by year, while this information was fully omitted in their study.<sup>3</sup> Not showing hospitalization rates can be problematic; thus, the readers are left in the dark because they cannot observe the different behaviors (eg, evolution over time) in hospitalization rates in their targeted cohort (Region of Valencia; Southeast Spain). In addition, the data shown by Orrico-Sánchez et al<sup>3</sup> did not show key findings from their statistical model; thereby their Table 3 did not show the effect of important variables, time in months from the start of the observation period, time from vaccine's licensure, and seasonality as the month of the year.

Second, our review<sup>2</sup> indicated that the multiple regression model used by Orrico-Sánchez et al<sup>3</sup> used a number of redundant variants, which could have led to an overfitting of their regression model. In our view, the arguments given by the authors<sup>1</sup>

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to support this decision are questionable, if not incorrect. To start with, they indicated<sup>2</sup> that controlling by confounders eliminated a non-adjusted significant association between RV vaccination and a reduction of seizure-related hospitalizations.<sup>3</sup> Turning this argument around, however, it could be argued that an overfitted model could instead foster undesirable false negative findings. Most noticeable is the fact that the model proposed by Orrico-Sánchez et al<sup>3</sup> included several variables that are intimately associated with vaccines, including vaccination coverage, time from vaccine licensure, and months from the start of the observation (eg, at the beginning of the study there was no vaccine, and as time went by the vaccination coverage will have increased). The use of these variables in a regression model is highly redundant, thus causing multi-collinearity, auto-correlation, statistical noise, and a lack of statistical power. The withdrawal of RV vaccination in 2010 alone does not justify the use of redundant variables<sup>1</sup> because such circumstance could even have contributed to a decrease (or at least not an increase) in vaccination coverage. A better strategy to deal with the risk of collinearity may have been to consider infant vaccination coverage as the unique covariable related to RV vaccine.

Much has been written with regard to the unsuitability of redundancy in regression models in general (eg, Yoo et al's study)<sup>5</sup>, and more specifically in the field of vaccines. For instance, the recent article by Xu et al<sup>6</sup> on vaccine safety points out that “[...] redundant risk factors significantly reduce the empirical power for detecting the association between the true risk factors and the outcome [...]”, and that “[...] correctly specifying the form of the relationship between risk factors and the outcome is crucial”. Additional studies have argued in the same direction, recommending to check for collinearity before incorporating variables in the regression model,<sup>7</sup> while other authors propose the use of alternative methodologies such as principal component analysis.<sup>8</sup>

Finally, our recently submitted article, which uses negative binomial regression for hospitalization rates considering covariables such as gender, age, population size, and month, does show clear significant results for “all kinds of seizures” and convulsions related to vaccine coverage (as shown in Figure 2 of our paper)<sup>2</sup> in the Galician population (Northwest Spain), thus further supporting our initial findings.<sup>4</sup>

## Disclosure

JGR reports personal fees from Merck Sharp & Dohme, personal fees from Glaxo Smithkline (GSK), and personal fees from Pfizer. The authors report no other conflicts of interest in this communication.

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