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Authors' response to 'Comment on "Guidelines for Use of the Approximate Beta-Poisson Dose-Response Model" – Previously Published Guidelines Continue to Be Ignored'

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We thank Dr. Philip J. Schmidt for his comment on our recently published article "Guidelines for Use of the Approximate Beta-Poisson Dose-Response Model" (Xie et al. 2016⁽¹⁾). This gives us an opportunity to have a deeper understanding of their work (Schmidt et al. 2013⁽²⁾) and a critical review of our work (Xie et al. 2016⁽¹⁾). Through this response and the discussions, we hope the issues around the valid use and the approximation performance assessment of the approximate beta-Poisson dose-response model can be further clarified to ensure the future applications of the beta-Poisson models to be more appropriate and efficient.

The statement of the setting of the research problem in Xie et al. 2016⁽¹⁾ is important for the subsequent discussions. It was assumed that the exact beta-Poisson model and the approximate beta-Poisson model were fitted to a set of dose-response data by following the maximum likelihood estimation (MLE) approach. The MLE parameter estimates were denoted as $\hat{\alpha}$ and $\hat{\beta}$ for the approximate model and $\hat{\alpha}_e$ and $\hat{\beta}_e$ for the exact model, assuming the true model parameters α and β unknown in real life situations. The research goal was to specify a rule-of-thumb in terms of $\hat{\alpha}$ and $\hat{\beta}$ for dose-response data analysis to ensure the validity and a good approximation for applying the approximate beta-Poisson model in place of the exact model.

In Xie et al. 2016⁽¹⁾, the validation criterion (i.e., the rule-of-thumb) was specified as $\hat{\beta} > (22 \hat{\alpha})^{0.50}$ for $0.02 < \hat{\alpha} < 2$ where $\hat{\alpha}$ and $\hat{\beta}$ are the maximum likelihood estimates of α and β in the approximate model. This rule-of-thumb was derived by explicitly referring to the contour curve of the probability $\Pr(0 < r < 1 | \alpha, \beta)$ where $r \sim \text{gamma}(\alpha, \beta)$ ¹. We claimed that, by meeting our validation criteria, the use of the approximate B-P model would be valid in terms of ensuring a good match with the exact model's dose-response curve (i.e., without visually identifiable discrepancies). We have justified our claims by applying our rule-of-thumb to all beta-Poisson dose-response models presented throughout QMRA Wiki⁽³⁾ at the time the article was written.

In Schmidt et al. 2013⁽²⁾, the validation criterion (i.e., the rule-of-thumb) was specified as $\beta > 31.13 \alpha$, essentially derived from the constraint condition $\frac{\alpha}{\beta} - \frac{\alpha}{\alpha+\beta} < 0.001$, although they did specify the constraint condition $\Pr(r > 1) < 0.001$. The quantity $\frac{\alpha}{\beta} - \frac{\alpha}{\alpha+\beta}$ was used as an indicator for approximation accuracy (i.e., the difference in $E(r)$ – the expected value of r). However, the distinction between the true model parameters (e.g., α and β) and model parameter estimates (e.g., $\hat{\alpha}$ and $\hat{\beta}$ or $\hat{\alpha}_e$ and $\hat{\beta}_e$) was not specified explicitly. With regard to applying $\frac{\alpha}{\beta} - \frac{\alpha}{\alpha+\beta}$ as an

¹ In terms of the probability density function (pdf) $f(r|\alpha, \beta) = \frac{\beta^\alpha}{\Gamma(\alpha)} r^{\alpha-1} \exp(-\beta r)$, which is equivalent to $r \sim \text{gamma}(\alpha, 1/\beta)$ based on the pdf adopted for the Microsoft Excel function *gamma.dist* as referred in the comment letter.

indicator measure for approximation accuracy, we make two observations: (1) the derived rule-of-thumb $\beta > 31.13 \alpha$ is not applicable for data analysis if α and β are unknown; (2) if the rule-of-thumb is actually meant to be $\hat{\beta} > 31.13 \hat{\alpha}$ or $\hat{\beta}_e > 31.13 \hat{\alpha}_e$, then the derivation deviates from the problem setting specified in Xie et al. 2016⁽¹⁾, because the difference in $E(r)$ should be evaluated as $\frac{\hat{\alpha}}{\hat{\beta}} - \frac{\hat{\alpha}_e}{\hat{\alpha}_e + \hat{\beta}_e}$ and $\hat{\alpha} \neq \hat{\alpha}_e$ and $\hat{\beta} \neq \hat{\beta}_e$. For the same reasons, the derivation of the percent bias $\alpha/\beta \times 100\%$ as specified in the comment letter could also be questionable². Therefore, it would be inappropriate using $\alpha/\beta \times 100\%$ as an indicator quantity for comparing the rule-of-thumb proposed in Schmidt et al. 2013⁽²⁾ against the rule-of-thumb proposed in Xie et al. 2016⁽¹⁾ unless the same problem setting is accepted. We suggest that, unless a better approximation performance assessment approach can be found, the comparison between the rules-of-thumb should be made in terms of ensuring a good match between the exact and the approximate models' dose-response curves (i.e., without visually identifiable discrepancies) as done in Xie et al. 2016⁽¹⁾.

An ideal rule-of-thumb should be able to include all 'good match' approximate models when the conditions are met and exclude any 'good match' approximate models when the conditions are not met. The fewer mis-categorisations of cases mean a better rule-of-thumb. For the 85 beta-Poisson models examined in Table II of Xie et al. 2016⁽¹⁾, it is straightforward to identify five models (cases 42, 53, 54, 55, and 78) that the approximation were considered acceptable by Xie et al. 2016⁽¹⁾ (i.e., $\hat{\beta} > (22 \hat{\alpha})^{0.50}$), but would be rejected by the Schmidt et al. 2013⁽²⁾ criterion (e.g., assuming $\hat{\beta} > 31.13 \hat{\alpha}$, despite the comments about the derivation process made above). For data analysis in general, application of the rule-of-thumb $\hat{\beta} > 31.13 \hat{\alpha}$ would potentially exclude a large number of good match approximate models (e.g., those models satisfy $\hat{\beta} > (22 \hat{\alpha})^{0.50}$ but fail to satisfy $\hat{\beta} > 31.13 \hat{\alpha}$ for $0.02 < \hat{\alpha} < 2$); and the impact of discrepancy due to approximation is practically negligible with these models.

Through Table 1 and Table 2, three examples are presented as empirical evidences to show: (1) the percent bias $\alpha/\beta \times 100\%$ should not be considered as a consistent measure for the discrepancy between the exact model and the approximate model for dose-response data analysis; (2) the impact of discrepancy is practically negligible with those models identified as invalid by rule $\hat{\beta} > 31.13 \hat{\alpha}$ but acceptable by rule $\hat{\beta} > (22 \hat{\alpha})^{0.50}$. Note that the first example (with parameter estimates $\hat{\alpha} = 0.0794$, $\hat{\beta} = 2.31$; $\hat{\alpha}_e = 0.0784$, $\hat{\beta}_e = 2.58$) is the case 78 model in Table II of Xie et al. 2016⁽¹⁾ (or the data set 78 case as presented in Table 1 of the comment letter). This example is presented here because it is the worst case in terms of bias $= \left(\frac{\hat{\alpha}_e}{\hat{\beta}_e} - \frac{\hat{\alpha}_e}{\hat{\alpha}_e + \hat{\beta}_e} \right) / \left(\frac{\hat{\alpha}_e}{\hat{\alpha}_e + \hat{\beta}_e} \right) = \frac{\hat{\alpha}_e}{\hat{\beta}_e}$ in all beta-Poisson models examined in Table II. The other two examples are based on simulated dose-response data sets which represent the possible extreme scenarios (e.g., $\hat{\alpha}$ (or $\hat{\alpha}_e$) is close to (but less than) 2 and $\hat{\beta}$ (or $\hat{\beta}_e$) marginally satisfies the rule $\hat{\beta} > (22 \hat{\alpha})^{0.50}$ (or $\hat{\beta}_e > (22 \hat{\alpha}_e)^{0.50}$). The results show clearly that the impact of discrepancy is practically negligible with those invalid models identified by applying rule $\hat{\beta} > 31.13 \hat{\alpha}$ but acceptable by the rule $\hat{\beta} > (22 \hat{\alpha})^{0.50}$.

Table 1 shows how inconsistent it could be of the conceptually different measure $\alpha/\beta \times 100\%$ (or $\hat{\alpha}/\hat{\beta} \times 100\%$, or $\hat{\alpha}_e/\hat{\beta}_e \times 100\%$) in comparison with the discrepancy measure $\left(\frac{\hat{\alpha}}{\hat{\beta}} - \frac{\hat{\alpha}_e}{\hat{\alpha}_e + \hat{\beta}_e} \right) /$

² According to Schmidt et al. 2013⁽²⁾ and the comment letter, the percent bias $\alpha/\beta \times 100\%$ can be derived as $\left(\frac{\alpha}{\beta} - \frac{\alpha}{\alpha + \beta} \right) / \left(\frac{\alpha}{\alpha + \beta} \right) \times 100\% = \frac{\alpha}{\beta} \times 100\%$.

$\left(\frac{\hat{\alpha}_e}{\hat{\alpha}_e + \hat{\beta}_e}\right) \times 100\%$. Table 2 further shows that, over the low mean dose range (e.g., the mean number of pathogen ranged from 0.001 to 10), the impact of discrepancy is practically negligible, i.e., either the relative error is $\leq 3\%$ or the absolute error is ≤ 0.003 if the relative error is more than 3%.

Table 1: Three examples to show the inconsistent results of using $\alpha/\beta \times 100\%$ (or $\hat{\alpha} / \hat{\beta} \times 100\%$, or $\hat{\alpha}_e / \hat{\beta}_e \times 100\%$) as an indicator quantity for measuring the difference in $E(r)$ between the exact model and the approximate model: the correct measure should be $\left(\frac{\hat{\alpha}}{\hat{\beta}} - \frac{\hat{\alpha}_e}{\hat{\alpha}_e + \hat{\beta}_e}\right) / \left(\frac{\hat{\alpha}_e}{\hat{\alpha}_e + \hat{\beta}_e}\right) \times 100\%$ based on the problem setting accepted in Xie et al. 2016⁽¹⁾.

model parameters and parameter estimates	α/β	$\hat{\alpha} / \hat{\beta}$	$\hat{\alpha}_e / \hat{\beta}_e$	$\left(\frac{\hat{\alpha}}{\hat{\beta}} - \frac{\hat{\alpha}_e}{\hat{\alpha}_e + \hat{\beta}_e}\right) / \left(\frac{\hat{\alpha}_e}{\hat{\alpha}_e + \hat{\beta}_e}\right)$
(α and β unknown) $\hat{\alpha}=0.0794, \hat{\beta}=2.31$; $\hat{\alpha}_e=0.0784, \hat{\beta}_e=2.58$	not applicable	3.44%	3.04%	16.6%
* $\alpha = 1.999, \beta = 6.637$; $\hat{\alpha}=2.30, \hat{\beta}=10.3$; $\hat{\alpha}_e=1.91, \hat{\beta}_e=6.76$	30.1%	22.3%	28.3%	1.36%
* $\alpha = 1.6, \beta = 4.5$; $\hat{\alpha}=1.93, \hat{\beta}=6.76$; $\hat{\alpha}_e=1.55, \hat{\beta}_e=4.03$	35.6%	28.6%	38.5%	2.78%

* α and β are the true model parameters used for generating simulated samples

Table 2: Three examples for investigating the impact of discrepancies in those invalid models identified by the rule $\hat{\beta} > 31.13 \hat{\alpha}$ (but identified as acceptable based on $\hat{\beta} > (22 \hat{\alpha})^{0.50}$). The ‘probability of infection’ is calculated based on the exact beta-Poisson model; ‘absolute difference’ is the difference between the exact model and the approximate model in terms of the probability of infection; ‘difference in %’ = ‘absolute difference’ / ‘probability of infection’ *100% (subject to rounding error).

mean dose(# of pathogen)		0.001	0.01	0.1	0.2	0.5	1	2	5	10
(α and β unknown) $\hat{\alpha}=0.0794, \hat{\beta}=2.31$; $\hat{\alpha}_e=0.0784, \hat{\beta}_e=2.58$	probability of infection	0.000	0.000	0.003	0.006	0.014	0.026	0.046	0.086	0.125
	absolute difference	0.000	0.000	0.000	0.001	0.002	0.002	0.003	0.001	0.000
	difference in %	16.5	16.5	15.6	14.7	12.4	9.5	5.9	1.6	-0.1
* $\alpha = 1.999, \beta = 6.637$; $\hat{\alpha}=2.30, \hat{\beta}=10.3$; $\hat{\alpha}_e=1.91, \hat{\beta}_e=6.76$	probability of infection	0.000	0.002	0.022	0.043	0.102	0.191	0.335	0.599	0.791
	absolute difference	0.000	0.000	0.000	0.001	0.001	0.001	0.000	-0.002	-0.001
	difference in %	1.4	1.4	1.3	1.2	0.9	0.6	0.1	-0.3	-0.2
* $\alpha = 1.6, \beta = 4.5$;	probability of infection	0.000	0.003	0.027	0.053	0.126	0.231	0.393	0.660	0.828

$\hat{\alpha} = 1.93,$ $\hat{\beta} = 6.76;$ $\hat{\alpha}_e = 1.55,$ $\hat{\beta}_e = 4.03$	absolute difference difference in %	0.000	0.000	0.001	0.001	0.002	0.002	0.001	-0.004	-0.002
		2.8	2.8	2.6	2.3	1.8	1.0	0.1	-0.5	-0.2

* α and β are the true model parameters used for generating simulated samples

With respect to Table 1 of the comment letter, we agree that the exact model MLE results $\hat{\alpha}_e$ and $\hat{\beta}_e$ for data set 7 (Rhinovirus(311)) and data set 13 (Rotavirus(125)) cases presented in Table II in Xie et al. 2016⁽¹⁾ need further investigation. On the other hand, we would like to point out that using the quantity $\frac{\hat{\alpha}_e}{\hat{\beta}_e} - \frac{\alpha_e}{\alpha_e + \beta_e}$ as an indicator measure for difference in means (i.e., difference in $E(r)$) is not consistent with the problem setting accepted in Xie et al. 2016⁽¹⁾ because it implies that the exact model and the approximate model have been fitted to two different data sets, respectively, so that the parameter estimates can possibly be the same. We would also argue that any rule-of-thumb for justification of the valid use of the approximate model should not involve $\hat{\alpha}_e$ and $\hat{\beta}_e$ because of the logic inconsistency in data analysis practice: knowing $\hat{\alpha}_e$ and $\hat{\beta}_e$ eliminates the need for specifying a rule for approximation.

In conclusion, we suggest that our newly proposed rule-of-thumb, $\hat{\beta} > (22 \hat{\alpha})^{0.50}$ (for $0.02 < \hat{\alpha} < 2$), is applicable and remains appropriate for dose-response data analysis. Further, meaningful comparisons between two different rules-of-thumb for the approximation of the beta-Poisson model should only be made based on a commonly accepted problem setting.

References:

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