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Dose-Response Models for Eastern US, Western US and Venezuelan Equine Encephalitis Viruses in Mice – Part II: Quantification of the Effects of Host Age on the Dose Response

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Abstract

Many infectious disease hazards demonstrate higher susceptibility with regards to younger host ages. This trend of increased susceptibility with decreasing host age can also lead to an increased likelihood of mortality, and prolonged/chronic health effects. For quantitative microbial risk assessment (QMRA) modeling, the ability to quantify the effect of host age in the dose response model can allow modelers to account for these effects mechanistically. Additionally, QMRA modelers using age-dependent dose response models can model entire populations within the dose-response itself rather than modeling age ranges using susceptibility factors. This research developed host-age dependent exponential and beta Poisson dose response models for Eastern, Western and Venezuelan encephalitis viruses (EEV, WEV and VEV respectively) for two routes – intracranial and intraperitoneal. Improvement in fit was statistically tested as a means of assessing the benefit of including age dependency into the dose response models. EEV demonstrated improvement in fit using host-age dependency only for the exponential model except for intracranial exposure. EEV demonstrated an improvement in fit when using age dependency in the beta Poisson dose response model for both exposure routes. VEV demonstrated an improvement in fit using age dependency for both exposure routes. WEV demonstrated an improvement in fit for intracranial exposure, but neither of the age dependent dose-response models provided a good fit for WEV intraperitoneal exposure.

Keywords

Dose response; encephalitis; virus; QMRA; age dependency; model

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1.0 Introduction

1.1 Dose Response Modeling

The dose-response relationship is the underlying mechanistic connection between an exposed dose and the resulting risk of a deleterious effect¹. For single-hit mechanistic dose-response models, they are derived based on an assumption of Poisson exposed dose, and Boolean likelihood of pathogen survival to initiate an infection^{1,2}. Additional factors beyond these derivational assumptions known to affect populations exposed to pathogens (*i.e.* host age, immune condition *etc.*) are not currently modeled in the most commonly used mechanistic dose response models, the exponential and beta Poisson¹.

While the standard single-hit dose response models cannot model additional factors in infection, illness and disease development, they are conducive to modification. The standard mechanistic dose response models have been adapted to quantitatively model the effects of: host age, diabetic populations, time post inoculation and host physiological dependencies³⁻⁶. The second generation of dose response models started with the age dependency for *Variola major* (*V. major*)³, and as with the other second generation models, are essentially structured as adaptations to the standard dose response models. The research performed in Part I of these twin manuscripts developed the standard dose response models for Eastern, Western and Venezuelan equine encephalitis viruses (EEV, WEV and VEV respectively). This research in Part II outlines the development, and testing of age dependent dose response models for these three equine encephalitis viruses.

1.2 Age Dependent Dose Response Models and Their Use in QMRA

Almost all pathogens have differential effects for sets of age groups within a single population, and encephalitis viruses are no different^{7,8}. Typically, younger and older ages present symptoms faster, with greater intensity and are more likely to result in mortality or debilitating effects. It is important to note that not all pathogens have the same underlying trend of reduced susceptibility with increased host age (up to a threshold age).

The concept of age dependency is not a simple one for all pathogens. Some pathogens such as the pandemic influenza of 1918 exhibited more severe effects on late adolescence/early adulthood age groups. This difference in effect was partially due to cramped living conditions in barracks and urban centers, but also via the pathogenesis of that influenza strain, and the human immune response to it^{9,10}. Age dependent dose response models allow for the development of QMRA models with two additional capacities:

1. Modeling sensitive sub-groups. This capacity allows the inherent differences in sensitive sub-groups such as children and their health responses to be captured mechanistically within the dose response model. This will also allow for additional factors such as circulation rate or reduced immune response to be more accurate and descriptive, since the dose response is already addressing the macro level of age dependency in the host response.

¹In this research the approximate form of the beta Poisson is used, owing to its improved familiarity and wider use with policy and engineering professionals.

2. Population level QMRA models. QMRA models can be developed for an entire population, rather than assuming that the dose response can accurately be used for the entire age range in the population. By using age dependent dose response models, the distribution of population ages (*e.g.* stratification of ages from census data) can be modeled directly in the dose response for the QMRA model. Additionally, if the age delineation of the population being modeled with the QMRA is known, then targeting outbreak predictions, mitigation options and communications strategies can be improved.

2.0 Theory/Calculation:

This research utilizes the underlying theory that the host age has an effect on the dose response relationship of infectious disease agents as noted clinically. This hypothesis expands to the concept of being able to model this host age dependency using the mechanistic physiologically plausible dose response models. The calculations include the identification and statistical verification of a trend between dose-response parameter and host age. Then the trend between host age and dose response parameter value is described using functional forms that are then optimized using the original dose response data, and the maximum likelihood estimation method.

3.0 Methods

3.1 Dose Response Data

The dose response data used in this research was the result of a literature review for equine encephalitis viruses. In¹¹ an experimental study was performed to determine the effect of host age – primarily juvenile in¹¹ – on host resistance to EEV, WEV and VEV.

The quantification of the effect of host age on the dose response relationship has been previously developed for *V. major*³. The data used in³ is similar in structure to that in¹¹, where mice of the same ages were grouped together and exposed to a known bolus dose. In the case of the data from¹¹ the dataset is very large as compared to those typically encountered in dose response modeling. In¹¹ a total of 41 dose groups were comprised of: three viruses, two exposure routes for each virus and five to seven dose groups per pathogen exposure route combination, and 6 to 10 animals per dose group. Therefore, these data required two separate research agenda: 1.) develop the standard dose response models for each age group with nested models of pooled ages without accounting for host-age dependency and 2.) model the host-age dependency of the dose response relationship. The dose response data and standard dose response modeling can be seen in Part I and summarized in the appendix for this manuscript.

3.2 Development of Age Dependent Sub-Models

This research uses the methods developed in³ for *V. major* to develop and test age dependent dose response models for EEV, VEV and WEV. Just as in previous research for *V. major*, the age dependency modeling is derived by modeling the trend between dose response parameter(s), and host age.

The methodology developed and used is analogous to multi-level or hierarchical modeling. By modeling the effect of age on the dose response parameters, a closed-form function is developed to describe how the parameter(s) change with host age. In the dose response models, the parameter(s) mechanistically describe the dose response relationship in the host. Therefore, a model that describes the relationship between parameter(s) and host age, will in turn model the relationship between host age and the dose response relationship. These models for the relationship between dose response parameter(s) and host age result in age dependent sub-models, herein referred to as sub-models.

Development of the sub-models starts with establishing the standard dose response values of the parameters for each host age group. This was performed in Part I and optimized parameter values were established at each host age for the exponential (Eq 1; parameter r) and the approximate form of the beta Poisson (Eq 2; parameters α and N_{50}).

$$P(R) = 1 - \exp(-r \cdot \text{dose}) \quad (1)$$

$$P(R) = 1 - \left[1 + \frac{\text{dose} \cdot (2^{1/\alpha} - 1)}{N_{50}} \right]^{-\alpha} \quad (2)$$

Once a trend between host age and dose response parameter value is determined, then the best means of modeling this trend is determined. As will be described in more detail in 3.2.1 and 3.2.2, the best means of modeling the age dependency is performed using linear regression. It is important to note that the sub-models' parameters are not optimized via the linear regression; the regression is only to identify a functional form for the trend. Rather, as will be explained in further detail in section 3.3, the maximum likelihood estimation (MLE) is used to optimize the sub-models' parameters using the same methods for optimizing the standard dose response. This distinction is important because this optimization method utilizes the underlying dose response relationship and data for the sub-model optimization. Therefore the age dependent dose response models maintain their primary dependence on the dose response relationship described in the data.

3.2.1 Exponential Parameter Sub Model—Each of the ages is considered a separate independent trial just as they were treated in the experimental design. First a visual assessment of the trend between r and host age was performed. Then a Cochran-Armitage trend test (equation 3) was implemented to determine if there is a statistically significant trend between the dose (d_j , independent variable), n adjusted doses ($\bar{d}$), number of animals in each dose group (n_j), number of positive responses (p_j) and the summed observed probability of response ($\bar{p}$ dependent variable). The summations in equation 3 are carried out from 1 to j doses in the dose response experiment [1] and the function results in a z-score value (z_{ca}) that must be below the Z-critical of a normal distribution at $\alpha = 0.05$.

$$Z_{ca} = \frac{\sum_{i=1}^k (d_i - \bar{d}) p_i}{\sqrt{\bar{p}(1 - \bar{p}) \sum_{i=1}^k n_i (d_i - \bar{d})^2}} \quad \text{where} \quad \begin{cases} \bar{d} = \frac{\sum_{i=1}^k n_i d_i}{\sum_{i=1}^k n_i} \\ \text{and} \\ \bar{p} = \frac{\sum_{i=1}^k p_i}{\sum_{i=1}^k n_i} \end{cases} \quad (3)$$

All pathogens had a well-defined trend between r and host age. Figure 1 shows the relationship between host age and r for EEV, WEV and VEV intracranial (IC) and intraperitoneal (IP) exposures.

The plots in figure 1 are the results of the MLE optimization of the standard dose response models (no age dependency added yet). Each age group was optimized separately resulting in an optimal r for the exponential model at each host age.

Once the existence of the trend was determined a linear regression was performed to determine the best fitting sub-model for r using the adjusted R^2 . linear regression was chosen since this can be considered a generalizable empirical model of the effects of age on the underlying dose response relationship.

3.2.2 Beta Poisson α and N_{50} Sub Models—Just as with the exponential r parameter each of the α and N_{50} parameters from the MLE optimizations for each age group were used to model the effect of host age on the parameters. The Cochran-Armitage trend test was enacted to verify the existence of a trend between α and host age, and N_{50} and host age. The relationship between beta Poisson parameters and host age are shown in figures 2 and 3 for IC and IP respectively.

3.3 Optimization of Age Dependent Sub-Models

The sub-models must be optimized in the same method as used for the standard dose response models. This is necessary since even though the dose response models are now age dependent, they are still dependent on the exposed dose, which was not used in the sub-model regression. Therefore, the age dependent forms of the dose response models must be used in the optimization of the age dependent dose response models.

Equations 8 and 9 are the age dependent forms of the exponential and beta Poisson models respectively. As can be seen the dose response parameters originally being a $f(d, \theta)$, where d is dose and θ is/are parameter(s), in age dependency this is changed to $f(d, \theta_A)$ where θ_A is/are the age dependent parameter(s). In turn the θ_A are $f(\text{Age}_H, \theta_A)$ where Age_H is the age of the host and where θ_A will be referred to using the nomenclature r_0 and r_1 for the age dependent exponential model and α_0 , α_1 , N_{50_0} and N_{50_1} for the age dependent beta Poisson model. In equation 8 r^* is the age dependent dose response model for the age dependent exponential dose response model. Equation 9 shows the age dependent beta Poisson dose response model where α^* and N_{50}^* are the age dependent dose response parameters.

$$P(R) = 1 - \exp(-r^* \cdot d) \quad (8)$$

$$P(R) = 1 - \left[1 + \frac{dose \cdot (2^{1/\alpha^*} - 1)}{N_{50}^*} \right]^{-\alpha^*} \quad (9)$$

The MLE method is used to optimize the age dependent dose response models by minimizing the deviance (Y ; equation 10). The Y statistic is a function of: predicted probability of response (π_i from the model), observed probability of response (π_i^o , from the data), number of positive responses (p_i) and number of hosts in each dose group (n_i). By optimizing for Y the test statistic for goodness of fit and best fitting model analyses is minimized, thereby allowing for rapid inferences from the optimization. As can be seen in the form of Y the functional form need not be altered for age dependent modeling. However, Y as programed in **R** is adapted to allow for optimization of the sub-model parameters in the MLE. The appendix demonstrates how this was performed in **R**.

$$Y = -2 \sum_{i=1}^n \left[p_i \ln \left(\frac{\pi_i}{\pi_i^o} \right) + (n_i - p_i) \ln \left(\frac{1 - \pi_i}{1 - \pi_i^o} \right) \right] \quad (10)$$

3.4 Bootstrapping of Age Dependent Models

This assessment of the parameter(s) of uncertainty is very important for inclusion into stochastic QMRA models. Therefore, the age dependent models and the age dependent parameters are bootstrapped to assess the uncertainty in their estimates. The bootstrap randomly samples with replacement the positive responses from dose response data that is used to optimize the age dependent dose response models at each iteration. The bootstrap method allows for the underlying distribution of the data to be leveraged to inform the uncertainty of the models' parameters^{12,13}.

4.0 Results

4.1 Age Dependent Exponential Model

Table 1 shows the results of the regressions which were performed in **R** (www.r-project.org) demonstrating that for EEV the power and inverse models for IC and IP respectively (equations 3 and 4) are the best options to model the effect of host age within the exponential dose response model. For VEV the inverse model is the best option to model the age dependency for both IC and IP exposures. WEV age dependency is best modeled using the power and inverse models for the IC and IP exposures respectively.

The age dependent exponential dose response models were optimized to the dose response data using the MLE method. An analysis to determine the improvement in fit or lack thereof from the age dependent model was undertaken, the null hypothesis (H_0) being that the simpler of the two models is the better choice. This analysis consists of determining the difference in the deviances between the age dependent and non-age dependent models (C).

With the χ^2 distribution being an upper tailed distribution, if χ^2 is greater than the χ^2 at set degrees of freedom (dof) and confidence level of 0.05 the analysis results in failing to accept the H_0 . In this analysis the dof is equal to the difference in the number of parameters between the simpler (fewer parameters) and more complex model. This comparison allows for the control of the number of parameters, where the addition of a parameter must be proven to statistically improve the fit, while accounting for the random chance of an improved fit. The exponential dose response model was statistically significantly improved by including age dependency for EEV IP, VEV IC, VEV IP and WEV IC, shown in table 2.

4.2 Age Dependent Beta Poisson Model

Table 3 shows the age dependent sub-models developed based on the trend between α and host age. For EEV IC and IP exposures equations 5 and 6 respectively show that the logarithmic and exponential models best describe α 's age dependency. The power and inverse models best describe α 's age dependency for VEV IC and IP exposures respectively. The exponential model best describes α 's age dependency for WEV IC and IP exposures respectively. There is a very weak fit for the age dependent sub-models for WEV IC and IP exposures, and this is very likely due to the poor fits for the beta Poisson model for these pathogen and exposure pairs at each age group from the standard dose response model optimization.

Table 4 shows the age dependent sub-models for N_{50}^* . Equation 7 shows that the linear model describes EEV IC age dependency and power models best describes EEV IP age dependency for N_{50} . The power and logarithmic models best describe N_{50} 's age dependency for VEV IC and IP exposures respectively. The logarithmic and power models best describe N_{50} 's age dependency for WEV IC and IP exposures respectively. EEV IP exposure showed a very poor fit for all models with the best options still having a poor adjusted R^2 for the fit. This could also be due to a poor fit for the beta Poisson for these age groups in this pathogen exposure set.

The age dependent beta Poisson dose response models were optimized to the dose response data using the MLE method. The same analysis used for the exponential r^* parameter to evaluate the improvement (or lack thereof) of including an age dependent model was used for α and N_{50} . Table 5 shows that for the beta Poisson model for all pathogens and exposure routes fit was improved using age dependent models. In some cases this improvement in fit was substantial.

4.3 Evaluation of Best Fitting Age Dependent Dose Response Models

The H_0 for the goodness of fit (gof) analysis is that there is no observed difference between observed and predicted probability of response. For the best fitting model analysis the H_0 is that the simpler (less parameterized) model is best. Table 6 shows the results of these analyses where, for clarity, the p -value is shown for the gof analysis and the χ^2 critical value at one dof for the best fitting model analysis. For gof the p -value is the probability of failing to reject the gof H_0 . For the best fitting analysis if the difference in the deviances () is greater than the critical value then the analysis fails to reject the H_0 .

Overall the age dependent beta Poisson model consistently shows a good fit and is the best fitting model when compared to the age dependent exponential model. In the cases of EEV IP and WEV IP neither age dependent dose response model is a good fit. This is interesting since there was also a very poor fit for the standard dose response models. This could be due to the exposure route used but there is insufficient information to take this beyond conjecture.

Table 7 shows the optimized age dependent dose response parameters from the MLE of the age dependent models. No parameters are given for those dose response models that did not show a good fit to the data. It should be noted that the EEV IC age dependent model did not show a statistically significant improvement in fit despite improving the minimized deviance slightly.

4.4 Bootstrapping of Age Dependent Models

The age dependent models were subjected to the bootstrap method to assess the uncertainty in the parameters. The bootstrap was operated for 10,000 iterations, but in the case of WEV IC only 9,562 iterations completed. Since the bootstrap samples with replacement from the positive responses of the data, any difficulties in optimization are exacerbated, thus the failure to achieve 10,000 iterations for WEV IC. Figure 4 shows the scatter plots and histograms for the EEV IC age dependent approximate beta Poisson model. As is expected there is a correlation between parameters with α_1 having the narrowest confidence bands similar to the *V. major* results³. Figure 5 shows a similar window-pane plot for the age dependent exponential dose response model showing narrow confidence bands for r_1 but with more potential outliers than r_0 . Figure 6 shows that for VEV IP, α_0 has the narrowest confidence bands and interesting stratification of N_{50_0} to N_{50_1} that may indicate additional factors that can be included from future research. Figure 7 shows for WEV IC the narrowest confidence bands correspond to α_1 and despite 9,562 iterations completed, those that did complete resulted in good fits.

4.5 Comparison of the Use of Encephalitis Age-Dependent Sub-Model to *V. major* Age-Dependent Dose Response Sub-Models

The age dependent dose response model for *V. major*³ was developed using the same methods as in this manuscript. Therefore, it is desired to determine if the methodology used develops a generalizable age dependent dose response model. A generalizable model can be illustrated as such: the exponential model (unaltered) can be used to model both pathogenic *Escherichia coli* as well as rotavirus, *i.e.* the model does not need to be derived again for a new pathogen or exposure route. While this method is likely not developing a generalized age dependent dose response model, this lack of generalizability should be proven statistically.

The comparison between the encephalitis specific age dependent sub-models and those for *V. major* was analyzed using the same method as in table 6. In this case the H_0 is: the smallpox age dependent sub-models provide a better fit to the data. This H_0 is essentially stating that the use of an age dependent dose response model developed for encephalitis

must be proven to provide a better fit than the original age dependent dose response model developed for *V. major*.

Table 8 shows that except for EEV IC the encephalitis specific age dependent sub-models provided a statistically significant improvement in fit for the exponential age dependent dose response model. Table 8 shows the same comparison for the beta Poisson age dependent dose response model demonstrating that except for WEV IC and IP there was a statistically significant improvement in fit using the encephalitis specific age dependent dose response model.

5.0 Discussion

The age delineated data from¹¹ was used to develop age dependent versions of the exponential and approximate beta Poisson dose response models. Except for the age dependent exponential dose response for EEV IC, WEV IC and WEV IP the age dependent dose response models developed in this research demonstrated an improvement in the fit to the data. In these cases despite the age dependent dose response models providing a lower *Y* to the pooled age data, these pathogen and exposure sets still did not allow for a good fit to the data using the age dependent or non-age dependent dose response models.

It is an interesting but unsurprising note that age dependency was incapable of improving the fit of the EEV IC exposure. As discussed in Part I, the EEV IC exposure data had the same observed probability of response for the first 3 of 8 age groups. This may indicate why the age dependency did not achieve an improvement in the fit since there were 3 sets with identical age dependent trends. This may give credence to the need for more research into the infectivity of EEV, age delineated or otherwise.

The encephalitis specific sub-models were better fitting to the data as opposed to using the *V. major* sub-models for all but EEV IC. This comparison was made since the *V. major* is the foundational model for this method for quantifying age dependency in the dose response for viruses. This indicates that quantifying age dependency in the dose response functions is not an easily transferrable method. If the *V. major* age dependent sub-models would have provided a better fit, or if the encephalitis sub-models would not have proven a statistically improved fit, then it could be surmised that the sub-models from *V. major* can be generalized to other pathogens. Rather given these results we can state that while the deviances are not drastically changed in all instances, there is sufficient evidence that for age dependent dose response models to be used it is best to have age delineated dose response data for which to construct them for those specific pathogens of interest. This result is to maintain the maximum amount of accuracy in the age dependent dose response model. However as a screening approach or first estimation to quantify age in the QMRA via the dose response, these models are viable options for other pathogens, as with any other use of a surrogate dose response model.

The quantification of age dependency is carried out by altering the parameter(s) of the respective dose response models. The parameter(s) of the dose response models are now functional forms that allow host age to be accepted as an independent variable. This

develops age dependent dose response parameters that in turn when optimized with dose response data develop age dependent dose response models. Future research for age dependent dose response models should focus on mechanistic models, thus providing a potentially generalizable age dependent dose response model.

These age dependent dose response models can be used for scoping population impacts from equine encephalitis exposures allowing for potentially improved: mitigation strategies, targeting of mitigation options, case burden preparation, outbreak estimation and risk communications. It is recommended that QMRA modelers use the age dependent dose response models for these viruses, due to their improved fit and ability to describe multiple age groups. Unlike chemical dose response, where corrections from host animal in the experiments must be made to use for humans, microbial dose response does not have this concern. If the animal is a competent host, and there are not cellular differences for the pathogen (*e.g. Legionella pneumophila* behaves differently in murine as opposed to human macrophages), then the dose response model optimized to animal data can be used for human QMRA modeling^{14,15}.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Age dependent dose response models were developed for equine encephalitis viruses
- Modeling accomplished via optimization of parameter trends with respect to host age
- The majority of data sets provided an improved fit using host age dependent models

Figure 1.

Plots demonstrating the trend between r and host age for both intracranial (IC) and intraperitoneal (IP) exposure, host ages are in days, dots represent optimized r parameter for each host age group. Trends can be seen in Table 1.

Figure 2. Plot demonstrating the trend between α and host age and N_{50} and host age for IC exposure, host age is in days. Trends can be seen in Table 2.

Figure 3.

Plot demonstrating the trend between α and host age and N_{50} and host age for IP exposure, host age is in days. Trends can be seen in Table 3.

Figure 4.

Window-pane view of parameters relationships with each other for the age dependent approximate beta Poisson model for EEV IC, the histograms are used when each parameter is compared just with itself.

Figure 5.
Age dependent exponential dose response model window-pane plot for VEV IC exposure.

Figure 6.
VEV IP age dependent approximate beta Poisson dose response model window-pane plot.

Figure 7.
WEV IC age dependent approximate beta Poisson dose response model window-pane plot.

Table 1.Age dependent sub-models for the exponential r parameter for all pathogens and exposure routes.

Pathogen/Exposure ^{*, **}	Sub-Model Tested	Adjusted R ²	Conclusion
EEV/IC	Linear	0.321	Power model is best option $r_{EEV/IC}^* = r_0 \cdot age^{r_1}$ (3)
	Logarithmic	0.679	
	Inverse	0.515	
	Power	0.796	
	Exponential	0.635	
EEV/IP	Linear	-0.95	Inverse model is best option $r_{EEV/IP}^* = r_0 \cdot \left(\frac{r_1}{age}\right)$ (4)
	Logarithmic	0.202	
	Inverse	0.730	
	Power	0.706	
	Exponential	0.361	
VEV/IC	Linear	-0.039	Inverse model is best option
	Logarithmic	0.396	
	Inverse	0.864	
	Power	0.577	
	Exponential	0.205	
VEV/IP	Linear	-0.110	Inverse model is best option
	Logarithmic	0.187	
	Inverse	0.784	
	Power	0.101	
	Exponential	-0.157	
WEV/IC	Linear	0.064	Power model is best option
	Logarithmic	0.009	
	Inverse	-0.162	
	Power	0.534	
	Exponential	0.239	
WEV/IP	Linear	0.436	Inverse model is best option
	Logarithmic	0.717	
	Inverse	0.910	
	Power	0.708	
	Exponential	0.821	

* - IC = Intracranial

** - IP = Intraperitoneal

Table 2.

Analysis of improvement or lack of improvement of fit by using age dependency modeling for the age dependent exponential dose response model.

Model	Group*	N _{doses}	Y	χ^2	dof	$\chi^2_{0.05,dof}$	Conclusion
Exponential	EEV IC Age Dependency	8	121.5	0.100	1	3.842	Age dependency does not provide better fit
	EEV IC No Age Dependency		121.6				
Exponential	EEV IP Age Dependency	7	892.7	286.3	1	3.842	Age dependency provides better fit
	EEV IP No Age Dependency		1179				
Exponential	VEV IC Age Dependency	7	18.70	14.72	1	3.842	Age dependency provides better fit
	VEV IC No Age Dependency		33.42				
Exponential	VEV IP Age Dependency	7	86.81	17.29	1	3.842	Age dependency provides better fit
	VEV IP No Age Dependency		104.1				
Exponential	WEV IC Age Dependency	6	22.94	12.66	1	3.842	Age dependency provides better fit
	WEV IC No Age Dependency		35.60				
Exponential	WEV IP Age Dependency	5	1424	-479	1	3.842	Age dependency does not provide better fit
	WEV IP No Age Dependency		945.5				

* - No age dependency is ages pooled for each pathogen and exposure route set

Table 3.

Age dependent sub-models for the beta Poisson α parameter for all pathogens and exposure routes. Note how the WEV sub-models are very weak in fit, potentially due to the very poor beta Poisson fits from the baseline dose response optimization.

Pathogen/Exposure ^{*,**}	Sub-Model Tested	Adjusted R ²	Conclusion
EEV/IC	Linear	0.356	Logarithmic model is best option $\alpha_{EEV_{IC}}^* = \alpha_0 \cdot [\alpha_1 \cdot \ln(age)]$ (5)
	Logarithmic	0.793	
	Inverse	0.318	
	Power	0.608	
	Exponential	0.426	
EEV/IP	Linear	-0.113	Exponential model is best option $\alpha_{EEV_{IP}}^* = \alpha_0 \cdot e^{\alpha_1 \cdot age}$ (6)
	Logarithmic	-0.089	
	Inverse	-0.134	
	Power	0.373	
	Exponential	0.647	
VEV/IC	Linear	0.135	Power model is best option
	Logarithmic	0.217	
	Inverse	0.064	
	Power	0.580	
	Exponential	0.481	
VEV/IP	Linear	-0.139	Inverse model is best option
	Logarithmic	0.133	
	Inverse	0.538	
	Power	-0.169	
	Exponential	-0.189	
WEV/IC	Linear	-0.188	Exponential model is best option although none show a good fit
	Logarithmic	-0.250	
	Inverse	-0.159	
	Power	-0.227	
	Exponential	-0.091	
WEV/IP	Linear	-0.169	Exponential model is best option although none show a good fit
	Logarithmic	-0.292	
	Inverse	-0.332	
	Power	-0.011	
	Exponential	0.193	

* IC = Intracerebral

** IP = Intraperitoneal

Table 4.

Age dependent sub-models for the beta Poisson N_{50} parameter for all pathogens and exposure routes. Note how the WEV IC sub-model is a very weak in fit, like with α this is potentially due to the very poor beta Poisson fits from the baseline dose response optimization.

Pathogen/Exposure ^{*, **}	Sub-Model Tested	Adjusted R ²	Conclusion
EEV/IC	Linear	0.510	Linear model is best option $N_{50}^{*}{}_{EEV\ IC} = N_{500} \cdot (N_{501} \cdot age)^{(7)}$
	Logarithmic	0.365	
	Inverse	0.072	
	Power	0.376	
	Exponential	0.314	
	Linear	-0.197	
EEV/IP	Logarithmic	-0.157	Power model is best option
	Inverse	-0.069	
	Power	0.117	
	Exponential	0.154	
	Linear	0.279	
VEV/IC	Logarithmic	0.452	Power model is best option
	Inverse	0.388	
	Power	0.457	
	Exponential	0.089	
	Linear	0.521	
VEV/IP	Logarithmic	0.780	Logarithmic model is best option
	Inverse	0.745	
	Power	0.459	
	Exponential	0.080	
	Linear	0.288	
WEV/IC	Logarithmic	0.471	Logarithmic model is best option
	Inverse	0.380	
	Power	0.324	
	Exponential	0.242	
	Linear	0.124	
WEV/IP	Logarithmic	0.178	Power model is best option
	Inverse	0.110	
	Power	0.677	
	Exponential	0.673	

* IC = Intracerebral

** IP = Intraperitoneal

Table 5.

Analysis of improvement or lack of improvement of fit by using age dependency modeling for the beta Poisson model.

Model	Group [*]	N _{doses}	Y	dof	$\chi^2_{0.05, \text{dof}}$	Conclusion	
Beta Poisson	EEV IC Age Dependency	8	28.8	13.4	2	5.99	Age dependency provides better fit
	EEV IC No Age Dependency		42.3				
Beta Poisson	EEV IP Age Dependency	7	106	97.1	2	5.99	Age dependency provides better fit
	EEV IP No Age Dependency		203				
Beta Poisson	VEV IC Age Dependency	7	20.3	10.5	2	5.99	Age dependency provides better fit
	VEV IC No Age Dependency		30.8				
Beta Poisson	VEV IP Age Dependency	7	41.2	9.24	2	5.99	Age dependency provides better fit
	VEV IP No Age Dependency		50.4				
Beta Poisson	WEV IC Age Dependency	6	22.4	10.63	2	5.99	Age dependency provides better fit
	WEV IC No Age Dependency		33.1				
Beta Poisson	WEV IP Age Dependency	5	104	16.90	2	5.99	Age dependency provides better fit
	WEV IP No Age Dependency		121				

* - No age dependency is ages pooled for each pathogen and exposure route set

Table 6.

Results of analysis of goodness of fit and best fitting age dependent dose response model for each pathogen and exposure route set.

Pathogen/Exposure	Model	<i>Y</i>		GOF <i>p</i> -value *	Best Fitting χ^2 crit **	Conclusions
EEV IC	Exponential	121.6	92.78	1.115 (10^{-10})	3.842	Exponential is not a good fit
	Beta Poisson	28.82		0.797		Beta Poisson is best fitting model
EEV IP	Exponential	892.8	786.2	0	3.842	Neither model is a good fit
	Beta Poisson	106.6		6.562 (10^{-09})		
VEV IC	Exponential	18.70	-10.09	0.996	3.842	Both models show a good fit
	Beta Poisson	28.79		0.797		Exponential model is best fitting model
VEV IP	Exponential	86.81	45.64	1.098 (10^{-05})	3.842	Exponential is not a good fit
	Beta Poisson	41.17		0.255		Beta Poisson is the best fitting model
WEV IC	Exponential	22.94	0.520	0.974	3.842	Both models show a good fit
	Beta Poisson	22.42		0.963		Exponential is best fitting model
WEV IP	Exponential	1424	1319	0	3.842	Neither model is a good fit
	Beta Poisson	104.6		1.303 (10^{-08})		

* - For χ^2 distribution dof of n-m (number of doses minus the number of model parameters), confidence level of 0.05

** - Critical value at 1 degree of freedom, confidence level of 0.05

Table 7.

Age dependent dose response parameters for the associated dose response and age dependent sub-models.

Pathogen / Exposure	Dose Response Model	Age-Dependent Sub-Model	Parameters
EEV IC	Beta Poisson	Logarithmic (eq. 5)	$\alpha_0 = 0.066$ $\alpha_I = -15.84$ $N_{50_0} = 2.903$
		Linear (eq. 7)	$N_{50_1} = 0.572$
		Neither age dependent model was a good fit	
		VEV IC	Exponential
Inverse (eq. 4)	$\alpha_0 = -0.364$ $\alpha_I = 2.695$		
	Beta Poisson		
VEV IP			
	Exponential (eq. 6)	$N_{50_0} = 2.546$	
	Power (eq. 3)	$N_{50_1} = -0.061$	
	Neither age dependent model was a good fit		

Table 8.

Assessment of use of *V. major* age dependent sub-models compared to encephalitis specific age dependent sub models for the exponential dose response models.

Pathogen/Exposure	Model	Y	Best Fitting χ^2 crit *		Conclusions
EEV IC	<i>V. major</i> age dependency	121.6	0.100	3.842	Encephalitis sub-models do not provide a better fit
	encephalitis age dependency	121.5			
EEV IP	<i>V. major</i> age dependency	1179	286.3	3.842	Encephalitis sub-models provide a better fit
	encephalitis age dependency	892.7			
VEV IC	<i>V. major</i> age dependency	33.42	14.72	3.842	Encephalitis sub-models provide a better fit
	encephalitis age dependency	18.70			
VEV IP	<i>V. major</i> age dependency	104.1	17.29	3.842	Encephalitis sub-models provide a better fit
	encephalitis age dependency	86.81			
WEV IC	<i>V. major</i> age dependency	35.60	12.65	3.842	Encephalitis sub-models provide a better fit
	encephalitis age dependency	22.95			
WEV IP	<i>V. major</i> age dependency	1574	150.0	3.842	Encephalitis sub-models provide a better fit
	encephalitis age dependency	1424			

Table 9.

Assessment of use of *V. major* age dependent compared to encephalitis specific age dependent sub models for the beta Poisson dose response models.

Pathogen/Exposure	Model	Y	Best Fitting χ^2 crit *		Conclusions
EEV IC	<i>V. major</i> age dependency	28.20	8.200	3.842	Encephalitis sub-models provide a better fit
	encephalitis age dependency	20.00			
EEV IP	<i>V. major</i> age dependency	163.7	57.10	3.842	Encephalitis sub-models provide a better fit
	encephalitis age dependency	106.6			
VEV IC	<i>V. major</i> age dependency	26.00	5.710	3.842	Encephalitis sub-models provide a better fit
	encephalitis age dependency	20.29			
VEV IP	<i>V. major</i> age dependency	50.40	9.240	3.842	Encephalitis sub-models provide a better fit
	encephalitis age dependency	41.16			
WEV IC	<i>V. major</i> age dependency	24.57	2.150	3.842	Encephalitis sub-models do not provide a better fit
	encephalitis age dependency	22.42			
WEV IP	<i>V. major</i> age dependency	104.6	0.000	3.842	Encephalitis sub-models do not provide a better fit
	encephalitis age dependency	104.6			