Microbial Risk Analysis xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Microbial Risk Analysis

journal homepage: www.elsevier.com/locate/mran

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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ARTICLE INFO

Keywords:
Dose response
Encephalitis
Virus
QMRA
Age dependency
Model

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.

1. 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 effect (Haas et al., 1999). 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 (Haas et al., 1999; Haas, 1983). 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 Poisson.[1]

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 dependencies (Weir and Haas, 2009; Tamrakar et al., 2011; Huang et al., 2009; Weir and Haas, 2011). The second generation of dose response models started with the age dependency for *Variola major* (*V. major*) (Weir and Haas, 2009), 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.

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

https://doi.org/10.1016/j.mran.2018.02.003
Received 17 August 2017; Received in revised form 2 January 2018; Accepted 22 February 2018

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 (Booss and Esiri, 2003; Fields and Knipe, 1990). 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 (Taubenberger et al., 2007; Van Hartesveldt, 1992). 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.
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. 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. 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. In Lennette and Koprowski (1943) an experimental study was performed to determine the effect of host age – primarily juvenile in Lennette and Koprowski (1943) – 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* (Weir and Haas, 2009). The data used in Weir and Haas (2009) is similar in structure to that in (Lennette and Koprowski, 1943), where mice of the same ages were grouped together and exposed to a known bolus dose. In the case of the data from (Lennette and Koprowski, 1943) the dataset is very large as compared to those typically encountered in dose response modeling. In Lennette and Koprowski (1943) 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 6–10 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 in Weir and Haas (2009) 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}).

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

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

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 Sections 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 (Eq. (3)) was implemented to determine if there is a statistically significant trend between the dose (d_i, independent variable), n adjusted doses ($\bar{d}$), number of animals in each dose group (n_i), number of positive responses (p_i) and the summed observed probability of response ($\bar{p}$ dependent variable). The summations in Eq. (3) are carried out from 1 to j doses in the dose response experiment