

Extrapolation and dosing recommendations for raxibacumab in children from birth to age <18 years

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Aims: The US Food and Drug Administration's Animal Rule allows for the approval of drugs when human efficacy studies are not ethical. While the therapeutic doses of raxibacumab, a monoclonal antibody for the prophylaxis and treatment of inhalational anthrax, have been based on pharmacokinetic data from adult subjects, its disposition in children has not been investigated in clinical trials. Here we evaluate the effect of demographic covariates and maturation processes on the pharmacokinetics of raxibacumab and explore opportunities for the optimisation of paediatric doses.

Methods: A population pharmacokinetic model was used as basis for the extrapolation of raxibacumab disposition from adults to children. Different extrapolation scenarios, including weight-banded dosing regimens, were considered to assess the effect of growth and maturation on the pharmacokinetic parameters of interest. Area under the concentration–time curve, maximum plasma concentration and the time of serum raxibacumab concentrations greater than or equimolar to the highest serum protective antigen concentrations observed for at least 28 days in any monkey challenged with *Bacillus anthracis* that died were derived and compared with the currently approved US doses.

Results: Based on practical considerations, a weight-banded dosing regimen consisting of 4 dose levels (75 mg/kg for individuals ≤ 1.5 kg, 55 mg/kg for individuals <10 kg, 45 mg/kg for individuals <50 kg, 40 mg/kg for all individuals >50 kg) was required to optimise target exposure across the paediatric population.

Conclusions: Age-related maturation processes may affect raxibacumab clearance in very young patients. The proposed dosing regimens take into account effects of body weight and maturation processes on the elimination of raxibacumab.

KEYWORDS

clinical trial simulations, maturation function, dose rationale, paediatric extrapolation, population pharmacokinetics, raxibacumab

1 | INTRODUCTION

The regulation commonly known as the Animal Rule^{1,2} allows for the approval of drugs when human efficacy studies are not ethical and

field trials to study the effectiveness of drugs or biological products are not feasible. Since 2003, 11 products have been approved by the US Food and Drug Administration based on the Animal Rule, among which is raxibacumab, a fully humanised monoclonal antibody (mAb)

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that blocks the protective antigen-receptor interaction of *Bacillus anthracis*.^{3,4} Over the same period, considerable insight has been gained with regard to the impact of developmental growth, maturation processes, and organ function on the pharmacokinetics of drugs used in children.⁵⁻⁸ Of note is the role of quantitative clinical pharmacology as a tool for the extrapolation of paediatric doses from adults.⁹⁻¹² Extrapolation approaches by modelling and simulation are increasingly being applied not only for drugs in development, but also for studies revisiting drugs already on the market. The concept has become equally important for the evaluation of younger subgroups in the paediatric population, in particular preterm and term neonates, who are likely to show the largest differences in drug disposition.

Raxibacumab was approved in both adults and children (between birth and age <18 years) for the treatment of inhalational anthrax in combination with appropriate antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. Furthermore, a recent study suggests a potential improvement of disease prevention when administered in combination with Anthrax Vaccine Adsorbed.¹³ It is recommended for administration in adult patients as a single intravenous dose of 40 mg/kg over 2 hours and 15 minutes after dilution in 0.9% sodium chloride (normal saline), to a final volume of 250 mL. In paediatric patients, the doses are as follows: 40 mg/kg for individuals above >40 kg; 60 mg/kg for individuals between 10 and 40 kg; and 80 mg/kg for individuals ≤10 kg. Raxibacumab is delivered over a similar infusion time as in adults after dilution with normal or half-normal saline to a final volume that varies from 7 to 150 mL depending on the weight of the patient. These doses have been selected under the assumption that drug disposition across the overall paediatric population from birth to age <18 years varies primarily due to developmental growth (i.e. by changes in body weight), which in turn are corrected by the use of dosing regimens in mg/kg.

Because of ethical constraints, evaluation of the pharmacokinetics of raxibacumab in healthy children, in particular neonates, infants and toddlers, is not possible. Given the advancement in current understanding of pharmacokinetics in children, it was considered appropriate to explore the implications of different allometric scaling concepts and explore how maturation and immunocompetence may affect the paediatric dose rationale for raxibacumab.¹⁴ In fact, despite limited evidence on the role of maturation and immunocompetence on the pharmacokinetics of mAbs, a comprehensive review of the pharmacokinetics of palivizumab, a humanised anti-respiratory syncytial virus mAb has shown that maturational processes in infants and preterm and term neonates have a strong effect on total clearance, with drug levels up to approximately 5-fold higher than what is predicted by allometric scaling methods only.¹⁵ The authors demonstrated that changes in exposure in this group of patients was affected by both chronological age and gestational age, with a maturation half-life of 41 months.

In the current analysis, we used population pharmacokinetic modelling and simulation in conjunction with extrapolation principles to assess whether maturation processes in neonates, infants, and toddlers, including preterm and term subjects may also

contribute significantly to changes in the disposition of raxibacumab. Simulation scenarios were subsequently implemented to evaluate the potential advantages of different weight-banded dosing regimens.

2 | METHODS

A previously developed population pharmacokinetic model in adult healthy subjects was used as the basis for the extrapolation of the disposition properties of raxibacumab in the paediatric population¹⁶ (*companion paper*). Despite the lack of specific data for this class of antibodies, stochastic parameter distributions have been assumed to be comparable across populations (i.e. propagated from adults to children). This implies that differences in drug disposition between the adult and paediatric population are attributable to the effect of maturation and developmental growth, rather than by other (random) causes.

Extrapolation of pharmacokinetic parameters was performed in conjunction with different simulation scenarios to explore the most appropriate doses and dosing regimens, i.e., which ensure area under the concentration–time curve (AUC) and maximum plasma concentration (C_{max}) within the range of values observed after intravenous administration of 40 mg/kg raxibacumab in adults. The ultimate goal was to define a regimen that meets the aforementioned target criteria, but that is simple enough to implement in emergency settings. Therefore, scenarios have been explored, in which doses are defined according to individual body weight, as currently defined in the US label, and according to weight bands.

As the base model used for extrapolation has been developed using healthy adult data, treatment response to raxibacumab has not been assessed in humans. Raxibacumab has been approved for human use under the assumption that antibody binding is specific to the anthrax toxin. Consequently, treatment response is expected not to vary due to interindividual differences in age or weight. Adjusting for changes in drug disposition should result in a response comparable to what has been observed in animal models.

2.1 | Allometric scaling and maturation processes

Different approaches were used to evaluate the effect of body size and ontogeny on the pharmacokinetic parameters of interest, in particular, the changes in clearance and volume of distribution.¹⁷⁻¹⁹ These approaches included:

- i. Use of pre-defined fixed allometric exponents (0.75 for clearance [CL] and intercompartmental clearance [Q] and 1 for central volume of distribution [V1] and peripheral volume of distribution [V2]).²⁰

In this case, the typical value of CL and V1 for a given body weight was defined as follows:

$$TVCL = \theta_{CL} \times \left(\frac{WT}{76.9}\right)^{0.75}$$

$$TVV1 = \theta_{V1} \times \left(\frac{WT}{76.9}\right)^1$$

where WT is the weight in kg and 76.9 kg is the reference weight of the adult population. V2 was scaled with the same exponent as V1, Q was scaled with the same exponent as CL.

- ii. Use of allometric exponents from Deng *et al.*,¹⁷ who proposed the use of allometric scaling of antibodies with a fixed exponent of 0.85 for CL:

$$TVCL = \theta_{CL} \times \left(\frac{WT}{76.9}\right)^{0.85}$$

where WT is the weight in kg and 76.9 kg is the reference weight of the adult population. Q was scaled with the same exponent as CL. V1 and V2 were scaled with an exponent of 1.

- iii. Use of allometric exponents, estimated from the population pharmacokinetic analysis of adult data (hereafter referred to as the *final estimated model*). In this case, modelling of the adult data was based on the following relationships for CL, Q, V, and V2:

$$TVV1 = \theta_{V1} \times \left(\frac{WT}{76.9}\right)^{0.7}$$

$$TVCL = \theta_{CL} \times \left(\frac{WT}{76.9}\right)^{0.83}$$

$$TVV2 = \theta_{V2} \times \left(\frac{WT}{76.9}\right)^{0.85}$$

$$TVQ = \theta_Q \times \left(\frac{WT}{76.9}\right)^{1.16}$$

where WT is the weight in kg and 76.9 kg is the reference weight of the adult population.

- iv. Use of the same maturation function estimated for palivizumab. Robbie *et al.*¹⁵ have used a combination of allometric scaling and a maturation function to describe the disposition of palivizumab in infants and young children. Assuming that the same mechanisms are involved in the maturation process of other antibodies, the following relationship can be applied:

$$TVCL = \theta_{CL} \times \left(\frac{WT}{70}\right)^{0.75} \times \left(1 - (1 - \beta) \times e^{-\left(\frac{PAGE-40}{4.35}\right) \times \left(\frac{\ln 2}{T_{CL}}\right)}\right)$$

$$TVV1 = \theta_{V1} \times \left(\frac{WT}{76.9}\right)^1$$

$$TVQ = \theta_Q \times \left(\frac{WT}{76.9}\right)^{0.75}$$

where PAGE is the combination of gestational and postnatal age in weeks, β (0.411) represents the fractional change in CL for a typical full-term (40-week PMA) and T_{CL} (62.3) is the maturation half-life for CL in months. WT is the weight in kg and 76.9 kg is the reference median weight for the adult population. V2 was scaled with the same exponent as V1.

Final model parameter estimates were used for V1, CL, V2 and Q along with the interindividual variability (IIV) estimates. IIV was identified for volume of distribution, clearance, peripheral volume of distribution and intercompartmental clearance. IIV was treated as log normally distributed for all pharmacokinetic parameters. The covariate effects of demographic (weight) and physiological (age) factors were added in a stepwise manner to the *base model*. Note that θ_{CL} values are rescaled to refer to the typical value of clearance for a 70 kg adult (instead of a 76.9 adult) in order to match the maturation formula used by Robbie *et al.*¹⁵

Given the assumptions required for each of these approaches, it is not possible to demonstrate which model provides the most accurate prediction of the pharmacokinetics in children. However, the working hypothesis was that changes in the disposition of raxibacumab are caused by developmental growth (allometry) as well as maturation processes. The magnitude of the effect of maturation on clearance could not be assessed formally other than by means of a sensitivity analysis. For the sake of completeness, all models were considered to ensure that potential differences in raxibacumab exposure were taken into account and factored into best case/worst case conditions. Table 1 provides an overview of the different models used in the analysis.

2.2 | Virtual paediatric population

To accurately characterise the effects of body size and developmental growth on the disposition of raxibacumab a relevant population has been created, in which age and body weight are represented.

A virtual trial cohort consisting of 250 000 subjects with age uniformly distributed within a range starting at 24 weeks of post-menstrual age to <18 years was created and used in the subsequent simulation scenarios. Weight was simulated using the demographic covariate model proposed by Sumpter *et al.*,²¹ which has age as the independent variable.

TABLE 1 List of models used for paediatric extrapolation

Model	Parameters scaled by allometry: (effect of body weight)	Parameters scaled by a maturation function: (effect of age)	Notes
Final estimation model	CL, Q, V_2 , V_3	N/A	Final model as estimated in healthy adults (FMHA) as reported in ¹⁶
Fixed allometric model	CL, Q, V_2 , V_3	N/A	FMHA but with allometric exponents fixed to literature values
Deng et al.	CL, Q, V_2 , V_3	N/A	FMHA with allometric exponents fixed to 0.85 for CL and Q and 1 for V_1 and V_2 , as reported in ¹⁷
Maturation model	CL, Q, V_2 , V_3	CL	FMHA with age and bodyweight effects as reported in ¹⁵

Overview of the different models used for extrapolation of the paediatric dose. CL, clearance; Q, intercompartmental clearance; V_2 , central volume of distribution; V_3 , peripheral volume of distribution.

2.3 | Secondary pharmacokinetic parameters

The secondary parameters of interest were AUC, C_{\max} and the time of serum raxibacumab concentrations greater than or equimolar to the highest serum protective antigen concentrations observed for at least 28 days in any adult monkey challenged with *B. anthracis* that died. Preclinical reference values were obtained from a prophylaxis study in cynomolgus macaques (*Macaca fascicularis*), in which 10 animals were randomly assigned to receive either placebo or raxibacumab at 10, 20 or 40 mg/kg on day -2. On day 0, all monkeys were exposed to *B. anthracis* spores at a target dose that was 100 times the median lethal dose. The study endpoint was survival at 28 days from challenge to death. The highest serum protective antigen concentrations observed for at least 28 days in any adult monkey challenged with *B. anthracis* that died was found to be 760 nM.²² Surviving adult monkeys had a minimum C_{\max} of 385 µg/mL and AUC of 2499 µg d/mL.

Secondary parameters were derived from the individually simulated profiles, C_{\max} was calculated by sampling the first concentration at the last point of infusion, while AUC values were obtained by the trapezoidal rule. The time above the monkey threshold was approximated in R^{23} using the individually simulated concentration vs time profiles.

2.4 | Simulation scenarios

Simulation scenarios included a range of assumptions regarding the extrapolation and prediction of raxibacumab disposition in paediatric patients from birth to age <18 years. In all scenarios, the paediatric dose selection is based on the attainment of systemic raxibacumab exposure corresponding to the (model-predicted) 95% confidence intervals for AUC and C_{\max} in adults after administration of a 40 mg/kg dose of raxibacumab. In addition, the dose rationale takes into account the duration of protective exposure levels in at least 95% of children (i.e. raxibacumab exposure should be equimolar or greater than the highest serum protective antigen concentrations observed for at least 28 days in any monkey challenged with *B. anthracis* that died [760 nM]). This was deemed a necessary cross-check to guard against outcomes of excessively high C_{\max} coupled with too rapid clearance,

resulting in an AUC within the acceptable range but insufficient duration of protective levels.

The following scenarios have been evaluated during the simulation procedures:

- Scenario 1: Three dose levels based on weight thresholds (40–80 mg/kg for all subjects based on weight: 80 mg/kg for individuals <10 kg; 60 mg/kg for individuals between 10 and 40 kg; and 40 mg/kg for individuals >40 kg).
- Scenario 2: Four dose levels based on weight thresholds (75 mg/kg for individuals ≤1.5 kg; 55 mg/kg for individuals >1.5 kg and ≤10 kg; 45 mg/kg for individuals >10 kg and ≤50 kg; 40 mg/kg for patients >50 kg).

Scenario 1 has been used for reference purposes, as it is the recommended dose according to the US prescribing information for raxibacumab approved in 2018. Other scenarios with more or fewer weight bands have also been evaluated but are not shown here. Each scenario had a different dosing scheme based on the number of weight bands. Doses were picked by visual inspection of simulated profiles and adjustment of the weight bands until an optimal dosing scheme was identified for each scenario. Dose schemes and weight bands were rounded in order to ensure prescriber-friendly recommendations. Table 2 provides an overview of the dose levels per weight band, for each of the scenarios.

Simulations consisted in generating raxibacumab concentrations up to 200 days post-administration of a single intravenous dose. Twenty sampling points were collected for each individual paediatric patient and used to derive secondary pharmacokinetic parameters. Simulated scenarios were summarised in terms of quantiles and median and were visually inspected. Scenarios not matching the required standards were discarded or adjusted.

3 | RESULTS

Allometric scaling and clearance maturation concepts were applied to characterise the effect of body size and developmental growth on the

TABLE 2 List of evaluated dosing scenarios

Body weight (kg)	Scenario 1 (dose in mg/kg)	Scenario 2 (dose in mg/kg)
≤1	80	75
1.1–1.5	80	75
1.6–2	80	55
2.1–3	80	55
3.1–4.9	80	55
5–10	80	55
11–15	60	45
16–30	60	45
31–40	60	45
41–50	40	45
>50	40	40

disposition of raxibacumab. Due to the uncertainty in the mechanisms determining drug distribution across the different age groups, several extrapolation models were evaluated (Table 1).

Body weight, irrespective of dose adjustment based on mg/kg, was found to affect the disposition of raxibacumab. However, based on known physiological mechanisms associated with antibody disposition and literature data regarding immunocompetence in infants, the inclusion of a maturation model was assumed to represent the most plausible scenario to establish the dose rationale in children. The maturation effect can be clearly seen when comparing the results of the allometric model with fixed exponents in Figure 1, where the entire paediatric population is treated according to the dosing recommendations in the US label.

Given that maturation processes only have an effect on CL, it can be anticipated that these will affect mainly the AUC estimates

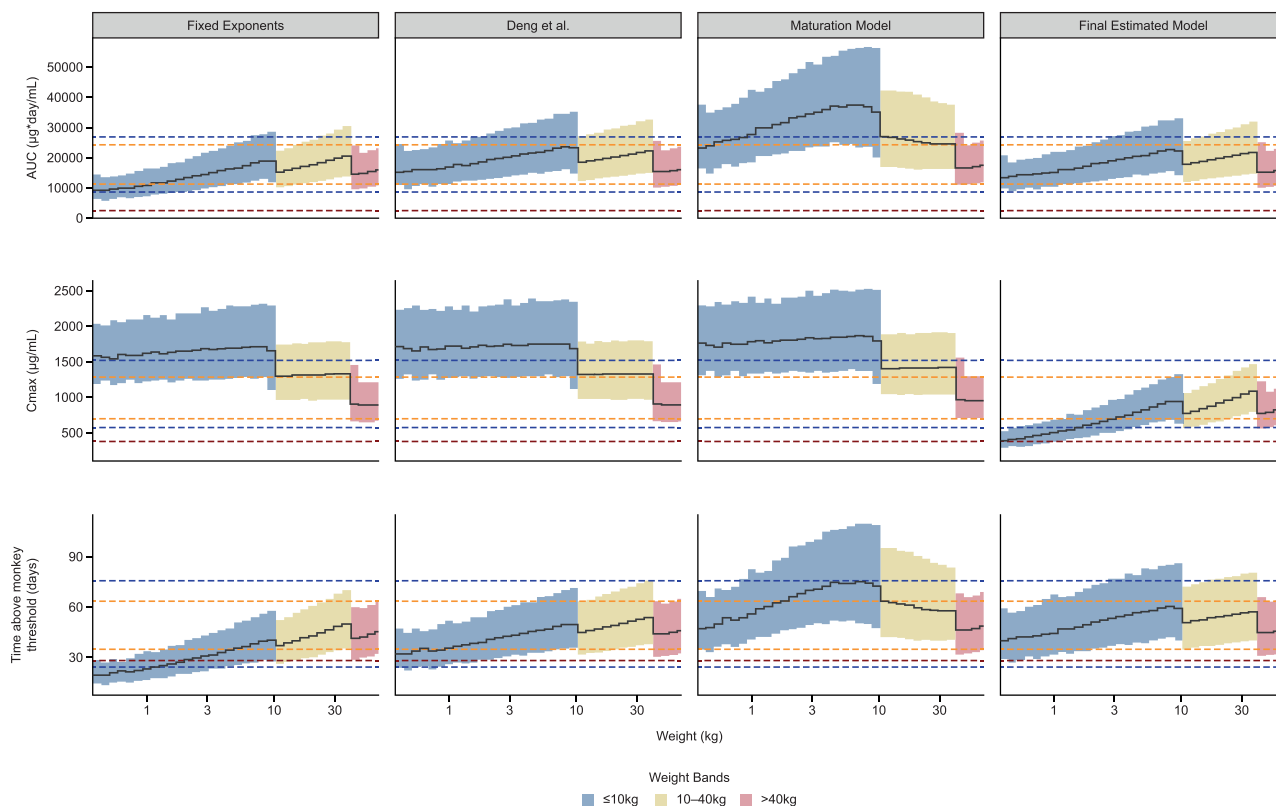


FIGURE 1 Simulation results for scenario 1. Shaded area represents the 2.5th and 97.5th quantiles of the simulated values. Solid line is the median value. Colours indicate the weight bands. Dashed lines are reference values. AUC panels: Dark red dashed line is the minimum AUC in surviving monkeys (2499 µg d/mL). Both dark blue dashed lines represent the maximum and minimum range observed in adults (i.e. 26 903 and 8680 µg d/mL, respectively). Both orange dashed lines represent the 2.5th and 97.5th percentiles of the observed data (i.e. 11 280 and 24 286 µg d/mL, respectively). C_{max} panels: Dark red dashed line is the minimum C_{max} in surviving monkeys (385 µg/mL). Both dark blue dashed lines represent the maximum and minimum range observed in adults (i.e. 1524 and 577 µg/mL, respectively). Both orange dashed lines represent the 2.5th and 97.5th percentiles of the observed data (i.e. 704 and 1288 µg/mL, respectively). Time above monkey threshold panels: Both dark blue dashed lines represent the maximum and minimum range observed in adults (i.e. 75.5 and 24.2 d, respectively). Both orange dashed lines represent the 5th and 95th percentiles of the observed data (i.e. 34.7 and 63.4 d, respectively). The red dashed line represents the 28-day target. *Threshold* refers to the highest observed protective antigen in any spore-challenged monkey that died. AUC, area under the concentration vs time curve; C_{max}, maximum plasma concentration

(i.e. AUC values will be higher in the lower weight range). In fact, differences with the final estimated model can be seen most clearly in the lower weight ranges where it predicts much lower exposure, as compared with the maturation model and allometric model with fixed exponents (Figure 1 and Figure 2). Model predictions between the final estimated model and Deng *et al.*¹⁷ model differ only slightly from each other.

As shown in Figure 1 and Figure 2, maturation processes have little impact on C_{max} . Predicted C_{max} values from the allometric model with fixed exponent proposed by Deng *et al.*¹⁷ did not differ significantly from the maturation model. By contrast, the final estimated model yields C_{max} values that are lower than any other simulation scenarios.

An immediate consequence of the assumption of maturation processes in neonates, infants and toddlers is that systemic clearance is reduced in this subgroup of patients. The maturation model predicted, therefore, the longest time (duration) above protective raxibacumab

concentrations, as compared with the other models (Figures 1 and 2). By contrast, in the absence of such processes, the predicted clearance was significantly higher for the same subgroup of patients. This was observed for the fixed allometric exponent model, which predicts shorter time above the protective raxibacumab concentration as body weight goes towards the lower end of the simulated weight range. The allometric model with fixed exponents proposed by Deng *et al.*¹⁷ yielded similar results, but concentrations were not as low as the allometric model with fixed exponents.

3.1 | Paediatric dosing recommendations

Simulations revealed that scenarios with multiple weight bands reach the predicted exposure ranges that are closer to what has been observed in adults (i.e. increasing the number of weight bands yielded treatment scenarios with higher proportion of patients within the

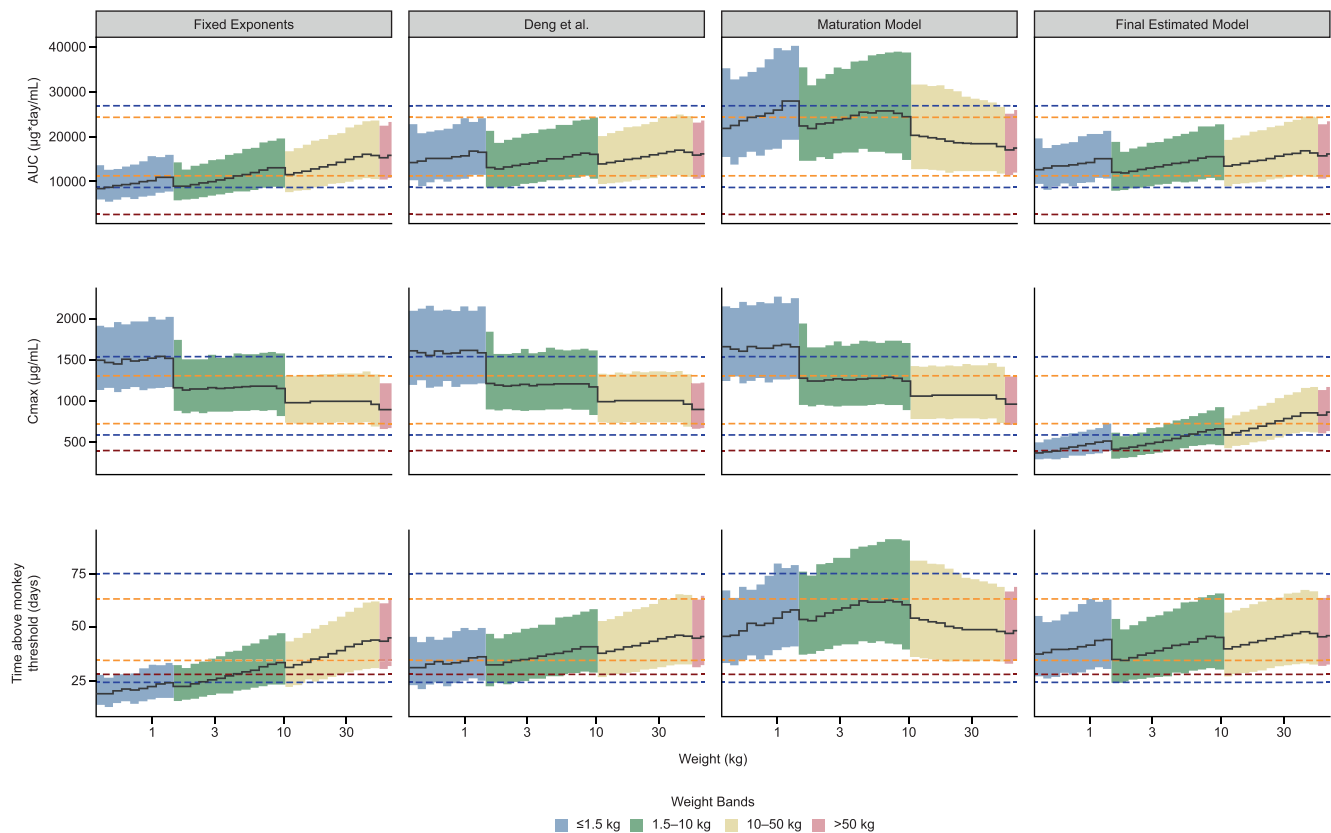


FIGURE 2 Simulation results for scenario 2. Shaded area represents the 2.5th and 97.5th quantiles of the simulated values. Solid line is the median value. Colours indicate the dosing weight band. Dashed lines are reference values. AUC panels: Dark red dashed line is the minimum AUC in surviving monkeys (2499 µg d/mL). Both dark blue dashed lines represent the maximum and minimum range observed in adults (i.e. 26 903 and 8680 µg d/mL, respectively). Both orange dashed lines represent the 2.5th and 97.5th percentiles of the observed data (i.e. 11 280 and 24 286 µg d/mL, respectively). C_{max} panels: Dark red dashed line is the minimum C_{max} in surviving monkeys (385 µg/mL). Both dark blue dashed lines represent the maximum and minimum range observed in adults (i.e. and 577 µg/mL, respectively). Both orange dashed lines represent the 2.5th and 97.5th percentiles of the observed data (i.e. 704 and 1288 µg/mL, respectively). Monkey threshold panels: Both dark blue dashed lines represent the maximum and minimum range observed time in adults (i.e. 75.5 and, 24.2 d, respectively). Both orange dashed lines represent the 5th and 95th percentiles of the observed data (i.e. 34.7 and 63.4 d, respectively). The red dashed line represents the 28-day target. *Threshold* refers to the highest observed protective antigen in any spore-challenged monkey that died. AUC, area under the concentration vs time curve; C_{max} , maximum plasma concentration

target exposure range). Based on practical considerations and on the need to ensure adequate target exposure across all age ranges, this analysis showed that this requirement can be met with 4 weight bands. The final dosing recommendations can be found in Table 3.

4 | DISCUSSION

Here we have used pharmacokinetic modelling and extrapolation in conjunction with simulation scenarios to explore the effect of developmental growth and putative maturational processes on the disposition characteristics of raxibacumab. While modelling and extrapolation concepts have been widely used as a tool for dose selection and prediction of the pharmacokinetics of small molecules in children across a wide range of ages, understanding of the effect of maturation and immunocompetence on the disposition of antibodies is not complete.²⁴ As very limited pharmacokinetic data are available in children younger than 2 years, inferences regarding the contribution of maturation processes, including immune system competence rely on current knowledge of both innate and adaptive immune responses, which are known to be age-dependent and variable due to numerous factors, including antigenic dose and mode of exposure.²⁵ In contrast to small molecules, which may undergo biotransformation, antibody elimination usually occurs by catabolism (proteolysis) in different organs, but mainly within the reticuloendothelial system. Also relevant is the elimination through target antigens (especially in the case of cell-bound target antigens), as well as a recycling process through binding to the neonatal Fc receptor that provides protection from lysosomal degradation. All these mechanisms may be altered by maturational processes during the first few months of life.

While 3 of the models are in agreement with each other, the final estimated model based on adult data showed significantly different results. The main differences were seen in C_{max} where the final

estimated model predicts concentrations below the target threshold. This effect is caused by the exponent obtained for the volume of distribution (i.e. 0.75), which is unlikely to predict well the effect of developmental growth and body size on the disposition of monoclonal antibodies. In children this exponent has usually a value of 1, as used in the other models.

Given the target paediatric population, the contribution of maturation processes to the pharmacokinetics of raxibacumab was deemed a plausible scenario for neonates, infants and possibly toddlers. Developmental growth was described by the changes in body size, as assessed by allometric principles, whereas maturation processes affecting expression of neonatal Fc receptor, the key mediator of raxibacumab clearance, was described by an empirical function that reflects the increase in the clearance of the biological molecule. Lastly, it was hypothesised that such processes represent system-specific changes rather than drug-specific properties. Hence, we have assumed that previous findings regarding the maturation function for palivizumab could be generalised to other molecules with similar disposition properties. We acknowledge that, unfortunately, the validity of this assumption cannot be demonstrated. A recent review of the population pharmacokinetic models for mAbs revealed that, apart from palivizumab, there are barely any published data on the role of maturation processes in the pharmacokinetics of mAbs in young children.²⁶⁻²⁹ By contrast, despite the lack of pharmacokinetic data in neonates and infants, it seems plausible to assume that drug disposition characteristics are altered due to the maturing immune system. A report on the evolution of the immune system in humans from infancy to old age³⁰ shows that development of the immune response through neonatal, infant and adult life is determined by a maturation process, normally described by the concept of immunocompetence. Similar considerations are presented by Dowling and Levy in their publication on the ontogeny of early life immunity.³¹

TABLE 3 Model-based raxibacumab dose recommendations in paediatric patients from birth to age <18 years^a

Body weight (kg)	Preparation			Administration	
	Dose (mg/kg)	Total infusion volume (mL)	Type of diluent	Infusion rate (mL/h) First 20 min	Infusion rate (mL/h) Remaining infusion
≤1	75	7	0.45% or 0.9% NaCl	0.5	3.5
1.1-1.5		15		1	7
1.6-2	55	15		1	7
2.1-3		20		1.2	10
3.1-4.9		25		1.5	12
5-10		40		3	20
11-15	45	50	0.9% NaCl	6	25
16-30		100		6	50
31-40		125		15	62.5
41-50		125		15	62.5
>50 or adult	40	150		15	75

^aThis table provides dose and infusion information stratified by body weight.

Irrespective of the magnitude of the effect of maturation processes on the disposition of raxibacumab in neonates, infants and very young children, the incorporation of a maturation function was shown to cause a considerable reduction in drug clearance and consequently an increase in exposure in all of the selected metrics. Such a change in clearance in this subgroup of patients raises the question about the need for a different dose or dosing regimen.

While the currently approved doses do account for the contribution of developmental growth and take into account the effect of varying body weight in the paediatric population, it does not seem to take into account the impact of maturation. This implies the possibility that, in neonates and infants, the exposure to raxibacumab may be significantly higher than predicted by allometric principles. However, given the life-threatening nature of the infection and the good tolerability profile of raxibacumab, one needs to consider potential biases in any attempt to optimise the dose.

Therefore, we have selected doses for neonates and infants, which account for higher or lower clearance values than what was obtained by the extrapolation procedures described here. In other words, overexposure to raxibacumab relative to the target range values was deemed preferable than underexposure. Whereas overexposure is the preferred choice given parameter uncertainty or bias, the assumption of maturation processes for neonates, infants and toddlers (i.e. preterm or term newborn to age 23 mo) was deemed the most biologically plausible scenario. Even though raxibacumab is well tolerated at cumulative doses of up to 80 mg/kg in adults, predicted exposure ranges in this subgroup of patients might exceed the observed clinical range if maturation processes is comparable to the changes in clearance observed for palivizumab.

The use of 4 weight bands compensates for the potential effect of maturation processes and allometric differences on the exposure to raxibacumab. This dosing regimen does not only consider the criteria for target exposure, but also the feasibility and practicalities for its implementation in a hospital setting. Increasing the number of weight bands would result in a higher proportion of individuals who are within the target exposure within each weight band. However, based on practical considerations, it was concluded that the requirement to ensure adequate target exposure across all age ranges was best met with 4 weight bands. It should be highlighted that, compared with the current dosing recommendations, the use of 4 weight bands represents an additional step for patients ≤ 1.5 kg.

In conclusion, maturational process may have significant effect on the elimination of raxibacumab if the mechanisms underpinning the observed changes in the disposition of palivizumab are applicable to other antibodies. In this case, dosing regimens should be selected taking into account the most biologically plausible scenario to ensure optimised raxibacumab exposure in neonates, infants and toddlers.

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COMPETING INTERESTS

S.P.O. declares no conflict of interest. O.D.P. is an employee of GSK and holds stocks/shares in GSK.

CONTRIBUTORS

S.P.O. analysed the data and wrote the manuscript. O.D.P. designed the research study, wrote the manuscript, and contributed to interpretation of results.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study. A copy of the control stream file used for the simulations is provided in the supplementary materials.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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