ARTICLE

Reducing Palivizumab Dose Requirements Through Rational Dose Regimen Design

Stephanie E. Reuter[1],*, Allan M. Evans[1] and Michael B. Ward[1]

Palivizumab for respiratory syncytial virus (RSV) immunoprophylaxis in premature infants poses a significant economic challenge. Although standard dosing of palivizumab results in unnecessary drug accumulation without additional clinical benefit, some clinicians have moved outside of evidence-based practice by implementing untested dose modifications, potentially jeopardizing efficacy. Using an industry-developed population pharmacokinetic model, this study evaluated the previously published alternate dosing regimens and developed a revised regimen that minimizes palivizumab dose requirements while maintaining established therapeutic concentrations. All published dose modifications resulted in unacceptably high proportions of infants not attaining minimum protective concentrations, compromising efficacy. Through intelligent dose regimen design, a clinically practical palivizumab regimen was devised that reduces drug use by 25%, while enabling a greater proportion of infants attaining early season target concentrations, particularly those at greatest risk of the consequences of RSV infection. This novel regimen has the potential to substantially change clinical practice and increase drug availability.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Healthcare systems worldwide are struggling with the economic challenges posed by using palivizumab for respiratory syncytial virus (RSV) immunoprophylaxis in premature and vulnerable infants. To reduce cost, alternate dose regimens have been proposed; however, an evidence basis for their use is lacking.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ A population pharmacokinetic model was used to evaluate and design alternate palivizumab dose regimens with reduced drug requirements with the intent of reducing treatment cost.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Previously published alternate regimens resulted in unacceptably high proportions of infants not attaining minimum protective palivizumab concentrations and, as such, are likely to compromise efficacy. A rationally designed, clinically practical palivizumab regimen was devised that reduces drug use by 25% and enables a greater proportion of infants to attain protective palivizumab concentration early in the RSV season.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ Through this novel dose regimen, reductions in the cost of palivizumab immunoprophylaxis can be achieved and, in doing so, provide the opportunity for enhanced access for this vulnerable patient group.

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infection and bronchiolitis in infants and young children.[1] RSV follows a distinct seasonal pattern in most regions, with peak prevalence during the winter months.[2] At present, there are no recommended pharmacological treatments for RSV disease[3]; the only option is prevention by passive immunoprophylaxis with palivizumab (Synagis). Palivizumab is approved for "the reduction of serious lower respiratory tract infection caused by respiratory syncytial virus (RSV) in children at increased risk of severe disease," including premature infants and infants at risk of RSV-related hospitalization because of hemodynamically significant congenital heart disease or chronic lung disease of prematurity.[4]

Because palivizumab only conveys passive immunity, protection against the virus is dependent on maintaining palivizumab serum concentrations for the duration of the RSV season, with a minimum protective serum

[1]School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia, Australia. *Correspondence: Stephanie E. Reuter (stephanie.reuter@unisa.edu.au)

concentration of 40 µg/mL having been specified by the manufacturer.[5,6] The approved dose of palivizumab is 15 mg/kg of body weight, administered intramuscularly once a month for 5 months and administered only during the anticipated periods of risk of infection with RSV within the community (i.e., the RSV season). It is recommended that the first dose of palivizumab is administered before the prevalence of RSV within the community begins to increase (denoting the commencement of the RSV season), with subsequent injections administered on a monthly schedule thereafter. This regimen is intended to provide protection against the virus across the period of peak prevalence of RSV within the community, through to the end of the season when RSV prevalence returns to low levels, at which time the treatment is ceased.

Significant drug cost presents a major barrier to palivizumab use worldwide.[7–10] As such, there exists a need to reduce the cost of palivizumab prophylaxis and in doing so provide the opportunity for enhanced access for this vulnerable patient group. Consequently, there has been interest in reducing the cost of palivizumab therapy through the design and in some cases implementation of modified dose regimens that reduce the amount of palivizumab required per patient, typically through the elimination of one or more doses from the regimen.[11–18] Analysis of the impact of these modified regimens on serum concentrations has typically been limited to extrapolation of mean concentration data and, where clinically evaluated, has been underpowered.

In 2012, a population pharmacokinetic model of palivizumab was developed using the data set acquired from 22 studies conducted during the clinical development program.[15] The model describes two-compartment pharmacokinetics, with first-order drug absorption from the site of intramuscular injection and first-order elimination from the central compartment. The model incorporates allometric scaling on clearance and volume parameters, PAGE (defined as gestational age + postnatal age), disease state (chronic lung disease of prematurity), and race as covariates on clearance and race as a covariate on central volume. To date, the full capacity of this model has not been exploited to address the cost of palivizumab therapy. The aim of this study was to use the established palivizumab population pharmacokinetic model to evaluate the published alternate dosing regimens (**Table 1**) and develop a revised dosing regimen that minimizes palivizumab dose requirements while maintaining established therapeutic concentrations.

METHODS
Pharmacokinetic model

Population pharmacokinetic simulation was conducted using NONMEM VII (ICON Development Solutions) software with an Intel Fortran complier and Wings for NONMEM interface (http://wfn.sourceforge.net); post-processing of data was conducted using R, Version 3.3.2 (https://www.r-project.org/).

The pharmacokinetic model was taken from that described by Robbie *et al.*[15] (incorporating clarifications by the authors), with model parameters defined as follows:

$$CL_i = \theta_{CL} \times \left(\frac{WT}{70}\right)^{0.75} \times \left(1 - (1-\beta) \times \exp^{-\left(\left(\frac{PAGE-40}{4.35}\right) \times \left(\frac{Ln(2)}{T_{CL}}\right)\right)}\right)$$
$$\times \theta_{RACE1}^{RACE[AfricanAmerican]} \times \theta_{RACE2}^{RACE[Hispanic]} \times \theta_{RACE3}^{RACE[Asian]}$$
$$\times \theta_{RACE4}^{RACE[Other]} \times \theta_{CLD}^{CLD} \times \exp^{\eta_{CL}} \quad (1)$$

$$V_{C_i} = \theta_{V_C} \times \left(\frac{WT}{70}\right)^{1.0} \times \theta_{RACE5}^{RACE[Hispanic]} \times \exp^{\eta_{V_C}} \quad (2)$$

$$V_{P_i} = \theta_{V_P} \times \left(\frac{WT}{70}\right)^{1.0} \quad (3)$$

$$Q_i = \theta_Q \times \left(\frac{WT}{70}\right)^{0.75} \quad (4)$$

Table 1 Published alternate palivizumab dose regimens

| Reference	Number of doses in regimen	Dose magnitude and schedule	Modifications to regimen			Reduction in palivizumab requirement (%)
			Number of doses	Dose magnitude	Interval	
Approved	5	15 mg/kg D0, D30, D60, D90, D120	–	–	–	–
14	4	15 mg/kg D0, D30, D60, D90	Y	–	–	20
14	3	15 mg/kg D0, D30, D90	Y	–	–	40
18	5	15 mg/kg D0 then 10 mg/kg D23, D53, D83, D113	–	Y	Y	25
12	4	15 mg/kg D0, D30, D75, D120	Y	–	Y	20
12	3	15 mg/kg D0, D30, D80	Y	–	Y	40
11	5	15 mg/kg D0, D29, D67, D105, D172	–	–	Y	0
11	4	15 mg/kg D0, D29, D67, D105	Y	–	Y	20
11	3	15 mg/kg D0, D29, D67	Y	–	Y	40

D, day; Y, yes.
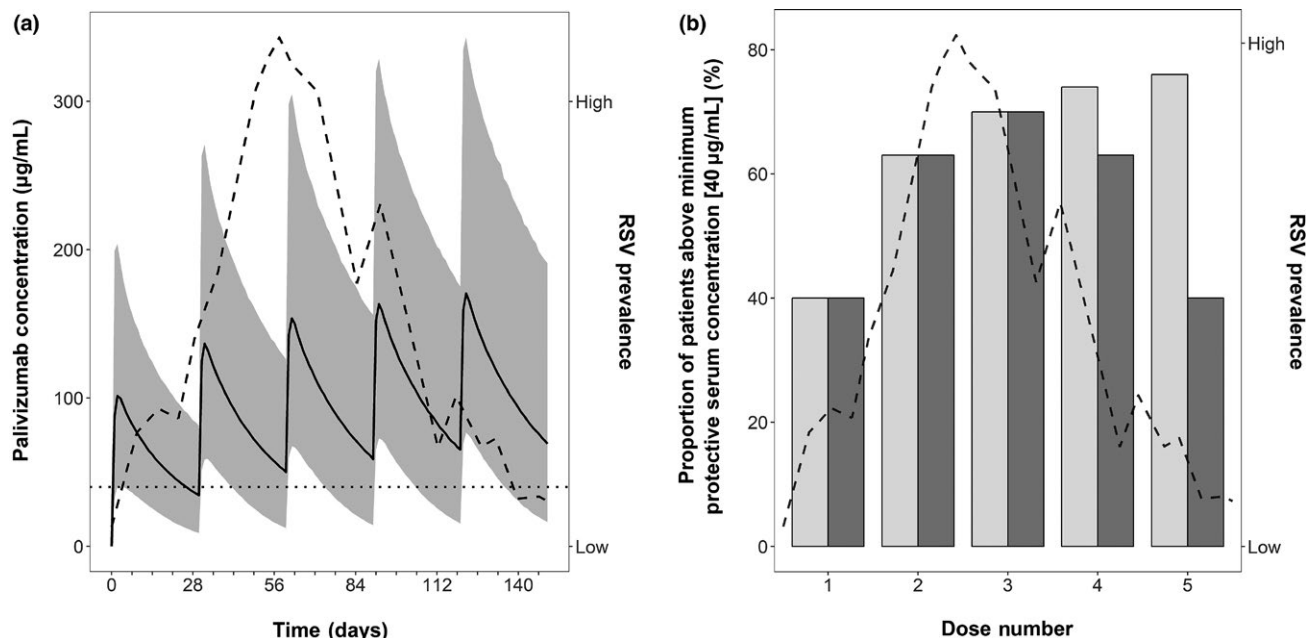
Figure 1 Evaluation of the approved dose regimen (15 mg/kg on D0, D30, D60, D90, and D120), overlayed with indicative respiratory syncytial virus (RSV) season prevalence (dashed), derived from Moore *et al.*[21] (**a**) Simulated population palivizumab concentration–time profiles for the approved dose regimen. Concentration–time data presented as median (solid) and 90% prediction interval (shaded). (**b**) Proportion of infants in the simulated patient cohort achieving the minimum protective serum palivizumab concentration (40 µg/mL) after administration of the approved dose regimen (light gray) and the defined acceptable targets (medium gray). Note: for intuitiveness, the figure indicates the proportion of patients attaining target concentrations; however, in assessing dose regimens, it is the proportion below target that is of concern and hence referred to as the criterion.

$$K_{A_i} = \theta_{K_A} \qquad (5)$$

$$F_i = \theta_F \qquad (6)$$

The full model code is presented within the Supplementary Material S1.

Simulated patient cohort
A patient cohort was constructed with the specific intent of describing the upper and lower limits of palivizumab exposure that would be expected to occur within the population for whom palivizumab is clinically indicated. Patient covariates were defined at baseline and matured over the 5-month palivizumab treatment period to reflect the significant changes in patient age and weight that occur in this specific population over that time. The patient cohort ranged in baseline PAGE from 26 to 78 weeks, consistent with recommendations for patients for whom palivizumab should be considered.[4] For each PAGE, the range of potential baseline body weights was described by the inclusion of individuals according to the 3rd and 97th percentiles, as defined by the INTERGROWTH-21st Project.[19] Throughout the simulated 5-month treatment period, PAGE and body weight were increased on a daily basis with weight obtained from the growth trajectories defined for the 3rd and 97th percentiles initially by the INTERGROWTH-21st Project (26–78 weeks PAGE) and subsequently by the World Health Organization (WHO) Child Growth Standards (>78 weeks PAGE).[20] This cohort

was then replicated for other factors in the pharmacokinetic model, including disease state (with and without chronic lung disease of prematurity) and race (white and Asian), resulting in a total of 424 unique individuals. Each individual was simulated 1,000 times to adequately characterize the potential variability, resulting in 424,000 simulated individuals from whom palivizumab dosing regimens were examined.

Criteria for assessment of dosing regimens
The approved regimen was used as the benchmark against which alternate regimens were assessed. Performance was evaluated on the basis of the proportion of simulated patients with palivizumab concentrations of at least 40 µg/mL at the end of each dose interval (i.e., trough) over the duration of a 5-month RSV season.

The approved regimen of 5-monthly doses of 15 mg/kg palivizumab results in considerable drug accumulation over the course of the RSV season, with median trough concentrations increasing from 35.9 µg/mL after the first dose to 72.1 µg/mL 1 month after the fifth dose (**Figure 1a**). Correspondingly, the proportion of infants with a palivizumab concentration <40 µg/mL at the end of each dose interval declines over the course of therapy. At the end of the first dosing period, palivizumab concentrations are predicted to be <40 µg/mL in 60% of patients compared with only 24% 1 month after the fifth and final dose.

These proportions are dramatically different despite equivalent risk of RSV exposure given the pattern of prevalence over the course of the RSV season. As such, the degree of
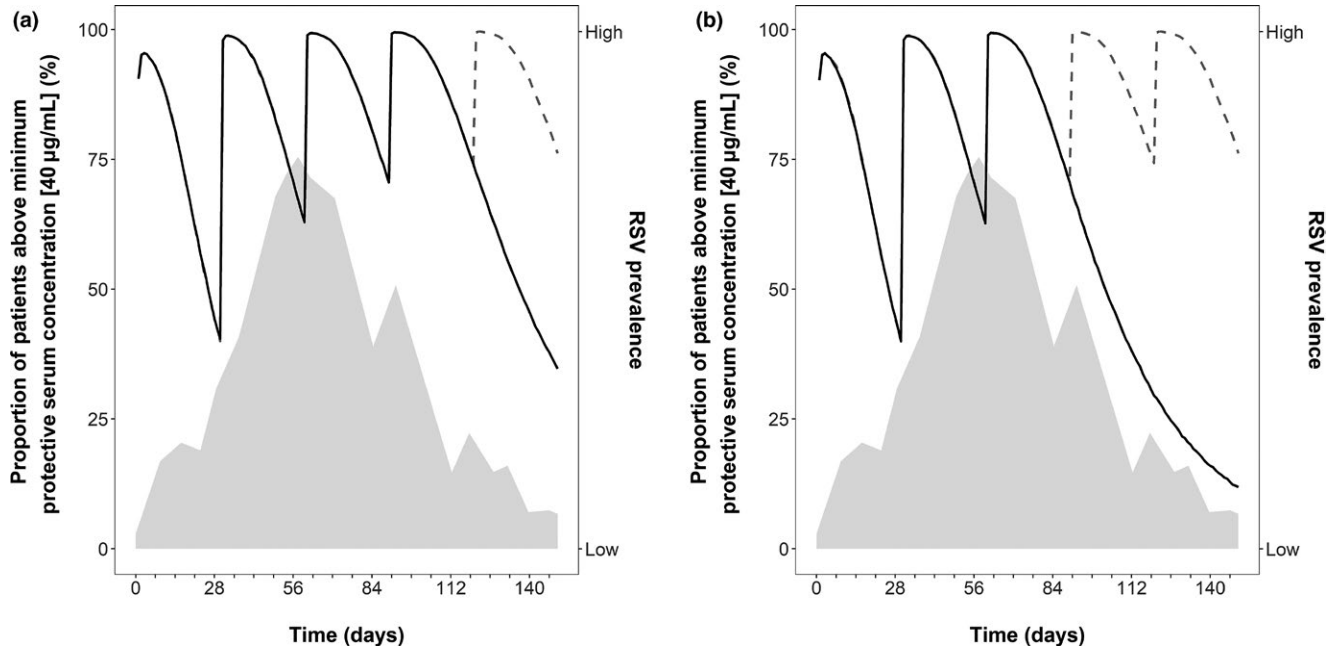
Figure 2 Proportion of infants in the simulated patient cohort achieving the minimum protective serum palivizumab concentration (40 μg/mL) over time after administration of the elimination dose regimen (black) compared with the approved regimen (gray, dashed), overlayed with indicative RSV season prevalence (shaded) derived from Moore *et al.*[21] (**a**) Elimination four-dose regimen (15 mg/kg on D0, D30, D60, and D90). (**b**) Elimination three-dose regimen (15 mg/kg on D0, D30, and D60).

overall protection against RSV in the cohort receiving palivizumab continues to increase over the final two doses of the approved regimen, despite the fact that there is a decreasing risk of exposure to RSV over that time period as the RSV season comes to an end.[21] This observation provides the basis for defining target values for the proportion of patients <40 μg/mL to be used in evaluating and designing new regimens. Target values were defined to ensure that early and peak season proportions were not compromised compared with the approved regimen, but late season values were reduced such that they were equivalent with those of the early season on the basis of equivalent RSV prevalence at those times in the RSV season (**Figure 1b**).[21]

Dose regimens that resulted in an increase in the proportion of patients with palivizumab concentrations <40 μg/mL relative to the defined target values were considered likely to compromise protection against infection, particularly if this occurred at the time of peak RSV prevalence when the risk that an individual will be exposed to RSV is at its greatest.

Assessment of cost savings

Cost savings for the alternate regimens were calculated relative to the approved regimen. Total drug use for each regimen was determined for the simulated patient cohort, with vial use calculated on the basis of administration using available 50- and 100-mg vial sizes.

RESULTS

When compared with the approved regimen and the defined target values, all previously published alternate dosing regimens resulted in an increase in the proportion of simulated patients with palivizumab concentrations <40 μg/mL (**Figures 2–4**). All regimens that deviated from the approved dose and frequency schedule over the first three doses increased the proportion of patients <40 μg/mL at the peak of the indicative RSV season (**Figures 3 and 4**). Therefore, identification of an optimal dose regimen was undertaken through the modification of dose magnitude, the number of doses, and/or the dose interval in accordance with the previously defined targets for proportion of infants not achieving palivizumab concentrations of 40 μg/mL.

On the basis of the clear clinical practicalities associated with a reduction in the number of doses, potential four-dose regimens were investigated; however, despite a 20% reduction in the number of doses administered, to attain acceptable proportions of patients attaining the minimum protective serum concentration, larger individual doses were required, resulting in only an overall 5% reduction in total palivizumab use (data not presented). Although an improvement on the existing approved regimen, this reduction was not considered sufficient; therefore, alternative five-dose regimens were investigated.

Potential five-dose regimens were explored through the adjustment of dose magnitude and dose interval. Adjusting the interval yielded minor improvements, and the feasibility of the inconsistent dose interval became clinically impractical. Therefore, modifications of the dose magnitude while maintaining a fixed 28-day dose interval for reasons of clinical practicality were explored. Through careful manipulation of the magnitude of each dose, a regimen was designed that results in a 21% reduction in palivizumab requirements. Although the devised dose regimen performed
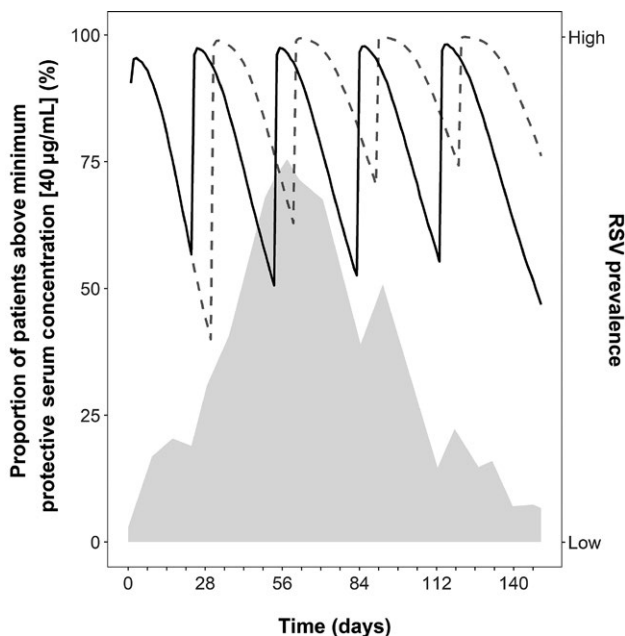
Figure 3 Proportion of infants in the simulated patient cohort achieving the minimum protective serum palivizumab concentration (40 µg/mL) over time after administration of the Zaaijer *et al.*[18] dose regimen (black; 15 mg/kg on D0, 10 mg/kg on D23, D53, D83, and D113), compared with the approved regimen (gray, dashed), overlayed with indicative RSV season prevalence (shaded), derived from Moore *et al.*[21]

age descriptor is an important component of the pharmacokinetic model, stratification based on baseline PAGE indicated distinct differences between the youngest and the oldest infants in the patient cohort (data not presented). Consequently, the final dose regimen is stratified into three groups based on PAGE at the commencement of therapy (**Table 2**). This regimen resulted in a 25% reduction in palivizumab requirements and, in comparison to the approved regimen, results in minimal drug accumulation across the five-dose treatment period. On the basis of the simulations, the revised dose regimen is predicted to meet or exceed the defined proportion targets at each timepoint and, compared with the approved regimen, results in an improvement in early season performance, with a 38% increase in the relative number of patients achieving target concentrations (**Figure 5**). Furthermore, this revised regimen resulted in a substantially higher total number of days above the minimum protective serum concentration over the RSV season for our patient cohort (82%) compared with that predicted for the alternate regimens that have previously been proposed (66–77%) and was comparable to that for the approved regimen (86%).

DISCUSSION

For RSV immunoprophylaxis, the current recommendation is administration of 5 × 15 mg/kg doses of palivizumab, with the first dose administered just before the start of the RSV season and subsequent doses administered monthly. This approved regimen has been designed to ensure increasing coverage alongside the increasing risk of RSV that occurs approaching the peak of the RSV season. However, in examining this regimen, it is immediately obvious that
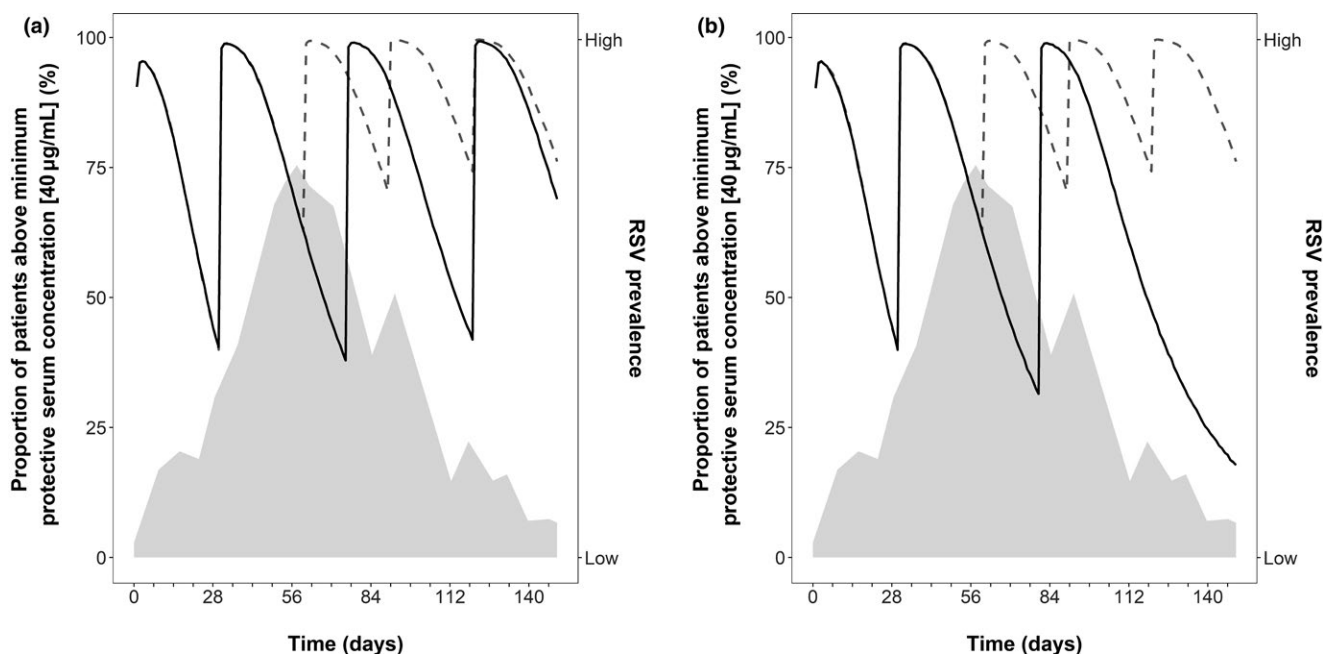
well across the cohort as a whole, evaluation of performance in specific patient subgroups for potential opportunities to further optimize the regimen was undertaken. Although an

Figure 4 Proportion of infants in the simulated patient cohort achieving the minimum protective serum palivizumab concentration (40 µg/mL) over time after administration of the Kwan and Solimano[12] dose regimen (black), compared with the approved regimen (gray, dashed), overlayed with indicative RSV season prevalence (shaded), derived from Moore *et al.*[21] (**a**) Kwan and Solimano[12] four-dose regimen (15 mg/kg on D0, D30, D75, and D120). (**b**) Kwan and Solimano[12] three-dose regimen (15 mg/kg on D0, D30, and D80).

Table 2 Final PAGE-stratified dose regimen

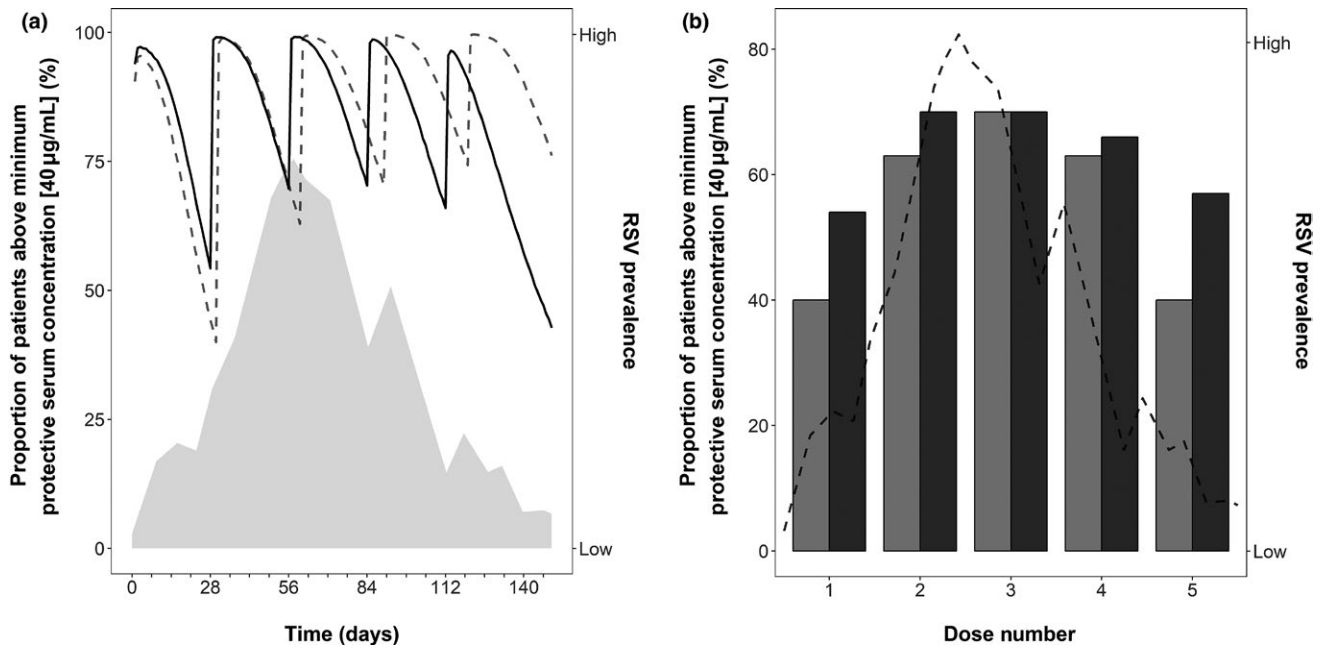| PAGE at treatment commencement (weeks PAGE)	Dose 1 (D0) (mg/kg)	Dose 2 (D28) (mg/kg)	Dose 3 (D56) (mg/kg)	Dose 4 (D84) (mg/kg)	Dose 5 (D112) (mg/kg)
26–39	20	17.5	15	12.5	10
40–65	17.5	15	12.5	10	7.5
66–78	15	12.5	10	7.5	5

D, day; PAGE, gestational age + postnatal age.

Figure 5 Proportion of infants in the simulated patient cohort achieving the minimum protective serum palivizumab concentration (40 µg/mL) after administration of the revised dose regimen. (**a**) Revised dose regimen (black) over time, compared with the approved regimen (gray, dashed), overlayed with indicative RSV season prevalence (shaded), derived from Moore *et al.*[21] (**b**) Revised dose regimen (dark gray) against the defined acceptable targets (medium gray), overlayed with indicative RSV season prevalence (dashed), derived from Moore *et al.*[21]

palivizumab concentrations at the end of the RSV season are significantly greater than those attained after the first dose (**Figure 1a**). In the context of the RSV season, these concentrations are occurring at a time when RSV prevalence is rapidly declining. These concentrations are a direct result of drug accumulation that occurs because of the long half-life of palivizumab; however, this accumulation is unlikely to result in any clinically meaningful benefit (because of low RSV risk) but represents excessive drug use. Preventing this excessive accumulation through more rational dose design presents a significant opportunity to reduce treatment cost without compromising efficacy.

To explore this further, a patient cohort was constructed with the express intent of examining dosing regimens for infants at the upper and lower limits of exposure, thereby ensuring adequate protection for the infants with the lowest predicted palivizumab concentrations, while minimizing drug use for those with the highest concentrations. Although simulations based on the constructed patient cohort are not necessarily reflective of the distribution of concentration–time profiles for the true patient population, it is expected

all individuals would be captured within the bounds of that examined.

Having constructed a suitable patient cohort and identified appropriate metrics against which to assess alternate dose regimens, each of the previously published dose regimens were examined, commencing with the most simplistic of modifications based on elimination of the final one or two doses from the approved treatment regimen. Because these approaches do not modify the initial doses, there is no impact on the percentage of patients achieving a concentration of 40 µg/mL in the early portion of the RSV season (**Figure 2**). However, the elimination of later doses results in the predictable increase in the number of patients falling below the minimum protective serum concentration, particularly toward the end of the season when the proportion reaches as high as 88%, well beyond the defined acceptable proportions.

Before the existence of the manufacturer's pharmacokinetic model, Zaaijer *et al.*[18] used an imprecise fixed estimate of palivizumab half-life (22 days) and a one-compartmental pharmacokinetic model to devise an improved palivizumab

dose regimen, using an initial 15 mg/kg dose, a reduction in subsequent doses to 10 mg/kg, and altered dose intervals. Unsurprisingly, targeting trough concentrations of 40 µg/mL using mean pharmacokinetic parameters results in ≈50% of patients falling below this value after each dose administration (**Figure 3**). This is particularly problematic when comparing against the 30% acceptable limit that is attained with the approved regimen at the peak of the RSV season. Subsequently, Gutfraind *et al.*[11] also used a fixed estimate of half-life (20 days) to develop three, four, and five dose regimens through adjustment of the dose interval. These regimens compromised the duration and extent of coverage when applied to our simulated patient cohort (data not presented). All of these regimens are further complicated by dose administration schedules that would be complex to clinically implement (e.g., the Gutfriand *et al.* regimens each require a precise combination of 29- and 38-day dosing intervals that are unlikely to be translated into clinical practice).

More recently, Kwan and Solimano[12] attempted to use the manufacturer's pharmacokinetic model to maintain the approved 15 mg/kg dose but increase the interval between doses to reduce the number of doses administered. However, this work was significantly compromised by major methodological errors. Most important, the authors oversimplified the model, disregarding key pharmacokinetic parameters, and ignored interpatient variability, one of the major strengths of the model. Consequently, the proposed three- and four-dose regimens were based on median data for a specific individual of 4.5 kg and 12.3 months PAGE. Simulating these regimens using the manufacturer's model and our patient cohort indicates that these regimens result in an unacceptably high proportion of patients (up to 82%) not attaining the minimum protective serum concentration for long periods, particularly during the peak of the RSV season when this value is ≈60%, double the previously specified target (**Figure 4**).

Through the application of the manufacturer's population pharmacokinetic model to all the previously published alternative dose regimens, it is clear that they result in unacceptably high proportions of patients not attaining the minimum protective serum concentration and, as such, are likely to compromise efficacy. As such, there existed a need to design a logical, clinically practical dose regimen that reduces drug use, while attaining the previously described acceptable proportion of patients achieving palivizumab concentrations >40 µg/mL.

Through examination of modifications of dose magnitude, the number of doses, and/or dose interval, a dose regimen was identified that reduces total palivizumab use by 25% relative to the approved regimen. When considering the available vial sizes, the doses required per individual, and assuming that vial sharing does not occur, this results in a real-world 20% reduction in the number of vials used. More important, because of injection site volume restriction, the revised regimen results in the added benefit of a substantial reduction in the number of infants who require more than one injection per session to achieve their requisite dose at any individual timepoint, particularly at the later doses (dose 5, 58% vs. 0% for the approved vs. revised regimens).

The final dose regimen is stratified into three groups based on PAGE at the commencement of therapy, with a simple 2.5 mg/kg stepwise reduction in dose throughout the treatment period (**Table 2**). Although this requires dose calculation at each administration timepoint, given the changing weight of the infant throughout the RSV season, this is no more complex or clinically arduous than the current weight-based palivizumab dose regimen. For the youngest infants, a group associated with increased risk of the consequences of RSV infection,[22] this PAGE-based optimization enabled a doubling in the proportion attaining early minimum protective serum concentrations compared with the approved dose regimen, while maintaining performance for the older age dose groups. The minor dose increase required in the youngest infants is offset by the savings obtained from the dose reduction in the older age group.

Healthcare systems worldwide are struggling with the economic challenges posed by the use of palivizumab for the prevention of RSV infection in premature and vulnerable infants. This study presents a logical, clinically practical palivizumab dose regimen that maximizes pharmacokinetic efficiency to reduce drug requirements by 25%. This regimen can be readily implemented with no additional clinical imposition compared with the approved regimen but has the potential to generate substantial cost savings and improve access to palivizumab worldwide. Generation of clinical evidence to support the implementation of this revised dosing regimen is required.

Author Contributions. S.E.R., A.M.E., and M.B.W. wrote the manuscript; S.E.R. and M.B.W. designed the research; S.E.R., A.M.E., and M.B.W. performed the research; S.E.R. and M.B.W. analyzed the data.

1. Baker, K.A. & Ryan, M.E. RSV infection in infants and young children: what's new in diagnosis, treatment, and prevention? *Postgrad. Med.* **106**, 97–99, 103-104, 107-108 passim (1999).
2. Centers for Disease Control and Prevention (CDC). Respiratory syncytial virus infection (RSV): U.S. Government, Department of Health and Human Services. <http://www.cdc.gov/rsv/clinical/> (2015). Accessed 15 February 2016.
3. Piedimonte, G. & Perez, M.K. Respiratory syncytial virus infection and bronchiolitis. *Pediatr. Rev.* **35**, 519–530 (2014).
4. American Academy of Pediatrics Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics* **134**, 5–420 (2014).
5. Johnson, S. *et al.* Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. *J. Infect. Dis.* **176**, 1215–1224 (1997).
6. Subramanian, K.N. *et al.* Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. *Pediatr. Infect. Dis. J.* **17**, 110–115 (1998).
7. Banerji, A. *et al.* Cost-effectiveness of palivizumab compared to no prophylaxis in term infants residing in the Canadian Arctic. *CMAJ Open* **4**, E623–E633 (2016).

8. Bentley, A., Filipovic, I., Gooch, K. & Busch, K. A cost-effectiveness analysis of respiratory syncytial virus (RSV) prophylaxis in infants in the United Kingdom. *Health Econ. Rev.* **3**, 18 (2013).

9. Blake, S.M., Tanaka, D., Bendz, L.M., Staebler, S. & Brandon, D. Evaluation of the financial and health burden of infants at risk for respiratory syncytial virus. *Adv. Neonatal. Care* **17**, 292–298 (2017).

10. Hussman, J.M., Lanctot, K.L. & Paes, B. The cost effectiveness of palivizumab in congenital heart disease: a review of the current evidence. *J. Med. Econ.* **16**, 115–124 (2013).

11. Gutfraind, A., Galvani, A.P. & Meyers, L.A. Efficacy and optimization of palivizumab injection regimens against respiratory syncytial virus infection. *JAMA Pediatr.* **169**, 341–348 (2015).

12. Kwan, E. & Solimano, A. Both three and four doses of palivizumab (PVZ) should be adequate for 5-months RSV season protection based on the published pharmacokinetic model. Pediatric Academic Societies and Asian Society for Pediatric Research Joint Meeting, Vancouver, Canada, 3-6 May 2014.

13. La Via, W.V. *et al.* Three monthly doses of palivizumab are not adequate for 5-month protection: a population pharmacokinetic analysis. *Pulm. Pharmacol. Ther.* **26**, 666–671 (2013).

14. Lavoie, P.M. *et al.* Outcomes of respiratory syncytial virus immunoprophylaxis in infants using an abbreviated dosing regimen of palivizumab. *JAMA Pediatr.* **170**, 174–176 (2016).

15. Robbie, G.J., Zhao, L., Mondick, J., Losonsky, G. & Roskos, L.K. Population pharmacokinetics of palivizumab, a humanized anti-respiratory syncytial virus monoclonal antibody, in adults and children. *Antimicrob. Agents Chemother.* **56**, 4927–4936 (2012).

16. Solimano, A. & Kwan, E. Revisiting palivizumab (PVZ) dosing recommendations based on published pharmacokinetics data. Pediatric Academic Societies Annual Meeting, Boston, MA, 28 April–1 May 2012.

17. Solimano, A. *et al.* RSV prophylaxis with palivizumab for risk-selected babies without chronic lung disease born at 32 to 34 weeks in British Columbia: three doses are as good as five per season. Pediatric Academic Societies Annual Meeting, Boston, MA, 28 April–1 May 2012.

18. Zaaijer, H.L., Vandenbroucke-Grauls, C.M. & Franssen, E.J. Optimum dosage regimen of palivizumab? *Ther. Drug Monit.* **24**, 444–445 (2002).

19. Villar, J. *et al.* Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21(st) Project. *Lancet Glob Health* **3**, e681–e691 (2015).

20. WHO Multicentre Growth Reference Study Group. *WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development* (World Health Organization, Geneva, 2006).

21. Moore, H.C., Jacoby, P., Hogan, A.B., Blyth, C.C. & Mercer, G.N. Modelling the seasonal epidemics of respiratory syncytial virus in young children. *PLoS ONE* **9**, e100422 (2014).

22. Sommer, C., Resch, B. & Simoes, E.A. Risk factors for severe respiratory syncytial virus lower respiratory tract infection. *Open Microbiol. J.* **5**, 144–154 (2011).