through nasogastric tubes or by i.v. lines, provided that the solubility of the drug is adequate. Liquid formulations often require the use of preservatives and excipients, and some of these can be incompatible with dosing to very young infants and neonates.[85] Altogether, while formulation factors need to be seriously considered as a hurdle, they are not insurmountable provided that they are considered and addressed early in the discovery and development process.

An additional complication for dosing in infants is efficacious dose selection, which is dependent on the absorption, distribution, metabolism and excretion properties of the drug. These characteristics need to be fully understood, preferably through adult Phase 1 studies, in order to predict accurately the appropriate starting dose for trials in infants. Given that newborns and the very young tend to have immature processes for metabolizing drugs due to differences in metabolic enzyme activities, a thorough understanding of hepatic clearance mechanisms is needed. Access to infant hepatocytes can be helpful in this respect for understanding metabolic properties in infants across the 0–2 year age range. Of course, this information is only valuable in the circumstance where hepatic metabolism is a relevant clearance mechanism for the drug in question.

Given all the challenges cited above, it is not surprising that no small-molecule drug has progressed into infant efficacy trials. Indeed, the development of drugs for just young infants below 2 years of age is extremely rare (surfactant being one example). The 'high bar' afforded by infant trials therefore presents a daunting obstacle for many pharmaceutical organizations to undertake. The monoclonal antibody therapeutics solve some of these issues because they are administered intravenously, have long half-lives avoiding some of the adult-infant scaling concerns, and would be considered highly selective and relatively safe, thereby minimizing risk. Palivizumab reduced viral load in the lower respiratory tract of infants, based on results from tracheal aspirates, but did not have an impact on upper respiratory tract virus levels.[41] Motavizumab, however, has been shown to be more potent that palivizumab in the cotton rat model. When tested in infants, a non-statistically significant antiviral impact on cultures from the upper respiratory tract on day 1 post-treatment was observed.[43] In addition, the duration of hospitalization from initiation of drug treatment was shorter for the motavizumab-treated group by almost 2 days but, once again, not statistically significant. These initial studies in infants are encouraging and it is anticipated that for an effective and safe fusion inhibitor in the future, treatment-based infant studies will be a potential option given the substantial benefit potential for these patients.

2.6.4 RSV Challenge Strain (Memphis 37)

Prompted by the challenges of using the age-diverse natural RSV-infected populations for clinical trials, an RSV challenge strain, Memphis 37, has emerged in recent years.[74] Arguably, this is the most significant event in the ability to develop small-molecule antivirals and fusion inhibitors for RSV. The