# RSV INFECTION AND WHEEZE IN MODERATE-TO-LATE PRETERM INFANTS

## PREDICTION AND COST-EFFECTIVENESS


MAARTEN O. BLANKEN

# RSV infection and wheeze in moderate-to-late preterm infants

Maarten O. Blanken

RSV infection and wheeze in moderate-to-late preterm infants
PhD thesis, Utrecht University, The Netherlands

© 2019 Maarten O. Blanken, Utrecht, The Netherlands
All rights reserved. No part of this thesis may be reproduced or transmitted in any form or by any means without prior written permission of the author. The copyright of the published papers has been transferred to the respective journals.

| | |
|---|---|
| ISBN | 978-90-393-7146-6 |
| Cover | Adapted from image of sculpture “What came first”, copyright Kyle Bean |
| Lay-out | Maarten Blanken / Proefschriftmaken.nl |
| Printed by | Proefschriftmaken.nl |

Printing of this thesis was kindly supported by Chipsoft, Chiesi, het Longfonds, Divisie Kinderen, Infection and Immunity Utrecht, ir. J.P. Blanken, ing. P.B. Blanken BBA

# RSV infection and wheeze in moderate-to-late preterm infants

## prediction and cost-effectiveness

Ziektelast van RSV infectie en wheeze in laat premature kinderen
predictie en kosteneffectiviteit

(met een samenvatting in het Nederlands)

**Proefschrift**

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het collega van promoties
in het openbaar te verdedigen op 2 juli 2019
des middags te 12:45

door

**Maarten Otto Blanken**
geboren op 18 mei 1981 te Groningen

Promotoren: Prof. Dr. L.J. Bont
Prof. Dr. M.M. Rovers

The research in this thesis was financially supported by a grant from the Netherlands Organization for Health Research and Development (NWO-AGIKO grant 920-035-89, to Dr. Blanken) and by grants from AbbVie (to Prof. Dr. L.J. Bont, paid to institution).

Publication of this thesis was financially supported by a grant from the Netherlands Organization for Health Research and Development (NWO-AGIKO grant 920-035-89, to Dr. Blanken).

## Table of contents

CHAPTER 1

# Introduction and Outline

This Introduction is an adaptation of a previously published paper by Maarten Blanken published in Early Human Development, June 2013, 89, Suppl 1: S37-9, a peer-reviewed Journal.

## Introduction and outline

### Moderate-to-late prematurity

Moderate-to-late preterm infants, defined as infants born from 32 weeks and 0 days to 35 weeks and 6 days gestational age, have long been considered a "major forgotten population" but we have seen a shift in attention in the last two decades. The World Health Organization published the Global Action Report on Preterm Birth identifying prematurity as a major global health issue mainly affecting countries with the lowest Human Development Index [1,2]. Every year more than 10% of all infants (more than 15 million infants) are born prematurely. The rate of prematurity is rising, in particular, in less affluent areas of the world where prematurity rates of 20% are reported. In developed countries investigators similarly reported a rising incidence of preterm birth from 5% in 1980 to 10% in 2008, with a gradual decline in the last decade [3,4]. This has been attributed to improved technological advancements in the management of early preterm infants. However, the greater majority of the preterm population still comprise moderate-to-late preterm infants [4]. Evidence-based interventions to minimize the risk of prematurity are limited. Moderate-to-late prematurity has significant socio-economic implications for the infant, the child's parents and society. In the USA, otherwise healthy moderate-to-late preterms have a three-fold higher mortality rate than healthy term neonates [5]. Even up to early adulthood, moderate-to-late prematurity is associated with an increased risk of mortality through cardiovascular morbidity, respiratory disease and other causes [6]. Moderate-to-late preterm infants have five-fold higher hospitalisation rates than term infants, with respiratory syncytial virus (RSV) bronchiolitis being the most frequent cause of re-hospitalisation in the first year of life [7–9]. The risk of respiratory morbidity is 22% in moderate-to-late preterm infants compared to 3% in term infants [10]. It is estimated that morbidity costs following hospital discharge after birth, up to 24 months of age, are three- to six-fold higher in moderate-to-late preterms compared to term infants [11,12]. In Canada, costs associated with mortality and morbidity in moderate-to-late preterms were estimated to be $2568 in the first two years of life compared to $1285 for term infants [13].

### Respiratory morbidity

Moderate-to-late preterm infants are often born without major respiratory distress. Oxygen supplementation and minimal respiratory support is required for a few days in the minority of

infants, probably due to delayed lung fluid clearance. Nevertheless, ample evidence exists that moderate-to-late preterm infants have decreased lung function [10,15]. They have incomplete alveolarization, pulmonary airway flows are restrictive and there is even evidence of impaired full catch-up lung growth [16]. Moderate-to-late preterms have decreased lung function, that persists up to seventeen years of age, [17]. In addition, they more often suffer from recurrent wheeze, in particular caused by respiratory viruses. Boyle et al. showed a higher prevalence of asthma in moderate-to-late preterm infants [8]. The mechanisms underlying decreased lung function and prolonged respiratory morbidity in moderate-to-late preterms are incompletely understood. Normal lung development in the intrauterine period (saccular and alveolar phase) is disrupted in preterm birth, although post-natal development occurs [10]. Alveolar walls of these infants may be thicker, impairing optimal gas exchange. Colin et al. proposed that preterm birth leads to decreased parenchymal elasticity and subsequent airway tethering, which compromises airway wall compliance and alveolar expansion [10]. Finally, the chest is overly compliant in moderate-to-late preterm infants, which necessitates exaggerated muscle effort for normal breathing.

**Respiratory syncytial virus**

Prematurely born infants are highly susceptible to severe RSV infections and respiratory tract illness caused by other respiratory viruses [18–21]. These other viruses, such as influenza or rhinovirus, are less often responsible for severe disease in preterm infants in the first year of life. RSV is a negative-stranded, non-segmented RNA pneumovirus of the family Paramyxoviridae, that is highly infectious and the leading cause of bronchiolitis in infants worldwide. RSV utilizes two envelope glycoproteins, RSV G protein (RSV-G) and RSV fusion protein (RSV-F), to initiate viral entry through the apical surface of airway epithelial cells. RSV-G protein is principally responsible for the initial attachment of the virus to the cells [22]. RSV-F is a trimeric viral envelope protein that enables fusion of the virus to the cell membrane, cell-to-cell transmission, and the formation of syncytia that results in the characteristic cytopathy of RSV infection [23].

RSV-F is a conserved type I transmembrane protein containing an N-terminal cleaved signal peptide and a C-terminal membrane anchor [23] (Figure 1).

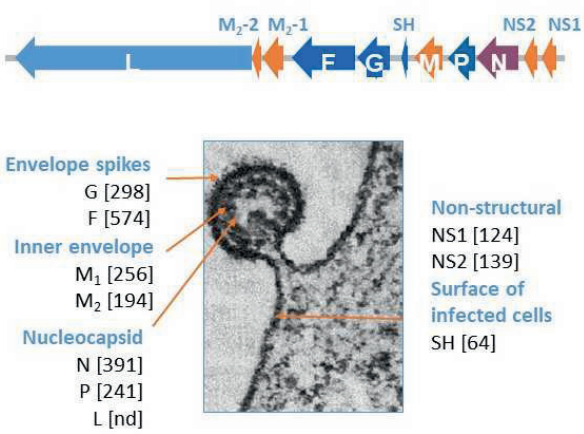



*Figure 1. Electron photomicrograph of budding virion (Peter Collins, 1989; Field's Virology 2nd edition, 1990)*

The variable sequences of the RSV-G gene define the two RSV subtypes, A and B. Administration of an antibody that binds RSV-F and blocks the ability of RSV to infect host cells is a clinically validated strategy, with Synagis® (palivizumab) representing the standard of care for prophylaxis against serious RSV infection in high-risk infants [24–28].

Virtually all infants will have had an RSV infection by the age of 2 years [29–32]. After entering the host via the nasopharyngeal and conjunctival mucosa, RSV spreads from the upper to the lower respiratory tract where it can cause acute disease characterized by edema and necrosis of respiratory mucosa leading to obstruction of the airways and reduced airflow [33] (Figure 2).

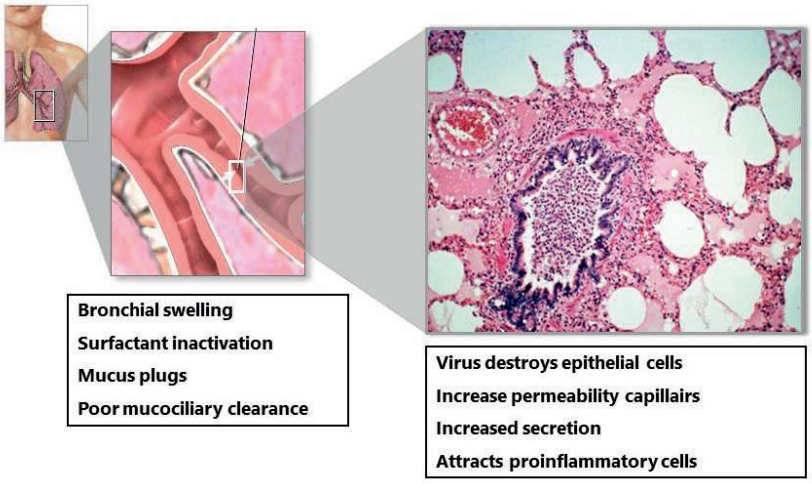



*Figure 2. RSV pathophysiology on a macroscopic and microscopic level. (http://www.adamimages.com/Bronchiolitis-Illustration/PI8096/F4)*

The incubation period is generally 4 to 6 days but ranges from 2 to 8 days [34]. RSV infection usually starts with upper respiratory illness presenting with nasal congestion, cough, and low-grade fever lasting 2 to 4 days. This may be followed by progression to the lower respiratory tract manifested by symptoms of bronchiolitis (wheezing, cyanosis and respiratory distress) [20,35]. Lower respiratory tract involvement occurs in 30% to 40% of infants with primary (first) RSV infection [20,35]. There is a substantial burden of RSV in the outpatient setting. In a study by Hall et al, symptoms were similar between infants that were hospitalised and those treated as outpatients with respect to labored respirations (95% vs. 73%), wheezing (78% vs. 65%), and fever (69% vs. 75%) [36]. RSV hospitalisation occurs in 0.5% to 3% of the annual birth cohort, with the youngest infants (<3 months) being at highest risk for RSV hospitalisation [29,37–40]. The incidence of RSV bronchiolitis requiring hospitalisation among moderate-to-late preterm infants is estimated at 3-6% [41–44]. The risk of life-threatening RSV infection appears relevant up to a post-conceptional age of 44 weeks [45], but risk of hospitalisation is significant up to the age of 1 year. A birth cohort study showed that most cases of RSV hospitalisation in moderate-to-late preterm infants are observed in the first 3–6 months of life [46]. Each year, about 28,000 infants require medical care for RSV bronchiolitis in the Netherlands, of which 1,500-2,000 require hospitalisation with costs of € 2,000-4,000 per patient [47–49].

Approximately 10 percent of these infants require mechanical ventilation in a pediatric intensive care unit. It is estimated that less than 5 infants die annually in the Netherlands from

RSV infection of which virtually 100% have severe comorbidities. The burden of RSV disease worldwide is immense. In a single year, an estimated 34 million episodes of RSV-associated lower respiratory tract infection may occur in infants younger than 5 years [50]. In developing countries, where more than 90% of all RSV infections occur, RSV is second only to malaria in causing death in infants [51]. Infants most at risk for severe disease are prematurely born infants either with or without chronic lung disease and infants with congenital heart disease. Major risk factors for a severe course of disease are high exposure to other infants, either by siblings or daycare attendance, cigarette smoke exposure, formula feeding and birth around the start of the RSV season. These risk factors have been used to design prediction models for severe RSV bronchiolitis in moderate-to-late preterm infants for disease prevention [44]. Validation of such a model for term infants is still warranted [40].

Passive immunisation with RSV neutralizing antibody is a safe and effective approach for reducing RSV related hospitalisations in infants, and has been in use for more than 15 years. Synagis (palivizumab), a humanized monoclonal antibody (moAb) against RSV-F, is the only agent currently available for prevention of RSV infections [25]. It was approved in the US in 1998 and in the EU in 1999 for the prevention of serious lower respiratory infection in infants at high risk for RSV disease. Palivizumab binds to RSV-F to block cell-to-cell and virus-to-cell fusion, inhibiting subsequent viral transcription [52]. However, palivizumab treatment is costly and requires monthly intramuscular injections. In 2016, the annual cost of the current RSV palivizumab prophylaxis program was € 12.5 million in the Netherlands [53]. These costs may be reduced by targeting RSV immunoprophylaxis to moderate-to-late preterm infants with additional risk factors [54]. The cost-effectiveness of RSV immunoprophylaxis in moderate-to-late preterm infants is however an ongoing debate. Conflicting reports have been published describing incremental cost-effectiveness ratios of RSV immunoprophylaxis varying from €20,236 to $1,228,260 per quality-adjusted life year gained [55–58]. The incremental cost-effective ratios of RSV immunoprophylaxis appear to be sensitive to variations in mortality rates from different sources. Therefore, the majority of infants at risk for RSV lower respiratory tract infection do not receive palivizumab [38]. Palivizumab is indicated for the high-risk pediatric population; however, widespread palivizumab prophylaxis is limited by high cost of therapy and inconvenient monthly dosing. The American Academy of Pediatrics (AAP) guideline recommends restricting its use to those infants in the highest risk category (premature infants <29 weeks gestational age and infants with chronic cardiopulmonary

conditions) that only comprise <5% of all infants at risk for RSV lower respiratory tract infections [59].

**Recurrent wheezing**

Viral respiratory tract infections, like RSV, have long-term consequences. In particular, during the winter season, infants with a history of RSV bronchiolitis suffer from respiratory ailments triggered by viral upper respiratory tract infections [60]. RSV bronchiolitis in term infants is often followed by recurrent episodes of wheeze. In particular in infants exhibiting signs of airflow limitation during the initial infection, the risk of recurrent wheeze is increased [61]. Recurrent wheeze after RSV bronchiolitis is associated with decreased health-related quality of life [62]. In very low birth weight infants RSV bronchiolitis has clearly been shown to be a predictor of major respiratory morbidity during later childhood [19]. It is not yet known whether the respiratory consequences are transient or persist into adulthood. Stein et al. reported that RSV lower respiratory tract illness during the first 3 years of life in a healthy birth cohort was associated with recurrent wheeze up to age 11 years [63]. At age 13, wheeze was no longer related to a history of RSV associated lower respiratory tract illness during the first 3 years of life [63]. Others have found that RSV bronchiolitis is associated with wheeze and asthma for a longer period, even up to 27 years [64,65]. The relationship between RSV bronchiolitis and recurrent wheeze has been established for term infants and very low birth weight preterm infants; this relationship is not yet well defined in moderate-to-late preterm infants [66]. Unfortunately, during RSV bronchiolitis no intervention has been proved to change the natural course of disease in term or preterm infants [67]. Prevention of the long-term effects of RSV in moderate-to-late preterm infants is not possible with inhaled steroids, although early initiated, high-dose inhaled fine particle beclomethasone, provides a transient partial reduction in post-bronchiolitis wheeze [68,69]. The mechanism underlying long-term airway morbidity following RSV bronchiolitis and recurrent wheeze is intriguing and has been described in two non-excluding hypotheses. On the one hand, moderate-to-late preterm infants are born with a susceptibility to wheeze by any respiratory viral infection (parallel hypothesis). In this hypothesis, RSV is only the first indicator of the propensity to wheeze. On the other hand, RSV infection could be the second hit required to develop recurrent wheeze (serial hypothesis). In the latter case, RSV infection may be causally related to recurrent wheeze. In the serial but not parallel hypothesis, RSV prevention would also result in

prevention of recurrent wheeze. Using RSV immunoprophylaxis with RSV-specific moAb, Simoes et al. showed that RSV prevention halted recurrent wheeze during the first years of life, in particular in non-atopic infants [70]. For a conclusive distinction between these two hypotheses, evidence from a randomised trial is needed.

**Objectives of the thesis**

The general aim of this thesis is to gain insight into the burden of RSV infection in moderate-to-late preterm infants, and to develop strategies to minimize this burden of disease.

More specific objectives are:

- To determine the effect of RSV prevention on the incidence of wheezing during the first year of life
- To determine the population attributable risks of risk factors for recurrent wheezing in the first year of life
- To determine risk factors for RSV hospitalisation in order to facilitate the development of a risk scoring tool in otherwise healthy moderate-to-late preterm infants
- To determine the cost-effectiveness of targeted RSV prevention in moderate-to-late preterm infants based on a risk scoring tool compared to no prophylaxis

**Outline of the thesis**

The studies reported in this thesis were performed within a network of hospitals, which I set-up collaboratively with my co-investigators, for the purpose of this thesis (the Dutch RSV Neonatal Network). **Chapter 2** describes the rationale and ethical considerations of our placebo controlled trial in otherwise healthy moderate-to-late preterm infants. **Chapter 3** outlines the effect of RSV prevention on the incidence of wheezing in moderate-to-late preterm infants. **Chapter 4** traces the population attributable risks (PAR) of risk factors for recurrent wheezing in the first year of life in otherwise healthy moderate-to-late preterm infants. **Chapter 5** delineates the development and validation of a risk scoring tool for the prediction of RSV hospitalisation in moderate-to-late preterm infants based on 4 risk factors. **Chapter 6** describes a large international collaborative research venture that was harmonized, to develop a prediction tool for RSV hospitalisation in moderate-to-late preterm infants in the Northern hemisphere based on 3 risk factors. **Chapter 7** outlines a systematic review of the literature on the cost-effectiveness of RSV prophylaxis in different subgroups. **Chapter 8**

details the cost-effectiveness of RSV prophylaxis targeted at high risk infants based on a risk scoring tool for RSV hospitalisation. The thesis ends with a general discussion (**chapter 9 )** and a summary of the findings.

**References**


1. Howson, C.P.; Kinney, M.V.; Lawn JE. *March of Dimes, PMNCH, Save the Children, Who. Born Too Soon: The Global Action Report on Preterm Birth*. Geneva; 2012.
2. Morisaki N, Ganchimeg T, Vogel JP, et al. Impact of stillbirths on international comparisons of preterm birth rates: a secondary analysis of the WHO multi-country survey of Maternal and Newborn Health. *BJOG*. 2017;124(9):1346-1354.
3. Baroutis G, Mousiolis A, Mesogitis S, Costalos C, Antsaklis A. Preterm birth trends in Greece, 1980-2008: a rising concern. *Acta Obstet Gynecol Scand*. 2013;92(5):575-582.
4. Purisch SE, Gyamfi-Bannerman C. Epidemiology of preterm birth. *Semin Perinatol*. 2017;41(7):387-391.
5. Reddy UM, Ko C-W, Raju TNK, Willinger M. Delivery indications at late-preterm gestations and infant mortality rates in the United States. *Pediatrics*. 2009;124(1):234-240.
6. Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational Age at Birth and Mortality in Young Adulthood. *JAMA*. 2011;306(11):1233.
7. McLaurin KK, Chatterjee A, Makari D. Modeling the Potential Impact of the 2014 American Academy of Pediatrics Respiratory Syncytial Virus Prophylaxis Guidance on Preterm Infant RSV Outcomes. *Infect Dis Ther*. 2015;4(4):503-511.
8. Boyle EM, Poulsen G, Field DJ, et al. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study. *BMJ*. 2012;344(mar01 2):e896-e896.
9. Isayama T, Lewis-Mikhael A-M, O'Reilly D, Beyene J, McDonald SD. Health Services Use by Late Preterm and Term Infants From Infancy to Adulthood: A Meta-analysis. *Pediatrics*. 2017;140(1):e20170266.
10. Colin AA, McEvoy C, Castile RG. Respiratory Morbidity and Lung Function in Preterm Infants of 32 to 36 Weeks' Gestational Age. *Pediatrics*. 2010;126(1):115-128.
11. McLaurin KK, Hall CB, Jackson EA, Owens O V, Mahadevia PJ. Persistence of morbidity and cost differences between late-preterm and term infants during the first year of life. *Pediatrics*. 2009;123(2):653-659.
12. Khan K, Petrou S, Dritsaki M, et al. Economic costs associated with moderate and late preterm birth: a prospective population-based study. *BJOG An Int J Obstet Gynaecol*. 2015;122(11):1495-1505.

13. Bérard A, Le Tiec M, De Vera MA. Study of the costs and morbidities of late-preterm birth. *Arch Dis Child - Fetal Neonatal Ed*. 2012;97(5):F329-F334.
14. Stephens AS, Lain SJ, Roberts CL, Bowen JR, Nassar N. Survival, Hospitalization, and Acute-Care Costs of Very and Moderate Preterm Infants in the First 6 Years of Life: A Population-Based Study. *J Pediatr*. 2016;169:61-68.e3.
15. McEvoy C, Venigalla S, Schilling D, Clay N, Spitale P, Nguyen T. Respiratory function in healthy late preterm infants delivered at 33-36 weeks of gestation. *J Pediatr*. 2013;162(3):464-469.
16. Friedrich L, Pitrez PMC, Stein RT, Goldani M, Tepper R, Jones MH. Growth Rate of Lung Function in Healthy Preterm Infants. *Am J Respir Crit Care Med*. 2007;176(12):1269-1273.
17. Kotecha SJ, Dunstan FD, Kotecha S. Long term respiratory outcomes of late preterm-born infants. *Semin Fetal Neonatal Med*. 2012;17(2):77-81.
18. Carbonell-Estrany X, Bont L, Doering G, Gouyon J-B, Lanari M. Clinical relevance of prevention of respiratory syncytial virus lower respiratory tract infection in preterm infants born between 33 and 35 weeks gestational age. *Eur J Clin Microbiol Infect Dis*. 2008;27(10):891-899.
19. Drysdale SB, Wilson T, Alcazar M, et al. Lung function prior to viral lower respiratory tract infections in prematurely born infants. *Thorax*. 2011;66(6):468-473.
20. Smyth RL, Openshaw PJ. Bronchiolitis. *Lancet*. 2006;368(9532):312-322.
21. Ricart S, Marcos MA, Sarda M, et al. Clinical risk factors are more relevant than respiratory viruses in predicting bronchiolitis severity. *Pediatr Pulmonol*. 2013;48(5):456-463.
22. Choppin PW, Scheid A. The role of viral glycoproteins in adsorption, penetration, and pathogenicity of viruses. *Rev Infect Dis*. 2(1):40-61.
23. Collins PL, Huang YT, Wertz GW. Nucleotide sequence of the gene encoding the fusion (F) glycoprotein of human respiratory syncytial virus. *Proc Natl Acad Sci U S A*. 1984;81(24):7683-7687.
24. Johnson S, Oliver C, Prince GA, 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*. 1997;176(5):1215-1224.

25. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. *Pediatrics*. 1998;102(3 Pt 1):531-537.
26. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr*. 2003;143(4):532-540.
27. Pedraz C, Carbonell-Estrany X, Figueras-Aloy J, Quero J, IRIS Study Group. Effect of palivizumab prophylaxis in decreasing respiratory syncytial virus hospitalizations in premature infants. *Pediatr Infect Dis J*. 2003;22(9):823-827.
28. Wu H, Pfarr DS, Johnson S, et al. Development of motavizumab, an ultra-potent antibody for the prevention of respiratory syncytial virus infection in the upper and lower respiratory tract. *J Mol Biol*. 2007;368(3):652-665.
29. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child*. 1986;140(6):543-546.
30. Dougherty NN, Meissner HC. Respiratory Syncytial Virus Immunoprophylaxis. *Pediatr Drugs*. 2000;2(2):127-132.
31. Hall CB. Respiratory Syncytial Virus and Parainfluenza Virus. *N Engl J Med*. 2001;344(25):1917-1928.
32. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA*. 1999;282(15):1440-1446.
33. Bruhn FW, Yeager AS. Respiratory syncytial virus in early infancy. Circulating antibody and the severity of infection. *Am J Dis Child*. 1977;131(2):145-148.
34. Wright M, Piedimonte G. Respiratory syncytial virus prevention and therapy: Past, present, and future. *Pediatr Pulmonol*. 2011;46(4):324-347.
35. Hall CB. Respiratory Syncytial Virus. In: *Mandell, Douglas, and Bennet's Principles and Practice of Infectious Disease*. Philadelphia, PA: Elsevier Health Sciences; 1999.
36. Hall CB, Weinberg GA, Iwane MK, et al. The Burden of Respiratory Syncytial Virus Infection in Young Children. *N Engl J Med*. 2009;360(6):588-598.
37. Hall CB, Geiman JM, Biggar R, Kotok DI, Hogan PM, Douglas RG. Respiratory Syncytial Virus Infections within Families. *N Engl J Med*. 1976;294(8):414-419.

38. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory Syncytial Virus-Associated Hospitalizations Among Children Less Than 24 Months of Age. *Pediatrics*. 2013;132(2):e341-e348.
39. Henderson FW, Collier AM, Clyde WA, Denny FW. Respiratory-syncytial-virus infections, reinfections and immunity. A prospective, longitudinal study in young children. *N Engl J Med*. 1979;300(10):530-534..
40. Houben ML, Bont L, Wilbrink B, et al. Clinical prediction rule for RSV bronchiolitis in healthy newborns: prognostic birth cohort study. *Pediatrics*. 2011;127(1):35-41. doi:10.1542/peds.2010-0581.
41. Boyce TG, Mellen BG, Mitchel EF, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. *J Pediatr*. 2000;137(6):865-870.
42. Law BJ, Langley JM, Allen U, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. *Pediatr Infect Dis J*. 2004;23(9):806-814.
43. Stensballe LG, Fullarton JR, Carbonell-Estrany X, Simões EAF. Population based external validation of a European predictive model for respiratory syncytial virus hospitalization of premature infants born 33 to 35 weeks of gestational age. *Pediatr Infect Dis J*. 2010;29(4):374-376.
44. Simões EA, Carbonell-Estrany X, Fullarton JR, et al. A predictive model for respiratory syncytial virus (RSV) hospitalisation of premature infants born at 33–35 weeks of gestational age, based on data from the Spanish FLIP study. *Respir Res*. 2008;9(1):78.
45. Bont L, van Vught AJ, Kimpen JL. Prophylaxis against respiratory syncytial virus in premature infants. *Lancet (London, England)*. 1999;354(9183):1003-1004.
46. Bont L, Houben ML. Commentary: why are young healthy term infants protected against respiratory syncytial virus bronchiolitis? *Pediatr Infect Dis J*. 2011;30(9):785-786.
47. Bos JM, Rietveld E, Moll HA, et al. The use of health economics to guide drug development decisions: Determining optimal values for an RSV-vaccine in a model-based scenario-analytic approach. *Vaccine*. 2007;25(39-40):6922-6929.

48. Rietveld E, De Jonge HCC, Polder JJ, et al. Anticipated costs of hospitalization for respiratory syncytial virus infection in young children at risk. *Pediatr Infect Dis J*. 2004;23(6):523-529.
49. Jansen AGSC, Sanders EAM, Hoes AW, van Loon AM, Hak E. Influenza- and respiratory syncytial virus-associated mortality and hospitalisations. *Eur Respir J*. 2007;30(6):1158-1166.
50. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet*. 2010;375(9725):1545-1555.
51. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet (London, England)*. 2012;380(9859):2095-2128.
52. Huang K, Incognito L, Cheng X, Ulbrandt ND, Wu H. Respiratory syncytial virus-neutralizing monoclonal antibodies motavizumab and palivizumab inhibit fusion. *J Virol*. 2010;84(16):8132-8140.
53. Zorginstituut Nederland / GIPdatabank. https://www.gipdatabank.nl/. Accessed January 28, 2019.
54. Wang D, Bayliss S, Meads C. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses. *Health Technol Assess*. 2011;15(5):iii-iv, 1-124.
55. ElHassan NO, Sorbero MES, Hall CB, Stevens TP, Dick AW. Cost-effectiveness Analysis of Palivizumab in Premature Infants Without Chronic Lung Disease. *Arch Pediatr Adolesc Med*. 2006;160(10):1070..
56. Joffe S, Ray GT, Escobar GJ, Black SB, Lieu TA. Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants. *Pediatrics*. 1999;104(3 Pt 1):419-427.
57. Lanctôt KL, Masoud ST, Paes BA, et al. The cost-effectiveness of palivizumab for respiratory syncytial virus prophylaxis in premature infants with a gestational age of 32–35 weeks: a Canadian-based analysis. *Curr Med Res Opin*. 2008;24(11):3223-3237.
58. Nuijten M, Lebmeier M, Wittenberg W. Cost effectiveness of palivizumab for RSV prevention in high-risk children in the Netherlands. *J Med Econ*. 2009;12(4):291-300.

59. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. *Pediatrics*. 2014;134(2):e620-e638.
60. Bont L, Steijn M, Van Aalderen WMC, et al. Seasonality of long term wheezing following respiratory syncytial virus lower respiratory tract infection. *Thorax*. 2004;59(6):512-516.
61. Bont L, Van Aalderen WM, Versteegh J, et al. Airflow limitation during respiratory syncytial virus lower respiratory tract infection predicts recurrent wheezing. *Pediatr Infect Dis J*. 2001;20(3):277-282.
62. Bont L, Steijn M, van Aalderen WMC, Kimpen JLL. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. *Pediatr Infect Dis J*. 2004;23(5):414-417.
63. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354(9178):541-545.
64. Ruotsalainen M, Piippo-Savolainen E, Hyvärinen MK, Korppi M. Adulthood asthma after wheezing in infancy: a questionnaire study at 27 years of age. *Allergy*. 2010;65(4):503-509.
65. Sigurs N, Aljassim F, Kjellman B, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax*. 2010;65(12):1045-1052.
66. Palmer L, Hall CB, Katkin JP, et al. Respiratory outcomes, utilization and costs 12 months following a respiratory syncytial virus diagnosis among commercially insured late-preterm infants. *Curr Med Res Opin*. 2011;27(2):403-412.
67. Lenney W, Boner AL, Bont L, et al. Medicines used in respiratory diseases only seen in children. *Eur Respir J*. 2009;34(3):531-551. doi:10.1183/09031936.00166508.
68. Ermers MJJ, Rovers MM, van Woensel JB, Kimpen JLL, Bont LJ, RSV Corticosteroid Study Group. The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: randomised double blind placebo controlled trial. *BMJ*. 2009;338(mar31 2):b897.

69. Blom DJ, Ermers M, Bont L, van Woensel JB, Van Aalderen WM. Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing. In: Blom DJ, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2007:CD004881.

70. Simões EAF, Carbonell-Estrany X, Rieger CHL, et al. The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. *J Allergy Clin Immunol*. 2010;126(2):256-262.

CHAPTER 2

# Ethical considerations and rationale of the MAKI trial: a multicenter double-blind randomized placebo-controlled trial into the preventive effect of palivizumab on recurrent wheezing associated with respiratory syncytial virus infection in children with a gestational age of 33-35 weeks

Maarten O. Blanken, Maroeska. M. Rovers, Elisabeth A.M. Sanders, Louis Bont

*Contemp Clin Trials. 2012 Nov;33(6):1287-92.*

**Abstract**

*Background*

Respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) is the most frequent cause of bronchiolitis during infancy. Long-term airway morbidity with recurrent post bronchiolitis wheezing (PBW) episodes, which are probably associated with respiratory infections, occurs in 30 to 70% of infants that were hospitalised with RSV LRTI.

*Methods*

We set up a multicenter, placebo-controlled double-blind randomized clinical trial in healthy preterm infants born between 33-35 weeks gestational age (WGA). The children received either one-monthly intramuscular palivizumab or placebo injection during the RSV season with a minimum of 2 injections.

*Results*

The primary objective was to determine the preventive effect of RSV immunoprophylaxis (palivizumab) on the development of recurrent wheezing during the first year of life. The primary outcome measure was the number of wheezing days during the first year of life as obtained by daily logs. As a secondary outcome nasal swabs were taken for viral analysis in case of respiratory symptoms. We will also examine wheezing at age 1, 3 and 6 years both reported by the parents and the general practitioner and quality of life as secondary outcomes. This trial is possible because RSV immunoprophylaxis, although effective in this population, is not completely used in the Netherlands due to its high costs.

*Conclusion*

The Institutional review board (IRB) concluded the study has high clinical relevance because the benefit of 50% chance of protection by palivizumab outweighs the risk of side adverse events due to intramuscular administration of placebo. (*Trial Registration*: Current Controlled Trials ISRCTN73641710)

**Introduction**

Respiratory syncytial virus (RSV) is a major cause of common colds in young children and most children are infected with RSV during the first year of life. RSV lower respiratory tract infection (LRTI) is the most frequent cause of bronchiolitis during infancy. During the winter season RSV bronchiolitis is the most common reason for hospitalisation of infants under the age of 12 months. The disease typically begins with signs of common cold, followed after a few days by coughing, dyspnea and an expiratory wheeze. A large population-based study showed that among hospitalised children under the age of 12 months and outpatients in emergency departments and primary care settings, 22-24% required medical attention for RSV bronchiolitis [1]. Hospitalisation in Europe and the United States is estimated to be 1-3% [2] of infants aged less than 13 months. Of these hospitalised children, about 10% of infants required mechanical ventilation at a Paediatric Intensive Care Unit [3-5]. After the acute illness, approximately 50% of children with RSV bronchiolitis will develop recurrent episodes of wheeze up to school age, associated with reduced health-related quality of life over a broad range of domains, including lung, gastrointestinal tract and sleeping domain [6;7]. Although the burden of disease is considerable, RSV-associated mortality in healthy term infants is probably low, published estimates vary between 0 and 8% [8-11]. Well known populations at high risk for RSV bronchiolitis are premature infants with or without chronic lung disease, infants with Down syndrome as well as infants with congenital heart disease and immunodeficiencies [12-15]. The only available intervention to prevent RSV bronchiolitis is passive immunization with monoclonal antibodies against the F-protein of RSV (16;17). The efficacy of palivizumab depends on the risk groups and varies from 39 to 80% in chronic lung disease and late preterms, respectively [16;18].

Long-term airway morbidity occurs in 30-70% of hospitalised infants with RSV LRTI, which is referred to as post-bronchiolitis wheeze (PBW). Evidence exists that milder forms of RSV LRTI, not requiring hospital admission, are also associated with PBW. The clinical picture of PBW is recurrent episodes of wheezing, generally associated with viral upper respiratory tract infection (URTI)(6). We found up to 10 episodes of wheezing during the first year after RSV LRTI hospitalisation [19;20]. A non-randomized trial suggested that RSV prophylaxis in preterm children 33-35 weeks gestational age (WGA) prevented 50 percent of recurrent wheezing [21].

This study showed lower long-term airway morbidity in children who received palivizumab immunoprophylaxis compared to a control group.

Two non-exclusive alternative mechanisms play a role in the pathogenesis of recurrent wheeze following RSV LRTI. First, pre-existent pulmonary, genetic and immunological mechanisms underlie the development of both RSV LRTI and PBW. For example, there is evidence that congenital decreased lung function precedes RSV LRTI [22]. Second, RSV causes direct damage to the lower airways, which is the incepting moment of lung function abnormalities and bronchial hyperresponsiveness. As an example, a causal relationship between RSV LRTI and PBW is supported by the non-randomized study by Simoes [21], but selection bias cannot be precluded. Consequently, this hypothesis of the pathogenesis of recurrent wheeze following RSV LRTI needs to be confirmed by a randomized placebo-controlled trial.

**Methods**

*Trial Design*

A multicenter, double-blind randomized placebo-controlled trial of palivizumab versus placebo.

*Aim*

The aim of this prospective randomized controlled trial was to provide insight into the preventive effect of palivizumab on recurrent wheezing during the first year of life. In this article we will describe the protocol of this trial.

*Investigator driven*

This trial was initiated by the principal investigator and both design and interpretation of results are performed independently by the researchers. The funding of this trial was provided by Abbott International.

*Regulation*

The study was conducted according to the principles of the Declaration of Helsinki (version 2000) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). The study was approved by the Institutional review board (IRB) of the University Medical Center Utrecht.

*Setting*

One tertiary and 15 secondary hospitals in the Netherlands.

**Population**

*Inclusion Criteria*

Healthy preterm infants with gestational age 33-35 weeks who were ≤ 6 months at the start of the RSV season were included at birth. Children born between April 1$^{st}$ and December 31$^{st}$ in 2008-2011 were included. The gestational age was further defined as children born from 32 weeks and 1 day to 35 weeks and 6 days. Inclusion took place at Pediatric Departments from secondary and tertiary hospitals in the Netherlands. Parents (or hereafter referred to and including legal guardians) were to have mastered the Dutch language.

*Exclusion Criteria*

Children with a known cardiac anomaly, Down syndrome(15), or other serious congenital disorders were excluded from the study. Also, children with physician-diagnosed wheeze before the start of the RSV season, defined as October 1st of the year of birth were excluded. Inclusion and exclusion criteria were reviewed and confirmed by a pediatrician.

*Approach*

Births of possible subjects were registered by the study pediatricians of secondary and tertiary hospitals. They informed the parents of the study. Parents received printed information and were thereafter contacted by a researcher (MB). Parents were asked if they were willing to participate. If they decided to participate, they were asked to return informed consent. The parents of children born before the start of the RSV season were contacted before the first appointment to re-check the inclusion and exclusion criteria, with special attention for physician-diagnosed wheezing before the start of the RSV season.

*Randomisation and Blinding*

Randomization was performed by an independent researcher. A randomization list was generated by an independent pharmacist before the start of the trial. Patients were coded by the investigator (MB) upon inclusion with a trial number and the intervention associated with this trial number was obtained from the randomization list by the research nurses who administered the treatment. The research nurses were therefore not blinded for the treatment (see Study Medication). The research investigators who performed the analyses and the parents were blinded to the interventions until all patients had reached the age of 1 year. This trial was judged by the IRB to be double-blind and not triple-blind since the research nurses were not blinded to the treatment.

*Treatment Regimen and Dosage*

Infants received intramuscular palivizumab 15 mg/kg or placebo during the RSV season from October 1st or from discharge until March. A minimum of 2 and a maximum of 5 injections were administered. As placebo a physiological saline solution (sodium chloride 0,9% solution) for intramuscular injection was used. The reconstituted palivizumab solution was indiscernible from the placebo saline solution.

*Study Medication*

Palivizumab is not an experimental drug. The efficacy of this drug in preventing severe disease caused by RSV LRTI is thoroughly described in previous studies(16;18). Palivizumab (MEDI-493, Synagis) is a humanised monoclonal IgG1κ antibody developed from a murine monoclonal antibody (Mab) - originally discovered by the NIH - directed against the antigenic site A on the fusion or F protein of RSV. It is produced as a lyophilised powder intended to be reconstituted with sterile water for injections to 100 mg/ml prior to intramuscular (IM) administration. An identical placebo, i.e. a powder for reconstitution, was not available. Therefore, a physiological saline solution as a placebo indiscernible from the reconstituted palivizumab solution, was used. After reconstitution palivizumab had to be administered within 3 hours. Therefore the treatment preparation was performed close before the home visit. It was not feasible to blind the research nurses for the preparation and administer the treatment at the patient's home within this accepted preservation time. The research nurses were, as a result, not blinded to the treatment. The research nurses were, according to IRB instructions, trained to tell parents that they didn't know to which intervention their child was randomized when asked. The research nurses only administer study medication and were not involved in reporting of end points and data analyses.

In the Netherlands, palivizumab is currently indicated for the prevention of serious lower respiratory tract disease requiring hospitalisation caused by RSV in children at high risk for RSV disease. Children considered at high risk are:

- Children born at 35 weeks of gestation or less and less than 6 months of age at the onset of the RSV season
- Children less than 2 years of age and requiring treatment for bronchopulmonary dysplasia (BPD) within the last 6 months.
- Children less than 2 years of age and with haemodynamically significant congenital heart disease (CHD).

*Endpoints*

The primary objective was to determine the preventive effect of palivizumab on the development of recurrent wheezing during the first year of life. Because the efficacy of palivizumab is explicitly described in previous studies the preventive effect of palivizumab on RSV LRTI was not an endpoint of this study [16;18]. The primary endpoint of the study was the

number of wheezing days during the first year of life. Data on baseline characteristics were collected from hospital charts and a standardized parental questionnaire, adapted from the KEA questionnaire [23]. Parents recorded airway symptoms, doctor's visits and the use of airway drugs in a daily log, as we have used previously [3;24;25]. The logs were kept from the start of intervention till the age of 1 year. They were returned to the investigators every three months. Parents were instructed on how to complete the logs by a single investigator. The primary intervention endpoint will be reached when the children reaches the age of 1 year. Secondary endpoints included: physician diagnoses of respiratory morbidity, questionnaires reporting wheezing at age 1, 3 and 6 years during the previous year by parents, send by mail, and an assessment of health-related quality of life and socio-economic consequences of RSV. Data on physician diagnoses of respiratory morbidity was collected by a survey send to the physician by mail, listing diagnosis of interest with corresponding ICD-9 codes. Health-related quality of life was measured with quarterly questionnaires developed by the Institute of Prevention and Health and the Leiden University Hospital (TNO-AZL) called the TNO-AZL Preschool children Quality of Life (TAPQOL) questionnaires [26]. Socio-economic consequences, including questions on labor participation, basic salary and work strain, were administered by the research nurses during the first home visit using a standard questionnaire developed by our research group (figure 1).

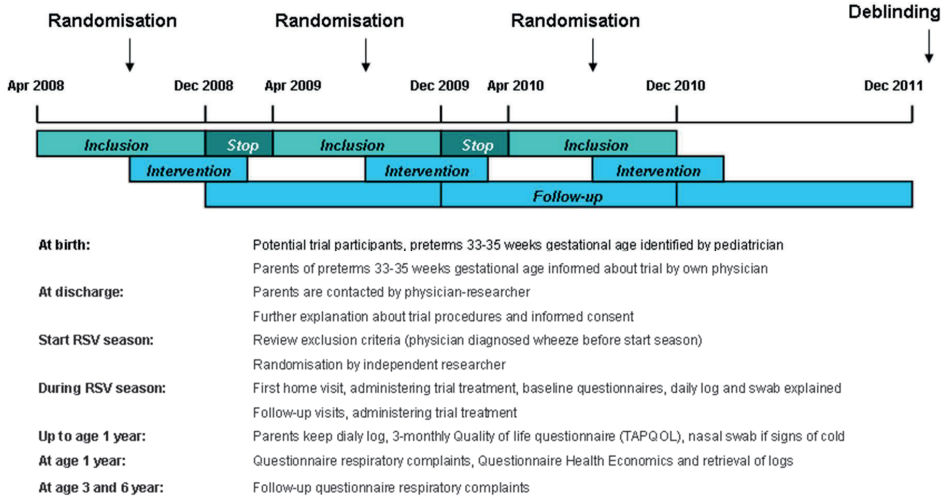



*Figure 1. Trial procedures over time.*

*Viral Sampling*

To determine whether RSV was the causal agent in the case of respiratory complaints a nasal swab was tested for respiratory viruses. Parents were instructed to take a nasopharyngeal swab in the case of respiratory complaints with duration of more than one day. The swab was placed in viral transport medium (VTM) and transported at ambient temperature by regular mail to the laboratory. The swab in VTM was vortexed and stored at -80°C until analysis. Before extraction of total nucleic acid from 200 µL of the supernatant they were spiked with 20 µL equine arteritis viruses (EAV) as extraction and inhibition internal control. Fifty µL total nucleic acid was extracted from the 200 µL aliquots using the MagNaPure® LC Total Nucleic Acid Isolation Kit (Roche), according to the Total NA External Lysis protocol (Roche). The transcription into cDNA and simultaneous detection and type-identification of RSV types A and B was done by Real Time reverse transcription (RT)-PCR, using the Taqman EZ-RT Core Reagents kit with specific primers and probes in a LightCycler 480 instrument (RSVA: 2050F TGA ACA ACC CAA AAG CAT CA, 2117R CCT AGG CCA GCA GCA TTG, 2086P AAT TTC CTC ACT TCT CCA GTG TAG TAT TAG G, Fam BHQ1; RSVB: 17 GAT GGC TCT TAG CAA AGT CAA GTT AA, 120 TGT CAA TAT TAT CTC CTG TAC TAC GTT GAA, PB45 TGA TAC ATT AAA TAA GGA TCA GCT GCT GTC ATC CA, YY-BHQ1; EAV: 2043F CTG TCG CTT GTG CTC AAT TTA C, 2193R AGC GTC CGA AGC ATC TC, 2102P-2 TGC AGC TTA TGT TCC TTG CAC TGT GTT C, TXR red -BHQ2). For internal quality control, real time RT-PCR reactions were also performed for detection of EAV. The real time RT-PCR assays were performed using 5 µL RNA and 20 uL reagent mix composed of Taqman EZ-RT Core Reagents according to manufacturer's protocol (Applied Biosystems). cDNA transcription was done at 55°C for 30 minutes. Amplifications were done with 45 cycles of denaturation at 94°C for 20 seconds and annealing-extension at 55°C for one minute. For RSV positive specimens, an additional analysis for co-infections was performed using the RespiFinder® SMART 22 Kit, a multiplex PCR test to detect and differentiate 17 RNA viruses, 1 DNA virus as well as 4 bacteria which can cause respiratory tract infections (www.pathofinder.com/products/respifindersmart22). According to manufacturer's protocol (PathoFinder BV), 10 µL of extracted total nucleic acid was used. Pre-amplification and probe hybridization and ligation were performed in a px2 Thermal Cycler (Thermo electron corporation) and PCR was performed in a LightCycler 480 instrument (Roche). The detection of pathogens was performed using a Melt Curve analysis, enabled by the combination of different labels and specific melting temperatures in three different detection channels for

the acquisition of the different fluorescent signals. It should be noted that prevention of severe disease caused by RSV infection was not an endpoint of this study because this effect was already established and the study was not powered to show this effect.

*Safety*

All adverse events reported spontaneously by the subject or observed by the investigator were recorded.

Palivizumab is generally safe and well tolerated when used as indicated. Local erythema has been reported at the site of injection and this was transient and generally mild in severity. Adverse events were monitored in all patients.

*Monitoring*

This study was yearly monitored according to current Good Clinical Practice (GCP) monitoring guidelines.

**Statistical methods**

*Sample size calculation*

The power calculation was based on a clinically relevant difference of 5 post bronchiolitis wheezing days (SD=15) during the first year of life [19;20;27]. Using an alpha of 0.05 and a power of 90% the number needed per treatment arm was 226, i.e. 452 in total.

*Statistical analysis*

All statistical analyses will be performed with the Statistical Package for Social Sciences (SPSS), version 20.0. Median number of wheezing days will be compared between the palivizumab and the placebo group. Since we expect that wheezing days will follow a Poisson distribution, we will use Poisson regression analysis to study the difference in wheezing days between both treatment arms [27]. With the results of viral sampling we will determine the effect of palivizumab on RSV positive wheezing episodes using Pearson's Chi-square test. Respiratory symptoms and physician diagnoses in the study population will be described. Continuous date will be presented as medians (interquartile range, IQR) if normality cannot be proven. Categorical data will be presented as fractions and percentages. Differences between the groups will be analysed using student t-test or Mann-Whitney U test for continuous variables and Pearson's Chi-square test for categorical variables. For Quality of Life, mean values

between the groups will be analysed using a student t-test. All analysis will be performed on an intention-to-treat basis. Furthermore, incremental cost-effectiveness ratio's (iCERs) will be calculated by dividing the estimated differences in costs by the differences in effects observed, i.e. costs per wheezing day avoided will be calculated. For these economic analyses only a short time horizon will be used and therefore no time preference or discount rate will be taken into account. Uncertainty will be addressed by means of bootstrapping. Considering the safe profile of the intervention no interim analyses were planned.

**Discussion**

*Trial description as a PICO*

*Patients*

Preterm infants with gestational age 33-35 weeks.

*Intervention*

Intramuscular palivizumab injections 15 mg/kg during the RSV season from October 1st or from discharge until March.

*Comparison*

Intramuscular placebo injections

*Outcome*

Number of wheezing days during the first year of life

**Significance of the Trial**

*Convincing arguments that there is no knowledge available to explain the problem*

There is evidence which relates RSV LRTI to PBW but this evidence needs to be confirmed by methodologically sound studies. With this trial we can study the preventive effect of RSV-immunoprophylaxis in a high-risk group on subsequent long-term respiratory tract morbidity.

*Which new information will this study provide*

This study will provide further insight into influences of palivizumab immunoprophylaxis on early RSV LRTI and the subsequent development of PBW and other long term respiratory tract morbidity in a high risk population. These respiratory morbidities are highly relevant as they 1) concern 30-70% of children with RSV LRTI 2) are associated with several general practitioner visits, 3) and are associated with decreased health-related quality of life over a broad range of domains, including lung, gastrointestinal tract and sleeping domain.

*Why this selected population*

A group of healthy preterm infants with gestational age 33-35 weeks was included. This group of infants has a higher risk of developing RSV LRTI and potentially a higher risk of subsequent development of long-term respiratory tract morbidity. Although RSV immunoprophylaxis has shown to be effective in preventing severe LRTI caused by RSV in preterm children born at 33-35 WGA in earlier studies, it is not completely reimbursed in the Netherlands. Instead, RSV immunoprophylaxis is only reimbursed and fully covered for preterm children born before 32

WGA and a selection of children with either BPD or CHD. Therefore this was a unique opportunity to study the preventive effect of palivizumab on post-bronchiolitis wheezing after respiratory syncytial virus infection in children with a gestational age of 33-35 weeks. A potential limitation of the study is that the primary objective is relying on parent-reported morbidity data as no objective measure to report wheezing is available. Given the potential benefit for participating children, parents with a positive family history for asthmatic complaints can create self-selection bias.

*Ethical issues*

As mentioned, RSV immunoprophylaxis has shown to be effective in preventing RSV LRTI in preterm children born at 33-35 WGA in earlier studies. Nevertheless, the Central Committee on Research involving Human Subjects (CCMO) has marked our study as a therapeutic study. In general medical trials in the Netherlands are covered by the Medical Research Involving Human Subjects Act (WMO). The WMO operates on the 'no, unless' principle with regard to studies on minors aged under 18: scientific research on such individuals is, in principle, prohibited. The only exception to this prohibition is research that could benefit the research subjects themselves (therapeutic) or where this is the only group on which the research can be conducted (group-based). Trials concerning subjects not capable of giving informed consent must either be reviewed by the CCMO or by the IRB. Only when there is a direct clinical advantage as a result of participation in the study and the study is therefore considered “therapeutic” can the study be reviewed by the IRB. Risks and burden for subjects participating in this trial were considered minimal. The favourable safety profile of palivizumab is well established. The intramuscular injections were administered by experienced professionals. A clear benefit of participating in the study was the prevention of severe RSV bronchiolitis for those children who received palivizumab. A possible additional benefit was the prevention of long-term airway morbidity for those children who received palivizumab. Therefore, the CCMO has marked the proposed study a therapeutic study because the effect of palivizumab on RSV LRTI has already proven beneficial and because the study focuses on therapeutic effects of palivizumab on PBW. The IRB has judged that the 50% chance of benefit of palivizumab outweighs the risk of moderate placebo-associated side effects due to the intramuscular administration and burden to participate in this trial. A placebo controlled control group was necessary because the primary objective will depend on parent-reported

daily scores of wheezing along with information from parent-reported questionnaires. This creates a possible limitation, because no other research group externally validated the logs kept by the parents. There is no alternative for reporting infant wheezing, since objective outcome measures are not available and physician reported wheezing is known to be biased [27]. The use of placebo was in the view of the IRB justified by the potential moderate harm of the intramuscular injection. The IRB concluded that the clinical relevance of the research question and the 50% chance of protection by palivizumab justified this risk.

*Funding*

This investigator driven study was funded by Abbott International. The investigators maintained control over any abstracts and presentations arising from the data and the rights to publish.

*Acknowledgements*

We thank the research nurses P. Winkler, L. Nibbelke and M. Polman and students for their help with this project. In addition to the authors, the following paediatricians participate in the MAKI trial: J. Schipper, St Antonius Hospital, Nieuwegein; C. Meijssen, Meander Medical Centre, Amersfoort; J. de Bie, Hofpoort Hospital, Woerden; W. de Waal, Diakonessenhuis, Utrecht; G. van Enk, Gelderse Vallei Hospital, Ede; M.Verboon-Maciolek, University Medical Center, Utrecht; D. van der Zwet-Fandri, Mesos Medical Center, Utrecht / St Antionius Hospital, Nieuwegein; R. Bruinsma, Gelre Hospital, Apeldoorn; R. Lubbers, Beatrix Hospital, Gorinchem; C. Crijns-Koers, Tergooi Hospitals, Blaricum; A. Zlotkowski, Hospital Rivierenland, Tiel; M. Bontemps, St Jansdal Hospital, Harderwijk; C. Dassel, Deventer Hospital, Deventer; R. van Gent, Maxima Medical Center, Veldhoven; C. Miedema, Catharina Hospital, Eindhoven; E. Smit-Kleinlugtenbeld, Albert Schweitzer Hospital, Dordrecht; C. Aleman, Ikazia Hospital, Rotterdam.

**References**


1. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009 Feb 5;360(6):588-98.
2. Smyth RL, Openshaw PJ. Bronchiolitis. Lancet 2006 Jul 22;368(9532):312-22.
3. Ermers MJ, Rovers MM, van Woensel JB, Kimpen JL, Bont LJ. The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: randomised double blind placebo controlled trial. BMJ 2009;338:b897.
4. Bont L, Kimpen JL. Immunological mechanisms of severe respiratory syncytial virus bronchiolitis. Intensive Care Med 2002 May;28(5):616-21.
5. Tissing WJE, Van Steensel-Moll HA, Offringa M. Risk factors for mechanical ventilation in respiratory syncytial virus infection. Eur J Pediatr 1993;152:125-7.
6. Bont L, Aalderen vWMC, Kimpen JLL. Long-term consequences of respiratory syncytial virus (RSV) bronchiolitis. Paediatr Respir Rev 2000;1(3):221-7.
7. Bont L, Steijn M, van Aalderen WM, Kimpen JL. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. PIDJ 2004 May;23(5):414-7.
8. Simon A, Ammann RA, Wilkesmann A, Eis-Hubinger AM, Schildgen O, Weimann E, et al. Respiratory syncytial virus infection in 406 hospitalized premature infants: results from a prospective German multicentre database. Eur J Pediatr 2007 Dec;166(12):1273-83.
9. Sampalis JS. Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants. J Pediatr 2003 Nov;143(5 Suppl):S150-S156.
10. Prais D, Schonfeld T, Amir J. Admission to the intensive care unit for respiratory syncytial virus bronchiolitis: a national survey before palivizumab use. Pediatrics 2003 Sep;112(3 Pt 1):548-52.
11. Stensballe LG, Devasundaram JK, Simoes EA. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. PIDJ 2003 Feb;22(2 Suppl):S21-S32.
12. Boyce TG, Mellen BG, Mitchel EF, Jr., Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr 2000 Dec;137(6):865-70.

13. Weisman LE. Populations at risk for developing respiratory syncytial virus and risk factors for respiratory syncytial virus severity: infants with predisposing conditions. PIDJ 2003 Feb;22(2 Suppl):S33-S37.
14. Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. J Pediatr 2003 Nov;143(5 Suppl):S112-S117.
15. Bloemers BL, van Furth AM, Weijerman ME, Gemke RJ, Broers CJ, van den EK, et al. Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis--a prospective birth-cohort study. Pediatrics 2007 Oct;120(4):e1076-e1081.
16. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics 1998 Sep;102(3 Pt 1):531-7.
17. Carbonell-Estrany X, Simoes EA, Dagan R, Hall CB, Harris B, Hultquist M, et al. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. Pediatrics 2010 Jan;125(1):e35-e51.
18. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH, Jr., et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003 Oct;143(4):532-40.
19. Bont L, Steijn M, van Aalderen WM, Brus F, Th Draaisma JM, Van Diemen-Steenvoorde RA, et al. Seasonality of long term wheezing following respiratory syncytial virus lower respiratory tract infection. Thorax 2004 Jun;59(6):512-6.
20. Bont L, van Aalderen WM, Versteegh J, Brus F, Draaisma JT, Pekelharing-Berghuis M, et al. Airflow limitation during respiratory syncytial virus lower respiratory tract infection predicts recurrent wheezing. PIDJ 2001 Mar;20(3):277-82.
21. Simoes EA, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, et al. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. J Pediatr 2007 Jul;151(1):34-42, 42.
22. Broughton S, Bhat R, Roberts A, Zuckerman M, Rafferty G, Greenough A. Diminished lung function, RSV infection, and respiratory morbidity in prematurely born infants. Arch Dis Child 2006 Jan;91(1):26-30.

23. Lakwijk N, Van Strien RT, Doekes G, Brunekreef B, Gerritsen J. Validation of a screening questionnaire for atopy with serum IgE tests in a population of pregnant Dutch women. Clin Exp Allergy 1998 Apr;28(4):454-8.

24. Bont L, Heijnen CJ, Kavelaars A, van Aalderen WM, Brus F, Draaisma JT, et al. Monocyte IL-10 production during respiratory syncytial virus bronchiolitis is associated with recurrent wheezing in a one-year follow-up study. Am J Respir Crit Care Med 2000 May;161(5):1518-23.

25. Bont L, Heijnen CJ, Kavelaars A, van Aalderen WM, Brus F, Draaisma JT, et al. Monocyte IL-10 production during respiratory syncytial virus bronchiolitis is associated with recurrent wheezing in a one-year follow-up study. Am J Respir Crit Care Med 2000 May;161(5):1518-23.

26. TAPQOL - TNO-AZL Questionnaire for Preschool Children's Health-Related Quality of Life. 2012.

27. Ermers MJ, Rovers MM, van Woensel JB, Kimpen JL, Bont LJ. The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: randomised double blind placebo controlled trial. BMJ 2009;338:b897.

CHAPTER 3

# Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants

Maarten O. Blanken, Maroeska M. Rovers, Jorine M. Molenaar, Pauline L. Winkler-Seinstra, Adam Meijer, Jan L. L. Kimpen, Louis Bont, on behalf of the Dutch RSV Neonatal Network

*N Engl J Med. 2013 May 9;368(19):1791-9*

**Abstract**

*Background*

Respiratory syncytial virus (RSV) infection is associated with subsequent recurrent wheeze. Observational studies cannot determine whether RSV infection is the cause of recurrent wheeze or the first indication of preexistent pulmonary vulnerability in preterm infants. The monoclonal antibody palivizumab has shown efficacy in preventing severe RSV infection in high-risk infants.

*Methods*

In the double-blind, placebo-controlled MAKI trial, we randomly assigned 429 otherwise healthy preterm infants born at a gestational age of 33 to 35 weeks to receive either monthly palivizumab injections (214 infants) or placebo (215 infants) during the RSV season. The prespecified primary outcome was the total number of parent-reported wheezing days in the first year of life. Nasopharyngeal swabs were taken during respiratory episodes for viral analysis.

*Results*

Palivizumab treatment resulted in a relative reduction of 61% (95% confidence interval, 56 to 65) in the total number of wheezing days during the first year of life (930 of 53,075 days in the RSV-prevention group [1.8%] vs. 2309 of 51,726 days [4.5%] in the placebo group). During this time, the proportion of infants with recurrent wheeze was 10 percentage points lower in patients treated with palivizumab (11% vs. 21%, P=0.01).

*Conclusions*

In otherwise healthy preterm infants, palivizumab treatment resulted in a significant reduction in wheezing days during the first year of life, even after the end of treatment. These findings implicate RSV infection as an important mechanism of recurrent wheeze during the first year of life in such infants. (ISRCTN73641710.)

**Introduction**

Illness of the lower respiratory tract that is caused by respiratory syncytial virus (RSV) is the most common cause of hospital admission in the winter season during the first year of life.[1] Severe RSV bronchiolitis has been associated with an increase in subsequent rates of early wheezing,[2,3] asthma, and possibly allergic sensitization later in life.[4-7] Early childhood wheeze after RSV infection has a high prevalence, influences quality of life, and generates substantial health care costs.[8-11] The pathogenesis of recurrent wheeze after RSV infection is still poorly understood. Gern and Busse distinguished two nonexclusive relationships between RSV infection and wheezing.[12] First, RSV bronchiolitis may interfere with normal lung development or immune maturation and subsequently cause recurrent episodes of wheezing. Second, RSV infection may be the earliest stimulus for wheezing in children who are predisposed to wheeze by genetic susceptibility or preexisting abnormal lung function at birth. A birth cohort study provided limited evidence for a causal relationship between RSV and recurrent wheeze, since the timing of birth in relationship to the annual winter RSV peak predicted the risk of recurrent wheeze.[13] So far, the potential causal role of RSV infection in the development of recurrent wheeze is debated, but strong empirical evidence is lacking.[14,15] Wu and Hartert therefore concluded that a randomized clinical trial using RSV prophylaxis was warranted to confirm a causal relationship between RSV infection and recurrent wheeze.[16] We performed the multicenter, double-blind, randomized, placebo-controlled MAKI trial to investigate the potential causal role of RSV infection in the pathogenesis of wheezing illness during the first year of life, using the commercially available monoclonal antibody palivizumab (Synagis, MedImmune) against RSV.

## Methods

*Patients*

From April 2008 through December 2010, we enrolled preterm infants (gestational age, 33 to 35 weeks) in pediatric departments of one university and 15 regional hospitals in the Netherlands. All the infants were otherwise healthy and 6 months of age or younger at the start of the RSV season. We excluded infants with congenital heart disease, bronchopulmonary dysplasia, Down's syndrome,[17] or other serious congenital disorders and infants who required mechanical ventilation at birth, who were treated with surfactant, or who had physician-diagnosed wheeze before the start of the RSV season. Parents provided written informed consent for study participation. The study was conducted according to the principles of the Declaration of Helsinki (version 2000). A yearly monitoring program that followed current Good Clinical Practice guidelines was run routinely.

*Ethical Issues*

Palivizumab is registered but not reimbursed in the Netherlands for preterm infants born at a gestational age of 33 to 35 weeks. Because RSV immunoprophylaxis is effective in preventing RSV lower respiratory tract illness in such preterm infants,[18] our study was marked as a therapeutic study. The institutional review board at the University Medical Center Utrecht decided that the 50% chance of benefit of RSV prevention with palivizumab outweighed the risk of moderate side effects caused by the intramuscular administration of placebo and the burden of participating in this trial. The protocol was reviewed and approved by the institutional review board at the University Medical Center Utrecht and at each participating hospital.

*Randomization*

Eligible infants were randomly assigned in a 1:1 ratio to receive either palivizumab (at a dose of 15 mg per kilogram of body weight) or placebo during the winter season (details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). The blinding of study-group assignment was performed with a randomization list that used a permuted-block design, which was generated by an independent pharmacist before the start of the trial. The randomization was stratified according to gestational age. Blinding was achieved with the use of a placebo matching the reconstituted palivizumab

solution. The researchers who received the logs and performed the analyses and the parents were unaware of study-group assignments until 1 year of follow-up was completed for all participants. The research nurses who administered the study drugs were aware of study-group assignments because it was not feasible to prepare and administer the treatment in a blinded fashion within 3 hours after reconstitution. The research nurses were trained to reveal no knowledge of the randomization to parents and were not involved in the reporting of data analyses. The research nurses worked with standard operating procedures and were carefully instructed to prevent possible unblinding.



*Study Outcomes and Follow-up*

The primary outcome was number of parent reported wheezing days in the first year of life. Using methods identical to those used in our previous trial, parents recorded airway symptoms, doctor visits, and the use of airway drugs in a daily log until their infant was 1 year of age.[19,20] Instructions for completing the log were given during the first home visit, and compliance was checked at each subsequent home visit. Secondary outcomes were the number of days with bronchodilator use, the number of RSV infections confirmed by means of a nasopharyngeal swab positive for RSV RNA with or without medical attention, the number of hospitalisations for laboratory-proven RSV infection, the number of wheezing episodes, and the prevalence of recurrent wheeze. Medical attention was defined as a visit to either a general practitioner or a hospital. A wheezing episode was defined as a respiratory episode with wheezing on more than 1 day. The interval between two episodes was defined as a period of at least 7 days without respiratory symptoms. Recurrent wheeze was defined as three or more episodes of wheezing during the first year of life. A family history of atopy was defined as a physician diagnosis of asthma, hay fever, or eczema in at least one of the parents.

*Laboratory Tests and Follow-up*

We defined the post-prophylaxis period as the follow-up from 2 months after the last treatment administration (three half-lives of palivizumab) up to the age of 1 year. In case of respiratory symptoms, primary care was left to the general practitioner. Parents were instructed to take a nasopharyngeal swab in case of the occurrence of respiratory symptoms with involvement of the upper or lower respiratory tract lasting more than 1 day. The swab was transported in a viral transport medium by regular mail to the laboratory and stored at −80°C until polymerase-chain-reaction (PCR) assays were performed. The presence of RSV

RNA was determined by multiplex real-time reverse-transcriptase–PCR with the use of previously published primers and probes for RSV-B21 and primers and probes for RSV-A that were developed in-house (details are provided in the Supplementary Appendix). We determined the presence of 16 respiratory viruses and 4 respiratory bacteria using the RespiFinder SMART 22 assay (PathoFinder).[22] Positive results on testing for rhinovirus or enterovirus are referred to as rhinovirus infection. All hospitalisations were evaluated, and any deaths were regarded as serious adverse events. Local injection-site reactions and physician visits for nonrespiratory symptoms were not recorded.

*Study Oversight*

The academic authors designed and conducted the study without input from the study sponsor (Abbott Laboratories, which markets palivizumab) other than financial support and donation of the palivizumab. All authors vouch for the accuracy and completeness of the data reported and for the fidelity of this report to the study protocol, available at NEJM.org. Statistical Analysis The sample-size calculation was based on a clinically relevant between-group difference of a mean (±SD) of 5±15 wheezing days during the first year of life.[20,23,24] The predefined target of 226 infants per study group provided a power of at least 90% to detect a clinically relevant difference in wheezing days with the use of an alpha level of 0.05. Since a typical Poisson distribution for probability arose, we used Poisson regression analysis to study potential differences in the number of days with wheeze.[20] Percentages and associated 95% confidence intervals of infants with wheezing or recurrent wheeze episodes were calculated. We used chi-square tests, Student's t-tests, and Mann–Whitney U tests to evaluate differences in percentages, mean values, and median values between the two study groups. All analyses were performed on an intention-to-treat basis. No imputation of missing data was performed, since the overall amount of missing data was less than 10%. Post hoc subgroup analyses were performed to assess wheezing days in subgroups of children with a family history of atopy or asthma. All statistical analyses were performed with SPSS software, version 20.0.

**Results**

We screened 1,550 late preterm infants of 33-35 wGA (32 weeks and 1 day to 35 weeks and 6 days) to include a total of 429 infants (Figure 1A). Median day of birth was August 22nd for included infants versus August 5th for non-included infants. Patients were randomly assigned to treatment or placebo. Groups were equally balanced for inclusion year, gestational age and birth month. Birth weight, family atopy, presence of siblings and other baseline characteristics were similar, except for gender (58% male gender in the RSV prevention group vs. 44% in the placebo group, Supplemental Table S1).By design children had no wheezing symptoms before enrollment. A median number of 4 injections during the RSV season was given to infants in both the RSV prevention group (range 1-5) and the placebo group (range 2-5). In the placebo group 92% of scheduled injections and 88% of the follow up were completed vs. 95% and 89% in the RSV prevention group. The median follow up duration was 10 months in the RSV prevention group (range 0-12) and the placebo group (range 0-12).

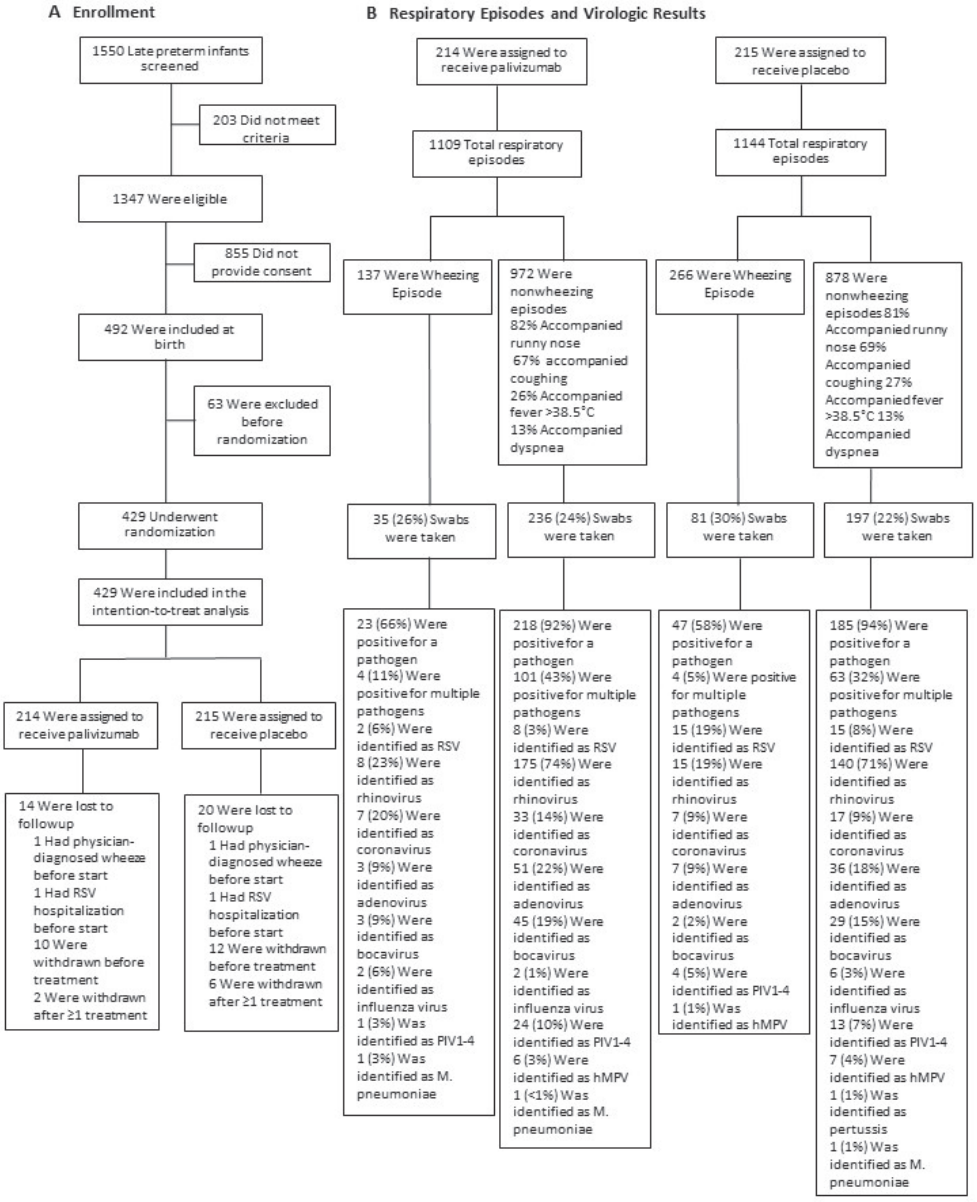



*Figure 1. Enrollment, Number of Respiratory Episodes, and Results of Virologic Analyses.*
Panel A shows enrollment and study outcomes for the 429 infants who were included in the intention-to-treat analysis. Panel B shows the total number of respiratory symptoms, which were based on parent records. A respiratory episode was defined as an episode of at least 2 consecutive days of upper or lower respiratory symptoms. Parents were instructed to take a nasopharyngeal swab on the second day of every respiratory episode. Respiratory syncytial virus (RSV) was detected with the use of in-house real-time reverse-transcriptase–polymerase-chain-reaction assays, and the RespiFinder SMART 22 assay was used for the detection of adenovirus, bocavirus, *Bordetella pertussis*, *Chlamydia pneumoniae*, coronavirus (229E, HKU1, NL63, and OC43), human metapneumovirus (hMPV), influenza virus type A, influenza virus A(H1N1)pdm09, influenza virus type B (influenza virus), *Legionella pneumophila*, *Mycoplasma pneumoniae*, parainfluenza virus types 1 through 4 (PIV1-4), RSV types A and B (RSV), and rhinovirus or enterovirus (rhinovirus).

*RSV infections*

We studied the occurrence and severity of RSV infections to confirm the efficacy of RSV immunoprophylaxis in our study population. We confirmed that infants treated with palivizumab had a lower incidence of RSV-related hospitalisations (0.9% v 5.1% of children, P=0.01).[18] The infants treated with palivizumab also had a lower incidence of medically attended non-hospitalised RSV infections (Table 1).



**Table 1. Proportion of Infants with Proven Respiratory Syncytial Virus (RSV) Infection.***

| Variable | Palivizumab (N = 214) | Placebo (N = 215) | Absolute Risk Reduction† | Relative Risk Reduction (95% CI)† | P Value |
|---|---|---|---|---|---|
| | *no. (%)* | | *percentage points* | *%* | |
| Total RSV infection | 10 (4.7) | 30 (14.0) | 9.3 | 67 (27 to 107) | 0.001 |
| Hospitalisation for RSV infection | 2 (0.9) | 11 (5.1) | 4.2 | 82 (18 to 157) | 0.01 |
| Medically attended RSV infection without hospitalisation | 2 (0.9) | 10 (4.7) | 3.7 | 80 (11 to 161) | 0.02 |
| RSV infection without medical attention | 6 (2.8) | 9 (4.2) | 1.4 | 33 (−56 to 126) | 0.40 |

* Medical attention was registered during the home visits and reported by parents on the daily log.
† The absolute and relative values for risk reduction are for the palivizumab group as compared with the placebo group.

*Primary and secondary outcomes*

The number of days with parent-reported wheeze was lower in the RSV-prevention group than in the placebo group (Table 2 and Fig. 2). This result was consistent for all 3 study years and independent of the number of injections of palivizumab or placebo. There was an absolute reduction of 2.7 percentage points in rates of wheezing in the RSV-prevention group versus the placebo group (930 of 53,075 days [1.8%] and 2309 of 51,726 days [4.5%], respectively), for a relative reduction of 61% (95% confidence interval [CI], 56 to 65).

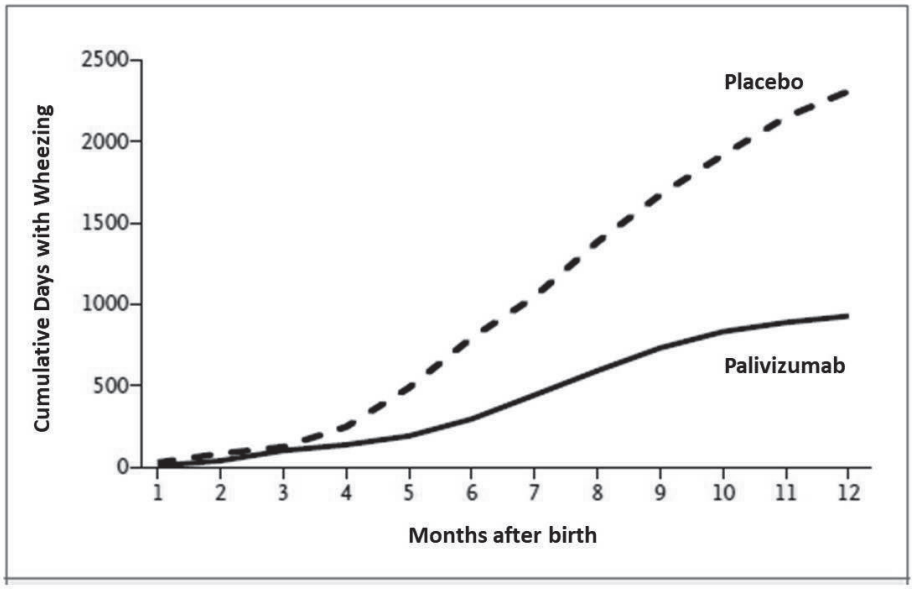



*Figure 2. Cumulative Wheezing Days for 429 Preterm Infants during the First Year of Life.*
P<0.001 for the comparison between palivizumab and placebo with the use of Poisson regression. The effect of RSV prevention on the number of wheezing days persisted during the post-prophylaxis period (i.e., starting at 2 months after the last injection), for a relative reduction of 73% (95% CI, 66 to 80). Similarly, there was a decrease in the number of wheezing days outside the RSV season in the RSV-prevention group (Table 2).

| Table 2. Days with wheezing in the first year of life.* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Palivizumab (n=214) | | | Placebo (n=215) | | | Absolute reduction | Relative Risk reduction (95% CI) |
| | Total log days | Total symptom days | Incidence per day | Total log days | Total symptom days | Incidence per day | | |
| | *no.* | | *%* | *no.* | | *%* | *no. of symptom days* | *%* |
| **Days with wheezing** | | | | | | | | |
| First year of life | 53 075 | 930 | 1.8% | 51 726 | 2309 | 4.5% | 1379 | 61% (56-65%) |
| <2 months after prophylaxis | 28 455 | 666 | 2.3% | 28 220 | 1382 | 4.9% | 716 | 52% (46-59%) |
| ≤ 2 months after prophylaxis | 24 620 | 264 | 1.1% | 23 506 | 927 | 3.9% | 663 | 73% (66-80%) |
| During RSV season* | 26 176 | 646 | 2.5% | 26 081 | 1348 | 5.2% | 702 | 52% (46-59%) |
| Outside RSV season* | 26 899 | 284 | 1.1% | 25 645 | 961 | 3.7% | 677 | 73% (66-80%) |

* The incidence of wheezing was calculated as the number of days with parent-reported airway symptoms divided by the number of log days during follow-up. P==0.006 for the category of less than 2 months after the end of prophylaxis.

† The values for absolute reduction and relative risk reduction are for the palivizumab group as compared with the placebo group.

‡ The RSV season was defined as October 1 to March 31.

Among children with any proven RSV infection, there was no significant between-group difference in the incidence of wheezing (23% in the RSV-prevention group and 30% in the placebo group) or in the mean number of wheezing days during the first year of life (8.2 days in the RSV-prevention group and 16 days in the placebo group). We did not detect RSV reinfection in either group. The proportion of infants with recurrent wheezing was lower in the RSV-prevention group than in the placebo group (11.2% vs. 20.9%, P=0.005) (Table 3). Similarly, the proportion of infants using bronchodilators was lower in the RSV-prevention group than in the placebo group (13% vs. 23%, P<0.001). The effect of RSV prevention on the total number of wheezing days was not significantly different (P=0.89) in children without a family history of atopy (72% reduction; 95% CI, 65 to 79), as compared with those with a family history of atopy (54% reduction; 95% CI, 47 to 60). A similar effect of RSV prevention was seen in children without and with parental asthma (68% reduction [95% CI, 62 to 73] vs. 35% reduction [95% CI, 23 to 47]). The total numbers of respiratory episodes were similar in the

two study groups. However, we found more coinfections during non-wheezing episodes in the RSV-prevention group than in the placebo group (101 of 236 swabs [43%] vs. 63 of 197 swabs [32%], P=0.02) (Fig. 1B).

**Table 3. Infants with wheezing.***

| Variable | Palivizumab (n=214) | Placebo (n=215) | Absolute reduction† | Relative Risk reduction (95% CI) † |
|---|---|---|---|---|
| Any wheezing – no. of infants (%) | 66 (31%) | 101 (47%) | 16% | 34% (14-53%) |
| Wheezing episodes – no. | 137 | 266 | 129 | 48% (32-62%) |
| Recurrent wheezing – no. of infants (%) | 24 (11%) | 45 (21%) | 10% | 47% (14-80%) |

* Any wheezing was defined as at least one episode of wheezing during the first year of life. A wheezing episode was defined as a respiratory episode with wheezing on more than 1 day. Recurrent wheezing was defined as three or more episodes of wheezing during the first year of life. P= 0.005 for recurrent wheezing.

† The values for absolute reduction are percentage points, and the values for relative risk reduction are numbers of episodes

*Adverse Events*

The proportion of patients with serious adverse events was lower in the RSV-prevention group than in the placebo group. We observed 32 hospitalisations in 27 children (12.6%) in the RSV-prevention group, as compared with 52 hospitalisations in 47 children (21.9%) in the placebo group (P=0.04). Reasons for hospitalisation in the RSV-prevention group were RSV infection (in 2 patients), other respiratory tract illness (in 6), gastroenteritis (in 6), surgery (in 6), failure to thrive (in 6), and other reasons (in 6). Reasons for hospitalisation in the placebo group were RSV infection (in 11 patients), other respiratory tract illness (in 6), gastroenteritis (in 10), surgery (in 13), failure to thrive (in 8), and other reasons (in 4). There were no deaths.

**Discussion**

In this proof-of-concept study, treatment with a monoclonal antibody for RSV prevention in late preterm infants greatly reduced the number of parent-reported wheezing days during the first year of life, even after the end of therapy and outside the RSV season. RSV prevention reduced wheezing, but wheezing was not eliminated. RSV prevention was associated with a relative reduction of 61% in the number of wheezing days, a finding that shows that RSV infection is an important mechanism in the pathogenesis of wheezing morbidity in this specific population. Our results are in line with other studies that acknowledge the relationship between RSV bronchiolitis and recurrent wheeze.[4,7,9,25-27] Wu et al.[13] found that the timing of birth date with respect to the peak of the winter bronchiolitis season was related to the risk of asthma. These findings suggest that asthma is most likely to develop in infants who are at highest risk for severe viral bronchiolitis. However, other studies have argued against RSV as the cause of pulmonary damage and subsequent early childhood wheezing.[2] The role of RSV in the development of asthma remains controversial, and our data cannot provide evidence in this discussion.[28] A previous nonrandomized trial suggested that the prevention of lower respiratory tract illness caused by RSV reduced subsequent recurrent wheeze in infants without a family history of atopy but showed no effect in infants with a family history of atopy.[29,30] We found that RSV prevention was associated with reduced wheezing in the first year of life, regardless of whether there was a family history of atopy. Our study underlines the important role that RSV plays in the pathogenesis of recurrent wheeze. We hypothesize that RSV primarily causes direct pulmonary epithelial damage and local immunologic alterations in the lungs, leading to longterm airway hyperresponsiveness and wheezing. A study in mice showed that RSV causes persistent airway hyperresponsiveness, chronic lung inflammation, and histopathological abnormalities.[31,32] Altered immune-response patterns have been described after RSV infection. Studies in mice and humans have suggested that local production of interleukin-10 during RSV infection is a key mechanism in the development of recurrent wheeze and airway hyperresponsiveness, although mechanisms independent of interleukin-10 have also been described.[19,33-36] We believe that alterations to the pulmonary environment and immunologic phenotype caused by RSV infection in early life eventually lead to long-term remodeling of the pulmonary system and hyperresponsiveness to respiratory viruses and nonspecific stimuli. In our study, the numbers of respiratory episodes were similar in the two study groups. However, in the RSV-prevention group, we found more coinfections

than in the placebo group. Previous studies have not addressed the effect of palivizumab on the acquisition or clearance of respiratory viruses other than RSV. RSV bronchiolitis is followed by a robust inflammatory response in the airways, which may persist for more than 1 month.[37] We speculate that this inflammatory response, including production of interferons, transiently protects against subsequent viral infection, resulting in fewer coinfections.[38,39] More research is needed to unravel how respiratory viruses interact at the mucosal level. The major strength of our study is the randomized design, which precludes bias from selection or confounding and which subsequently provided unbiased and conclusive evidence regarding the mechanism of RSV infection in the pathogenesis of infant wheezing. Some potential limitations should also be discussed. First, parents with an atopic history may have been more likely to participate in the study. However, since the stratified results did not differ between infants of parents with and those without an atopic history, our conclusions are generalizable. Second, although nasopharyngeal swabs were obtained by parents to increase compliance of sampling,[40] swabs were obtained in approximately 30% of all respiratory episodes. This is similar to the range of percentages (24 to 43%) obtained in a study with a similar approach to parental swab collection.[40,41] Consequently, we may underestimate the incidence of RSV infection. However, since the trial was double-blind and randomized, we do not believe this factor had an effect on the overall conclusions. Third, preterm infants are at higher risk for recurrent episodes of wheezing than are term infants.[42] Therefore, we do not know whether our results can be generalized to healthy term infants. Fourth, we had to rely on parent-reported morbidity data, since no objective measure of wheezing was available. Identifying wheezing is problematic even for trained clinicians.[43,44] However, since the parents were unaware of study-group assignments, we believe that any misclassification of wheezing was random in the two groups. In summary, we have shown that the administration of palivizumab for RSV prevention reduced the total number of wheezing days in the first year of life among preterm infants with a gestational age of 33 to 35 weeks. The postprophylaxis effect of RSV prevention on wheezing illness is evidence that RSV infection is an important mechanism in the pathogenesis of wheezing during the first year of life among late preterm infants.

*Disclosure*

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

*Acknowledgements*

We thank Loes Nibbelke and Shireen Jenny for their assistance in recruiting children, data collection, and virological analyses for the MAKI trial. We also thank the children and their families who graciously provided their time and effort to participate in the MAKI trial.

We thank all collaborating nurses, nurse practitioners, supporting staff and pediatricians in the hospitals of the RSV Neonatal Network Netherlands who collaborated in the study: M.A. Verboon, M.D., Ph.D. (University Medical Center Utrecht); W.J. de Waal, M.D., Ph.D. (Diakonessenhuis Utrecht); J.A. Schipper, M.D., Ph.D. (St. Antonius hospital Nieuwegein); J.H. de Bie, M.D. (Zuwe Hofpoort hospital Woerden); C.B. Meijssen, M.D. (Meander Medical Center Amersfoort); J.G. van Enk, M.D., Ph.D. (Hospital Gelderse Vallei Ede); A. Zlotkowski, M.D. (Hospital Rivierenland Tiel); R.A. Bruinsma, M.D. (Gelre hospital Apeldoorn); C.E. Crijns-Koers, M.D. (Tergooi hospitals Blaricum); R.P.H. Lubbers, M.D. (Rivas Beatrix hospitals Gorkum); A.C.M. Dassel, M.D., Ph.D. (Deventer hospital Deventer); C. Aleman, M.D. (Ikazia hospital Rotterdam); C.M.M.L. Bontemps, M.D. (St. Jansdal hospital Harderwijk); C.J. Miedema, M.D. (Catharina hospital Eindhoven); E.A. Smit-Kleinlugtenbeld, M.D. (Albert Schweitzer hospital Dordrecht); R. van Gent, M.D., Ph.D. (Maxima Medical Center Veldhoven).

The study was funded by an unrestricted grant by Abbott Laboratories and the Netherlands Organization for Health Research and Development (ZonMw), NWO-AGIKO grant 920-035-89 (M.O. Blanken).

*Ethical approval*

Our protocol was reviewed and approved by the Institutional Review Board (IRB) of the University Medical Center Utrecht (IRB UMCU METC-08-118) and by the IRB of each participating hospital.

**References**


1. Hall CB, Weinberg GA, Iwane MK et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009;360(6):588-598.
2. Stensballe LG, Simonsen JB, Thomsen SF et al. The causal direction in the association between respiratory syncytial virus hospitalization and asthma. J Allergy Clin Immunol 2009;123(1):131-137.
3. Carroll KN, Wu P, Gebretsadik T et al. Season of infant bronchiolitis and estimates of subsequent risk and burden of early childhood asthma. J Allergy Clin Immunol 2009;123(4):964-966.
4. Henderson J, Hilliard TN, Sherriff A, Stalker D, Al SN, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. Pediatr Allergy Immunol 2005;16(5):386-392.
5. Bacharier LB, Cohen R, Schweiger T et al. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. J Allergy Clin Immunol 2012;130(1):91-100.
6. Stein RT, Sherrill D, Morgan WJ et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999;354(9178):541-545.
7. Sigurs N, Aljassim F, Kjellman B et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. Thorax 2010;65(12):1045-1052.
8. Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? Lancet 2001;357(9271):1821-1825.
9. Bont L, Aalderen WM, Kimpen JL. Long-term consequences of respiratory syncytial virus (RSV) bronchiolitis. Paediatr Respir Rev 2000;1(3):221-227.
10. Bont L, Steijn M, Van Aalderen WM, Kimpen JL. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. Pediatr Infect Dis J 2004;23(5):414-417.
11. Miedema CJ, Kors AW, Tjon ATW, Kimpen JL. Medical consumption and socioeconomic effects of infection with respiratory syncytial virus in The Netherlands. Pediatr Infect Dis J 2001;20(2):160-163.
12. Gern JE, Busse WW. Relationship of viral infections to wheezing illnesses and asthma. Nat Rev Immunol 2002;2(2):132-138.

13. Wu P, Dupont WD, Griffin MR et al. Evidence of a causal role of winter virus infection during infancy in early childhood asthma. Am J Respir Crit Care Med 2008;178(11):1123-1129.
14. Edwards MR, Bartlett NW, Hussell T, Openshaw P, Johnston SL. The microbiology of asthma. Nat Rev Microbiol 2012;10(7):459-471.
15. Martinez FD. Respiratory syncytial virus bronchiolitis and the pathogenesis of childhood asthma. Pediatr Infect Dis J 2003;22(2 Suppl):S76-S82.
16. Wu P, Hartert TV. Evidence for a causal relationship between respiratory syncytial virus infection and asthma. Expert Rev Anti Infect Ther 2011;9(9):731-745.
17. Bloemers BL, van Furth AM, Weijerman ME et al. Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis--a prospective birth-cohort study. Pediatrics 2007;120(4):e1076-e1081.
18. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics 1998;102(3 Pt 1):531-537.
19. Bont L, Heijnen CJ, Kavelaars A et al. Monocyte IL-10 production during respiratory syncytial virus bronchiolitis is associated with recurrent wheezing in a one-year follow-up study. Am J Respir Crit Care Med 2000;161(5):1518-1523.
20. Ermers MJ, Rovers MM, van Woensel JB, Kimpen JL, Bont LJ. The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: randomised double blind placebo controlled trial. BMJ 2009;338:b897.
21. Hu A, Colella M, Tam JS, Rappaport R, Cheng SM. Simultaneous detection, subgrouping, and quantitation of respiratory syncytial virus A and B by real-time PCR. J Clin Microbiol 2003;41(1):149-154.
22. Loens K, van Loon AM, Coenjaerts F et al. Performance of different mono- and multiplex nucleic acid amplification tests on a multipathogen external quality assessment panel. J CLIN MICROBIOL 2012;50(3):977-987.
23. Bont L, Van Aalderen WM, Versteegh J et al. Airflow limitation during respiratory syncytial virus lower respiratory tract infection predicts recurrent wheezing. Pediatr Infect Dis J 2001;20(3):277-282.
24. Bont L, Steijn M, Van Aalderen WM et al. Seasonality of long term wheezing following respiratory syncytial virus lower respiratory tract infection. Thorax 2004;59(6):512-516.

25. Hall CB, Hall WJ, Gala CL, MaGill FB, Leddy JP. Long-term prospective study in children after respiratory syncytial virus infection. J Pediatr 1984;105(3):358-364.
26. Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. Br Med J (Clin Res Ed) 1982;284(6330):1665-1669.
27. Eisen AH, Bacal HL. The relationship of acute bronchiolitis to bronchial asthma: a 4 to 14 year followup. Pediatrics 1963;31:859-861.
28. Welliver RC. RSV and chronic asthma. Lancet 1995;346(8978):789-790.
29. Simoes EA, Groothuis JR, Carbonell-Estrany X et al. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. J Pediatr 2007;151(1):34-42, 42.
30. Simoes EA, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick L, Groothuis JR. The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. J Allergy Clin Immunol 2010;126(2):256-262.
31. Jafri HS, Chavez-Bueno S, Mejias A et al. Respiratory syncytial virus induces pneumonia, cytokine response, airway obstruction, and chronic inflammatory infiltrates associated with long-term airway hyperresponsiveness in mice. J Infect Dis 2004;189(10):1856-1865.
32. Mejias A, Chavez-Bueno S, Rios AM et al. Comparative effects of two neutralizing anti-respiratory syncytial virus (RSV) monoclonal antibodies in the RSV murine model: time versus potency. Antimicrob Agents Chemother 2005;49(11):4700-4707.
33. Schuurhof A, Janssen R, de GH et al. Local interleukin-10 production during respiratory syncytial virus bronchiolitis is associated with post-bronchiolitis wheeze. Respir Res 2011;12:121.
34. Makela MJ, Kanehiro A, Dakhama A et al. The failure of interleukin-10-deficient mice to develop airway hyperresponsiveness is overcome by respiratory syncytial virus infection in allergen-sensitized/challenged mice. Am J Respir Crit Care Med 2002;165(6):824-831.
35. Makela MJ, Kanehiro A, Borish L et al. IL-10 is necessary for the expression of airway hyperresponsiveness but not pulmonary inflammation after allergic sensitization. Proc Natl Acad Sci U S A 2000;97(11):6007-6012.

36. Loebbermann J, Schnoeller C, Thornton H et al. IL-10 regulates viral lung immunopathology during acute respiratory syncytial virus infection in mice. PLoS One 2012;7(2):e32371.
37. Bermejo-Martin JF, Garcia-Arevalo MC, Alonso A et al. Persistence of proinflammatory response after severe respiratory syncytial virus disease in children. J Allergy Clin Immunol 2007;119(6):1547-1550.
38. Casalegno JS, Bouscambert-Duchamp M, Morfin F, Lina B, Escuret V. Rhinoviruses, A(H1N1)v, RVS: the race for hivernal pandemics, France 2009-2010. Euro Surveill 2009;14(44).
39. Linde A, Rotzen-Ostlund M, Zweygberg-Wirgart B, Rubinova S, Brytting M. Does viral interference affect spread of influenza? Euro Surveill 2009;14(40).
40. van der Zalm MM, Uiterwaal CS, de Jong BM, Wilbrink B, van der Ent CK. Viral specimen collection by parents increases response rate in population-based virus studies. J Allergy Clin Immunol 2006;117(4):955-956.
41. van der Zalm MM, Uiterwaal CS, Wilbrink B et al. Respiratory pathogens in respiratory tract illnesses during the first year of life: a birth cohort study. Pediatr Infect Dis J 2009;28(6):472-476.
42. Colin AA, McEvoy C, Castile RG. Respiratory morbidity and lung function in preterm infants of 32 to 36 weeks' gestational age. Pediatrics 2010;126(1):115-128.
43. Brand PL, Baraldi E, Bisgaard H et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J 2008;32(4):1096-1110.
44. Elphick HE, Sherlock P, Foxall G et al. Survey of respiratory sounds in infants. Arch Dis Child 2001;84(1):35-39.

**Supplemental Methods**

- Study Intervention
- Supplemental Methods: RSV PCR
- Supplemental Table S1

**Methods**

*Study Intervention*

Palivizumab is a humanized monoclonal antibody directed against the fusion protein of RSV and prevents hospitalisation for RSV infection.[1, 2] Interventions were intramuscular injections of palivizumab 15 mg/kg or placebo during one RSV season from October 1st or from discharge from the neonatal unit until March 10th. A minimum of 2 and a maximum of 5 injections were given. The RSV season was defined as running from October 1st through March 31st based on virological data obtained from the National Institute of Public Health and the Environment (RIVM). For subjects randomized to placebo, physiological sodium chloride 0.9% solution for intramuscular injection was used. Treatment was started at the patient's home from the first week of October or within 72 hours after discharge from the neonatal hospitalisation. All injections were administered at the patient's home and home visits ended after the last injection.

RSV PCR

Total nucleic acid was extracted from 200 µl specimen using the MagNA Pure 96 platform (Roche) and MagNA Pure 96 DNA and Viral NA Small Volume Kit 05 467 497 001 (Roche). For RSV types A and B detection a duplex real-time onestep RT-PCR was performed on 5 µl total nucleic acid, using the one-step TaqMan EZ RT-PCR kit (ABI) in a final volume of 25 µl on a Lightcycler 480 (Roche). The copy DNA synthesis and amplification protocol consisted of 2 minutes at 50°C (decontamination using Uracil N-glycosylase), 30 minutes at 55°C (reverse transcription), 5 minutes at 95°C (inactivation Uracil N-glycosylase) and 45 cycles of 20 seconds at 94°C and 1 minute at 55°C, with primers 5'-TGA ACA ACC CAA AAG CAT CA-3' and 5'-CCT AGG CCA GCA GCA TTG-3' and probe 5'-6Fam-AAT TTC CTC ACT TCT CCA GTG TAG TAT TAG G-BHQ1-3' for RSV type A (in house design) and primers 5-GAT GGC TCT TAG CAA AGT CAA GTT AA-3' and 5'-TGT CAA TAT TAT CTC CTG TAC TAC GTT GAA-3' and probe 5'-YY-TGA TAC ATT AAA TAA GGA TCA GCT GCT GTC ATC CA-BHQ1-3' for RSV type B[3], both PCRs targeting the nucleocapsid gene of RSV.

| Table S1: Baseline Characteristics | | |
|---|---|---|
| | **Palivizumab (n=214)** | **Placebo (n=215)** |
| Male (%)** | 125 (58%) | 94 (44%) |
| Birth Weight – gram (95%CI) | 2294 (1363-3325) | 2289 (1385-3358) |
| Gestational Age – weeks (95%CI) | 34+3 (32+2-35+6) | 34+3 (32+3-35+6) |
| Multiple birth (%) | 38 (19%) | 36 (18%) |
| Type of feeding (%) | | |
| Breastfeeding and formula | 90 (44%) | 107 (53%) |
| Breastfeeding | 59 (29%) | 49 (24%) |
| Formula | 54 (27%) | 46 (23%) |
| Maternal smoking during pregnancy (%) | 32 (15%) | 34 (16%) |
| Parental smoking | | |
| Mother (%) | 33 (15%) | 36 (17%) |
| Father (%) | 57(27%) | 62 (29%) |
| Siblings (%) | 82 (44%) | 85 (45%) |
| Age mother (median (range) | 31 (19-48) | 32 (18-44) |
| Age father (median (range) | 34 (21-55) | 35 (22-52) |
| Atopy Mother (%) | 85 (40%) | 72 (34%) |
| Physician diagnosis Asthma | 22 (11%) | 24 (12%) |
| Physician diagnosis Hay fever | 48 (24%) | 45 (23%) |
| Physician diagnosis Eczema | 48 (24%) | 30 (15%) |
| Atopy Father (%) | 73 (34%) | 80 (37%) |
| Physician diagnosis Asthma | 27 (14%) | 21 (11%) |
| Physician diagnosis Hay fever | 44 (22%) | 52 (26%) |
| Physician diagnosis Eczema | 29 (15%) | 27 (14%) |
| Household pets (%) | 97 (48%) | 98 (49%) |
| Daycare attendance (%)<br>Sibling attending daycare (%) | 103 (48%)<br>75 (37%) | 113 (53%)<br>79 (40%) |
| Doses palivizumab received (median (range) | 4 (1-5) | 4 (2-5) |

**: p<0.01

**References**

1. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics 1998;102(3 Pt 1):531-537.
2. Feltes TF, Cabalka AK, Meissner HC et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003;143(4):532-540.
3. Hu A, Colella M, Tam JS, Rappaport R, Cheng SM. Simultaneous detection, subgrouping, and quantitation of respiratory syncytial virus A and B by real-time PCR. J Clin Microbiol 2003;41(1):149-154.

CHAPTER 4

# Population-Attributable Risk of Risk Factors for Recurrent Wheezing in Moderate Preterm Infants During the First Year of Life

Maarten O. Blanken, Koos Korsten, Niek A. Achten, Saskia Tamminga, Loes Nibbelke, Lieke Sanders, Jet Smit H.A, Rolf Groenwold, Louis Bont, on behalf of the Dutch RSV Neonatal Network

*Paediatr Perinat Epidemiol. 2016 Jul;30(4):376-85*

**Abstract**

*Background*

Recurrent wheezing in young infants has a high prevalence, influences quality of life, and generates substantial health care costs. We previously showed that respiratory syncytial virus infection is an important mechanism of recurrent wheezing in moderate preterm infants. We aimed to provide population-attributable risks (PAR) of risk factors for recurrent wheezing during the first year of life in otherwise healthy moderate preterm infants.

*Methods*

RISK is a multicentre prospective birth cohort study of 4424 moderate preterm infants born at 32–35 weeks gestation. We estimated PAR of risk factors for recurrent wheezing, which was defined as three or more parent-reported wheezing episodes during the first year of life.

*Results*

We evaluated 3952 (89%) children at 1 year of age, of whom 705 infants (18%) developed recurrent wheezing. Fourteen variables were independently associated with recurrent wheezing. Hospitalisation for respiratory syncytial virus bronchiolitis had a strong relationship with recurrent wheezing (RR 2.6; 95% confidence interval, CI, 2.2, 3.1), but a relative modest PAR (8%; 95% CI 6, 11%) which can be explained by a low prevalence (13%). Day-care attendance showed a strong relationship with recurrent wheezing (RR 1.9; 95% CI, 1.7, 2.2) and the highest PAR (32%; 95% CI 23, 37%) due to a high prevalence (67%). The combined adjusted PAR for the 14 risk factors associated with recurrent wheezing was 49% (95% CI 46, 52%).

*Conclusions*

In moderate preterm infants, day-care attendance has the largest PAR for recurrent wheezing. Trial evidence is needed to determine the potential benefit of delayed day-care attendance in this population.

**Introduction**

Recurrent wheezing (RW) in young infants has a high prevalence, influences quality of life, and generates substantial healthcare costs [1-3]. It is estimated that per child annual costs to society associated with preschool asthma amounts to CDN$ 1386 for infants under four years of age [4]. In the UK it was estimated that the economic impact of medically attended preschool asthma and wheezing in children aged 1-5 years was 53 million GBP annually [5]. Around one-third of children aged 1–6 years in Europe and the USA report current or recent wheezing [6,7]. It was recently established that respiratory syncytial virus (RSV) infections are an important cause of RW during the first year of life in otherwise healthy moderate preterm infants 32-35 weeks gestational age (wGA)[8]. Our recent randomized clinical trial showed that RSV prevention leads to a reduction of wheezing in the first year of life, strongly suggestive of a causal link between RSV infection and first year wheezing in healthy moderate preterm infants 32-35 wGA [8]. In addition, several studies have shown that infants who experienced wheezing illness caused by human rhinovirus infection are at increased risk of RW development in early childhood and of wheezing and asthma through 13 years of age [9,10]. Viral infections and the exposure to viruses is potentially modifiable by preventive treatment and lifestyle changes but several other risk factors associated with RW are non-modifiable. The heterogeneity in causes of RW is based on multiple interactions between the child's genetic makeup, age, anatomy and prenatal and postnatal environmental factors. As an example of a non-modifiable risk factor, prematurity is associated with increased susceptibility for viral infections, but also with chronic airway morbidity [11]. Several birth cohort studies have described the association between impaired lung function at one month of age and later airway morbidity, an example of an anatomical factor [12,13]. Life style factors like day care attendance or the presence of siblings [14], environmental exposure to tobacco smoking[15] and formula feeding instead of breast feeding[16] are other factors associated with RW risk. Prevention of viral infections or the exposure to viruses, but also environmental factors, can be an important strategy to decreasing the burden of disease of recurrent wheezing and potentially asthma. Therefore, it is essential to identify potentially modifiable risk factors and to determine their potential impact on RW morbidity. One way to define the proportion of disease that can be attributed to a risk factor or set of factors is to quantify the population attributable risk (PAR) as a burden of disease measure [17]. This implies that if exposure to a risk factor could be totally prevented, i.e. is modifiable, the burden of disease would be reduced

by that proportion. PAR is widely used in burden of disease studies to determine risk factor attribution [18,19]. We hypothesized that potentially modifiable viral exposure variables like day care attendance and bronchiolitis hospitalisations strongly contribute to burden of disease of RW. The goal of this prospective birth cohort study was aimed on risk factors for RSV hospitalisation and this follow up study focused on risk factors for RW in the first year of life. The objective of this study was to provide PAR estimates of risk factors for parent-reported RW during the first year of life in otherwise healthy moderate preterm infants.

**Materials and Methods**

*Study design*

This study is based on data from the RISK study, an ongoing prospective study in moderate preterm infants (defined as infants born at 32 weeks and 1 day to 35 weeks and 6 days gestational age, referred to as 32–35 wGA) in 1 university hospital and 40 regional hospitals of the Dutch RSV Neonatal Network in the Netherlands. Infants were included between June 2008 and February 2014. Children with gross congenital abnormalities (n=6) (e.g. Down syndrome), those who received palivizumab (n=186) for any reason and children with incomplete data or when no telephone contact could be made at one year of age were excluded from the current data analyses (n=472).



The RISK study protocol was approved by the Institutional Review Board (IRB) of University Medical Center Utrecht. All parents or legal guardians provided written informed consent for study participation. The RISK study was conducted in compliance with the Declaration of Helsinki and standards of Good Clinical Practice.

*Data collection*

We described data collection procedures and risk factor identification in our previous publication[20]. In summary, at birth, clinical data were obtained from patient charts. The parents or legal guardians completed a standardized questionnaire containing questions on family history, maternal characteristics and other household details. At one year of age parents were contacted by telephone for an interview based on a standardized questionnaire containing questions to determine whether hospitalisation for respiratory disease had occurred and to determine the incidence of day care attendance and other risk factors[21]. In the questionnaire at 1 year of age, the International Study of Asthma and Allergies in Childhood (ISAAC)[22] standardized questions on wheezing were phrased as follows: “Did your child experience wheezing in the last 12 months?” and “How many episodes of wheezing did your child experience?”. Airway medication use and physician’s visits were asked as follows: “Did your child use airway medication prescribed by a physician in the last 12 months, please specify?” and “Did your child visit a pediatrician or general practitioner for other reasons than prematurity, please specify?” which all could be answered by “yes” or “no.” Low parental education was defined as none of the parents having a university of applied sciences degree. Hospital records were retrieved to verify hospitalisation details. Infants with incomplete data

were not included in the analyses. Laboratory virology testing was performed according to routine practice at the hospital where the patient had been admitted. RSV bronchiolitis hospitalisation was defined as hospitalisation for lower respiratory tract infection with proven RSV infection.

*Outcome definition*

The primary outcome was parent-reported RW similar to the primary outcome definition in previous trials [8,23]. RW was defined as three or more parent-reported episodes of wheezing during the first year of life. In line with our previous trials the interval between two episodes was defined as a period of at least 7 days without respiratory symptoms [8,23]. Medically attended RW defined as RW plus any airway medication in the first year of life, as reported by the parents, was considered a secondary outcome. PAR as a burden of disease measure was used to quantify the proportion in population disease that can be attributed to the contributing effects of identified risk factors [17,24].

*Statistical analysis*

Percentages and associated 95% confidence intervals of infants with RW were calculated. We used $\chi 2$ tests, Student's t tests, and Mann Whitney U tests to determine statistical differences between the group of infants with and without RW. All variables with p-value <0.20 in univariate analyses were included in multivariable analysis. Poisson regression analysis with a robust variance estimator was used to determine multivariable-adjusted relative risks (RR) for RW. Data analysis was carried out using SPSS IBM 20.0 (SPSS Inc, Chicago, Ill)

*Population attributable risk*

Adjusted independent relative risks were used to quantify the PAR and corresponding 95% confidence intervals. The PAR for each risk factor was calculated using aggregated adjusted association measures via the following formula: ((RR-1)/RR) x $P^d$ (where $P^d$ is the proportion of the cases being exposed) [17]. Based on the prospective cohort study design and the large sample size we used Walter's formula to calculate the 95% confidence intervals for the PAR[25]. The combined weighted estimate of the PAR, accounting for correlation between risk factors, was calculated with the formula: $PAR_{AdjustedCombined} = 1 - \Pi (1 - (w \times PAR))$ (where $\Pi$ is the product of a sequence from i=1 to m, over $(1\text{-}w_i \times PAR_i)$, where i indicates a risk factor, and m is the total number of risk factors considered) [26]. The PAR for each risk factor was weighed

where the weight ($w_i$) was determined using the estimate of 1 minus the proportion of the variance shared with the other risk factors (i.e., communality). The communality for each risk factor was determined via principal components analysis of the risk factor correlation matrix. The communality was calculated as the square of the loadings on the first five principal components based on Monte Carlo parallel analysis criteria (eigenvalues) [27]. Principal component analysis was justified since the Kaiser-Meyer-Olkin measure of sampling adequacy was 0.56, Bartlett's test showed a $p<0{\cdot}001$. The estimated amount of overlap between the eleven risk factors ranged from 40.6% to 62.3% (Supplementary Table 1). Together, the first five principal components explained 54% of the total variance between the risk factors, which suggests substantial overlap.

**Results**

In total 4424 moderate preterm infants born in the 41 participating hospitals were in study at age 1 (Figure 1). Of these, 472 infants (10%) were lost to follow up or had incomplete data of which three infants died of causes that were not related to RW. Baseline characteristics for patients lost to follow up compared to included infants showed that these patients were more likely to be single birth females and more subject to maternal smoking during pregnancy. [Supplemental Table 3]."We retrospectively excluded 186 infants (4%) receiving palivizumab and 6 infants (<1%) infants with gross congenital abnormalities not known or present at birth. Of the 3952 infants included in the analyses, 705 infants (18%) had developed RW during the first year of life. Baseline characteristics of children with RW and without RW (control children) are shown in Table 1.

*Recurrent wheezing*

Table 2 shows the distribution of risk factors for RW. Multivariable regression analysis showed that RSV, non-RSV and non-tested hospitalisation were the strongest independent determinants of RW (RR 2.6, 95%CI 2.2, 3.1; RR 2.7, 95% CI 2.1, 3.5 and RR 3.4, 95%CI 2.6, 4.5). Other important determinants of RW were day care attendance, male gender, presence of siblings, maternal smoking and maternal childhood wheezing (Table 2, Supplemental Figure 1). A subgroup analysis showed that both early onset (<3 months of age) of day care attendance and late onset (>6 months of age) of day care attendance had a similar relative risk (RR 2.0, 95% CI 1.5, 2,6; and RR 1.7 95% CI 1.3, 2.2).

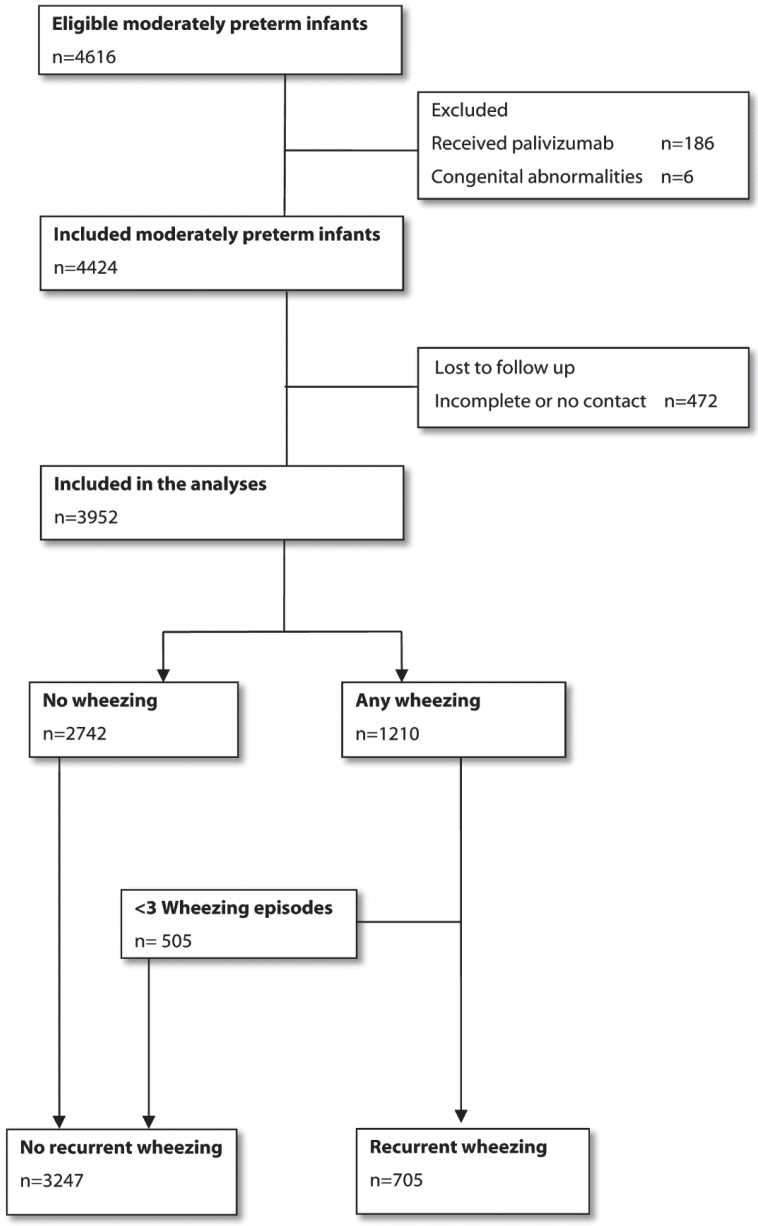



*Figure 1. Flowchart RISK study*

*Population-Attributable Risks*

Based on adjusted independent relative risks, the PAR of RW could to a large part be attributed to variables associated with viral exposure. Day care attendance (PAR 31.7%, 95% CI 23, 37%) and presence of siblings (PAR 10.4%, 95% CI 6, 17%) had a major attribution to the risk of RW. (Table 2) Male gender (PAR 21.7%, 95% CI 13, 28%) and gestational age (PAR 11.5%, 95% CI 3, 21%) also attributed considerably to RW. The proportion of RW that could be attributed to hospitalisation for bronchiolitis caused by RSV or another pathogen was substantially lower. Several socioeconomic and genetic variables, like maternal low education and parental asthma or hay fever, also independently attributed to the incidence of RW. Respiratory support contributes to the burden of disease of RW with a PAR of 4.5% [95% CI 2, 10%]. To assess the robustness of our results, we performed a sensitivity analysis of our data using medically attended RW (n=255) as a more strict outcome.

Multivariable regression analysis yielded similar RRs and PARs for the risk factors tested as found in the model using RW as the outcome (Supplementary Table 2). The estimate of the combined PAR for all risk factors attributed to 49% [95% CI 46, 52%] of RW cases in the moderate preterm infants. Potentially modifiable risk factors (day care attendance, bronchiolitis and maternal smoking) together accounted for 24% [95% CI 22, 26%] of RW cases.

**Table 1**. Characteristics of children with and without recurrent wheezing in the RISK study. Data from univariate analyses

| Characteristic N (%) | Recurrent wheezing N = 705 | No Recurrent wheezing N = 3247 | p value† |
|---|---|---|---|
| Maternal characteristics | | | |
| Maternal smoking during pregnancy | 95 (14%) | 382 (12%) | 0.21 |
| Caesarean section | 254 (36%) | 1168 (36%) | 0.98 |
| Supplemental vitamins during pregnancy | 235/480 (49%) | 969/1912 (51%) | 0.50 |
| No breastfeeding | 206 (29%) | 849 (26%) | 0.10 |
| Breastfeeding <= 6 months | 630 (89%) | 2786 (86%) | 0.01 |
| Maternal smoking | 144 (20%) | 505 (16%) | 0.002 |
| Maternal atopy | 303 (43%) | 1130 (35%) | <0.001 |
| Hay fever | 181 (26%) | 629 (19%) | <0.001 |
| Eczema | 146 (21%) | 530 (16%) | 0.005 |
| Asthma | 113 (16%) | 332 (10%) | <0.001 |
| Maternal childhood wheezing | 91 (13%) | 205 (6%) | <0.001 |
| Low education mother | 395 (56%) | 1706 (53%) | 0.09 |
| Infant characteristics | | | |
| Male sex | 456 (65%) | 1740 (53%) | <0.001 |
| Multiple birth | 222 (32%) | 1108 (34%) | 0.19 |
| Birth weight <p10 | 71 (10%) | 371 (11%) | 0.30 |
| Birth weight >p90 | 51 (7%) | 231 (7%) | 0.91 |
| Gestational age | | | |
| 32 weeks | 70 (10%) | 291 (9%) | 0.40 |
| 33 weeks | 176 (25%) | 730 (23%) | 0.14 |
| 34 weeks | 240 (34%) | 1060 (33%) | 0.43 |
| 35 weeks | 215 (31%) | 1160 (36%) | 0.01 |
| Born Aug 15$^{th}$ – Dec 1$^{st}$ | 225 (32%) | 1036 (32%) | 0.94 |
| Apgar 1 min <5 | 58 (8%) | 280 (9%) | 0.73 |
| Apgar 5 min <7 | 20 (3%) | 110 (3%) | 0.46 |
| Respiratory support | 188 (27%) | 682 (21%) | 0.001 |
| Mechanical ventilation | 23 (3%) | 97 (3%) | 0.70 |
| CPAP | 145 (21%) | 542 (17%) | 0.014 |
| Supplemental oxygen | 94 (13%) | 323 (10%) | 0.008 |
| Bronchiolitis hospitalisation | 145 (21%) | 143 (4%) | <0.001 |
| RSV bronchiolitis hospitalisation | 90 (13%) | 91 (3%) | <0.001 |
| Non-RSV bronchiolitis hospitalisation | 32 (5%) | 35 (1%) | <0.001 |
| Non tested bronchiolitis hospitalisation | 23 (3%) | 17 (1%) | <0.001 |
| Day care attendance | 474 (67%) | 1627 (50%) | <0.001 |
| Age of onset of day care attendance , mnth | 4.6 (1.7) | 5.0 (2.2) | 0.06 |
| Early onset (≤ 3 months of age) | 105 (22%) | 367 (23%) | 0.74 |
| Late onset (≥ 6 months of age) | 118 (25%) | 490 (30%) | 0.03 |
| Paternal characteristics | | | |
| Paternal smoking | 182 (26%) | 885 (27%) | 0.44 |
| Paternal atopy | 255 (36%) | 984 (30%) | 0.002 |
| Hay fever | 148 (21%) | 598 (18%) | 0.11 |
| Eczema | 101 (14%) | 378 (12%) | 0.05 |
| Asthma | 104 (15%) | 274 (8%) | <0.001 |
| Paternal childhood wheezing | 82 (12%) | 234 (7%) | <0.001 |
| Low education father | 404 (57%) | 1876 (58%) | 0.82 |
| Household characteristics | | | |
| Presence of siblings | 318 (45%) | 1184 (37%) | <0.001 |
| Presence of fur bearing pets | 331 (47%) | 1524 (47%) | 0.99 |

† differences between the groups were assessed using $\chi^2$ tests, Student's t tests, or Mann Whitney U tests as appropriate.

**Table 2.** Clinical determinants of recurrent wheezing ranked according to adjusted population attributable risk (PAR).

| Risk factor | Prevalence N(%) | RR [95%CI] | PAR# [95%CI] |
|---|---|---|---|
| Day care attendance | 474 (67%) | 1.9[1.7, 2.2] | 31.7% [23, 37%] |
| Male sex | 456 (65%) | 1.5[1.3, 1.7] | 21.7% [13, 28%] |
| Bronchiolitis hospitalisation | 145 (21%) | 2.8[2.4, 3.2] | 13.5% [11, 17%] |
| RSV bronchiolitis hospitalisation | 90 (13%) | 2.6[2.2, 3.1] | 8.0% [6, 11%] |
| Non-RSV bronchiolitis hospitalisation | 32 (5%) | 2.7[2.1, 3.5] | 3.1% [2, 4%] |
| Non tested bronchiolitis hospitalisation | 23 (3%) | 3.4[2.6, 4.5] | 2.1% [1, 3%] |
| GA <35 weeks | 490 (69%) | 1.2[1.0, 1.3] | 11.5% [3, 21%] |
| Presence of siblings | 318 (45%) | 1.3[1.2, 1.5] | 10.4% [6, 17%] |
| Low education mother | 395 (56%) | 1.2[1.1, 1.4] | 9.3% [2, 16%] |
| Paternal asthma | 104 (15%) | 1.5[1.2, 1.7] | 5.0% [3, 8%] |
| Maternal childhood wheezing | 91 (13%) | 1.6[1.3, 1.9] | 4.9% [4, 8%] |
| Maternal smoking | 144 (20%) | 1.3[1.2, 1.6] | 4.6% [2, 8%] |
| Respiratory support | 188 (27%) | 1.2[1.0, 1.4] | 4.5% [2, 10%] |
| Maternal hay fever | 181 (26%) | 1.2[1.0, 1.4] | 4.3% [2, 10%] |
| | | | |
| Adjusted combined* | | | 49.1% [46, 52%] |

RR: relative risk, adjusted for all other risk factors listed; PAR: population-attributable risk; GA: gestational age; 95%CI: 95% confidence interval #The PAR for each risk factor was calculated using adjusted relative risks derived from multivariable analysis via the following formula: ((RR-1)/RR) x $P^d$ (where $P^d$ is the proportion of the cases exposed).*The combined weighted estimate of the PAR, accounting for correlation between risk factors, was calculated with the formula: $PAR_{AdjustedCombined} = 1 - \Pi( 1 - (w \times PAR))$.

**Discussion**

We recently showed in a randomized controlled trial that RSV prevention with monoclonal RSV antibody induced an important decrease in wheezing in the first year, establishing the causal link between RSV and wheezing[8]. We showed in this prospective preterm birth cohort that potentially modifiable risk factors associated viral infections and factors associated with viral exposure like day care attendance and bronchiolitis hospitalisation are important risk factors for RW during the first year of life of otherwise healthy moderate preterm infants as reflected by the relative risk and PAR of these factors. To our knowledge this is the first study to calculate PARs of independent risk factors for RW in the first year of life for moderate preterm infants. In addition, this study combined and quantified the joint PAR of potentially modifiable risk factors, being approximately 25% of RW cases.



Our results are in line with other studies in term infants and preterm infants that acknowledge the relationship between viral exposure and childhood wheezing [9,10,28]. In the recent 10 years the association of day care attendance with the development of wheezing was described thoroughly in term infants[14,29-31]. The observed incidence of RW in our study and the risk factors for RW like day care attendance, presence of siblings and male gender were comparable to other prospective studies [8,30]. It is important to note that the prevalence of day care attendance is high in the Netherlands as compared to other European countries. In a recent study by Herr et al male gender and a parental history of asthma were also identified as risk factors in children with the atopic wheezing phenotype, whereas factors related to respiratory tract infections were the strongest risk factors for the non-atopic wheezing phenotype [30]. The protective effect of early day care on later asthma development is disputed. Ball et al and others found that day care protects against the development of asthma and frequent wheezing later in childhood [14,31]. A recent large cohort study however showed that infants who attend day care do not develop fewer asthma symptoms or allergies at age 8 years [29]. In this study we found a positive association between both early and late onset of day care attendance and the incidence of RW. The pathogenesis of RW following viral infections is still poorly understood. It is disputed whether viral infection is the incepting moment for pulmonary damage and subsequent wheezing or a symptom of genetic, pulmonary or immunological predisposition [6,14] . Martinez et al. showed that as infant's airways grow in absolute size with age, they may become less apt to have wheezing during viral infections [6].

We describe and quantify that viral exposure variables, especially day care attendance as a surrogate for viral exposure, play a large role in RW incidence. In our study we showed for the first time the separate and combined contribution of these factors to RW morbidity in moderate preterm infants.

This study has several major strengths, first the size and uniqueness of our prospective cohort of moderate preterm infants (>4000 infants) and the consistent and accurate retrieval of all baseline data with minimal missing data. Second, we quantify for the first time the PAR of day care attendance, bronchiolitis and the presence of siblings to the risk of RW. Third, the methods we used to calculate PAR accounted for the correlation between risk factors by using a weighted method for combined PAR to provide a robust estimate of the combined PAR of RW risk factors[26]. We are not aware that this method is used by other groups than Norton et al. but we feel confident that the use of adjusted PAR provides a more reliable combined PAR than the use of unadjusted PAR. Furthermore, although no graded risk classification for PAR exists we have arbitrarily presented PARs of 9% and higher as major relative to the PARs of other risk factors in this study. Potential limitations should also be discussed. First, interpreting PAR assumes a causal association between risk factors and RW. This study was not designed to determine causation of risk factors for RW. This would require an intervention study with adequate follow up, this however would be costly and challenging to perform. The main focus of this study was therefore on the risk factors related to viral exposure, for which a recent randomized controlled trial suggested causality [8]. Furthermore, this study could not establish the temporal relationship between exposure and outcome. PAR estimates based on a causal relationship and not on associations would be stronger evidence. Second, a small underestimation of RSV hospitalisation may have occurred, because not all children hospitalised for respiratory tract infections were routinely tested for RSV. This could have influenced the PAR because although no big differences in RR were seen between bronchiolitis hospitalisations there was a difference in prevalence between the three groups. Third, we used a standardized parental questionnaire to determine the outcome of this study since there is no gold standard for RW during early childhood and valid lung function tests are not yet available for this age group. To increase reliability of the parental report of airway morbidity, e.g. use of airway medication and physician visits, we used the standardized questions derived from the ISAAC questionnaire [22]. Because the 1 year questionnaire included both risk factors and the primary outcome RW this reduced the advantage of the cohort

design. Furthermore, the parental report of risk factors could have resulted in a recall bias because parental history of asthma or wheeze and parental education level could have influenced recall of RW. Fourth, the study population consisted of moderate preterm infants and the result might not be generalizable to early preterm infants or term infants. Fifth, this study was performed in the Netherlands, where infants attend day care from an early age, this may have impacted the PAR of day care attendance. The transferability of the results is therefore dependent on local day care prevalence. Sixth, we had to rely on parent-reported morbidity data, since no objective measure of wheezing was available. Identifying wheezing is problematic even for trained clinicians [32-33]. Seventh, 10.6% of included patients could not be contacted despite extended efforts and were considered lost to follow-up. Maternal smoking during pregnancy was higher in this population which could have resulted in an underestimation of this effect on recurrent wheezing. As a cautionary note it should be emphasized that as RW is distinct from asthma, this study was not designed to determine risk factors for asthma. Future studies in this population are needed to determine the effect of viral infections on asthma risk.



*Conclusion*

This prospective birth cohort provides compelling evidence that the majority of the PAR of RW in moderate preterm infants is related to modifiable viral exposure variables, like day care attendance. By measuring PAR we quantify that a large proportion of RW incidence is explained by viral exposure. Understanding the etiology of RW in moderate preterm infants is important to design preventive strategies because outpatient and inpatient visits related to RW have a high economic impact[5]. Many diseases are caused by multiple risk factors, and individual risk factors may interact in their impact on overall risk of disease. Despite a strong relationship with RW, RSV bronchiolitis requiring hospitalisation had a relative modest contribution to the overall risk of RW. Trial evidence is needed to determine whether specific interventions, such as delayed day care attendance, may prevent long-term airway disease in this specific high risk population.

*Funding*

This investigator driven study was funded by a grant from the Netherlands Organization for Health Research and Development (NWO-AGIKO grant 920-035-89, to Dr. Blanken) and by an unrestricted grant from AbbVie. The study hypothesis, data collection, analysis and interpretation were performed independently by the researchers. The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

*Financial disclosure statement*

LB reports grants for investigator initiated studies from MedImmune and from AbbVie. All other authors have indicated they have no financial relationships relevant to this article to disclose.

*Conflict of interest*

LB reports consulting fees from Janssen, Gilead, Okairos, Mabxience, Alios, AIT, during the conduct of the study; MOB reports consulting fees from AbbVie. All other authors have indicated they have no potential conflicts of interest to disclose.

*Acknowledgments*

We thank Katrien Castelijns, Annemiek de Nooijer, Loek Crefcoeur en Leanne de Vries who helped in data collection. We also thank the infants and their families who graciously provided their time and effort to participate in this study.

We thank all collaborating nurses, nurse practitioners, supporting staff and pediatricians in the hospitals of the Dutch RSV Neonatal Network who collaborated in the study. Members of the Dutch RSV Neonatal Network: M.A. Breukels, Elkerliek hospital Helmond; M.M. Pestman-Harms, St. Anna hospital Geldrop; M. Westra, Zaans Medical Center Zaandam; A.O.A. Adeel, Kennemer Gasthuis Haarlem; J.T.C.M Verhallen, St. Franciscus Gasthuis Rotterdam; J.G.C.M. van Zoest, Diaconessenhuis Leiden; H. Rijk-van Gent, Antonius hospital Sneek; G.W. ten Tusscher, Westfries Gasthuis Hoorn; A.E. Hoffman-van der Meer, St. Franciscus hospital Roosendaal; C.C.J.M. Smeets, St.Elisabeth hospital Tilburg; E.H.G. van Leer, Groene Hart hospital Gouda; A.A.M.W. van Kempen, Onze Lieve Vrouwe Gasthuis Amsterdam; R. Van Gent, Maxima Medical Center Veldhoven; C.J. Miedema, Catharina hospital Eindhoven; E.P. de

Groot, Isala Klinieken Zwolle; A.H.P.M. Essink, Jeroen Bosch hospital 's Hertogenbosch; G.J. Blok, Medical Center Alkmaar; J.C. Smal, Hospital Rijnstate Arnhem; M.J. Oele, Medical Center Haaglanden Westeinde Den Haag; L.H. van der Meer-Kappelle, Reinier de Graaf Gasthuis Delft; T. Hubregtse, Laurentius hospital Roermond; M.A.M. Jacobs, Slingeland hospital Doetinchem; T.E. Faber, Medical Center Leeuwarden; J.P. de Winter, Spaarne hospital Hoofddorp; A.C.M. van Kessel, Diaconessenhuis Meppel; P.P.R. Rosias, Orbis Medical Center Sittard; S.L. Schellekens, Bernhoven hospital Veghel; K.D. Liem, University Medical Center St. Radboud; A.J. Sprij, Juliana Children's Hospital Den Haag; P.W.T. van Rijssel, Maashospital Pantein Boxmeer; I.A. von Rosenstiel, Slotervaart hospital Amsterdam; E.I.M. Blankman, Bovenij hospital Amsterdam; J.J.B. Rehbock, Lange Land hospital Zoetermeer; C.G. Massar, Waterland hospital Purmerend; C.L.M. Geesing, Bernhoven hospital Oss; W.F. Heikens, Hospital Tjongerschans Heerenveen; J.C. Bakker, Streekhospital Midden-Twente Hengelo; K.M. Dolman, St. Lucas Andreas hospital Amsterdam; J.H. Kreijen-Meinesz, Bronovo hospital Den Haag; E.A. Smit-Kleinlugtenbeld, Albert Schweitzer hospital Dordrecht

**References**


1. Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? *Lancet* 2001 Jun;357(9271):1821-5.
2. Bont L, Steijn M, van Aalderen WM, Kimpen JL. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. *Pediatric Infectious Diseases Journal* 2004 May;23(5):414-7.
3. Bisgaard H, Szefler S. Prevalence of asthma-like symptoms in young children. *Pediatric Pulmonology* 2007 Aug;42(8):723-8.
4. Ungar WJ, Coyte PC. Prospective study of the patient-level cost of asthma care in children. *Pediatric Pulmonology* 2001 Aug;32(2):101-8.
5. Stevens CA, Turner D, Kuehni CE, Couriel JM, Silverman M. The economic impact of preschool asthma and wheeze. *European Respiratory Journal* 2003 Jun;21(6):1000-6.
6. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *New England Journal of Medicine* 1995 Jan;332(3):133-8.
7. Heymann PW, Carper HT, Murphy DD, Platts-Mills TA, Patrie J, McLaughlin AP, et al. Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. *Journal of Allergy and Clinical Immunology* 2004 Aug;114(2):239-47.
8. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *New England Journal of Medicine* 2013 May;368(19):1791-9.
9. Lemanske RF, Jr., Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *Journal of Allergy and Clinical Immunology* 2005 Sep;116(3):571-7.
10. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *American Journal of Respiratory and Critical Care Medicine* 2008 Oct;178(7):667-72.
11. Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Medicine* 2014 Jan;11(1):e1001596.

12. Bisgaard H, Jensen SM, Bonnelykke K. Interaction between asthma and lung function growth in early life. *American Journal of Respiratory and Critical Care Medicine* 2012 Jun;185(11):1183-9.
13. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *New England Journal of Medicine* 1988 Oct;319(17):1112-7.
14. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *New England Journal of Medicine* 2000 Aug;343(8):538-43.
15. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. *Journal of Allergy and Clinical Immunology* 2003 Apr;111(4):661-75.
16. Dogaru CM, Strippoli MP, Spycher BD, Frey U, Beardsmore CS, Silverman M, et al. Breastfeeding and lung function at school age: does maternal asthma modify the effect? *American Journal of Respiratory and Critical Care Medicine* 2012 Apr;185(8):874-80.
17. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *American Journal of Public Health* 1998 Jan;88(1):15-9.
18. Pinart M, Benet M, Annesi-Maesano I, von BA, Berdel D, Carlsen KC, Carlsen KH, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based cohort study. *Lancet Respiratory Medicine* 2014 Feb;2(2):131-40.
19. Bisgaard H, Hermansen MN, Buchvald F, Loland L, Halkjaer LB, Bonnelykke K, et al. Childhood asthma after bacterial colonization of the airway in neonates. *New England Journal of Medicine* 2007 Oct;357(15):1487-95.
20. Blanken MO, Koffijberg H, Nibbelke EE, Rovers MM, Bont L. Prospective validation of a prognostic model for respiratory syncytial virus bronchiolitis in late preterm infants: a multicenter birth cohort study. *PLoS One* 2013;8(3):e59161.
21. Lakwijk N, Van Strien RT, Doekes G, Brunekreef B, Gerritsen J. Validation of a screening questionnaire for atopy with serum IgE tests in a population of pregnant Dutch women. *Clinical and Experimental Allergy* 1998 Apr;28(4):454-8.

22. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *European Respiratory Journal* 1995 Mar;8(3):483-91.
23. Ermers MJ, Rovers MM, van Woensel JB, Kimpen JL, Bont LJ. The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: randomised double blind placebo controlled trial. *British Medical Journal* 2009;338:b897.
24. Benichou J. A review of adjusted estimators of attributable risk. *Statistical Methods of Medical Research* 2001 Jun;10(3):195-216.
25. Walter SD. Calculation of attributable risks from epidemiological data. *International Journal of Epidemiology* 1978 Jun;7(2):175-82.
26. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurology* 2014 Aug;13(8):788-94.
27. Watkins MW. Determining Parallel Analysis Criteria. *Journal of Modern Applied Statistical Methods* 2006;5(2).
28. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999 Aug;354(9178):541-5.
29. Caudri D, Wijga A, Scholtens S, Kerkhof M, Gerritsen J, Ruskamp JM, et al. Early daycare is associated with an increase in airway symptoms in early childhood but is no protection against asthma or atopy at 8 years. *American Journal of Respiratory and Critical Care Medicine* 2009 Sep;180(6):491-8.
30. Herr M, Just J, Nikasinovic L, Foucault C, Le Marec AM, Giordanella JP, et al. Risk factors and characteristics of respiratory and allergic phenotypes in early childhood. *Journal of Allergy and Clinical Immunology* 2012 Aug;130(2):389-96.
31. Nicolaou NC, Simpson A, Lowe LA, Murray CS, Woodcock A, Custovic A. Day-care attendance, position in sibship, and early childhood wheezing: a population-based birth cohort study. *Journal of Allergy and Clinical Immunology* 2008 Sep;122(3):500-6.
32. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *European Respiratory Journal* 2008;32:1096-110.

33. Elphick HE, Sherlock P, Foxall G, Simpson EJ, Shiell NA, Primhak RA et al. Survey of respiratory sounds in infants. *Archives of Diseases in Childhood* 2001;84:35-9.

## Supporting Information

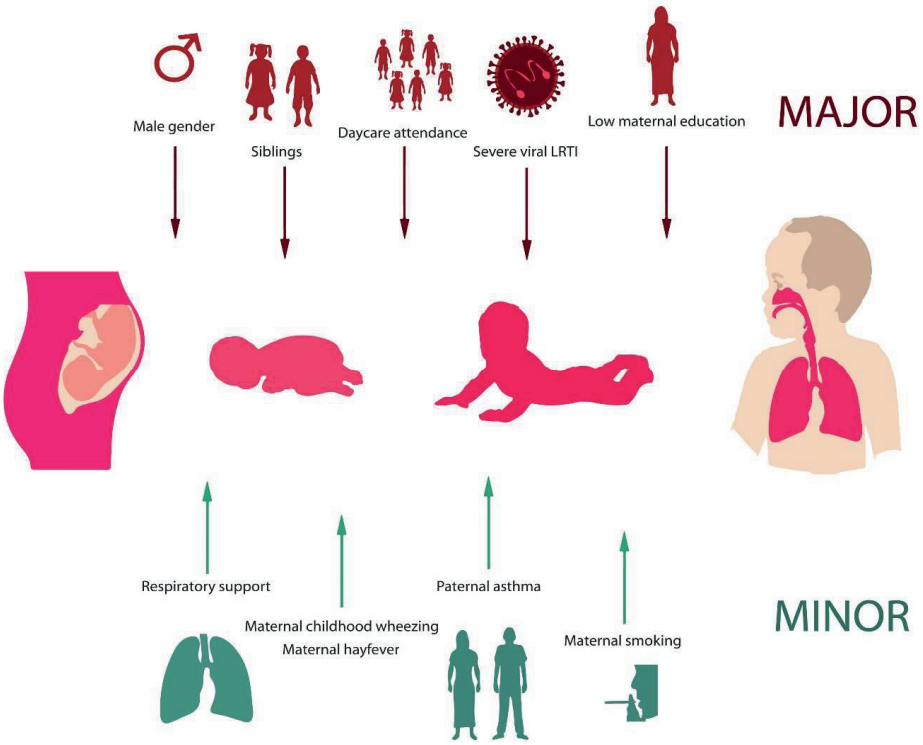



*Figure S1. Major and minor contributors to recurrent wheezing during the first year of life ranked according to adjusted population-attributable risk (PAR). PAR calculation was based on adjusted independent relative risks and prevalence rates derived in this article. PARs of 9% and higher are presented as major relative to the PARs of other risk factors in this study (PAR ≤5%).*

Table S1. Shared variance between risk factors.

| **Risk factor** | **Communality** |
|---|---|
| Day care attendance | 49.7% |
| Male sex | 47.9% |
| Bronchiolitis hospitalisations | 62.3% |
| Low education mother | 54.0% |
| Presence of siblings | 57.5% |
| Paternal asthma | 51.1% |
| Maternal hay fever | 56.0% |
| Maternal smoking | 40.6% |
| Respiratory support | 58.6% |
| Maternal childhood wheezing | 55.0% |
| GA <35 weeks | 59.5% |

Table S2. Clinical determinants of medically attended recurrent wheezing ranked according to adjusted population-attributable risk (PAR).

| **Characteristic N (%)** | **MA Recurrent wheezing N = 255** | **No Recurrent wheezing N = 3691** | **RR [95%CI]** | **PAR[#] [95%CI]** |
|---|---|---|---|---|
| Day care attendance | 171 (67%) | 1933 (52%) | 2.1[1.7, 2.7] | 35.1% [24, 46%] |
| Male sex | 179 (70%) | 1692 (46%) | 1.9[1.5, 2.4] | 33.2% [21, 45%] |
| Low education mother | 165 (65%) | 1942 (52%) | 1.7[1.3, 2.2] | 26.8% [15, 39%] |
| Bronchiolitis hospitalisations | 72 (28%) | 216 (6%) | 4.0 [3.1, 5.1] | 21.0% [16, 28%] |
| RSV bronchiolitis hospitalisation | 47 (18%) | 135 (4%) | 3.9[3.0, 5.2] | 13.4% [9, 19%] |
| Non-RSV bronchiolitis hospitalisation | 18 (7%) | 49 (1%) | 4.6[3.0, 7.0] | 5.5% [2, 8%] |
| Non tested bronchiolitis hospitalisation | 7 (3%) | 32 (1%) | 3.3[1.8, 6.0] | 2.1% [0, 4%] |
| Presence of siblings | 132 (52%) | 1369 (37%) | 1.6[1.3, 2.1] | 19.5% [10, 30%] |
| Paternal asthma | 52 (20%) | 326 (9%) | 2.1[1.6, 2.7] | 10.5% [5, 15%] |
| Maternal hay fever | 79 (31%) | 730 (20%) | 1.5[1.2, 1.9] | 10.3% [3, 17%] |
| Maternal smoking | 64 (25%) | 587 (16%) | 1.6[1.2, 2.1] | 9.4% [3, 16%] |
| Respiratory support | 74 (29%) | 799 (22%) | 1.4[1.1, 1.7] | 8.3% [1, 15%] |
| Maternal childhood wheezing | 43 (17%) | 254 (7%) | 1.9[1.4, 2.6] | 8.1% [3, 13%] |
| GA <35 weeks | 168 (66%) | 2404 (65%) | NS | NS |
| Adjusted combined* | | | | 64·3% [59, 70%] |

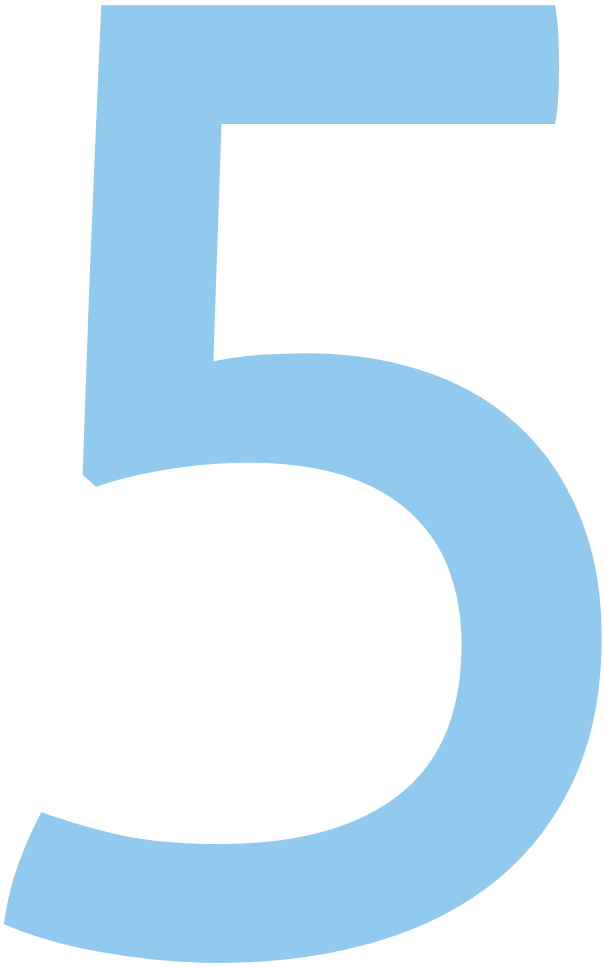
Abbreviations: MA RW current: recurrent wheezing plus current airway medication usage (fluticasone, salbutamol/albuterol, beclomethasone, ipratropium; RR: relative risk, adjusted for all other risk factors listed; PAR: population-attributable risk; GA: gestational age; 95%CI: 95% confidence interval [#]The PAR for each risk factor was calculated using adjusted relative risks derived from multivariable analysis via the following formula: ((RR-1)/RR) x $P^d$ (where $P^d$ is the proportion of the cases exposed).*The combined weighted estimate of the PAR, accounting for correlation between risk factors, was calculated with the formula: $PAR_{AdjustedCombined} = 1 - \Pi (1 - (w \times PAR))$.

Table S3. Distribution of characteristics of infants lost to follow-up compared with infants with complete data (n(%)).

| | **Lost to follow-up (N = 472)** | **Complete data (N= 3952)** |
|---|---|---|
| Clinical data | **N (%)** | **N (%)** |
| Gender male | 234 (50%) | 2196 (56%)* |
| Gestational age mean (weeks + days) | 34+2 | 34+2 |
| Birth weight (grams) (mean(SD)) | 2183 (446) | 2198 (448) |
| Multiple birth | 137 (29%) | 1330 (34%)* |
| Caesarean section | 157 (33%) | 1422 (36%) |
| Neonatal respiratory support ◊ | 94 (20%) | 870 (22%) |
| Mechanical ventilation | 4 (1%) | 120 (3%)* |
| Birth from August 14th - December 1st | 138 (29%) | 1261 (32%) |
| Breastfeeding Δ | 333 (71%) | 2897 (73%) |
| Presence of siblings | 180 (38%) | 1502 (38%) |
| Day care attendance | 236 (50%) | 2101 (53%) |
| Maternal smoking during pregnancy | 98 (21%) | 477 (12%)* |

* Baseline difference between excluded and included infants $p<0.05$ ◊ Oxygen/nasal mask/CPAP and/or mechanical ventilation. Δ predicted, either exclusive/mixed with formula feeding. # hay fever/asthma and/or eczema. † One parent completed at least a university of applied sciences.

CHAPTER 5



# Prospective validation of a prognostic model for respiratory syncytial virus bronchiolitis in late preterm infants: a multicenter birth cohort study

Maarten O. Blanken, Erik Koffijberg, Loes Nibbelke, Maroeska M. Rovers, Louis Bont, on behalf of the Dutch RSV Neonatal Network

*PLoS One. 2013;8(3):e59161*

**Abstract**

*Objectives*

This study aimed to update and validate a prediction rule for respiratory syncytial virus (RSV) hospitalisation in preterm infants 33–35 weeks gestational age (WGA).

*Study Design*

The RISK study consisted of 2 multicenter prospective birth cohorts in 41 hospitals. Risk factors were assessed at birth among healthy preterm infants 33–35 WGA. All hospitalisations for respiratory tract infection were screened for proven RSV infection by immunofluorescence or polymerase chain reaction. Multivariate logistic regression analysis was used to update an existing prediction model in the derivation cohort (n = 1,227). In the validation cohort (n = 1,194), predicted versus actual RSV hospitalisation rates were compared to determine validity of the model.

*Results*

RSV hospitalisation risk in both cohorts was comparable (5.7% versus 4.9%). In the derivation cohort, a prediction rule to determine probability of RSV hospitalisation was developed using 4 predictors: family atopy (OR 1.9; 95%CI, 1.1–3.2), birth period (OR 2.6; 1.6–4.2), breastfeeding (OR 1.7; 1.0–2.7) and siblings or daycare attendance (OR 4.7; 1.7–13.1). The model showed good discrimination (c-statistic 0.703; 0.64–0.76, 0.702 after bootstrapping). External validation showed good discrimination and calibration (c-statistic 0.678; 0.61–0.74).

*Conclusions*

Our prospectively validated prediction rule identifies infants at increased RSV hospitalisation risk, who may benefit from targeted preventive interventions. This prediction rule can facilitate country-specific, cost-effective use of RSV prophylaxis in late preterm infants.

**Introduction**

Respiratory syncytial virus (RSV) bronchiolitis is one of the most common causes of infant hospitalisation during the winter season and is associated with a large burden of disease and high costs [1–5]. Hospitalisation for RSV lower respiratory tract infection in Europe and the United States is estimated to be 1-3% of all infants aged less than 13 months. Important risk groups for RSV bronchiolitis are infants with prematurity with or without chronic lung disease, congenital heart disease, Down syndrome and immunodeficiencies [6–9]. Although risk groups for RSV bronchiolitis have been identified, the precise incidence of hospitalisation for RSV bronchiolitis in these patient populations is generally not known. There is no effective therapy for RSV infection, so treatment is mainly symptomatic [10]. Due to the increased risk most high risk groups receive RSV immunoprophylaxis to prevent RSV infection. Palivizumab, a humanized immunoglobin monoclonal antibody, specific for RSV, has been proven effective and safe for preterm infants with gestational age ≤35 weeks, infants with bronchopulmonary dysplasia and infants with congenital heart disease [11,12]. Efficacy of 55% of RSV prophylaxis has been demonstrated for late preterm infants 33-35 weeks gestational age (WGA). Subgroup analysis showed 80% efficacy of RSV prophylaxis in 32-35 WGA preterm infants [12]. In many countries RSV immunoprophylaxis is not used in late preterm infants 33-35 WGA because of high costs [13]. Within health care, limited budgets force the need to selectively apply high cost treatments to a proportion of infants identified as having increased risk for severe disease. Costs may be reduced by targeting RSV immunoprophylaxis to 33-35 WGA late preterm infants with additional risk factors.[14] Several environmental and clinical risk factors have been described which compound the risk for severe RSV disease. Presence of siblings, daycare attendance, month of birth and protective factors like breastfeeding have been described as independent risk factors for severe disease due to RSV infection.[15–21] In a recent paper it was emphasized that validated prediction rules are required to improve the care of our patients with infectious diseases.[22] Two prediction rules for late preterm infants 33-35 WGA have been published but these have not yet been validated prospectively.[23,24] To develop a practical and accurate prediction model for the Netherlands the prediction rule previously developed by Simoes et al. may have inferior performance in countries, such as the Netherlands, in which most children visit daycare facilities.[24] We therefore aimed to update and validate a RSV prediction rule for 33-35 WGA late preterm infants using 2 prospective birth cohorts.[24]

**Methods**

*Study design*

RISK is an ongoing study prospectively performed in late preterm infants born at 32 weeks and 1 day to 35 weeks and 6 days weeks gestational age (referred to as 33-35 WGA) in 41 hospitals of the RSV Neonatal Network in the Netherlands. Between June 2008 and January 2011 infants were included in hospitals located across the Netherlands. The study population consisted of newborn infants born at 33-35 WGA from 1 university hospital and 40 regional hospitals. Infants with gross abnormalities or Down syndrome, and those who received palivizumab for any reason were excluded. The study consists of 2 subsequent birth cohorts: a derivation cohort and a validation cohort.

*Ethics statement*

The study was reviewed and approved by the Institutional Review Board of the University Medical Center Utrecht and subsequently approved by Institutional Review Boards of all participating hospitals. All parents provided written informed consent for screening of hospital records. The study was conducted in compliance with the Declaration of Helsinki and the standards of Good Clinical Practice.

*Data collection*

At birth, a questionnaire containing questions on family history of wheeze, asthma and hay fever, smoking during pregnancy and in the household, the number of siblings and their age, parental education level, potential breastfeeding, potential day-care attendance, household pets and pregnancy details was filled out by parents. Clinical data on the mode of delivery, gestational age, respiratory support, birth weight, Apgar score and delivery details were derived from patient charts. The following 7 variables from the prediction rule previously developed by Simoes et al. were noted:"birth within 10 weeks of the start of the season," "birth weight," "breast-feeding ≤2 months," "number of siblings ≥2 years of age," "number of family members with atopy," "male sex," and "number of family members with wheeze"[24]. Breast-feeding was defined as either exclusive breastfeeding or mixed with formula feeding. Atopy was defined as the presence of asthma, eczema or hay fever. At one year of age, parents were contacted by telephone to determine whether hospitalisation for respiratory disease had occurred. If any data were missing from questionnaires completed by the parents/legal

guardians or from the clinical records, the respective physician was contacted for information, which ensured that all baseline data were assembled. If the parents could not be reached by telephone, the hospital and general practitioner were contacted for updated information. If no valid telephone number was available, an e-mail or letter was sent to the parents.

*Outcome definition*

When parents reported hospitalisation for respiratory disease during the first year of life, we analysed the medical hospital record for RSV hospitalisation, including routine virology results. The main study endpoint, hospitalisation for RSV bronchiolitis was defined as hospitalisation for lower respiratory tract infection with proven RSV infection determined by routine practice laboratory testing in the participating hospitals, i.e. either by rapid RSV immunofluorescence test or polymerase chain reaction.

*Statistical analysis*

Sample size calculation: According to a generally accepted rule of thumb that at least 10 cases are required per variable in the prediction rule. For a 7-variable model we calculated a priori, a sample size of 70 infants hospitalised for RSV bronchiolitis. [24] With an estimated incidence of 4%, the projected sample size of the derivation cohort was 1,750. To validate a 4-variable prediction rule, the estimated sample size of the validation cohort was 1,000.

*Derivation and validation of the prediction rule*

We assessed the test performance of the clinical prediction rule to identify infants at high risk for hospitalisation with RSV bronchiolitis. To evaluate the models' calibration, the Hosmer-Lemeshow statistic was used in which observations are grouped based on deciles of predicted probability and compared with the observed risk of RSV bronchiolitis in the derivation and validation cohort. This was graphically assessed with a calibration plot and tested with the Hosmer-Lemeshow statistic, where a non-significant test indicated good model fit.[25,26] Discrimination is the ability of the rule to distinguish between infants hospitalised from those not hospitalised for RSV bronchiolitis, and will be quantified with the Area Under the Receiver Operating Characteristic curve (AUROC). An AUROC area ranges from 0.5 (no discrimination.) to 1.0 (perfect discrimination).

We anticipated that the prediction rule previously developed by Simoes et al. may have inferior performance in countries, such as the Netherlands, in which most children visit day

care facilities. Therefore we planned to update the model. Multivariable logistic regression was used to update the independent contribution of each of the variables to the discrimination of the model. The updated model was reduced by excluding variables from the model with univariate p-values >0.15, using the log likelihood ratio test. The AUROC was used to determine whether the variables provided added predictive value beyond the existent prediction rule.[27] Other, additional variables with a univariate p-value of <0.15 not included in the original prediction rule were added to increase the discrimination and reliability of the prediction rule. Subsequently, the model shrinkage was applied in the derivation dataset using bootstrapping, to adjust the model's estimated regression coefficients in order to reduce overfitting.[25,28] We repeated the modelling process in 1,000 bootstrap samples. For each individual infant the risk score was calculated using the bootstrap-corrected coefficients of the updated prediction rule. The value of each risk factor was multiplied by its coefficient and the sum of all resulting values and the model intercept, i.e. the linear predictor, was calculated. The results of the validation were examined primarily by classification tables and by calculating the AUROC. To make the model easy to use in a clinical setting we calculated a point score.

The updated prediction rule was externally validated in a new cohort of infants. The two cohorts were derived by making a non-randomized split according to birth date. [29]

We defined our derivation cohort as all infants born between June 2008 and September 2009, and our validation cohort as all infants born between September 2009 and January 2011. We calculated performance of the rule as sensitivity, specificity, positive likelihood ratio and negative likelihood ratio. Statistical analysis was performed by using SPSS 15.0. (SPSS Inc, Chicago, Ill).

## Results

*Patient characteristics*

In total, 2,703 infants born in the 41 participating hospitals were included (figure 1, table 1); 186 infants (7%) were lost to follow-up after a year. Three infants died of RSV-unrelated causes. Of the 2,514 included infants, 198 parents reported hospitalisation for respiratory tract symptoms during the first year of life and these were verified through hospital medical records. For these 198 hospitalisations, tests for RSV were positive in 129 instances (5.1%) and negative in another 41 (1.6%). Testing for RSV was not performed in 28 cases.

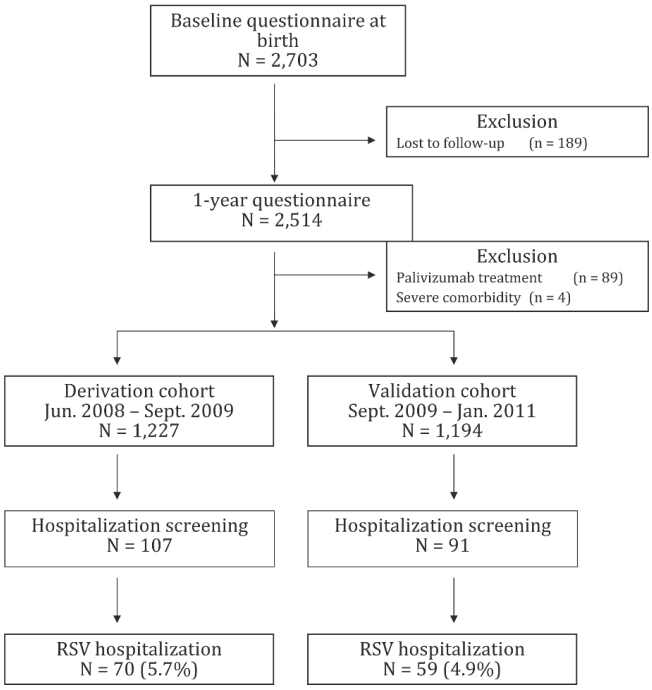



*Figure 1. Patient flowchart derivation and validation cohort.*

**Table 1.** Distribution of Baseline Patient Characteristics in the Derivation and Validation Cohort (Number(percentage)).

| | Derivation cohort (n=1,227) | Validation cohort (n=1,194) |
|---|---|---|
| Male gender | 676 (55.1%) | 659 (55.2%) |
| Gestational age (wk) | 34 +2 days | 34 + 2 days |
| 32 | 115 (9.4%) | 124 (10.4%) |
| 33 | 296 (24.1%) | 240 (20.1%) |
| 34 | 371 (30.2%) | 429 (35.9%) |
| 35 | 445 (36.3%) | 401 (33.6%) |
| Birth Weight (g) (Mean(SD)) | 2214 (452) | 2225 (427) |
| Multiple pregnancy | 426 (34.7%) | 422 (35.3%) |
| Caesarean section | 409 (33.3%) | 436 (36.5%) |
| Continuous positive airway pressure | 166 (13.5%) | 217 (18.2%) |
| Mechanical ventilation | 46 (3.7%) | 35 (2.9%) |
| Born Aug 14th to Dec 1st | 324 (26.4%) | 496 (41.5%) |
| Breastfeeding less than 2months or not # | 416 (33.9%) | 376 (31.5%) |
| Presence of siblings | 504 (41.1%) | 463 (38.8%) |
| Atopy in 1st degree family member | 642 (52.3%) | 729 (61.1%) |
| Fur bearing pets | 571 (46.5%) | 548 (45.9%) |
| Maternal smoking during pregancy | 164 (13.4%) | 136 (11.4%) |
| Subject daycare attendance # | 730 (59.5%) | 714 (59.8%) |
| Number of house hold residents (Median (95%CI)) | 3 (2-4) | 3 (2-4) |
| Siblings or subject daycare attendance | 959 (78.2%) | 918 (76.9%) |

*No infants developed BPD ** either exclusive breastfeeding or mixed with formula feeding # predicted by parents at birth.

*Derivation of the prediction rule*

Table 2 shows the distribution of potential predictors of RSV bronchiolitis. In the derivation cohort we updated a previously published prediction rule.[24] Of the seven predictors in this original model the following four variables “birth within 10 weeks of the start of the season,” “breast-feeding ≤2 months”, “number of siblings ≥2 years of age”, “number of family members with atopy”, contributed significantly.

**Table 2.** Distribution of potential predictors across cases and non-cases in the derivation and validation cohort.

| | Derivation cohort (n=1,227) | | Validation cohort (n=1,194) | |
|---|---|---|---|---|
| Characteristic (Number (%)) | RSV hospitalisation (n=70) | Controls (n=1,157) | RSV hospitalisation n=59 | Controls (n=1,135) |
| Born Aug 14th to Dec 1st | 32 (45.7%) | 292 (25.2%) | 35 (59.3%) | 461 (40.6%) |
| Gestational age (weeks + days) (Median (95%CI)) | 34+2 (32+1-35+6) | 34+2 (32+1-35+6) | 34+1(32+1-35+6) | 34+2 (32+1-35+6) |
| Birth weight, gr (Mean (SD)) | 2216 (483) | 2214 (450) | 2215 (395) | 2200 (428) |
| Breast fed ≤ 2 months or not# | 32 (45.7%) | 384 (33.2%) | 20 (33.9%) | 356 (31.4%) |
| Presence of siblings | 46 (65.7%) | 458 (39.6) | 33 (55.9%) | 430 (37.9%) |
| Atopy in 1st degree family member | 46 (65.7%) | 596 (51.5%) | 41 (69.5%) | 688 (60.6%) |
| Male gender | 39 (55.7%) | 637 (55.1%) | 29 (49.2%) | 630 (55.5%) |
| Fur bearing pets | 27 (38.6%) | 544 (47.0%) | 22 (37.3%) | 526 (46.3%) |
| Maternal smoking during pregancy | 11 (15.7%) | 153 (13.2%) | 9 (15.3%) | 127 (11.2%) |
| Subject daycare attendance# | 47 (67.1%) | 683 (59.0%) | 41 (70.7%) | 673 (59.4%) |
| Number of residents | 3.1 (0.84) | 2.8 (0.80) | 3.0 (0.80) | 3.0 (0.80) |
| Siblings or subject daycare attendance | 66 (94.3%) | 893 (77.2%) | 55 (93.2%) | 863 (76.0%) |
| Multiple birth | 25 (35.7%) | 401 (34.7%) | 14 (23.7%) | 408 (36.1%) |

* either exclusive breastfeeding or mixed with formula feeding # predicted by parents at birth.

Updating the model by adjusting the four original variables to increase discrimination and by stepwise backward selection in the derivation cohort resulted in the final 4-variable model including "born Aug 14th to Dec 1st", "presence of siblings or day care attendance", "atopy in a 1st degree family member" and "breast-feeding ≤2 months". The AUROC of this updated model was 0.703 (95% CI 0.64-0.76) before bootstrapping and 0.702 (0.64-0.76) afterwards (Table 3). We used point values generated from the five times multiplied and rounded regression coefficients to develop a score. We entered the scores of each patient in a logistic regression model to generate the individual predicted probability of RSV hospitalisation. For scores ≥16 mean predicted probabilities were 10.0% (95% CI 7.0-14.2%) versus 3.5% in scores <16.

**Table 3.** Results of the multivariable logistic regression analyses in the derivation cohort (n = 1227) and the performance of the model in the validation cohort (n = 1194): predictors for RSV hospitalisation after bootstrapping.

| Characteristics | RISK model† | | | RISK point score |
|---|---|---|---|---|
| | Regression coefficient | Odds ratio (95% CI) | p-value | |
| *Born Aug 14th to Dec 1st* | 0.96 | 2.6 (1.6-4.2) | <0.001 | 5 |
| *Presence of siblings or subject daycare attendance#* | 1.65 | 4.7 (1.7-13.1) | 0.003 | 8 |
| *Breast fed 2months or not#* | 0.51 | 1.7 (1.0-2.7) | 0.04 | 3 |
| *Atopy in 1st degree family member* | 0.67 | 1.9 (1.1-3.2) | 0.01 | 3 |
| | | | | |
| *Intercept* | -4.20 | | | |
| ROC area (95%CI) derivation cohort | | 0.702 (0.64-0.76) | | |
| ROC area (95%CI) validation cohort | | 0.678 (0.61-0.74) | | |

* either exclusive breastfeeding or mixed with formula feeding # predicted by parents at birth.

*Validation of the prediction rule*

In our independent validation sample, the updated prediction rule demonstrated satisfactory discrimination (AUROC, 0.678; 95% CI 0.61-0.74) (Table 3). In the calibration plot, the intercept was 0.0, the slope was 1.0, indicating good calibration. The Hosmer-Lemeshow test resulted in a p-value of 0.26, and the average absolute difference in predicted and calibrated probabilities was 0.008. We calculated sensitivity, specificity and diagnostic likelihood ratios for each score defined as high-risk categories (Table 4). Using a threshold score ≥16 we observed that 27 infants (positive predictive value 10%) were hospitalised for RSV bronchiolitis in the validation cohort. We calculated the following other characteristics of the RISK prediction rule: negative predictive value of 96%, sensitivity of 46% (95% CI 34-58%), a specificity of 79% (95% CI 76-81%), a positive likelihood ratio of 2.1 (95% CI 1.6-2.9) and a negative likelihood ratio of 0.7 (95% CI 0.5-0.9).

**Table 4**. Operating Characteristics for Each Threshold of the RISK model in the validation cohort (n = 1194).

| | RISK score | | | |
|---|---|---|---|---|
| | ≥ 8 | ≥11 | ≥16 | ≥19 |
| True positive | 56 (4.7%) | 53 (4.4%) | 27 (2.3%) | 8 (0.7%) |
| False positive | 957 (80%) | 745 (62%) | 243 (20%) | 62 (5.0%) |
| True negative | 178 (15%) | 390 (33%) | 892 (75%) | 1073 (90%) |
| False negative | 3 (0.2%) | 6 (0.5%) | 32 (2.6%) | 51 (5.0%) |
| | | | | |
| Sensitivity | 0.95 | 0.90 | 0.46 | 0.14 |
| Specificity | 0.16 | 0.34 | 0.79 | 0.95 |
| Positive likelihood ratio | 1.1 | 1.4 | 2.1 | 2.5 |
| Negative likelihood ratio | 0.3 | 0.3 | 0.7 | 0.9 |

**Discussion**

We showed that the overall RSV hospitalisation risk was 5.1% in this population of healthy late preterm infants 33-35 WGA. As far as we are aware, this is the first prospective validation study for RSV hospitalisation in late preterm infants. The sample size was large enough for both updating and validating the updated prediction rule. The 4-variable prediction rule can be used to further target preventive interventions at those infants who have the highest risk for hospitalisation caused by RSV infection.

Two previous studies described prediction rules for RSV hospitalisation in late preterm infants.[23,24] The group of Figueras-Aloy developed a 7-variable prediction rule for RSV hospitalisation in a group of late preterms born between 33-35 weeks of gestation. This model was retrospectively validated in French, Italian and Danish cohort studies or case-control studies.[30–33] We updated the Spanish prediction rule aiming to produce a model which is both valid and practical in clinical use. The predictors in our prediction rule are also in agreement with a Canadian prediction model.[31] This model was retrospectively validated in the case-control study used to develop the Spanish prediction rule.[23] Although the Canadian study has not been prospectively validated, this study is used for targeted prophylaxis in Canada. The performance of the RISK prediction model is remarkably similar to the actual impact of the Canadian model as it targets 22% of the late preterm cohort which is comparable to the performance of the prediction rule used in Canada which targets 18% of late preterms of 33-35 WGA.[31]

The major strengths of our study include: that data from 2 large prospective cohorts were collected allowing further validation of an existing RSV prediction rule, the retrieval of complete baseline data, and palivizumab was used by less than 5% in our study population because it is not reimbursed. The majority of infants who received palivizumab in our study population had either a congenital anomaly or chronic lung disease. Some potential limitations included the following. First, an underestimation of RSV hospitalisation may have occurred, because not all infants hospitalised for respiratory tract infections were routinely tested. Underestimation of the risk of RSV hospitalisation is unlikely to have affected the AUROC of the prediction rule, but would result in an underestimation of the positive predictive value. Second, of all infants with a score <16, 3.5% will be hospitalised for RSV bronchiolitis while not classified as high risk. Third, 6.1% of parents could not be contacted after 1 year despite attempts to obtain contact details via the hospital, general practitioner or a web-

based search and this could be a potential selection bias. Since the vast majority of parents were contacted we believe this does not significantly jeopardize the conclusions of this study. Fourth, this study does not answer the on-going question of cost-effectiveness of RSV immunoprophylaxis in late preterm infants.[13,14,34–39] Conflicting reports on this matter have recently been published.[36,40–42] However, applying the RISK prediction rule will certainly improve cost-effectiveness of RSV prophylaxis. Five, because there is no gold standard for RSV prediction we were unable to assess the criterion validity of the RISK prediction model. Content, construct and face validity were accounted for because our analyses covered all relevant RSV risk factors and the outcome of our model is based on laboratory confirmed RSV hospitalisations. Since we externally validated the prediction model in a prospective and independent second cohort we believe the model was sufficiently validated.

The RISK prediction model incorporates four simple clinical variables which combined can be used for risk stratification in the birth period among late preterm infants. The RISK model provides an important foundation for targeted prevention for those infants most at risk for severe RSV disease. With the RISK prediction rule a high risk group can be identified with a hospitalisation risk >10% which is comparable to the hospitalisation risk in preterm infants <32 weeks gestational age and other high risk groups [6,7] If a risk score of 16 is applied, then infants with a risk score exceeding this threshold comprise 22% of all preterm infants 33-35 weeks gestational age. By targeting only 22% of this large birth cohort of late preterm infants for prophylaxis, the potential impact of our model is not dissimilar to the Canadian findings.[31] Future research should focus on the confirmation of the impact of the RISK prediction rule during implementation in clinical guidelines.



*Conclusion*

The risk of hospitalisation for RSV bronchiolitis in late preterms is 5.1%. The RISK prediction rule is a simple clinical rule identifying a subgroup of 33-35 WGA late preterm infants with increased risk of hospitalisation for RSV bronchiolitis. Implementation of the RISK prediction rule will further improve cost-effectiveness of RSV prophylaxis.

*Acknowledgements*

We thank Niek Achten, Koos Korsten, Katrien Castelijns and Annemiek de Nooijer who helped in data collection. We also thank the infants and their families who graciously provided their time and effort to participate in this study.

We thank all collaborating nurses, nurse practitioners, supporting staff and pediatricians in the hospitals of the Dutch RSV Neonatal Network who collaborated in the study: M.A. Breukels, Elkerliek hospital Helmond; M.M. Pestman-Harms, St. Anna hospital Geldrop; M. Westra, Zaans Medical Center Zaandam; A.O.A. Adeel, Kennemer Gasthuis Haarlem; J.T.C.M Verhallen, St. Franciscus Gasthuis Rotterdam; J.G.C.M. van Zoest, Diaconessenhuis Leiden; H. Rijk-van Gent, Antonius hospital Sneek; G.W. ten Tusscher, Westfries Gasthuis Hoorn; A.E. Hoffman-van der Meer, St. Franciscus hospital Roosendaal; C.C.J.M. Smeets, St. Elisabeth hospital Tilburg; E.H.G. van Leer, Groene Hart hospital Gouda; A.A.M.W. van Kempen, Onze Lieve Vrouwe Gasthuis Amsterdam; R. van Gent, Máxima Medical Center Veldhoven; C.J. Miedema, Catharina hospital Eindhoven; E.P. de Groot, Isala Klinieken Zwolle; A.H.P.M. Essink, Jeroen Bosch hospital 's Hertogenbosch; G.J. Blok, Medical Center Alkmaar;. J.C. Smal, Hospital Rijnstate Arnhem; M.J. Oele, Medical Center Haaglanden Westeinde Den Haag; L.H. van der Meer-Kappelle, Reinier de Graaf Gasthuis Delft; T. Hubregtse, Laurentius hospital Roermond; M.A.M. Jacobs, Slingeland hospital Doetinchem; T.E. Faber, Medical Center Leeuwarden; J.P. de Winter, Spaarne hospital Hoofddorp; A.C.M. van Kessel, Diaconessenhuis Meppel; P.P.R. Rosias, Orbis Medical Center Sittard; S.L. Schellekens, Bernhoven hospital Veghel; K.D. Liem, University Medical Center St. Radboud; A.J. Sprij, Juliana Children's Hospital Den Haag; P.W.T. van Rijssel, Maashospital Pantein Boxmeer; I.A. von Rosenstiel, Slotervaart hospital Amsterdam; E.I.M. Blankman, Bovenij hospital Amsterdam; J.J.B. Rehbock, Lange Land hospital Zoetermeer; C.G. Massar, Waterland hospital Purmerend; C.L.M. Geesing, Bernhoven hospital Oss; W.F. Heikens, Hospital Tjongerschans Heerenveen; J.C. Bakker, Streekhospital Midden-Twente Hengelo; K.M. Dolman, St. Lucas Andreas hospital Amsterdam; J.H. Kreijen-Meinesz, Bronovo hospital Den Haag; E.A. Smit-Kleinlugtenbeld, Albert Schweitzer hospital Dordrecht

**References**


1. Bos JM, Rietveld E, Moll HA, Steyerberg EW, Luytjes W et al. (2007) The use of health economics to guide drug development decisions: Determining optimal values for an RSV-vaccine in a model-based scenario-analytic approach. Vaccine 25: 6922-6929.
2. Jansen AG, Sanders EA, Hoes AW, van Loon AM, Hak E (2007) Influenza- and respiratory syncytial virus-associated mortality and hospitalisations. Eur Respir J 30: 1158-1166.
3. Rietveld E, De Jonge HC, Polder JJ, Vergouwe Y, Veeze HJ et al. (2004) Anticipated costs of hospitalization for respiratory syncytial virus infection in young children at risk. PIDJ 23: 523-529.
4. Smyth RL, Openshaw PJ (2006) Bronchiolitis. Lancet 368: 312-322.
5. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM et al. (2009) The burden of respiratory syncytial virus infection in young children. N Engl J Med 360: 588-598.
6. Bloemers BL, van Furth AM, Weijerman ME, Gemke RJ, Broers CJ et al. (2007) Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis--a prospective birth-cohort study. Pediatrics 120: e1076-e1081.
7. Boyce TG, Mellen BG, Mitchel EF, Jr., Wright PF, Griffin MR (2000) Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr 137: 865-870.
8. Weisman LE (2003) Populations at risk for developing respiratory syncytial virus and risk factors for respiratory syncytial virus severity: infants with predisposing conditions. PIDJ 22: S33-S37.
9. Welliver RC (2003) Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. J Pediatr 143: S112-S117.
10. Lenney W, Boner AL, Bont L, Bush A, Carlsen KH et al. (2009) Medicines used in respiratory diseases only seen in children. Eur Respir J 34: 531-551.
11. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA et al. (2003) Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 143: 532-540.
12. The IMpact-RSV study group (1998) Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 102: 531-537.

13. Wang D, Cummins C, Bayliss S, Sandercock J, Burls A (2008) Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: A systematic review and economic evaluation. Health Technol Assess 12.
14. Wang D, Bayliss S, Meads C (2011) Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses. Health Technol Assess 15: iii-124.
15. Carbonell-Estrany X, Figueras-Aloy J, Law BJ (2004) Identifying risk factors for severe respiratory syncytial virus among infants born after 33 through 35 completed weeks of gestation: different methodologies yield consistent findings. PIDJ 23: S193-S201.
16. Chantry CJ, Howard CR, Auinger P (2006) Full breastfeeding duration and associated decrease in respiratory tract infection in US children. Pediatrics 117: 425-432.
17. Doering G, Gusenleitner W, Belohradsky BH, Burdach S, Resch B et al. (2006) The risk of respiratory syncytial virus-related hospitalizations in preterm infants of 29 to 35 weeks' gestational age. PIDJ 25: 1188-1190.
18. Houben ML, Bont L, Wilbrink B, Belderbos ME, Kimpen JL et al. (2011) Clinical prediction rule for RSV bronchiolitis in healthy newborns: prognostic birth cohort study. Pediatrics 127: 35-41.
19. Lanari M, Giovannini M, Giuffre L, Marini A, Rondini G et al. (2002) Prevalence of respiratory syncytial virus infection in Italian infants hospitalized for acute lower respiratory tract infections, and association between respiratory syncytial virus infection risk factors and disease severity. Pediatr Pulmonol 33: 458-465.
20. Law BJ, Langley JM, Allen U, Paes B, Lee DS et al. (2004) The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. PIDJ 23: 806-814.
21. Sinha A, Madden J, Ross-Degnan D, Soumerai S, Platt R (2003) Reduced risk of neonatal respiratory infections among breastfed girls but not boys. Pediatrics 112: e303.
22. Ferrero F, Nascimento-Carvalho CM (2012) Clinical prediction rules and pediatric infectious diseases. Pediatr Infect Dis J 31: 628-629.

23. Sampalis JS, Langley J, Carbonell-Estrany X, Paes B, O'Brien K et al. (2008) Development and validation of a risk scoring tool to predict respiratory syncytial virus hospitalization in premature infants born at 33 through 35 completed weeks of gestation. Med Decis Making 28: 471-480. 0272989X08315238 [pii];10.1177/0272989X08315238 [doi].
24. Simoes EA, Carbonell-Estrany X, Fullarton JR, Liese JG, Figueras-Aloy J et al. (2008) A predictive model for respiratory syncytial virus (RSV) hospitalisation of premature infants born at 33-35 weeks of gestational age, based on data from the Spanish FLIP Study. Respir Res 9: 78.
25. Harrell FE, Jr., Lee KL, Mark DB (1996) Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15: 361-387.
26. Hosmer, D. W. and Lemeshow S. (1989) Applied Logistic Regression. New York: John Wiley & Sons, Inc.
27. Janssen KJ, Vergouwe Y, Kalkman CJ, Grobbee DE, Moons KG (2009) A simple method to adjust clinical prediction models to local circumstances. Can J Anaesth 56: 194-201.
28. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y et al. (2001) Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 54: 774-781.
29. Steyerberg EW, Neville BA, Koppert LB, Lemmens VE, Tilanus HW et al. (2006) Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. J Clin Oncol 24: 4277-4284.
30. Stensballe LG, Fullarton JR, Carbonell-Estrany X, Simoes EA (2010) Population based external validation of a European predictive model for respiratory syncytial virus hospitalization of premature infants born 33 to 35 weeks of gestational age. Pediatr Infect Dis J 29: 374-376.
31. Paes B, Steele S, Janes M, Pinelli J (2009) Risk-scoring tool for respiratory syncytial virus prophylaxis in premature infants born at 33-35 completed weeks' gestational age in Canada. Curr Med Res Opin 25: 1585-1591.
32. Carbonell-Estrany X, Simoes EA, Fullarton JR, Ferdynus C, Gouyon JB (2010) Validation of a model to predict hospitalization due to RSV of infants born at 33-35 weeks' gestation. J Perinat Med 38: 411-417.

33. Simoes EA, Carbonell-Estrany X, Fullarton JR, Rossi GA, Barberi I et al. (2011) European risk factors' model to predict hospitalization of premature infants born 33-35 weeks' gestational age with respiratory syncytial virus: validation with Italian data. J Matern Fetal Neonatal Med 24: 152-157.
34. Carbonell-Estrany X, de Mercado PL (2009) Health economics and RSV. Paediatr Respir Rev Jun; 10 Supll. 1: 12-13.
35. Resch B, Sommer C, Nuijten MJ, Seidinger S, Walter E et al. (2012) Cost-effectiveness of palivizumab for respiratory syncytial virus infection in high-risk children, based on long-term epidemiologic data from Austria. Pediatr Infect Dis J 31: e1-e8.
36. Lanctot KL, Masoud ST, Paes BA, Tarride JE, Chiu A et al. (2008) The cost-effectiveness of palivizumab for respiratory syncytial virus prophylaxis in premature infants with a gestational age of 32-35 weeks: A Canadian-based analysis. Curr Med Res Opin 24: 3223-3237.
37. Prescott WA, Jr., Doloresco F, Brown J, Paladino JA (2010) Cost effectiveness of respiratory syncytial virus prophylaxis: a critical and systematic review. Pharmacoeconomics 28: 279-293.
38. Krilov LR, Weiner LB, Yogev R, Fergie J, Katz BZ et al. (2009) The 2009 COID recommendations for RSV prophylaxis: issues of efficacy, cost, and evidence-based medicine. Pediatrics 124: 1682-1684.
39. Meissner HC, Bocchini JA, Jr., Brady MT, Hall CB, Kimberlin DW et al. (2009) The role of immunoprophylaxis in the reduction of disease attributable to respiratory syncytial virus. Pediatrics 124: 1676-1679.
40. Elhassan NO, Sorbero MES, Hall CB, Stevens TP, Dick AW (2006) Cost-effectiveness analysis of palivizumab in premature infants without chronic lung disease. Arch Pediatr Adolesc Med 160: 1070-1076.
41. Joffe S, Ray GT, Escobar GJ, Black SB, Lieu TA (1999) Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants. Pediatrics 104: 419-427.
42. Nuijten M, Lebmeier M, Wittenberg W (2009) Cost effectiveness of palivizumab for RSV prevention in high-risk children in the Netherlands. J Med Econ .

CHAPTER 6

# Risk scoring tool to predict respiratory syncytial virus hospitalization in premature infants

Maarten O. Blanken, Bosco Paes, Evan Anderson, Marco Lanari, Margeret Sheridan-Pereira, Scot Buchan, John Fullarton, Elizabeth Grubb E, Gerard Notario, Barry Rodgers-Gray, Xavier Carbonell-Estrany

*Pediatric Pulmonology, 2018 May;53(5):605-612*

**Abstract**

*Background*

The objective was to develop a risk scoring tool which predicts respiratory syncytial virus hospitalisation (RSVH) in moderate-late preterm infants (32-35 weeks' gestational age) in the Northern Hemisphere.

*Methods*

Risk factors for RSVH were pooled from six observational studies of infants born 32 weeks and 0 days to 35 weeks and 6 days without comorbidity from 2000-2014. Of 13,475 infants, 484 had RSVH in the first year of life. Logistic regression was used to identify the most predictive risk factors, based on area under the receiver operating characteristic curve (AUROC). The model was validated internally by 100-fold bootstrapping and externally with data from a seventh observational study. The model coefficients were converted into rounded multipliers, stratified into risk groups, and number needed to treat (NNT) calculated.

*Results*

The risk factors identified in the model included: a) proximity of birth to the RSV season; b) second-hand smoke exposure; and, c) siblings and/or daycare. The AUROC was 0·773 (sensitivity: 68·9%; specificity: 73·0%). The mean AUROC from internal bootstrapping was 0·773. For external validation with data from Ireland, the AUROC was 0·707 using Irish coefficients and 0·681 using source model coefficients. Cut-off scores for RSVH were ≤19 for low- (1·0%), 20-45 for moderate- (3·3%), and 50-56 (9·5%) for high-risk infants. The high-risk group captured 62·0% of RSVHs within 23·6% of the total population (NNT 15.3).

*Conclusions*

This risk scoring tool has good predictive accuracy and can improve targeting for RSVH prevention in moderate-late preterm infants.

**Introduction**

Respiratory syncytial virus (RSV) is the predominant cause of lower respiratory tract infection (LRTI) in early childhood, accounting for 340,000 hospitalisations annually in children <5 years in industrialised countries.[1,2] It places a considerable strain on healthcare services, particularly during the winter months when the virus is most prevalent, with costs estimated at $545 million in the USA alone in 2009.[3] Moderate-late preterm infants (defined as 32 to 33-35 weeks' completed gestation at birth [wGA]) are at higher risk of severe RSV LRTI and greater morbidity than full-term infants.[4] Studies show that they also incur higher healthcare utilisation costs over the first 2 years of life,[5,6] and more frequent recurrent wheezing through 6 years of age compared to non-RSV hospitalised infants.[7] A pooled-analysis of seven prospective, observational studies comprising 7,820 infants born at 33-35 wGA during the RSV season, reported an incidence rate of 3.4% for first confirmed RSV hospitalisation (RSVH), with 22.2% requiring intensive care and 12.7% needing mechanical ventilation.[8]

At present, palivizumab is the only licensed therapy for reducing RSVH rates,[9,10] though there are several new monoclonal antibodies on the horizon.[11,12] In order to effectively manage healthcare budgets, sub-populations of moderate-late preterms at particular risk need to be identified for intervention.[13,14] Large studies across the Northern Hemisphere have established risk factors associated with severe RSV LRTI in moderate-late preterm infants, including those related to RSV exposure (e.g. daycare attendance), biological factors (e.g. male sex), and social/environmental factors (e.g. exposure to tobacco smoke).[15-21] Several risk scoring tools (RST) using data from these studies, identify moderate-late preterm infants at risk for RSVH in order to target RSV prophylaxis judiciously.[13,14,22-24]

The models demonstrate good sensitivity (~70%) and specificity (~70%),[13,14,22,23] with the Canadian model proven to be cost-effective in clinical practice.[25,26] A model for general applicability across multiple countries has not been developed. The objective of the current study was to use a pooled dataset of studies to develop a simple and validated risk factor tool with improved performance, applicable across the Northern Hemisphere.

**Methods**

*Pooled dataset used for modelling*

Individual patient-linked data from six prospective, observational studies across the Northern Hemisphere were used to develop the predictive model underpinning the RST: 'Risk Factors Linked to Respiratory Syncytial Virus Infection Requiring Hospitalisation in Premature Infants Study' (FLIP-2, Spain);[17] 'RISK' (Netherlands);[13] 'Pediatric Investigators Collaborative Network on Infections in Canada' (PICNIC, Canada);[15] 'Italian National Birth Cohort' (IBC, Italy);[19] 'Respiratory Syncytial Virus (RSV) Respiratory Events Among Preterm Infants Outcomes and Risk Tracking Study' (REPORT, USA);[18] and 'Predictors Associated with RSV Hospitalisation in Nonprophylaxed, Premature Infants' (PONI, multinational)[20] (Table 1). These studies had been previously identified by a systematic review of the literature undertaken in 2015.[8] The key inclusion criteria for studies were: multicentre, observational, prospective design; assessed >1,000 moderate-late preterm (32-35 wGA) infants at risk for severe RSV disease (defined as the need for hospitalisation); included infants with laboratory-confirmed RSV infection; and ≤15% of infants received palivizumab prophylaxis (to ensure a standardised and unbiased population). An updated search of the literature (to 18 December 2017) identified no additional studies meeting the inclusion criteria.

*Data extraction, recasting, verification and analysis*

Data for infants (≤1 year) born at 32 weeks and 0 days ($32^0$) to 35 weeks and 6 days ($35^6$) gestation were extracted from each study, including information on first confirmed RSVH and corresponding risk factors. To ensure homogeneity, infants were excluded if they were born at $<32^0$ or $>35^6$ wGA, had received RSV prophylaxis, or had a relevant comorbidity (e.g. congenital heart disease, bronchopulmonary dysplasia/chronic lung disease). All data were anonymised. To ensure sufficient data for analysis, the collection/recording of a risk variable in at least four studies was a requisite for inclusion in the pooled dataset. Included risk factors were recast, where necessary, into a common format across studies. To verify each study's data before inclusion, the extracted datasets were checked and approved by key study investigators and personnel (XCE, MB, BP, ML, EJA; also see acknowledgements). The quantity of data available for three risk factor variables from each dataset were further confirmed against the original study publication. A heterogeneity test for the dichotomous variables present in all contributory datasets was performed by comparing odds ratios (ORs) using the

Breslaw-Day method. For categoric variables (>2 categories), data were converted to ranks and analysis of variance (ANOVA) conducted on the differences from mean rank in hospitalised and non-hospitalised infants. Heterogeneity for continuous variables was assessed by comparing the significance of difference between hospitalised and non-hospitalised infants using parametric t-test. Statistical significance of individual variables in the pooled dataset was assessed by two-tailed t-test (parametric data) and Mann-Whitney U-test and Mantel-Haenzel test (categoric data).

*Development of the predictive model*

Logistic regression was used to develop a preliminary risk factor model that included all risk factors in the pooled dataset. RSVH was the dependent variable and the risk factors were the covariates. Where risk factor data were missing for an infant, average values for that dataset were used, or when all values for a particular risk factor were missing from a dataset, the combined data average was applied. Alternative approaches using a new category for a missing value or neutral, non-discriminatory values were also tested. The model was optimised by several mechanisms: i) sequential removal and reinsertion of each risk factor variable from the dataset to establish its impact on predicting RSVH; ii) using Wald test significance and exp(beta) to determine which covariates to test at each stage of removal; iii) assessing risk factors in combination versus use as individual predictors; and iv) assessing different cut-off values for risk factors, where applicable. Risk factors were expressed as either dichotomous (i.e. yes/no) or, if used in combination, categorical (i.e. neither, one, both etc.) variables. The overall goal was to find the combination of risk factors that provided the best balance between predictive accuracy and simplicity in terms of number and type of risk factors. Predictive accuracy was assessed by a receiver operating characteristic (ROC) curve, plotting sensitivity against 1-specificity, with an area under the ROC curve (AUROC) of ≥0.75 considered 'good'.[27] The point of maximum sensitivity and specificity was also calculated for the final model using the Youden's J statistic. Lastly, for each variable in the final model, the increased adjusted risk of RSVH was expressed as an OR.

*Validation of the final model*

Three main approaches were used to validate the final model. First, the model was generated in the FLIP-2,[17] PICNIC,[15] RISK[13] and PONI[20] datasets and compared to the published models for those studies (IBC[19] and REPORT[18] do not have published models).[13,22,24] Second, 100-fold

bootstrapping validation was performed on the pooled dataset.[28] The pooled dataset was sampled with replacement 100 times and the model coefficients used to calculate the predictive probabilities for each case in the 100 samples. ROC curves were constructed for each sample, the AUROC values calculated, and the dispersion statistics (standard deviation and range) across the 100 samples assessed. A low level of dispersion indicates an internally consistent model. The Kolmogorov-Smirnov test was used to assess normality in the distribution of AUROCs from the samples (non-significance indicates a normal distribution) and skewness was also calculated (0.0 = absolute symmetry). Finally, the model was validated externally against data from the recently published RSV Preterm Risk Estimation Measure for RSVH in Ireland study (RSV-PREMI)[21], which was identified in the same systematic review as the studies in the pooled dataset (Table 1).[8] Data were verified by study personnel (MS-P and Acknowledgements), including three variables checked against the study publication, and heterogeneity assessed as previously described. The model was tested in two ways against the RSV-PREMI data: i) generating a model from the RSV-PREMI data itself using the same risk factors as for the final model; and ii) the coefficients from the pooled dataset were applied to the RSV-PREMI data. For both analyses, predictive accuracy was assessed by AUROC.

*Development of the RST*

To convert the final model into a RST, the logistic regression coefficient(s) for each variable was assigned a rounded multiplier with a positive value. The rounded multiplier provides a measure of the influence of a particular risk factor on the probability of RSVH relative to that of the other risk factors in the model (the higher the value, the greater the influence). The sum of the rounded multipliers, taking into consideration any categorical variables that may have more than one multiplier, represented the maximum score of the tool.

Cut-off scores for low-, moderate-, and high-risk groups were determined based on RSVH rates of <2%, 2-10%, and >10%, respectively, in line with the RSTs developed in Canada[22] and the Netherlands[13,14] (the FLIP-2[24] and PONI[20] models did not include cut-offs). The RSVH rate was also plotted against the risk score to determine if there were any apparent inflections in the curve from which to refine the cut-off values. A very high-risk group was defined by examining a score that would limit the RST to capturing approximately 10% of the total population. The relative risk and ORs for RSVH were compared between risk groups, positive predictive values (PPV) and negative predictive values (NPV) determined, and numbers needed to treat (NNT)

calculated, assuming a palivizumab efficacy rate of 80% for 32-35 wGA infants, based on randomised controlled trials.[9,29]

All analyses were performed using SPSS for Windows version 15.0 (IBM Corporation, New York, USA), Microsoft Access 2010 SQL (Microsoft Corporation, Washington, USA), and Microsoft Access/Excel VBScript 2010 (Microsoft Corporation, Washington, USA).

*Transparency of reporting*

The *Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis* (TRIPOD) statement was followed for this manuscript (E-Table 1).[30] The TRIPOD statement provides a framework for the full and clear reporting of a prediction model study, such that risk of bias and potential usefulness can be adequately assessed.[30]

**Results**

*Pooled dataset*

The six studies (FLIP-2,[17] RISK,[13] PICNIC,[15] IBC,[19] REPORT,[18] PONI[20]) contained individual patient-linked data collected from 2000 to 2014 for a total of 15,862 infants, of whom 13,475 were born between $32^0$-$35^6$ wGA and met the inclusion criteria for the pooled dataset (Table 1). The primary reasons for exclusion were birth ≥36 wGA (n=1,184), receiving RSV prophylaxis (n=693), and having an exclusionary comorbidity (n=490). Each study contributed at least 1,000 infants to the pooled dataset, with all providing data for infants born at 33-35 wGA and three studies contributing data as well for 32 wGA infants (FLIP-2,[17] RISK,[13] REPORT[18]). The overall distribution by wGA was: 32 wGA (6.9%), 33 wGA (24.4%), 34 wGA (38.1%), and 35 wGA (30.7%).

Of the 13,475 infants in the pooled dataset, 484 (3.6%) had a confirmed RSVH within the first year of life. A total of 18 possible risk factors for RSVH were present in four of the six studies and were recast to a common format (E-Table 2). Prior to inclusion in the pooled dataset, the extracted data for each study were confirmed and verified against the published data with no apparent discrepancies (E-Table 3). Heterogeneity tests revealed no significant differences for 11 of the 12 risk factor variables present in all six datasets; smokers in the household differed significantly (p=0.04) between studies, with rates varying between 4-67% across studies (E-Table 4).

*Risk factor model*

The final logistic regression model comprised three variables, combining a total of five risk factors: birth between three months before and two months after season start date; smokers in the household and/or maternal smoking whilst pregnant; and siblings (excluding multiple births) and/or daycare attendance (recorded as 'planned', reflecting how the RST would be used in practice). Treating all risk factors as categorical covariates (i.e. assigning into groups and treating as non-linear scales), the derived model had an AUROC of 0.773 (95% confidence interval [CI] 0.753-0.792) and a maximum sensitivity and specificity of 0.689 and 0.730, respectively (Figure 1). The most predictive variable was the combination of siblings and daycare, though age relative to the start of the RSV season was the single most powerful risk factor (Table 2). Refining the siblings variable to pre-school age (<6 years), which is a highly significant risk factor for RSVH,[18,20] increased the AUROC minimally to 0.775. It was considered

more practical to exclude a sibling age criterion, particularly when 'pre-school age' is defined differently across countries. Substituting (any) siblings for a broader 'crowding' variable of >4 in the household including infant, >4 being the most predictive cut-off, or adding this variable to the model did not increase overall predictive accuracy (AUROC 0.764 for both substitution and addition). Unlike the other five datasets, PONI recorded only month (not day) of birth.[20] The age variable birth between three months before and two months after season start date was intended to simplify the calculated 13 weeks before to 8.5 weeks after the start of the RSV season. The use of a new category or imputation of neutral, non-discriminatory values for missing data resulted in models with similar discrimination (new category, AUROC 0.773; non-discriminatory, AUROC 0.770), confirming the absence of unrecognised bias associated with using average values.

**Validation of the risk factor model**

*Generation of the model in individual datasets*

Generating the final model in the individual datasets resulted in functions that were more powerful in FLIP-2: AUROC 0.762 vs. 0.687,[24] respectively, and in the other cases was within 3-12% of the predictive power of the published models (PICNIC: 0.673 vs. 0.762;[22] RISK: 0.680 vs. 0.703;[13] PONI: 0.701 vs. 0.755[20]) (E-Table 5).



*Internal validation*

The bootstrap validation resulted in a tight distribution of results for the 100 samples (total of ~1.35 million infants), with the median AUROC being 0.773 (range 0.753-0.805; interquartile range 0.01) (E-Figure 1). The Kolmogorov-Smirnov test indicated that the distribution of AUROCs from the samples was normal (0.059, degrees of freedom 100; p=0.200), whilst the Skewness statistic showed a symmetrical distribution containing a slightly greater number of larger values (0.322±0.241).

*External validation*

RSV-PREMI[21] included 1,078 infants born $32^0$-$35^6$ wGA of whom 46 (4.3%) were hospitalised with RSV LRTI in the first year of life (Table 1). All risk factors comprising the final model were available in RSV-PREMI and were recast in exactly the same format as the pooled dataset. Analysis revealed no apparent discrepancies between the extracted and published data for

RSV-PREMI (E-Table 3). The risk factors in the final model were shown to behave similarly within RSV-PREMI and the pooled dataset (E-Table 4).

Generating a model in the RSV-PREMI[21] data comprised of the risk factors included in the final model produced an AUROC of 0.707 (95% CI 0.637-0.778) (E-Figure 2A). Applying the coefficients from the final model from the pooled dataset to the RSV-PREMI data resulted in an AUROC of 0.681 (95% CI 0.588-0.773) (E-Figure 2B).

*RST*

Converting the logistic regression coefficients for each variable in the final model into rounded multipliers resulted in a maximum risk score of 56 (Table 2 & Figure 2A&B). The RST was created as a nomogram with a score ≤19 representing a low-risk of RSVH (average risk 1.0%), 20-45 representing a moderate-risk (average risk 3.3%), and ≥50 representing high-risk (average risk 9.5%). Plotting the RSVH rate against the risk score resulted in a curve with a natural inflection at a score of ~45 (E-Figure 3). This was set as the medium/high risk boundary. The high-risk group identified 62.0% of all RSVHs whilst selecting 23.6% of the total study population. The corresponding figures for the moderate- and low-risk groups were 23.2%/25.1% and 14.8%/51.3%, respectively. The high- and moderate-risk groups both had a significantly higher RSVH risk than the low risk group (OR 10.1, 95% CI 7.9-12.9, p<0.001; and OR 3.3, 95% CI 2.5-4.4, p<0.001, respectively; combined high- and moderate-risk: OR 6.4, 95% CI 5.1-8.2, p<0.001). The NNT for the high-risk group was 15.3, while the combined high- and moderate-risk group had a NNT of 33.3. A very high-risk group was defined as a score of 56, which captured 39.3% of RSVHs whilst selecting 11.9% of the total population, with a corresponding NNT of 10.8.

**Discussion**

A simple RST was developed for predicting the risk of RSVH in moderate-late ($32^0$-$35^6$ wGA) preterm infants in the Northern Hemisphere, from six large datasets and validated in a seventh large dataset. Three risk factor variables – birth between three months before and two months after season start date, smokers in the household and/or maternal smoking whilst pregnant, and siblings (excluding multiples) and/or (planned) daycare attendance – were shown to accurately and reliably predict RSVH. The RST is practical and can facilitate decision making for clinicians, parents, and policy makers regarding RSV prophylaxis. Importantly, two out of the five identified risk factors in our model – smoking in the household and daycare – are modifiable and the tool could be used accordingly to educate parents.

The model underpinning the RST compares favourably in terms of simplicity and predictive accuracy with other published models in moderate-late preterm infants, including those contained within the pooled dataset: AUROC of 0.773 with three variables vs. 0.791 with seven variables (Spanish [FLIP][23]); 0.762 with seven variables (Canadian [PICNIC][22]); 0.755 with six variables (PONI[20]); 0.72 with five variables (Dutch [RISK-II][14]); 0.703 with four variables (Dutch [RISK][13]); and 0.687 with four variables (Spanish [FLIP-2][24]). All of the models included variables associated with age relative to the RSV season and siblings/daycare, highlighting the importance of these risk factors in determining RSVH risk. The combination of siblings and daycare is particularly powerful and non-linear (individual score: 14 vs. combined score: 39), suggesting that these risk factors reinforce each other in terms of exposure to RSV and in combination, increase discrimination in the model. Smoking, the other risk factor included in the pooled model, was also part of previously published models (FLIP-2,[24] PICNIC,[22] and PONI[20]). The combined smoking variable is approximately linear and less powerful (individual score: 5; combined score: 11) than siblings/daycare, despite similar ORs (1.4-1.7 vs. 1.6, respectively). This may partly be due to greater overlap in the variance explained by the two smoking risk factors within the model, since average values were imputed for smoking whilst pregnant in PICNIC[15] and REPORT[18], which only captured smokers in the household. Combined with the validation against the RSV-PREMI dataset and the homogeneity of risk factor data across all studies, this reinforces the universal applicability of the RST across the Northern Hemisphere.

The key strength of this RST was the development from a pooled dataset of six independent, multicentre, observational, prospective studies involving >14,500 infants with both internal and external validation. However, certain limitations should be addressed. The individual studies varied in objectives and design, which influenced the included gestational age range of infants and how and what risk factors were collected. Of the six studies, only three included data on 32 wGA infants, but these represented Europe (FLIP-2,[17] RISK[13]) and North America (REPORT[18]). In total, >900 32 wGA infants were included in the pooled dataset and, importantly, the RSV-PREMI[21] validation dataset involved 32 wGA infants. Whilst the FLIP-2[17] dataset provided around one third of infants in the pooled dataset, each study contributed >1,000 infants. Recasting risk factors to a simpler, common format results in loss of some statistical power; however, this was justified by the objective to create a user-friendly tool. All of the risk factors in the final model were available in all the datasets, except for smoking whilst pregnant. The PONI[20] dataset captured only month not day of birth, which could have weakened the birth between three months before and two months after season start date variable, although rounding to whole months helped to mitigate this effect. The studies spanned 15 years (2000-2014), with likely variations in hospital practice and RSV testing. Our ability to develop a robust predictive model suggests intrinsic compatibility amongst the datasets and supports the high predictive value of these risk factors. The internal and external validations demonstrated that the model is internally consistent, not overly-optimistic (i.e. there is little or no over-fitting), and can be applied effectively across the Northern Hemisphere.

The RST has a scale of 0-56 with defined cut-off scores for low- (≤19), moderate- (20-45) and high-risk (≥50) infants. The cumulative RSVH risk was 3.6% (484/13,475) in the pooled dataset, with the combined moderate- and high-risk groups being 6.3%, the high-risk group 9.5%, and the very high risk group (score of 56) 11.9%. The NNT for the combined high- and moderate-risk groups was 33.3, which falls to 15.3 in the high-risk group and 10.8 for very high-risk infants. A balance must be struck between the cost-effectiveness of palivizumab versus potential therapeutic benefits, with the very high risk group having a compelling NNT, but missing 60% of predicted RSVHs. Ultimately, the final decision regarding appropriate cut-offs should be made locally, taking into consideration the overall risk-cost-benefit relative to each clinical setting.

The validated RST described herein is simple and has good predictive accuracy to assess RSVH risk in moderate-late preterm infants. Developing the tool from six datasets confirms its predictive capabilities, generalisability, and applicability across the Northern Hemisphere. The RST is a powerful instrument to determine RSVH risk and direct RSV therapies cost-effectively to the most vulnerable moderate-late preterm infants.

*Acknowledgements*

The authors would like to thank the following individuals for their contributions to the dataset transfers and quality control for analysis respectively: Dr Fulvio Adorni (IBC), Institute of Biomedical Technologies, Milan, Italy; Dr Massimo Musicco (IBC), National Research Council, Milan, Italy; the Dutch RSV Neonatal Network (RISK); Dr Joan Murphy (RSV-PREMI), Coombe Women and Infants University Hospital, Dublin, Ireland; Dr Xionghua Wu (REPORT), MedImmune, MD, USA; Dr Pamela Vo and Fiona Campbell, former employees of AbbVie, USA; Dr Elisabeth Rouffiac, former employee of AbbVie Biopharmaceuticals SARL. The authors would also like to thank Dr Joanne Smith, Strategen Ltd, Basingstoke, UK for her assistance with the statistical analysis and editing of this manuscript.

EJA, ML, XC-E, MB, MS-P, BP have received research funding and/or compensation as advisor/lecturer from AbbVie. EJA has received research funding from MedImmune, Regeneron, and NovaVax. SB, JF, BRG are employees of Strategen, a company which has received payment from AbbVie for work on various projects. EG is an employee of AbbVie and may hold AbbVie stock or stock options. GN is a former employee of AbbVie and may hold AbbVie stock or stock options.

**References**


1. Shi T, McAllister DA, O'Brien KL, Simões EAF, Madhi SA, Gessner BD, Polack FP, Balsells E, Acacio S, Aguayo C, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017;390:946-958.
2. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, Stockmann C, Anderson EJ, Grijalva CG, Self WH, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015;372:835-845.
3. Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA Jr. Trends in bronchiolitis hospitalizations in the United States, 2000-2009. Pediatrics 2013;132:28-36.
4. Figueras-Aloy J, Manzoni P, Paes B, Simões EA, Bont L, Checchia PA, Fauroux B, Carbonell-Estrany X. Defining the risk and associated morbidity and mortality of severe respiratory syncytial virus infection among preterm infants without chronic lung disease or congenital heart disease. Infect Dis Ther 2016;5:417-452.
5. Palmer L, Hall CB, Katkin JP, Shi N, Masaquel AS, McLaurin KK, Mahadevia PJ. Respiratory outcomes, utilization and cost 12 months following a respiratory syncytial virus diagnosis among commercially insured late-preterm infants. Curr Med Res Opin 2011;27:403-412.
6. Shefali-Patel D, Paris MA, Watson F, Peacock JL, Campbell M, Greenough A. RSV hospitalisation and healthcare utilisation in moderately prematurely born infants. Eur J Pediatr 2012;171:1055-1061.
7. Carbonell-Estrany X, Pérez-Yarza EG, García LS, Guzmán Cabañas JM, Bòria EV, Atienza BB, IRIS Study Group. Long-term burden and respiratory effects of respiratory syncytial virus hospitalization in preterm infants-the SPRING study. PLoS One 2015;10:e0125422.
8. Anderson EJ, Carbonell-Estrany X, Blanken M, Lanari M, Sheridan-Pereira M, Rodgers-Gray B, Fullarton J, Rouffiac E, Vo P, Notario G, et al. Burden of severe respiratory syncytial virus disease among 33-35 weeks gestational age infants born during multiple respiratory syncytial virus seasons. Pediatr Infect Dis J 2017;36:160-167.

9. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998;102:531-537.
10. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH Jr, Connor EM, Sondheimer HM, Cardiac Synagis Study Group. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003;143:532-540.
11. Simões EA, DeVincenzo JP, Boeckh M, Bont L, Crowe JE Jr, Griffiths P, Hayden FG, Hodinka RL, Smyth RL, Spencer K, et al. Challenges and opportunities in developing respiratory syncytial virus therapeutics. J Infect Dis 2015;211:S1-S20.
12. Rezaee F, Linfield DT, Harford TJ, Piedimonte G. Ongoing developments in RSV prophylaxis: a clinician's analysis. Curr Opin Virol 2017;24:70-78.
13. Blanken MO, Koffijberg H, Nibbelke EE, Rovers MM, Bont L, Dutch RSV Neonatal Network. Prospective validation of a prognostic model for respiratory syncytial virus bronchiolitis in late preterm infants: a multicenter birth cohort study. PLoS One 2013;8:e59161.
14. Korsten K, Blanken MO, Nibbelke EE, Moons KG, Bont L, Dutch RSV Neonatal Network. Prediction model of RSV-hospitalization in late preterm infants: an update and validation study. Early Hum Dev 2016;95:35-40.
15. Law BJ, Langley JM, Allen U, Paes B, Lee DS, Mitchell I, Sampalis J, Walti H, Robinson J, O'Brien K, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. Pediatr Infect Dis J 2004;23:806-814.
16. Figueras-Aloy J, Carbonell-Estrany X, Quero J, IRIS Study Group. Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33–35 weeks in Spain. Pediatr Infect Dis J 2004;23:815-820.

17. Figueras-Aloy J, Carbonell-Estrany X, Quero-Jimenez J, Fernández-Colomer B, Guzmán-Cabañas J, Echaniz-Urcelay I, Doménech-Martínez E, IRIS Study Group. FLIP-2 Study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in Spain at a gestational age of 32 to 35 weeks. Pediatr Infect Dis J 2008;27:788-793.
18. Ambrose CS, Anderson EJ, Simões EA, Wu X, Elhefni H, Park CL, Sifakis F, Groothuis JR. Respiratory syncytial virus disease in preterm infants in the U.S. born at 32-35 weeks gestation not receiving immunoprophylaxis. Pediatr Infect Dis J 2014;33:576-582.
19. Lanari M, Prinelli F, Adorni F, Di Santo S, Vandini S, Silvestri M, Massimo Musicco, Study Group of Italian Society of Neonatology on Risk Factors for RSV Hospitalization. Risk factors for bronchiolitis hospitalization during the first year of life in a multicentre Italian birth cohort. Ital J Pediatr 2015; 41:40.
20. Straňák Z, Saliba E, Kosma P, Posfay-Barbe K, Yunis K, Farstad T, Unnebrink K, van Wyk J, Wegzyn C, Notario G, et al. Predictors of RSV LRTI hospitalization in infants born at 33 to 35 weeks gestational age: a large multinational study (PONI). PLoS One 2016;11:e0157446.
21. Sheridan-Pereira M, Murphy J, Sloan J, Crispino G, Leahy A, Corcoran JD, Dempsey E, Elnazir B, Gavin P, Sharif F, et al. Respiratory Syncytial Virus preterm (32-36 completed weeks' gestation) risk estimation measure for RSV hospitalization in Ireland: A prospective study. Pediatr Infect Dis J 2016;35:19-24.
22. Sampalis JS, Langley J, Carbonell-Estrany X, Paes B, O'Brien K, Allen U, Mitchell I, Aloy JF, Pedraz C, Michaliszyn AF. Development and validation of a risk scoring tool to predict respiratory syncytial virus hospitalization in premature infants born at 33 through 35 completed weeks of gestation. Med Decis Making 2008;28:471-480.
23. Simões EA, Carbonell-Estrany X, Fullarton JR, Liese JG, Figueras-Aloy J, Doering G, Guzman J, European RSV Risk Factor Study Group. A predictive model for respiratory syncytial virus (RSV) hospitalisation of premature infants born at 33–35 weeks of gestational age, based on data from the Spanish FLIP study. Respir Res 2008;9:78.
24. Figueras-Aloy J, Quero-Jiménez J, Fernández-Colomer B, Guzmán-Cabañas J, Echaniz-Urcelay I, Doménech-Martínez E, IRIS Study Group. Usefulness of different risk factor associations in predicting admissions due to respiratory syncytial virus in premature newborns of 32 to 35 weeks gestation in Spain. An Pediatr (Barc) 2009;71:47-53.

25. Paes B, Steele S, Janes M, Pinelli J. Risk-scoring tool for respiratory syncytial virus prophylaxis in premature infants born at 33-35 completed weeks' gestational age in Canada. Curr Med Res Opin 2009;25:1585-1591.
26. Lanctôt KL, Masoud ST, Paes BA, Tarride JE, Chiu A, Hui C, Francis PL, Oh PI. The cost-effectiveness of palivizumab for respiratory syncytial virus prophylaxis in premature infants with a gestational age of 32-35 weeks: a Canadian-based analysis. Curr Med Res Opin 2008;24:3223-3237.
27. Brubaker PH. Do not be statistically cenophobic: time to roc and roll! J Cardiopulm Rehabil Prev 2008;28:420-421.
28. Efron B, Tibshirani RJ. 1993. An introduction to the bootstrap. London: Chapman and Hall.
29. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, Bont L, Dutch RSV Neonatal Network. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med 2013;368:1791-1799.
30. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015;350:g7594.

**Online Supporting information (E-Supplementary Information):**

E-Table 1: TRIPOD checklist: prediction model development and validation

E-Table 2: Risk factors included in pooled dataset

E-Table 3: Data verification - comparison of the quantity of data for three risk factor variables in pooled dataset ('Dataset') vs. study publications ('Paper')

E-Table 4: Heterogeneity Tests

E-Table 5: Comparison of final model generated in individual datasets vs. published models

E-Figure 1: Results of 100-fold bootstrapping using pooled dataset

E-Figure 2: Validation of final model derived from pooled dataset against RSV-PREMI dataset

E-Figure 3: Plot of RSVH rate vs. risk score

Table 1: Overview of studies included in developing and validating the risk factor model

| Dataset | Demographics | | | | | | Exclusions | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Country | Study Years | Duration of follow up | RSV Season | wGA[a] Range | Total N | wGA[a] >35$^6$ | Comorbid | Prophylaxed | Other | N included |
| **PICNIC**[15] | Canada | 2000-2002 | 1 month post-RSV season | 1 Nov-30 Apr | $33^0$-$35^6$ | 1,758 | 0 | 232 | 0 | 9[b] | 1517 |
| **FLIP-2**[17] | Spain | 2005-2007 | End of May | 1 Oct–30 Apr | $32^1$-$35^0$ | 5,441 | 0 | 193 | 693 | 0 | 4555 |
| **RISK**[13] | Netherlands | 2008-2012 | 1 year of age | 1 Oct-31 Mar | $32^1$-$35^6$ | 2,421 | 0 | 0 | 0 | 11[c] | 2410 |
| **REPORT**[18] | USA | 2009-2011 | End of May | 1 Nov-31 Mar | $32^0$-$35^6$ | 1,642 | 0 | 0 | 0 | 0 | 1642 |
| **IBC**[19] | Italy | 2009-2013 | 1 year of age | 1 Nov-31 Mar | $\geq 33^0$ | 2,210 | 1184 | 0 | 0 | 0 | 1026 |
| **PONI**[20] | Europe, America Asia/Middle East[d] | 2013-2014 | End of Apr | 1 Oct-30 Apr | $33^0$-$35^6$ | 2,390 | 0 | 65 | 0 | 0 | 2325 |
| | | | | **TOTAL (POOLED DATASET)** | | **15,862** | **1,184** | **490** | **693** | **20** | **13,475** |
| **PREMI**[21] | Ireland | 2011-2014 | 1 year of age | 1 Oct-31 Mar | $32^0$-$36^6$ | 1,807 | 718 | 11 | 0 | 0 | 1078 |
| | | | | **TOTAL (VALIDATION DATASET)** | | **1,807** | **718** | **11** | **0** | **0** | **1078** |

[a] wGA = weeks' gestational age [b] 9 cases not hospital confirmed [c] No recorded wGA [d] 23 countries in Western Europe (Austria, France, Norway, Portugal, Sweden, and Switzerland), Eastern Europe (Bosnia, Bulgaria, Czech Republic, Estonia, Latvia, Lithuania, Slovakia, and Slovenia) and Russia, South Korea, Mexico, and the Middle East (Bahrain, Egypt, Jordan, Lebanon, Oman, and Saudi Arabia)

Table 2: Variables in the final logistic regression model for the risk scoring tool derived from the pooled dataset

| Variable | Odds ratio (95% CI), *P*-value[a] | Logistic regression coefficient | Score (rounded integer) |
|---|---|---|---|
| Birth between 3 months before and 2 months after season start date [yes or no] | 2.0 (1.7-2.5), p<0.001 | 0.338 | 6 |
| Smokers in household and/or while pregnant [neither, either, or both] | Household: 1.4 (1.2-1.7), p=0.001<br>Pregnant: 1.7 (1.3-2.1); p<0.001 | Either: 0.209<br>Both: 0.479 | Either: 5<br>Both: 11 |
| Siblings (excluding multiple birth siblings) and/or (planned) day care [neither, either, or both] | Siblings: 1.6 (1.4-2.0), p<0.001<br>Daycare: 1.6 (1.3-1.9), p<0.001 | Either: 0.740<br>Both: 1.639 | Either: 14<br>Both: 39 |

[a] Increased adjusted risk of respiratory syncytial virus hospitalisation for individual variables

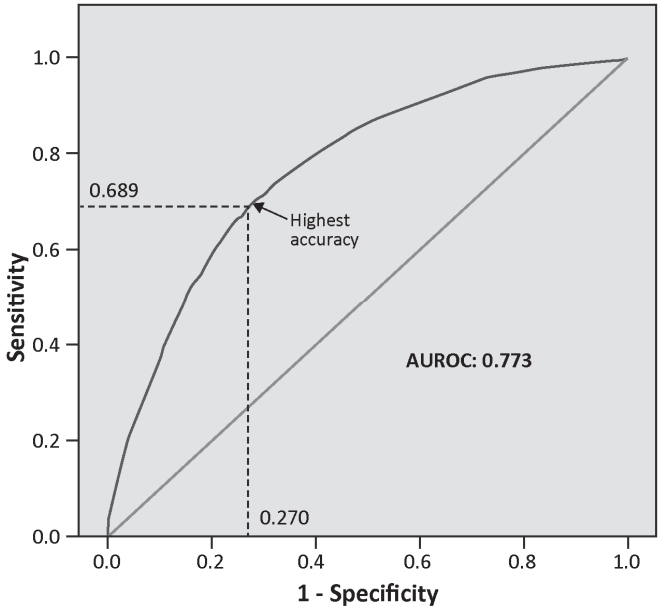



*Figure 1: Receiver operating characteristic (ROC) curve for the final three-variable model derived from the pooled dataset*

AUROC = area under the receiver operating characteristic curve

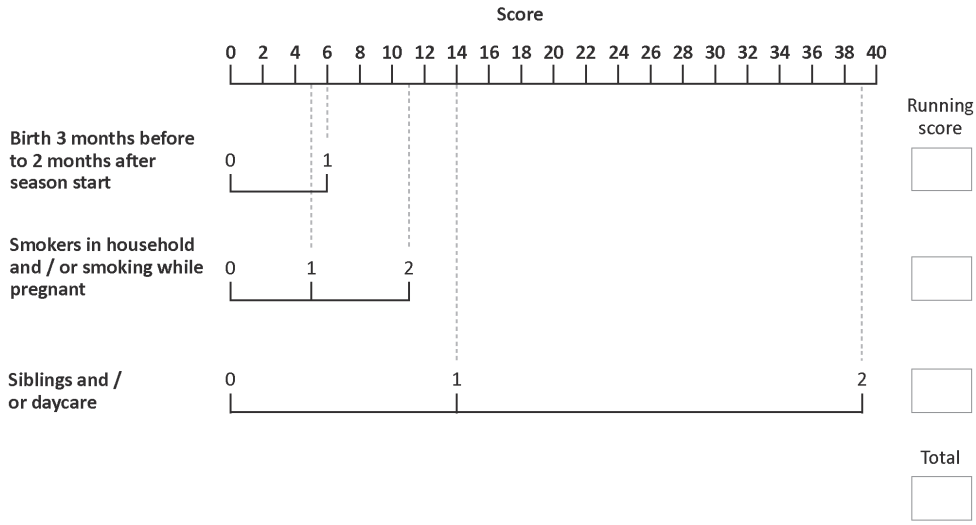



*Figure 2A: Risk factor scoring tool*

0 = No/Not Present; 1 = Yes/Present for one risk factor; 2 = Yes/Present for both risk factors

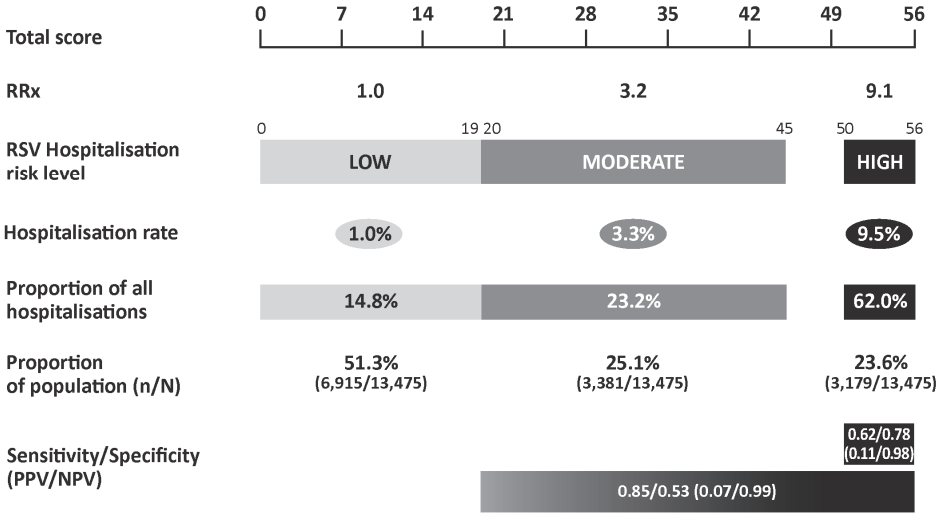



*Figure 2B: Interpretation of risk score and risk group characteristics**

RR = relative risk compared to low risk group; PPV = positive predictive value; NPV = negative predictive value *Please note that it is not possible to achieve a score of 46-49 base

CHAPTER 7

# The Cost-Effectiveness of Palivizumab in the Prevention of Respiratory Syncytial Virus Bronchiolitis: A Systematic Review

Maarten O. Blanken, Louis Bont, Maroeska M. Rovers

*Curr Respir Med Rev. 2011 Jun; 7(3,: 203-212(10) and*
*MSc thesis Health Economics, Policy and Law, Erasmus University (2012)*

**Abstract**

*Background*

RSV bronchiolitis is the most common cause of infant morbidity during the winter season and is associated with a large burden of disease and high costs. The cost-effectiveness of RSV immunoprophylaxis with the only available preventive treatment, palivizumab is subject of vigorous debate. It is recognised that a policy of using palivizumab for all children who meet the licensed indication is not cost-effective, but most clinicians feel that its use is justified in certain subgroups.

*Objective*

To systematically review the literature on the cost-effectiveness of palivizumab prophylaxis in the following subgroups: 1) preterm infants born before 32 weeks gestational age (WGA), 2) preterm infants born between 32 and 35 WGA, 3) children with chronic lung disease (CLD), and 4) children with congenital heart disease (CHD).

*Methods*

We searched Pubmed, EMBASE, and the latest versions of the DARE, NHS EED and HTA databases from inception to June 2012. Relevant studies were first selected on title and abstract and full text of the selected papers was reviewed.

*Results*

Nineteen studies evaluating the cost-effectiveness of palivizumab performed in 13 different countries were included. The cost-effectiveness of palivizumab for the subgroups of children born before 32 WGA, children born between 32 and 35 WGA, children with CLD, and children with CHD was studied in 9, 9, 8, and 7 studies, respectively. The incremental cost-effectiveness ratios varied considerably both within and between subgroups. Sensitivity analyses showed that cost-effectiveness was mainly driven by the mortality rate due to RSV infection. Differences in hospitalisation rates, industry sponsoring and study year were also associated with differences in cost-effectiveness, but these differences could be attributed to differences in mortality rates.

*Conclusion*

The cost-effectiveness of prophylactic treatment of RSV infection with palivizumab in subgroups varies considerably. The cost-effectiveness is mainly sensitive to mortality rates of RSV infection. This systematic review indicates that future research should focus on the major uncertainties in cost-effectiveness, particularly RSV-related mortality rate, high-risk populations and long term sequelae. Interpretation of RSV cost-effectiveness studies should be done cautiously due to transferability issues.

Key Words: Respiratory syncytial virus, palivizumab, prophylaxis, cost-effectiveness

**List of definitions**

**Economic evaluation:** Economic evaluation is the comparison of two or more alternative courses of action in terms of both their costs and consequences [1]. Economists usually distinguish several types of economic evaluation, differing in how consequences are measured: cost-minimization analysis, cost-effectiveness analysis and cost-utility analysis.

**Cost-effectiveness analysis (CEA):** is a form of economic analysis that compares the relative costs and outcomes (effects) of two or more courses of action. Typically the CEA is expressed in terms of a ratio where the denominator is a gain in health from a measure (years of life, premature births averted, sight-years gained) and the numerator is the cost associated with the health gain. The most commonly used outcome measure is quality-adjusted life years (QALY).

**Cost-utility analysis (CUA)**: is a form of economic analysis used to guide budget decisions. The purpose of CUA is to estimate the ratio between the cost of a health-related intervention and the benefit it produces in terms of the number of years lived in full health by the beneficiaries.

**Payer's perspective:** a perspective that can be used in a health economic evaluation to count all costs that are relevant from the viewpoint of the health payer. In an analysis conducted from the payer's perspective for example, the patients travel costs are excluded as well as indirect costs due to production losses. For example, this viewpoint is used in the study by Reeve et al. where only direct medical cost are considered[2].

**Societal perspective:** a perspective from which an economic evaluation is conducted that takes into account all costs to society as a whole, regardless who incurs them. It includes all costs and effects that are relevant as seen from the viewpoint of society, including indirect costs caused by the disease under investigation, such as production losses. For example, this viewpoint is used in the study by Nuijten et al. where not only direct medical cost but also costs associated with asthma, non-medical costs and long term indirect costs are taken into account[3].

**Discounting:** Economic concept to handle time-preference, using a method of calculation by which costs and benefits occurring at different moments in time can be compared. Discounting converts the value of future costs and benefits into their present value to account for positive time preferences for benefits (preference for current benefits as compared to future benefits) and negative time preferences for costs (preference for future costs as compared to current costs).

**Incremental cost-effectiveness ratio (ICER)**: is defined as the ratio of the change in costs of a therapeutic intervention (compared to the alternative, such as doing nothing or using the best available alternative treatment) to the change in effects of the intervention.

**Hospital admission prevented (HAP)**: is used to describe the prevention of a single hospital admission by a given intervention. This outcome is regarded inferior to both QALY and LYG and mainly used as surrogate outcome due to relevance to clinical practice.

**Quality adjusted life year (QALY)**: is a measure of disease burden and is based on the number of years of life that would be added by the intervention. Each year in perfect health is assigned the value of 1.0 down to a value of 0.0 for death. If the extra years would not be lived in full health, for example if the patient would be blind or have to use a wheelchair, then the extra life-years are given a value between 0 and 1 to account for this.

**Life year gained (LYG)**: refers to a single year prolongation of a patient's life by means of a certain intervention. In contrast with QALY morbidity is not included in this measure.

**Introduction**

RSV bronchiolitis is the most common cause of infant morbidity during the winter season and is associated with a large burden of disease and high costs. Most children are infected with RSV during the first year of life. A recent population-based study showed that 30-50% of all children require medical attention for RSV bronchiolitis in the first year of life [4]. RSV infection is worldwide the most common cause of infant morbidity during the winter season and is associated with a large burden of disease and high costs. Each year, 10-14% of all children below 1 year of age require medical care for RSV bronchiolitis in the Netherlands adding up to about 25,000 infants each year [5]. A total of 1,500-2,000 of these children are hospitalised with RSV bronchiolitis in the Netherlands annually, with corresponding mean hospitalisation costs of € 3,000-4,000 per patient [6-8].

The disease typically begins with signs of common cold, followed after a few days by coughing, dyspnoea and an expiratory wheeze [9]. Hospitalisation in Europe and the United States is estimated to be 1-3%(10) of all infants aged less than 13 months. Of these hospitalised children, about 10% of infants require mechanical ventilation at a Paediatric Intensive Care Unit [11-13]. After the acute illness, approximately 50% of children with RSV bronchiolitis will develop recurrent episodes of wheeze up to school age which is associated with reduced health-related quality of life [14;15]. Although the burden of disease is considerable, RSV-associated mortality in healthy term infants is probably low, but published estimates vary between 0 and 8% [16-19].

Important risk factors for RSV bronchiolitis are prematurity with or without chronic lung disease, congenital heart disease, Down syndrome and immunodeficiencies [20-23]. Long-term airway morbidity during childhood occurs in 30-70% of hospitalised infants with RSV LRTI, which is referred to as post-bronchiolitis wheeze. The clinical picture of post-bronchiolitis wheeze is recurrent episodes of wheezing, generally associated with viral upper respiratory tract infection [14]. It has been shown that post-bronchiolitis wheeze is associated with decreased health-related quality of life over a broad range of domains, including lung, gastrointestinal tract and sleeping domain [24].

The only effective intervention to prevent RSV bronchiolitis is passive immunoprophylaxis with palivizumab, a monoclonal antibody against the F-protein of RSV. However, this is costly and requires monthly intramuscular injections. Due to high costs RSV immunoprophylaxis is only registered for use in selected populations during the first year of life with the exception

of children with chronic lung disease (CLD) on home oxygen (2 years). The average medical cost of palivizumab prophylaxis at the recommended dose of 15 mg/kg is 4,600 Euro during a 5 month prophylaxis period per patient, which currently leads to a total of 14 million Euro for RSV prevention annually (online GIPdatabank). The efficacy of palivizumab depends on the risk groups and varies from 39 to 80% in chronic lung disease and late preterms, respectively [25;26]. The average medical cost of palivizumab prophylaxis at the recommended dose of 15 mg/kg is 4400 Euro during a 5 month prophylaxis period per patient [27].

Due to these high costs, the cost-effectiveness of palivizumab is subject of vigorous debate [28;29]. Most countries, like The Netherlands, have therefore restricted this treatment to specific high risk groups, i.e. preterm infants born before 32 weeks gestational age and younger than 6 months at the start of the RSV season, children with hemodynamically significant congenital heart disease (CHD), and children with CLD.

However, even the cost-effectiveness studies performed within these high risk groups used different perspectives, outcomes (HAP, QALY or LYG), populations, follow-up, and extra risk factors. The objective of this study therefore is to systematically review the literature on the cost-effectiveness of palivizumab prophylaxis in the following subgroups: 1) preterm infants born before 32 weeks gestational age (WGA), 2) preterm infants born between 32 and 35 WGA, 3) children with CLD, and 4) children with CHD.

**Methods**

*Search strategy*

We searched Pubmed and EMBASE from inception to week 15 2012 and the latest versions of the DARE, NHS EED and HTA databases using the terms cost, cost-effectiveness, respiratory syncytial virus and palivizumab (see Appendix for the complete search syntax) to identify articles reporting on the cost-effectiveness of palivizumab. In addition, a reference and related article search was performed.

*Study selection*

We screened identified titles and abstracts without blinding to authorship or journal. Potentially relevant studies were obtained and the full text examined. Criteria for inclusion in this survey were:

- Respiratory syncytial virus
- Palivizumab
- Children
- Cost-utility analysis using quality adjusted life years (QALY) or cost-effectiveness analysis using either life years gained (LYG) or hospitalisation prevented (HAP)
- Analysis with comparator
- ICER

*Data extraction and synthesis*

Information was gathered for each study on study design, population, and ICER outcomes measured. Because there was significant heterogeneity between the identified studies, pooling of the major outcomes was not possible. The results of the studies are therefore described separately. Where possible ICER values where used which included direct medical and non-medical costs and mortality consequences. The following subgroups where analysed separately 1) preterm infants born before 32 WGA, 2) preterm infants born between 32 and 35 WGA, 3) children with CLD, and 4) children with CHD.

*Study quality*

Two authors (MB, MR) independently assessed the quality of all included studies using Drummond's check-list for assessing economic evaluations [1]**.** Ten specific domains were addressed, i.e. research question, competing alternatives, effectiveness, relevant cost and

consequences, cost and consequence measures, unit measures, values, discounting, incremental analysis, sensitivity analysis and overall considerations. By answering pre-specified questions we reported the execution of the study and judged the quality for each domain. The original quality scores, between brackets, were adapted to Good (Yes), Acceptable (Yes) and Poor (No/Can't tell) to be able to make a further quality assessment possible for the quality score "Yes" in the original Drummond score model. The new quality scores for each domain was 1) good, 2) acceptable, or 3) poor or unclear. Disagreement was resolved by discussion (MB, MR).

*Analyses*

All ICER values were inflated to 2009 values using country specific inflation rates, and converted to Euro values using mean conversion rates for the currency in the year of publication with foreign exchange databases [30-36].

To study the influence of some important factors we performed sensitivity analyses with these factors, i.e. hospitalisation rates, mortality rates and sponsoring, study year and country of origin. For the comparison analyses, only the ICER values for the preterm children born before 35 WGA are shown because the number of studies focusing on the CLD and CHD subgroup were too low. Because no internationally accepted threshold for cost-effectiveness is available no threshold was adopted but cost-effectiveness levels were derived from the conclusions of the authors in the selected papers.

**Results**

*Study selection*

Our search retrieved a total of 339 articles. A total of 19 articles were included in this review (Figure 1). No additional studies were identified by checking the bibliographies of the selected studies. Main reasons to exclude studies were that the articles did not cover respiratory syncytial virus or palivizumab or because the articles did not include an economic evaluation. Other studies that were not included were studies about elderly and replicate studies.

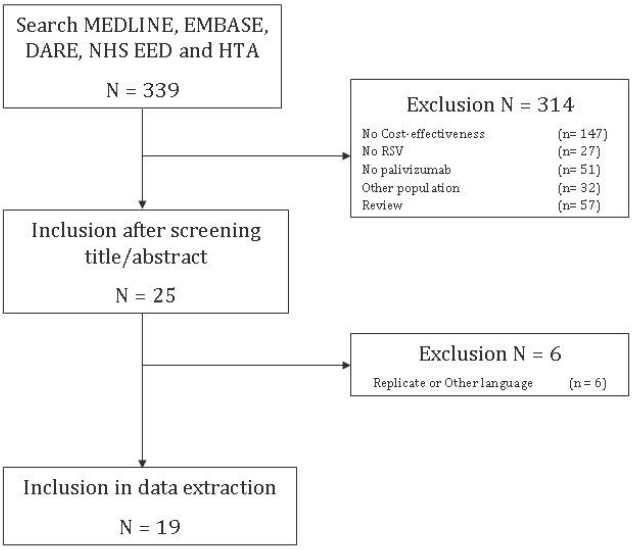



*Figure 1. Flow chart showing identification of economic evaluations.*

*Study quality*

Figure 2 shows the results of the quality assessment according to Drummond's check-list for assessing economic evaluations. All studies performed incremental analysis as this was an inclusion criterion. In 3 out of 19 studies (16%) the research question was not accurately described. In two studies (10%) the effectiveness of palivizumab was not adequately covered. Different cost and consequences were well described by most studies (69%). Only three studies (16%) did not use discounting, and two other studies did not describe it properly.

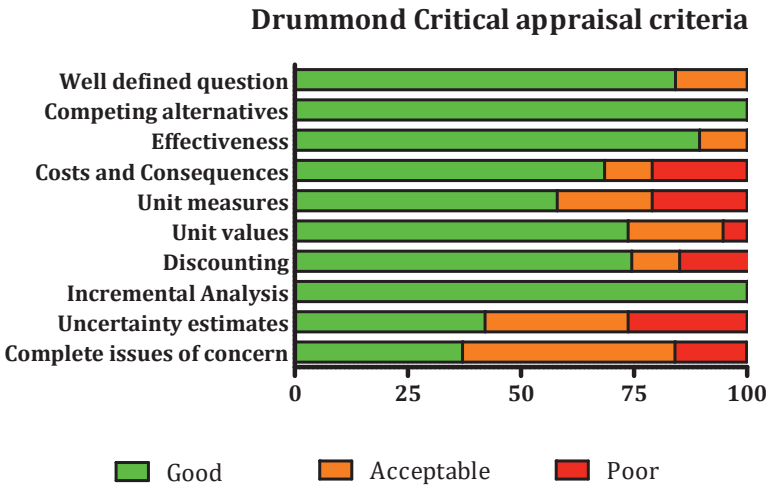



*Figure 2. Critical appraisal of the included studies using Drummond criteria (n=19)* adapted to Good (Yes), Acceptable (Can't tell) and Poor (No/Can't tell) [1].

The reported outcomes of the included studies differed considerably. Of the 19 articles, 8 reported ICER per HAP, 2 reported ICER per QALY, 1 reported both ICER per HAP and ICER per LYG and 8 reported both ICER per QALY and ICER per LYG. The ICERs vary from € 7,372 to 344,617/HAP, from € 7,067 to € 104,532/QALY and from € 4,332 to € 985,485/LYG.

*Effectiveness*

Eleven studies derived the clinical effectiveness of palivizumab from the previously performed phase III trials [25;26]. For preterm children, children with CHD and children with CLD they reported a reduction of the hospitalisation rate of 78%, 45% and 39% with palivizumab treatment versus no-prophylaxis, respectively. The effectiveness used in the other 8 studies was based on longitudinal birth cohort studies.

*Costs*

Nine studies did only report on direct costs associated with respiratory syncytial virus infection. The other nine studies reported on both direct and indirect costs.

*Comparison of subgroups*

Figure 3a-d and Table 1 show the ICER values of the different subgroups. Nine studies [2;37-43] assessed the cost-effectiveness of palivizumab for the subgroup of children born before 32 WGA. The ICER values varied from €9,380 to €1,041742/QALY. Of these nine studies only three

studies considered treatment with palivizumab to be cost-effective with an ICER of respectively €9,380, 12,814 and 19,146/QALY (Table 2). Nine studies assessed the cost-effectiveness for the subgroup of children born between 32 and 35 WGA. Five studies [3;37;41;44;45] considered treatment with palivizumab for this subgroup to be cost-effective with ICER values ranging from €11,759 to €23,060/QALY. The other five studies [39;46-49] concluded that prophylactic treatment is not cost-effective with ICER values varying from €31,522 to €985,485/LYG (Table 3). Eight studies [37;39;41-44;48;49] assessed the cost-effectiveness of palivizumab for the subgroup of children with chronic lung disease. The ICER values varied from €2,731 to €32,465/QALY, €4,332 to €167,168/LYG and €7,372 to €68,448/HAP. Four studies considered palivizumab prophylaxis in this subgroup cost-effective (Table 4). Seven studies assessed the cost-effectiveness of palivizumab for the subgroup of children with congenital heart disease [3;41;44;50-53]. Four studies considered treatment with palivizumab to be cost-effective with ICER values varying from €7,067 to 22,955/QALY. The other three studies reported that palivizumab for this subgroup is not cost-effective with ICER of €165,545/HAP , 188.906/HAP and 104,532/QALY, respectively (Table 5).

Table 1.ICER ranges of the selected subgroups. All values in 2009 € values. WGA: weeks gestational age; CHD: congenital heart disease; BPD: bronchopulmonary dysplasia; CLD: chronic lung disease.

| | <32 WGA | 32-35 WGA | CHD | BPD/CLD |
|---|---|---|---|---|
| HAP | 38 404-130 591 | 37 427-344617 | 165 545-188 906 | 7 372-68 448 |
| LYG | 17 886-362 755 | 16 780-985 485 | 12 139-91 743 | 4 332-167 168 |
| QALY | 9 380-104 1742 | 11 759-20 236 | 7067-104 532 | 2 731-32 465 |

Table 2. Summary of study characteristics of the systematic review of economic evaluations of palivizumab for the subgroup of children born before 32 weeks gestational age.

| Author, publication year | country | N | CEA / CUA | hospitalisation palivizumab group | hospitalisation control group | reduction hospitalisation | hospital mortality | time horizon | perspective | ICER | Conversion and inflation to 2009 € values |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chirico, 2009 | Italy | model | CEA/CUA | 2.0% | 10.3% | 80.0% | 4.0% | 2 years | payers | €17,886/LYG^<br>€9,380/QALY^ | €17,886/LYG^<br>€9,380/QALY^ |
| Elhassan, 2006‡ | USA | model | CUA | 2.9% | 13.2% | 78.0% | n.a. | 8 years | societal | $1,228,260/QALY | €1,041,742/QALY |
| Joffe, 1999§ | USA | 1721 | CEA | 2.5% | 5.5% | 55.0% | 1.2% | lifetime | societal | $108,000/HAP<br>$300,000/LYG | €130,591/HAP<br>€362,755/LYG |
| Nuijten, 2009 | Spain | model | CEA/CUA | 3.9% | 13.4% | 71.0% | 1.4% | lifetime | payers | €18,872/LYG<br>€12,814/QALY | €18,872/LYG<br>€12,814/QALY |
| Reeve, 2006 | Australia | 12171 | CEA | 0.8% | 4.0% | 80.0% | n.a. | 1 year | payers | A$98,818/HAP | €64,659/HAP |
| Resch, 2008 | Austria | model | CEA/CUA | 1.8% | 8.1% | 78.0% | 8.1% | lifetime | payers | €41,242/LYG<br>€28,939/QALY | €41,406/LYG<br>€29,054/QALY |
| Salinas, 2012 | Mexico | model | CUA | 4.9% | 10.1% | 51.5% | 0.23% / 0.99%° | lifetime | payers | $27,333/LYG<br>$19,146/QALY | $27,333/LYG<br>$19,146/QALY |
| Stevens, 2000 | USA | 1029 | CEA | 4.1% | 9.2% | 55.0% | n.a. | 1 year | payers | $32,792/HAP | €44,326/HAP |
| Vogel, 2002 | New Zealand | 437 | CEA | 2.9% | 13.4% | 78.0% | n.a. | 1 year | societal | NZ$65,000/HAP | €38,404/HAP |

§= ≤32WGA values derived from the mean of groups C and D ‡= values derived from mean values of groups 26 WGA, 27-28WGA, 29-30WGA and 31-32WGA. ^= asthma costs were included in the ICER. ° different mortality rates adopted for palivizumab and control group respectively (model= decision analytical model; n.a.= not applicable; CEA= cost-effectiveness analysis, CUA= cost-utility analysis, ICER= incremental cost-effectiveness ratio, LYG= life years gained, QALY=quality adjusted life year, HAP= hospital admission prevented)

Table 3. Summary of study characteristics of the systematic review of economic evaluations of palivizumab for the subgroup of children born before between 32 and 35 weeks gestational age.

| Author, publication year | country | N | CEA / CUA | hospitalisation palivizumab | hospitalisation control | reduction hospitalisation | hospital mortality | time horizon | perspective | ICER | Conversion and inflation to 2009 € values |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chirico, 2009 | Italy | model | CEA/CUA | 1.5% | 9.8% | 85.0% | 4.0% | 2 years | payers | €28,417/LYG^<br>€14,937/QALY^ | €28,417/LYG^<br>€14,937/QALY^ |
| Joffe, 1999 § | USA | 1721 | CEA | 1.0% | 2.2% | 55.0% | 1.2% | lifetime | societal | $285,000/HAP<br>$815,000/LYG | €344,617/HAP<br>€985,485/LYG |
| Lanctot, 2008 | Canada | model | CEA/CUA | 1.8% | 10.0% | 80.0% | 8.1% | lifetime | payers | CAN$ 44,237/LYG<br>CAN$ 30,618/QALY | €29,053/LYG<br>€20,109/QALY |
| Resch, 2008 | Austria | model | CEA/CUA | 1.8% | 8.1% | 78.0% | 8.1% | lifetime | payers | €16,714/LYG<br>€11,713/QALY | €16,780/LYG<br>€11,759/QALY |
| Lofland, 2000† | USA | model | CEA | 5.0% | 12.0% | 59.0% | n.a. | 1 year | payers | $53,777/HAP | €72,693/HAP |
| Nuijten, 2009 | Netherlands | model | CUA | 4.8% | 10.6% | 55.0% | 8.1% | lifetime | societal | €20,236/QALY^ | €20,236/QALY^ |
| Nuijten, 2007 | UK | model | CEA/CUA | 1.8% | 8.1% | 78.0% | 8.1% | lifetime | payers | £20,344/LYG^<br>£14,883/QALY^ | €31,522/LYG^<br>€23,060/QALY^ |
| Rodriguez, 2008 | Argentina | 159 | CEA | 3.5% | 16.5% | 79.0% | n.a. | 1 year | payers | $51,550/HAP | €37,427/HAP |
| Roeckl-Wiedmann, 2003^^ | Germany | model | CEA | 5.8% | 12.8% | 55.0% | 1.2% | 1 year | societal | €94,270/HAP | €104,691/HAP |

Data described are derived from the subgroups of children born <35 WGA and children born between 32 and 35 WGA. §= 32-35 values derived from the mean of groups G and H, CLD values derived from groups A, B, E and F. †= ≤35WGA values used most comparable to 55% efficacy rate for the preterm subgroup; ICER values included indirect medical costs (asthma costs). ^= asthma costs were included in the ICER. ^^= all children had one of the risk factors: male, siblings or birth month Oct-Dec., ≤35WGA values were derived from the mean of groups B to D. (model= decision analytical model; n.a.= not applicable; CEA= cost-effectiveness analysis, CUA= cost-utility analysis, ICER= incremental cost-effectiveness ratio, LYG= life years gained, QALY=quality adjusted life year, HAP= hospital admission prevented)

Table 4. Summary of study characteristics of the systematic review of economic evaluations of palivizumab for the subgroup of children with bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD).

| Author, publication year | country | N | CEA / CUA | hospitalisation palivizumab group | hospitalisation control group | reduction hospitalisation | hospital mortality | time horizon | perspective | ICER | Conversion and inflation to 2009 € values |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chirico, 2009 | Italy | model | CEA/CUA | 5.6% | 18.4% | 70.0% | 4.0% | 2 years | payers | €4,332/LYG^<br>€2,731/QALY^ | €4,332/LYG^<br>€2,731/QALY^ |
| Joffe, 1999* | USA | 1721 | CEA | 5.7% | 12.7% | 55.0% | 1.2% | lifetime | societal | $49,750/HAP<br>$138,250/LYG | €55,319/HAP<br>€167,168/LYG |
| Nuijten, 2007 | UK | model | CEA/CUA | 7.9% | 12.8% | 39.0% | 8.1% | lifetime | payers | £28,569/LYG^<br>£20,953/QALY^ | €44,266/LYG^<br>€32,465/QALY^ |
| Resch, 2008 | Austria | model | CEA/CUA | 7.9% | 12.8% | 39.0% | 8.1% | lifetime | payers | €45,369/LYG<br>€31,867/QALY | €45,550/LYG<br>€31,994/QALY |
| Rodriguez, 2008 | Argentina | 159 | CEA | 16.5% | 28.0% | 41.0% | n.a. | 1 year | payers | $32,089/HAP | €23,297/HAP |
| Roeckl-Wiedmann, 2003^^ | Germany | model | CEA | 24.3% | 53.9% | 55.0% | 1.2% | 1 year | societal | €6,639/HAP | €7,372/HAP |
| Stevens, 2000 | USA | 1029 | CEA | 14.8% | 24.4% | 39.0% | n.a. | 1 year | payers | $16,851/HAP | €22,778/HAP |
| Vogel, 2002 | New Zealand | 437 | CEA | 10.0% | 16.5% | 39.0% | n.a. | 1 year | societal | NZ$115,850/HAP | €68,448/HAP |

§= CLD values derived from groups A, B, E and F. *= defined as ≥ 28 days oxygen. ^= asthma costs were included in the ICER. ^^= all children had one of the risk factors: male, siblings or birth month Oct-Dec. Children in the CLD group had all three risk factors. CLD values were derived from group A. (model= decision analytical model; n.a.= not applicable; CEA= cost-effectiveness analysis, CUA= cost-utility analysis, ICER= incremental cost-effectiveness ratio, LYG= life years gained, QALY=quality adjusted life year, HAP= hospital admission prevented)

Table 5. Summary of study characteristics of the systematic review of economic evaluations of palivizumab for the subgroup of children with congenital heart disease (CHD)

| Author, publication year | country | N | CEA / CUA | hospitalisation palivizumab group | hospitalisation control group | reduction hospitalisation | hospital mortality | time horizon | perspective | ICER | Conversion and inflation to 2009 € values |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Harris, 2011 | Canada | 704 | CEA | 1.7% | 2.9% | 41.4% | 5.9% | 1 year | societal | $188,906/HAP ~ | $188,906/HAP ~ |
| Meberg, 2006 | Norway | 43470 | CEA | 5.0% | 9.2% | 45.0% | n.a. | 1 year | payers | $195,000/HAP | €165,545/HAP |
| Nuijten, 2009 | Germany | model | CEA/CUA | 5.3% | 9.7% | 45.0% | 4.5%** | lifetime | societal | €19,391/LYG<br>€18,266/QALY | €19,391/LYG<br>€18,266/QALY |
| Nuijten, 2009 | Netherlands | model | CUA | 5.3% | 9.7% | 45.0% | 4.5%** | lifetime | societal | €7,067/QALY^ | €7,067/QALY^ |
| Nuijten, 2007 | UK | model | CEA/CUA | 5.6% | 7.9% | 29.0% | 4.5% | lifetime | payers | £15,575/LYG^<br>£14,816/QALY^ | €24,132/LYG^<br>€22,955/QALY^ |
| Resch, 2008 | Austria | model | CEA/CUA | 5.3% | 9.7% | 45.0% | 4.5%** | lifetime | payers | €12,091/LYG<br>€11,390/QALY | €12,139/LYG<br>€11,435/QALY |
| Yount, 2004 | USA | model | CEA/CUA | 5.3% | 9.7% | 45.0% | 3.0% | lifetime | societal | $100,338/LYG<br>$114,337/QALY | €91,734/LYG<br>€104,532/QALY |

**= based on analysis by Nuijten et al. (Nuijten et al. Pharmacoeconomics 07). ~ derived from the mean hospitalisation duration and the incremental cost to prevent 1 day of hospitalisation ^= asthma costs were included in the ICER. (model= decision analytical model; n.a.= not applicable; CEA= cost-effectiveness analysis, CUA= cost-utility analysis, ICER= incremental cost-effectiveness ratio, LYG= life years gained, QALY=quality adjusted life year, HAP= hospital admission prevented)

*Sensitivity analyses*

The results of our sensitivity analyses are shown in figures 4-9. Figure 4 shows the relation between the hospitalisation rate and the cost-effectiveness for the subgroup of children born before 32 WGA and children born between 32 and 35 WGA. Studies adopting an efficacy rate of approximately 80% for prophylactic treatment tend to be more cost-effective than studies using an efficacy rate of 55% as derived from the original palivizumab effectiveness study, the IMpact trial [25].

Figure 5 shows the relation between the mortality rate and cost-effectiveness. The mortality rates for children hospitalised with RSV infection varied from 0.5 to 8.1 %, and especially the latter rate has a tremendous effect on the cost-effectiveness. Studies with 8.1% mortality rate tend to be more cost-effective than studies using lower mortality rates. Figure 6 shows the relation between potential sponsoring by pharmaceutical companies and the cost-effectiveness. Sponsored studies show a tendency to be more cost-effective. Figure 7 shows the relation between year of publication and cost-effectiveness. Economic evaluations from recent years tend to be more cost-effective. Figure 8 shows the geographic location of the various economic evaluations and the outcome of the analyses. The majority of studies performed in Europe appear to show more cost-effectiveness than the studies from America.

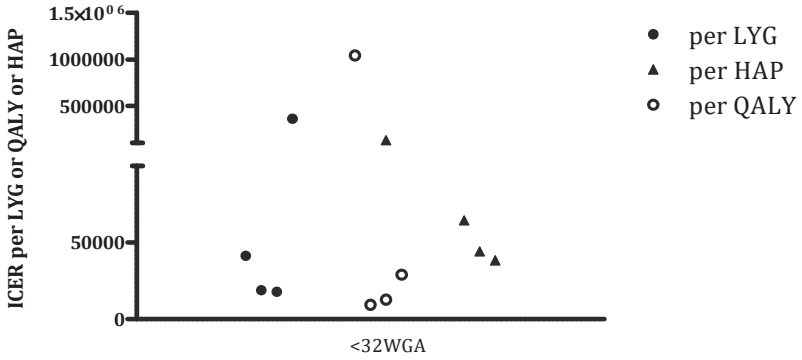



*Figure 3a. The cost-effectiveness of palivizumab for the subgroup of children born before 32 weeks gestational age.*

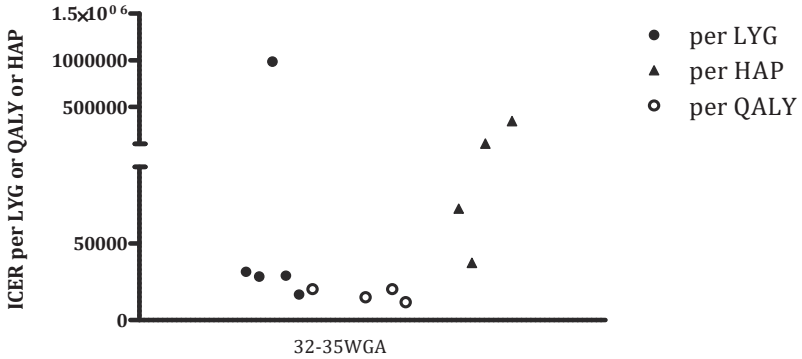



*Figure 3b. The cost-effectiveness of palivizumab for the subgroup of children born at 32 - 35 weeks gestational age.*

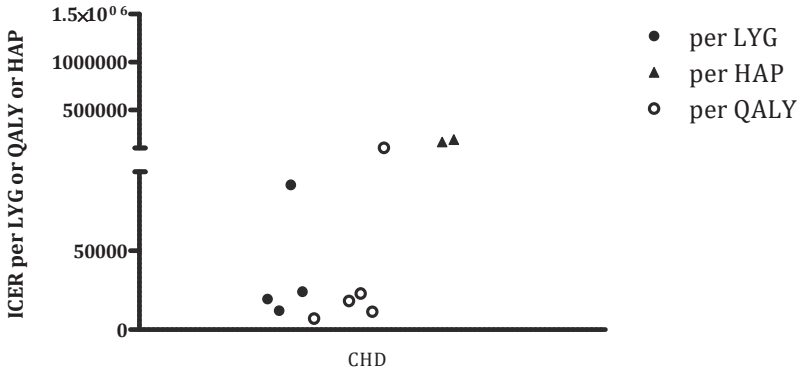


*Figure 3c. The cost-effectiveness of palivizumab for the subgroup of children with congenital heart disease.*

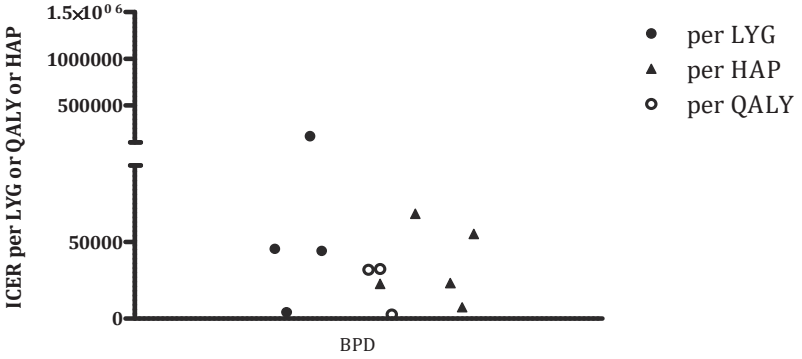



*Figure 3d. The cost-effectiveness of palivizumab for the subgroup of children with bronchopulmonary dysplasia.*

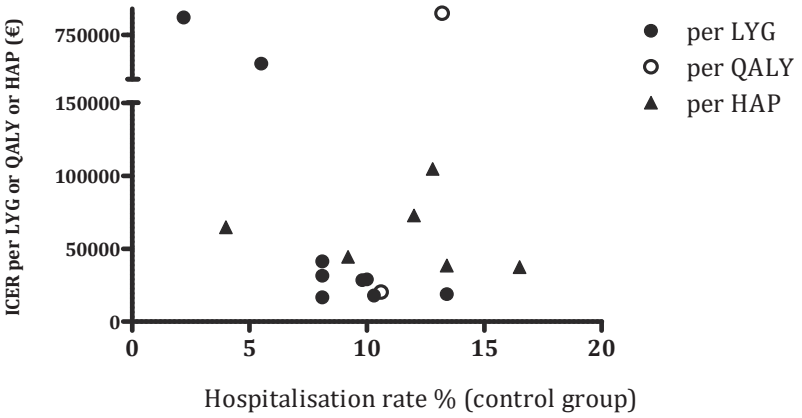



*Figure 4. The relation between the hospitalisation rates used in the economic analyses and the measured ICER values for the subgroup of children born before 35 weeks gestational age.*

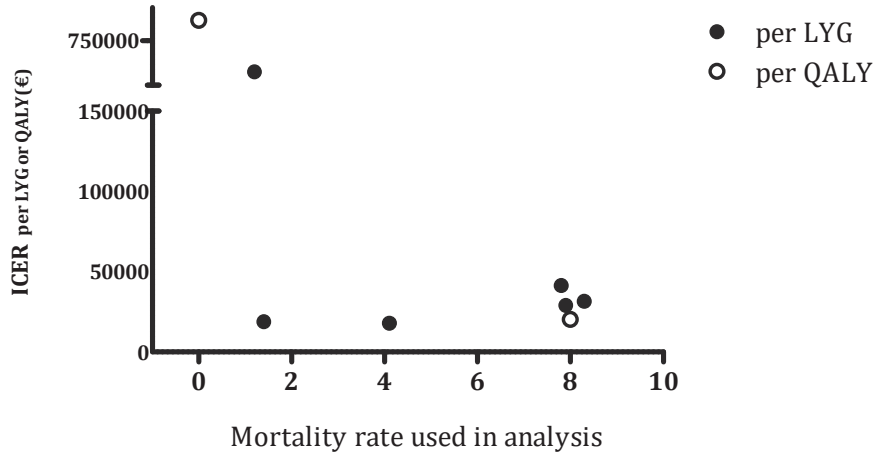



*Figure 5. The relation between the mortality rate for hospitalised children in the economic analysis and the measured ICER values for the subgroup of children born before 35 weeks gestational age.*

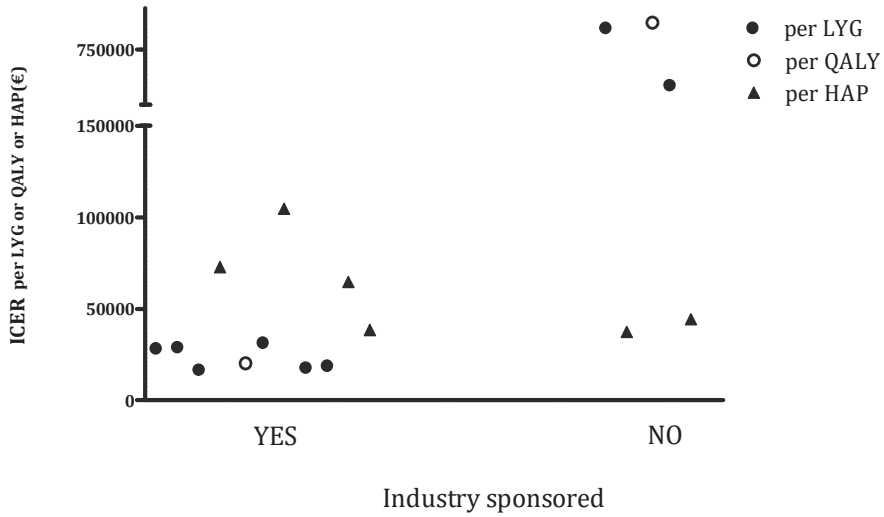



*Figure 6. The relation between the economic analysis sponsored by the pharmaceutical industry and the measured ICER values for the subgroup of children born before 35 weeks gestational age.*

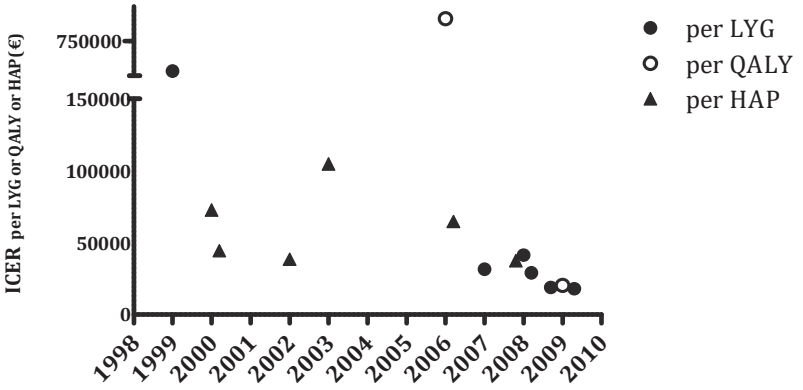



*Figure 7. The relation between the cost-effectiveness of palivizumab and the year of publication for the subgroup of children born before 35 weeks gestational age.*

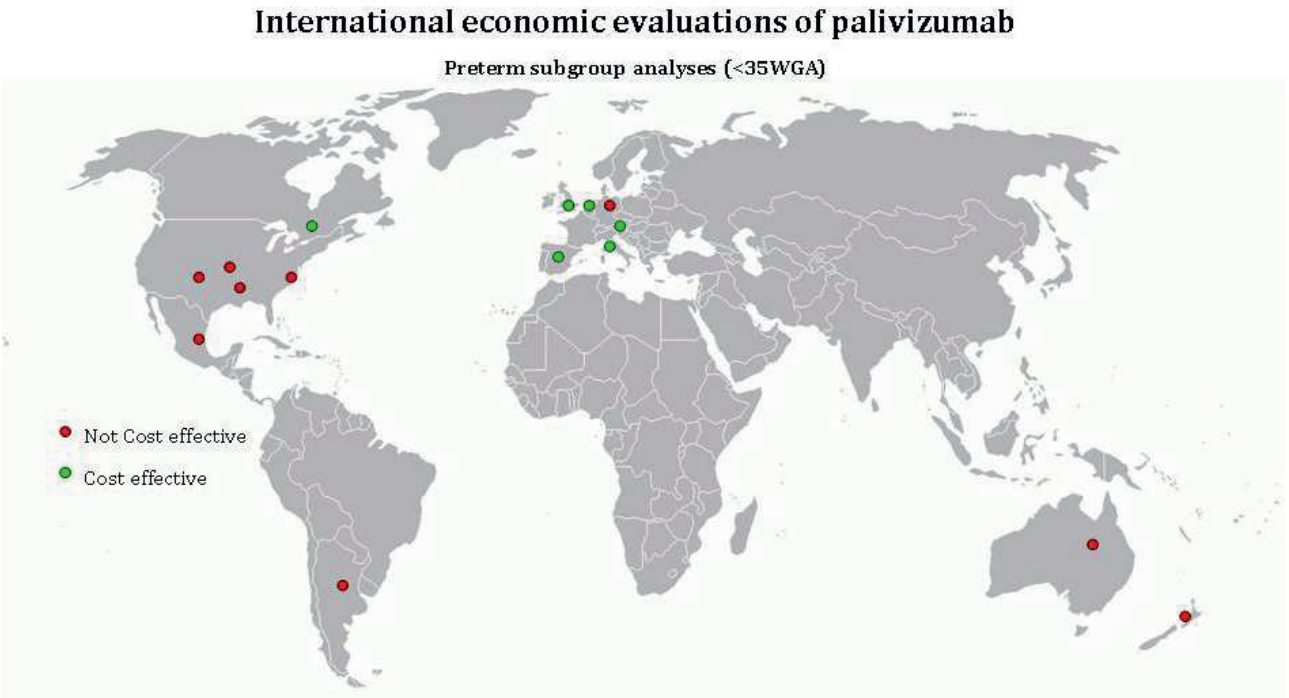



*Figure 8. The presented conclusion of cost-effectiveness studies of palivizumab shown per country for subgroup of children born before 35 weeks gestational age.*

**Discussion**

The evidence regarding the cost-effectiveness of prophylactic treatment of RSV infection with palivizumab in subgroups varies considerably. This is in agreement with the results of other reviews [54-56]. Due to this high variability between studies and the broad ranges in all outcome measures conclusive recommendations are currently not possible.

The most important driver of cost-effectiveness seems the mortality rate, and even the other variations associated with cost-effectiveness, can often be attributed to differences in mortality. This is also reflected in sponsored studies, although we are not the first to describe the influence of industry sponsoring on cost-effectiveness [57]. For example, most of the sponsored studies used a high mortality rate and productivity losses of children within a life time horizon, which are also based on mortality. These high mortality rates have a large impact on cost-effectiveness when ICERs are reported for LYGs or QALYs. Every percent increase in mortality will mean that more life years or QALYs are gained despite the cost of palivizumab. As a result, the cost-effectiveness ratio will be lower. A recent study from Denmark suggests that the mortality rate of RSV probably does not exceed 1% [58]. The high mortality rate used is based on the study of Sampalis, in which there was a high amount of children with sudden or otherwise unexplained death for which the causal relation with RSV infection has not been proven [59]. The European studies, which are the more recent studies, also generally use the higher mortality rate. The need for solid RSV mortality rates is evident and should be an important RSV research subject.

The major strength of our systematic review is the diversity of the included studies with respect to localization, year of analysis and the subgroups studied. Nevertheless, some of our findings deserve further discussion. First, the included studies reported LYG, QALY or HAP, which cannot be compared directly. Cost per HAP as even considered an inferior outcome measure compared to cost per LYG or QALY but we included it in our systematic review as morbidity and especially hospitalisation is a much bigger issue than mortality in RSV infection and thus regarding a highly relevant outcome. Second, some studies [3;40;41;44;51] looked at different subgroups but used identical modelling data (both costs and effects), and are therefore not independent as suggested in the figures. Third, cost data for palivizumab are generally based on 5 doses of palivizumab and no drug wastage, but in daily practice it is not unusual that more doses are given and is there considerable drug wastage because of the limited time a vial is usable after opening (3 hours). The real cost will thus often be higher than

reported in most papers, although vial sharing becomes increasingly used. Fourth, one of our inclusion criteria was the presence of an ICER as outcome measure. This created a possible selection bias and we might have missed important studies for which the ICER could be calculated. Fifth, as our quality analysis shows, there were differences in study quality. Some studies used data derived from small cohort studies as a measure of effectiveness of palivizumab. The associated cost-effectiveness ratios are therefore not based on the best available evidence. This should be taken into account when comparing these studies to cost-effectiveness studies with a better approach. The original quality scores of the Drummond Critical appraisal criteria, between brackets, were adapted to Good (Yes), Acceptable (Yes) and Poor (No/Can't tell) to be able to make a further quality assessment possible for the quality score "Yes" in the original Drummond score model. The authors chose this approach because a high variability in quality in the "Yes" area. Although this provided additional insight in study quality we don't recommend further use of this approach as domains should either be appropriately discussed, i.e. "Yes", or not, i.e. "No"/"Can't tell".

Evidence derived from cost-effectiveness studies is used to inform decisions about the reimbursement of medical interventions in an increasing number of countries. Cost-effectiveness and cost-utility thresholds have either been explicitly specified by authorities or can be implicitly determined from examining past reimbursement decisions. However, the use of thresholds is disputed and alternative approaches to assess the value of a health technology have been proposed, such as the fixed budget approach, fixed trade off approach and flexible trade off approach. Although an explicit threshold approach will not be end of equity discussions within and between countries it will certainly help increase transparency of reimbursement decisions. Currently, interpreting the results of cost effectiveness analysis can be problematic, making it difficult to decide whether to adopt an intervention. The threshold for adoption is thought to be somewhere between €20 000/QALY and €100 000/QALY, with thresholds of €50-60 000/QALY frequently proposed [60]. Because there is still no consensus regarding an international threshold we have refrained from adopting a threshold for this systematic review. Another issue that needs discussion is the transferability of cost effectiveness data between countries. Because it is not feasible to assess the cost effectiveness of every intervention in every country, reimbursement decisions in one country could be based on the results of a cost effectiveness study in another country. Unfortunately, decision-makers need to assess whether, and to what extent, the assessment and analysis

from this other country applies to their own country. In a recent systematic review treatment effects were considered to have high transferability whereas especially baseline risk, resource use and unit costs have low transferability [61]. This is highly relevant for the guidelines for cost effectiveness studies regarding choices for input data. It is for example generally accepted to adopt clinical data from trials performed in another setting as the source of the relative treatment effect, while absolute risk estimates or resource consumption from these studies are difficult to transfer. There are several systems, processes and approaches for assessing the transferability of cost effectiveness studies or guidelines for transferring economic evaluation data between countries, although the proposed approached varied substantially [62]. There is general agreement on the approach to first consider critical criteria like study quality, transparency of methods the level of reporting of methods and results and the applicability of the treatment comparators to the target country followed by the assessment of non-critical criteria for which is the list is long and diverse. A consensus on the approach of transferability in national guidelines and regularly updating these guidelines would a big step forward to cost effective use of the results of cost effectiveness studies between countries.

In this review we did not focus on targeting high risk populations with additional risk factors within preterm infants or infants with CHD or CLD. This is a main focus for future RSV research and subsequent economic evaluation studies. For example although RSV immunoprophylaxis has shown to be effective in preventing RSV LRTI in preterm children born at 32-35 WGA, it is not reimbursed in the Netherlands. Due to high costs, the willingness to pay for palivizumab is too low for use in late preterm infants 32-35 WGA in the Netherlands indiscriminately. However, cost-effectiveness of providing immunoprophylaxis to a subgroup of preterm infants 32-35 WGA at highest risk to develop RSV bronchiolitis based on individualized risk prediction may be acceptable. I have recently discovered that every year 5.1% of all late preterm infants 32-35 WGA are hospitalised for RSV infection in the Netherlands (PIDJ in review). Because 6000 preterm infants 32-35 WGA are born annually in the Netherlands, an annual country-specific RSV hospitalisation rate of 306 is estimated. RSV disease burden is not only a direct burden for the child. During the acute illness parents experience stress on both private and working life. After the acute illness the child could develop wheezing complaints with significant morbidity and decreased quality of life. This underlines the importance of developing guidelines to target the disease burden caused by RSV infection in the highest risk groups based on risk stratification.

Future RSV cost-effectiveness analyses should make use of country specific epidemiological cost and effectiveness data and describe all input data on both unit and value level. This demands both large cohort studies, accurate RSV related mortality estimates and attention for short and long term consequences with respect to morbidity and indirect costs of productivity losses of parents and future productivity losses of children. Also, to increase legitimacy and decrease potential bias, the analyses should be performed independent from the influence of pharmaceutical companies.

**Conclusion**

The cost-effectiveness of prophylactic treatment of RSV infection with palivizumab in subgroups varies importantly, and is certainly not always below the threshold. The cost-effectiveness is mainly affected by mortality rates of RSV infection. Future research should focus on the major uncertainties in cost-effectiveness, particularly RSV-related mortality rate.

**References**


1. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the Economic Evaluation of Health Care Programmes. 3 ed. Oxford University Press; 2005.
2. Reeve CA, Whitehall JS, Buettner PG, Norton R, Reeve DM, Francis F. Cost-effectiveness of respiratory syncytial virus prophylaxis with palivizumab. J Paediatr Child Health 2006;42(5):253-8.
3. Nuijten M, Lebmeier M, Wittenberg W. Cost effectiveness of palivizumab for RSV prevention in high-risk children in the Netherlands. J Med Econ 2009 Oct 8.
4. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009 Feb 5;360(6):588-98.
5. Houben ML, Bont L, Wilbrink B, Belderbos ME, Kimpen JL, Visser GH, et al. Clinical prediction rule for RSV bronchiolitis in healthy newborns: prognostic birth cohort study. Pediatrics 2011 Jan;127(1):35-41.
6. Bos JM, Rietveld E, Moll HA, Steyerberg EW, Luytjes W, Wilschut JC, et al. The use of health economics to guide drug development decisions: Determining optimal values for an RSV-vaccine in a model-based scenario-analytic approach. Vaccine 2007 Sep 28;25(39-40):6922-9.
7. Jansen AG, Sanders EA, Hoes AW, van Loon AM, Hak E. Influenza- and respiratory syncytial virus-associated mortality and hospitalisations. Eur Respir J 2007 Dec;30(6):1158-66.
8. Rietveld E, De Jonge HC, Polder JJ, Vergouwe Y, Veeze HJ, Moll HA, et al. Anticipated costs of hospitalization for respiratory syncytial virus infection in young children at risk. PIDJ 2004 Jun;23(6):523-9.
9. Smyth RL, Openshaw PJ. Bronchiolitis. Lancet 2006 Jul 22;368(9532):312-22.
10. Smyth RL, Openshaw PJ. Bronchiolitis. Lancet 2006 Jul 22;368(9532):312-22.
11. Ermers MJ, Rovers MM, van Woensel JB, Kimpen JL, Bont LJ. The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: randomised double blind placebo controlled trial. BMJ 2009;338:b897.
12. Bont L, Kimpen JL. Immunological mechanisms of severe respiratory syncytial virus bronchiolitis. Intensive Care Med 2002 May;28(5):616-21.

13. Tissing WJE, Van Steensel-Moll HA, Offringa M. Risk factors for mechanical ventilation in respiratory syncytial virus infection. Eur J Pediatr 1993;152:125-7.
14. Bont L, Aalderen vWMC, Kimpen JLL. Long-term consequences of respiratory syncytial virus (RSV) bronchiolitis. Paediatr Respir Rev 2000;1(3):221-7.
15. Bont L, Steijn M, van Aalderen WM, Kimpen JL. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. PIDJ 2004 May;23(5):414-7.
16. Simon A, Ammann RA, Wilkesmann A, Eis-Hubinger AM, Schildgen O, Weimann E, et al. Respiratory syncytial virus infection in 406 hospitalized premature infants: results from a prospective German multicentre database. Eur J Pediatr 2007 Dec;166(12):1273-83.
17. Sampalis JS. Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants. J Pediatr 2003 Nov;143(5 Suppl):S150-S156.
18. Prais D, Schonfeld T, Amir J. Admission to the intensive care unit for respiratory syncytial virus bronchiolitis: a national survey before palivizumab use. Pediatrics 2003 Sep;112(3 Pt 1):548-52.
19. Stensballe LG, Devasundaram JK, Simoes EA. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. Pediatr Infect Dis J 2003 Feb;22(2 Suppl):S21-S32.
20. Bloemers BL, van Furth AM, Weijerman ME, Gemke RJ, Broers CJ, van den EK, et al. Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis--a prospective birth-cohort study. Pediatrics 2007 Oct;120(4):e1076-e1081.
21. Boyce TG, Mellen BG, Mitchel EF, Jr., Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr 2000 Dec;137(6):865-70.
22. Weisman LE. Populations at risk for developing respiratory syncytial virus and risk factors for respiratory syncytial virus severity: infants with predisposing conditions. Pediatr Infect Dis J 2003 Feb;22(2 Suppl):S33-S37.
23. Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. J Pediatr 2003 Nov;143(5 Suppl):S112-S117.
24. Bont L, Steijn M, van Aalderen WM, Kimpen JL. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. PIDJ 2004 May;23(5):414-7.

25. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics 1998 Sep;102(3 Pt 1):531-7.
26. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH, Jr., et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003 Oct;143(4):532-40.
27. GIP database, Dutch database of medical resources and medicines. GIP database, Drug Information System of the Health Care Insurance Board 2010 [cited 2010 Feb 2];Available from: URL: http://www.gipdatabank.nl/
28. Isaacs D. Palivizumab. An example of indication creep. BMJ 2009;339:b2724.
29. Meissner HC, Bocchini JA, Jr., Brady MT, Hall CB, Kimberlin DW, Pickering LK. The role of immunoprophylaxis in the reduction of disease attributable to respiratory syncytial virus. Pediatrics 2009 Dec;124(6):1676-9.
30. FXHistory; Historical Exchange rates. OANDA 2010 [cited 2010 Feb 2];Available from: URL: http://www.oanda.com/currency/historical-rates
31. Eurostat. Eurostat 2010 [cited 2010 Feb 2];Available from: URL: http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/
32. United States Department of Labor. Bureau of Labor Statistics 2010 [cited 2010 Feb 2];Available from: URL: http://www.bls.gov/CPI/
33. Australian Bureau of Statistics. Australian Bureau of Statistics 2010 [cited 2010 Feb 2];Available from: URL: http://www.abs.gov.au/
34. Reserve Bank of New Zealand. Reserve Bank of New Zealand 2010 [cited 2010 Feb 2];Available from: URL: http://www.rbnz.govt.nz/statistics/
35. Statistics Canada. Statistics Canada 2010 [cited 2010 Feb 2];Available from: URL: http://www.statcan.gc.ca/
36. Institutio Nacional de Estadistica y Censos. Institutio Nacional de Estadistica y Censos 2010 [cited 2010 Feb 2];Available from: URL: http://www.indec.mecon.ar/
37. Chirico G, Ravasio R, Sbarigia U. Cost-utility analysis of palivizumab in Italy: Results from a simulation model in the prophylaxis of respiratory syncytial virus infection (RSV) among high-risk preterm infants. Ital J Pediat 2009;35(4).

38. Elhassan NO, Sorbero MES, Hall CB, Stevens TP, Dick AW. Cost-effectiveness analysis of palivizumab in premature infants without chronic lung disease. Arch Pediatr Adolesc Med 2006;160(10):1070-6.
39. Joffe S, Ray GT, Escobar GJ, Black SB, Lieu TA. Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants. Pediatrics 1999;104(3 I):419-27.
40. Nuijten MJ, Wittenberg W. Cost effectiveness of palivizumab in Spain: an analysis using observational data. Eur J Health Econ 2009;1-11.
41. Resch B, Gusenleitner W, Nuijten MJC, Lebmeier M, Wittenberg W. Cost-effectiveness of palivizumab against respiratory syncytial viral infection in high-risk children in Austria. Clin Ther 2008;30(4):749-60.
42. Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM. Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: Hospitalization and economic implications of prophylaxis. Arch Pediatr Adolesc Med 2000;154(1):55-61.
43. Vogel AM, McKinlay MJ, Ashton T, Lennon DR, Harding JE, Pinnock R, et al. Cost-effectiveness of palivizumab in New Zealand. J Paediatr Child Health 2002;38(4):352-7.
44. Nuijten MJC, Wittenberg W, Lebmeier M. Cost effectiveness of palivizumab for respiratory syncytial virus prophylaxis in high-risk children: A UK analysis. PharmacoEconomics 2007;25(1):55-71.
45. Salinas-Escudero G, Martinez-Valverde S, Reyes-Lopez A, Garduno-Espinosa J, Munoz-Hernandez O, Granados-Garcia V, et al. Cost-effectiveness analysis of the use of palivizumab in the prophylaxis of preterm patients in Mexico. Salud Publica Mex 2012 Jan;54(1):47-59.
46. Lanctot KL, Masoud ST, Paes BA, Tarride JE, Chiu A, Hui C, et al. The cost-effectiveness of palivizumab for respiratory syncytial virus prophylaxis in premature infants with a gestational age of 32-35 weeks: A Canadian-based analysis. Curr Med Res Opin 2008;24(11):3223-37.
47. Lofland JH, Touch SM, O'Connor JP, Chatterton ML, Moxey ED, Paddock LE, et al. Palivizumab for respiratory syncytial virus prophylaxis in high-risk infants: A cost-effectiveness analysis. Clin Ther 2000;22(11):1357-69.

48. Rodriguez SP, Farina D, Bauer G. Respiratory Syncytial Virus Prophylaxis in a High-Risk Population in Argentina: A Cost-Effectiveness Analysis. Pediatr Infect Dis J 2008;27(7):660-1.
49. Roeckl-Wiedmann I, Liese JG, Grill E, Fischer B, Carr D, Belohradsky BH. Economic evaluation of possible prevention of RSV-related hospitalizations in premature infants in Germany. Eur J Pediatr 2003;162(4):237-44.
50. Meberg A, Bruu AL. Respiratory syncytial virus infections in congenital heart defects - Hospitalizations and costs. Acta Paediatr Int J Paediatr 2006;95(4):404-6.
51. Nuijten M, Lebmeier M, Wittenberg W. Cost effectiveness of palivizumab in children with congenital heart disease in Germany. J Med Econ 2009 Oct 8.
52. Yount LE, Mahle WT. Economic analysis of palivizumab in infants with congenital heart disease. Pediatrics 2004;114(6):1606-11.
53. Harris KC, Anis AH, Crosby MC, Cender LM, Potts JE, Human DG. Economic evaluation of palivizumab in children with congenital heart disease: a Canadian perspective. Can J Cardiol 2011 Jul;27(4):523-5.
54. Wang D, Cummins C, Bayliss S, Sandercock J, Burls A. Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: A systematic review and economic evaluation. Health Technol Assess 2008;12(36).
55. Prescott WA, Jr., Doloresco F, Brown J, Paladino JA. Cost effectiveness of respiratory syncytial virus prophylaxis: a critical and systematic review. Pharmacoeconomics 2010 Apr 1;28(4):279-93.
56. Embleton ND, Harkensee C, Mckean MC. Palivizumab for preterm infants. Is it worth it? Arch Dis Child Fetal Neonatal Ed 2005 Jul;90(4):F286-F289.
57. Bell CM, Urbach DR, Ray JG, Bayoumi A, Rosen AB, Greenberg D, et al. Bias in published cost effectiveness studies: systematic review. BMJ 2006 Mar 25;332(7543):699-703.
58. Thorburn K. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. Arch Dis Child 2009 Feb;94(2):99-103.
59. Sampalis JS. Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants. J Pediatr 2003 Nov;143(5 Suppl):S150-S156.

60. Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 2004 Sep;7(5):518-28.
61. Barbieri M, Drummond M, Rutten F, Cook J, Glick HA, Lis J, et al. What do international pharmacoeconomic guidelines say about economic data transferability? Value Health 2010 Dec;13(8):1028-37.
62. Goeree R, He J, O'Reilly D, Tarride JE, Xie F, Lim M, et al. Transferability of health technology assessments and economic evaluations: a systematic review of approaches for assessment and application. Clinicoecon Outcomes Res 2011;3:89-104.

**Appendix 1**

*Search strategy*

A systematic search was conducted in Pubmed (Ovid), EMBASE(Ovid) and the DARE, NHS EED and HTA databases in week 5 2010, this search was updated in week 15 2012 . Searches were not restricted by date or language. We used the following search terms with corresponding synonyms:

- cost
- cost-effectiveness
- cost utility
- cost benefit
- decision making
- palivizumab
- synagis
- monoclonal antibody
- vaccine
- prevent*
- immunotherapy
- immunoprophylaxis
- respiratory syncytial virus
- bronchiolitis

*Exclusion criteria*

- not about children
- not about respiratory syncytial virus
- not about palivizumab
- no comparator
- no full text available
- other immunoprophylaxis

*Specific database search strategies*

**PUBMED**

((cost[title/abstract] OR costs[title/abstract] OR cost-effectiveness[title/abstract] OR cost-utility[title/abstract] OR cost-benefit[title/abstract] OR decision analys*[title/abstract]) AND (palivizumab[title/abstract] OR synagis[title/abstract] OR monoclonal antibod* [title/abstract] OR vaccin*[title/abstract] OR prevent*[title/abstract] OR immunotherapy[title/abstract] OR immunoprophylaxis[title/abstract]) AND (RSV[title/abstract] OR respiratory syncytial virus[title/abstract] OR bronchiolitis[title/abstract])) OR ((cost[title/abstract] OR costs[title/abstract] OR cost-effectiveness[title/abstract] OR cost-utility[title/abstract] OR cost-benefit[title/abstract] OR decision analys*[title/abstract]) AND (palivizumab[title/abstract] OR synagis[title/abstract]))

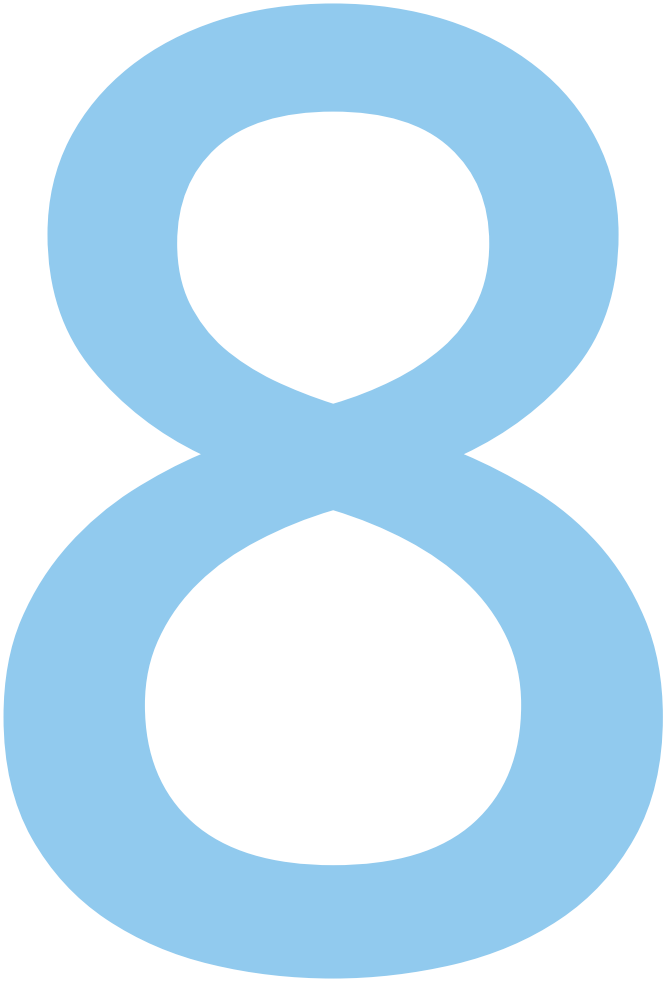
**EMBASE**

((cost:ab,ti OR 'cost-effectiveness':ab,ti OR 'cost utility':ab,ti OR 'cost benefit':ab,ti OR 'decision making':ab,ti) AND (palivizumab:ab,ti OR synagis:ab,ti OR 'monoclonal antibody':ab,ti OR vaccin*:ab,ti OR prevent*:ab,ti OR immunotherapy:ab,ti OR immunoprophylaxis:ab,ti) AND ('syncytial respiratory virus'/exp OR 'syncytial respiratory virus':ab,ti OR bronchiolitis:ab,ti)) OR ((cost:ab,ti OR 'cost effectiveness':ab,ti OR 'cost utility':ab,ti OR 'cost benefit':ab,ti OR 'decision making':ab,ti) AND (palivizumab:ab,ti OR synagis:ab,ti))

**CRD (DARE, NHS EED, HTA)**

((cost OR costs OR cost-effectiveness OR cost-utility OR cost-benefit OR decision analys*) AND (palivizumab OR synagis OR monoclonal antibod* OR vaccin* OR prevent* OR immunotherapy OR immunoprophylaxis) AND (RSV OR respiratory syncytial virus OR bronchiolitis)) OR ((cost OR costs OR cost-effectiveness OR cost-utility OR cost-benefit OR decision analys*) AND (palivizumab OR synagis))

CHAPTER 8



# Cost-effectiveness of rule-based immunoprophylaxis against respiratory syncytial virus infections in preterm infants

Maarten O. Blanken, Geert Frederix, Loes Nibbelke, Erik Koffijberg, Lieke Sanders, Maroeska M. Rovers, Louis Bont, on behalf of the Dutch RSV Neonatal Network.

*Eur J Pediatr. 2018 Jan;177(1):133-144*

**Abstract**

*Objectives*

To assess the cost-effectiveness of targeted respiratory syncytial virus(RSV)-prophylaxis based on a validated prediction rule with one-year time horizon in moderately preterm infants compared to no prophylaxis.

*Methods*

Data on health care consumption were derived from a randomized clinical trial on wheeze reduction following RSV-prophylaxis and a large birth cohort study on risk prediction of RSV hospitalisation. We calculated the incremental cost-effectiveness ratio(ICER) of targeted RSV-prophylaxis vs. no prophylaxis per quality-adjusted life year(QALYs) using a societal perspective, including medical and parental costs and effects. Costs and health outcomes were modelled in a decision tree analysis with sensitivity analyses.

*Results*

Targeted RSV-prophylaxis in infants with a first-year RSV-hospitalisation risk of >10% resulted in a QALY gain of 0.02(0.931 vs 0.929) per patient against additional cost of €472 compared to no prophylaxis(ICER €214.748/QALY). The ICER falls below a threshold of €80.000 per QALY when RSV-prophylaxis cost would be lowered from €928(baseline) to €406 per unit. At a unit cost of €97 RSV-prophylaxis would be cost saving.

*Conclusions*

Targeted RSV-prophylaxis is not cost effective in reducing RSV burden of disease in moderately preterm infants, but it can become cost-effective if lower priced biosimilar palivizumab or a vaccine would be available.

**Introduction**

Respiratory syncytial virus (RSV) bronchiolitis is a major cause of infant morbidity in both high income and low-and middle income countries and is associated with a large burden of disease and high costs [1–4]. A systematic review estimated the global incidence among children <1 year of age at 19.19 per 1000 infants per year and a threefold higher rate for preterm infants[5]. Each year, about 28.000 infants require medical care for RSV bronchiolitis in the Netherlands [6,7], of which approximately 2.000 require hospitalisation with costs of €2.000-4.000 per patient [8–10]. In moderately preterm infants born at 32-35 weeks gestational age (WGA), we recently reported that about 9% of infants require mechanical ventilation at a Paediatric Intensive Care Unit(PICU) [11].

Children most at risk for severe disease are prematurely born infants either with or without chronic lung disease (CLD) and children with congenital heart disease (CHD) [12]. RSV prevention is possible with a RSV specific biological, palivizumab. RSV-prophylaxis has shown to be effective in preventing RSV infection in preterm infants <35 WGA [13,14]. We showed in our randomized clinical trial that RSV infection has a causal relation with recurrent wheeze during the first year of life in such infants[14]. Although the burden of disease is considerable, RSV-associated mortality in healthy term infants is probably low, but published estimates vary between 0 and 8% [2,4,5,15–17].

Meijboom estimated the total annual cost to society in the Netherlands due to RSV to be €7.7 million if no vaccination is undertaken [6]. Due to high costs, the cost-effectiveness of RSV-prophylaxis is subject of vigorous debate[18–21]. Several systematic reviews of the cost-effectiveness of palivizumab conclude that results vary considerable and are sensitive to poor quality input values, especially the RSV associated mortality rate [19,22,23]. The current RSV-prophylaxis program with palivizumab for preterm infants born before 32 WGA and infants with CLD or CHD includes 2.994 users in the Netherlands and the total annual cost was €14.0 million for 2015 [24].

Following the publication of the MAKI trial(no acronym) we raised the issue to perform a formal cost effectiveness analysis based on trial data and including impact and prevention of recurrent wheeze [25,26]. Our trial provided us with a population of preterm infants 33-35 WGA randomly assigned to RSV prophylaxis or placebo with associated detailed follow up of RSV burden of disease and health care consumption. We further integrated incidence data of the large RISK birth cohort study in preterm infants 32-35 WGA designed to develop a validated

prediction rule for RSV hospitalisation risk. To approximate real-time health care choices we included in our base case analysis the risk prediction at birth to determine the impact of targeted RSV-prophylaxis in preterms with a >10% hospitalisation risk [11]. Integration of decision rules and targeted treatment programmes in recent cost-effectiveness analyses to define cost-effective or even cost-saving strategies in a time of health care budget constraints is an accepted approach but remains rare[27–30]. Because our trial spanned 3 subsequent RSV seasons (2008-2011) and the RISK birth cohort study spanned 7 consecutive RSV seasons (2008-2014) our data reflects the heterogeneity of RSV seasonality. The aim of this study is to determine the cost-effectiveness of targeted RSV-prophylaxis in late preterm infants 32-35 WGA using a prospectively validated prediction rule compared to standard care, i.e. no prophylaxis.

**Methods**

*Model*

This cost-effectiveness study was performed based on the MAKI randomized, double blind, placebo-controlled, multicenter trial and the RISK birth cohort study, reported in more detail elsewhere [11,14]. A cost-utility analyses (CUA) was conducted to assess the economic benefit of targeted RSV-prophylaxis with humanized monoclonal antibody palivizumab compared to no prophylaxis in moderately preterm infants born at 32-35 WGA for reducing the burden of RSV infection. The outcome of the CUA was incremental costs per quality adjusted life year (QALY) gained. This analysis reflects the extra costs of preventive treatment, i.e. RSV prophylaxis, minus the prevented health care cost in relation to the prevented decrease in health care burden due to RSV related illness, i.e. QALY gain by prevention of RSV hospitalisation and subsequent wheezing. The analysis was performed from a societal perspective, which include not only medical costs but also societal costs as made by parents. For the base-case analysis, for which input values were not yet varied, a time horizon of 1 year was used which matches the time horizon of the MAKI trial. We choose to build a decision tree to avoid substantial, and potentially unreliable, extrapolation of trial data and implemented a validated prediction rule to target RSV-prophylaxis at infants with increased risk of severe RSV disease (Figure 1) [11,31]. No discounting, a technique to correct cost and outcome inputs derived from different time period, was necessary due to the 1-year horizon. The decision tree model was build using TreeAge Pro (2017, TreeAge Software Inc., Williamstown, Mass, USA).

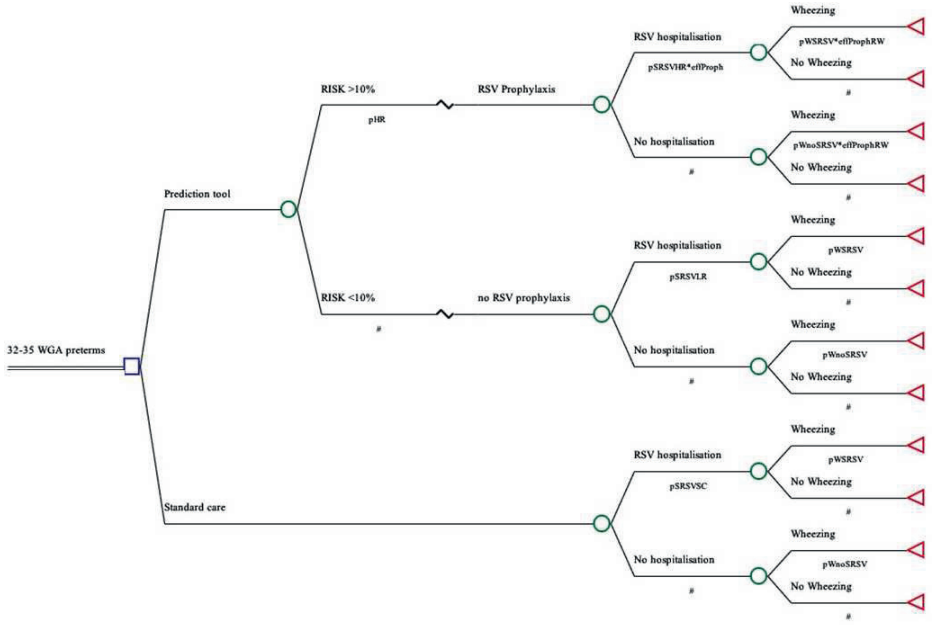



*Figure 1. Decision tree analysis for targeted RSV prophylaxis in Moderate preterm infants*

*Participants and randomization*

In short, in the MAKI trail 429 moderately preterm infants(gestational age, 33 to 35 weeks) were recruited in pediatric departments of one university hospital and 15 regional hospitals in the Netherlands. Eligible infants were randomly assigned in a 1:1 ratio to receive either monthly intramuscular palivizumab injections or placebo during the winter season[14].

In short, in the RISK study, a multicenter prospective birth cohort in 41 hospitals in the Netherlands, we validated a prediction rule (area under the receiver operating curve 0.72(95% CI 0.65-0,78) in 4.088 moderately preterm infants to identify a high risk group with a hospitalisation risk >=10% in the first year of life which is comparable to the hospitalisation risk in preterm infants, <32 WGA and other high risk groups [11,31]. Risk factors(e.g. day care attendance, presence of siblings, birth period) were assessed at birth among healthy preterm infants 32–35 WGA. All hospitalisations for respiratory tract infection were screened for laboratory proven RSV infection.

*Probabilities and clinical data*

Probabilities on disease incidence were derived from the MAKI trial and the RISK birth cohort study (Table 1). The MAKI trial was designed and powered to determine wheezing incidence, therefore incidence of recurrent wheeze was derived from this source. Because the incidence of RSV hospitalisations was low in the MAKI trial we derived probabilities and duration of RSV admission and PICU admission from the RISK study. We included mortality estimates that were derived from the Dutch RSV Mortality Study, a study on RSV-associated mortality. This study provided Dutch RSV mortality estimates derived from hospital PICU administration and the Dutch Central Bureau of Statistics (CBS) (Supplemental information).

| Table 1. Model inputs: morbidity probabilities used in base case and sensitivity analyses. | | | | |
|---|---|---|---|---|
| **Model input** | **Base case value** | **SA range for one way sensitivity analyses** [a] | **Distribution** | **Source** |
| Probability | | | | |
| | | | | |
| Prediction rule | | | | |
| High risk ( >10% RSV hospitalisation risk) | 0.112 | 0.08-0.14 | β (SD 0.01) | Korsten et al. |
| | | | | |
| RSV prophylaxis group | | | | |
| Recurrent wheezing, no RSV hospitalisation[¶] | 0.19 | 0.15-0.24 | β (SD 0.02) | Blanken |
| Recurrent wheezing, RSV hospitalisation[¶] | 0.55 | 0.41-0.68 | β (SD 0.05) | Blanken |
| RSV hospitalisation, given high risk | 0.126 | 0.095-0.158 | β (SD 0.01) | Korsten |
| PICU, given hospitalisation[§] | 0.088 | 0.07-0.11 | β (SD 0.01) | Korsten |
| Mortality, given PICU admission[§] | 0.01 | 0.008-0.013 | β (SD 0.001) | Supplement |
| | | | | |
| Placebo group | | | | |
| Recurrent wheezing, no RSV hospitalisation | 0.19 | 0.15-0.24 | β (SD 0.02) | Blanken |
| Recurrent wheezing, RSV hospitalisation | 0.55 | 0.41-0.68 | β (SD 0.05) | Blanken |
| RSV hospitalisation, given low risk | 0.034 | 0.026-0.043 | β (SD 0.005) | Korsten |
| PICU, given hospitalisation | 0.088 | 0.07-0.11 | β (SD 0.01) | Korsten |
| | | | | |
| Standard care | | | | |
| Recurrent wheezing, no RSV hospitalisation | 0.19 | 0.15-0.24 | β (SD 0.02) | Blanken |
| Recurrent wheezing, RSV hospitalisation | 0.55 | 0.41-0.68 | β (SD 0.05) | Blanken |
| RSV hospitalisation | 0.044 | 0.033-0.055 | β (SD 0.005) | Korsten |
| PICU, given hospitalisation | 0.088 | 0.07-0.11 | β (SD 0.01) | Korsten |
| | | | | |
| Utility (positive)/Disutility(negative) | | | | |
| No RSV hospitalisation, baseline | 0.95 | 0.71-1.00 | Gamma (SD 0.1) | Greenough |
| RSV hospitalisation | -0.07 | -0.05--0.09 | Gamma (SD 0.01) | Greenough |
| PICU admission[§] | -0.15 | -0.17--0.28 | Gamma (SD 0.02) | Jones |
| Wheezing, QALY reduction | -0.08 | -0.06--0.1 | Gamma (SD 0.01) | RIVM |
| | | | | |
| Prophylaxis effectiveness | | | | |
| Reduction of RSV hospitalisation | 0.82 | 0.62-1.03 | β (SD 0.08) | Blanken |
| Reduction of recurrent wheezing | 0.47 | 0.35-0.59 | β (SD 0.05) | Blanken |
| | | | | |

SA range= sensitivity analysis range, SD= standard deviation; [a] univariate sensitivity analyses ranges were derived by increasing and decreasing baseline values by 25%; [¶] Recurrent wheezing following RSV GP visit in the RSV prophylaxis group was assumed equal to recurrent wheezing following RSV GP visit in the placebo group because the trial data suggested an inconsistent probability of 1.0 following RSV GP visit in the RSV prophylaxis group (n=2). [§] Potential utility loss and costs due to PICU admission and mortality was included in all RSV hospitalisation based on the probability of PICU admission and mortality following RSV hospitalisation.

*Follow up*

In the MAKI trial, parents recorded airway symptoms, doctor visits, hospitalisations and the use of airway medication in a daily log until their infant was 1 year of age. General practitioners (GP) recorded number of GP visits and number of prescriptions of short acting beta agonist as relief medication (first choice test treatment Dutch college of GPs)[32]. In this model we included recurrent wheeze in the first year of life. Recurrent wheeze was defined as three or more episodes of wheezing during the first year of life. The number of hospitalisations for laboratory-proven RSV infection was assessed during the first year of life in both the MAKI trial and the RISK study.

*Measurement of effectiveness*

The efficacy of RSV-prophylaxis with palivizumab in reducing hospital admission in infants born at 32-35 weeks gestational age was set at 82% (95% CI 18-157%) reduction as retrieved from 2 randomized clinical trials [13,14]. Additionally, the MAKI trial provided the efficacy of RSV-prophylaxis in reducing recurrent wheeze which was set a 47% reduction [14].

*High risk group identification*

For the use of targeted RSV-prophylaxis we considered 11% of the palivizumab group as high risk, with a cut-off of a >10% hospitalisation risk, following the proportion of the RSV prediction rule paper [11]. The MAKI trial data did not permit us to do individualized prediction because of missing baseline data for the prediction rule and the low percentage of hospitalisations [14].

*Cost estimates*

We valued the use of health care resources for both treatment groups in the MAKI trial with Dutch reference prices and calculated total costs from the total quantity of health care resources consumed and the unit cost of those resources [33]. Cost of medication were obtained from the Dutch Formulary, including a pharmacist fee for each subscription. Use of bronchodilators (short acting beta agonist, 1st choice salbutamol/albuterol) was calculated for a trial course of 2 weeks, followed by symptom relief treatment based on reported symptoms in the diary, according to national asthma guidelines for this age group [32]. Over the counter drugs were not measured in the trial and not included in this model because of lack of reliable data in this population. Used health care resources did not include administration cost for

RSV-prophylaxis as this is a free of charge service as part of palivizumab reimbursement in the Netherlands. In case of PICU admission ambulance transfer was taken into account because PICU admissions in the Netherlands generally occur after a transfer from a secondary to a tertiary care hospital. Parental transportation costs were calculated based on the estimate of 189 travelled kilometers (km) per admission and reference costs of € 0,9 per km [33,34]. Other costs included productivity losses by caretakers as a result of care giving to children suffering from RSV-infections. It has been estimated that on average two parental workdays are lost as the result of a RSV related hospitalisation [34].

*Health outcomes*

In the model utilities were defined for all health states, and using the health state durations (i.e. modelled at one year) QALYs were calculated for each strategy to determine the QALY gains for the targeted RSV-prophylaxis strategy compared to no prophylaxis. One study by Greenough et al. provides utilities for RSV health states for preterm children with a RSV hospitalisation. In this study, quality-of-life in children, aged 2–4 years, with a history of preterm birth and RSV hospitalisation were compared with a control group of preterm children without a history of RSV hospitalisation [35]. The median Health Utilities Index (HUI 2) multi-attribute utility function was 0.88 in children with a confirmed RSV infection and a history of chronic lung disease, as compared to 0.95 in the control group. For quality of life loss following a PICU admission we included the HUI 2 score of 0.73 from a study of 1.455 children, mean age 4 years, who were followed up until 6 months after discharge [36]. To prevent double counting we assumed that this decrease in quality of life due to a PICU admission is not additive to the QALY decrease due to a RSV admission because this PICU admission would also include an initial hospital admission. QALY decreases due to recurrent wheezing was not separately assessed in these studies therefore we based the quality-of-life decrease on the best estimate as derived from QALY decrease for asthma of 0.08 based on a Dutch national reference study [37].

*Sensitivity analyses*

It is important to evaluate to uncertainty of the input values used in a cost effectiveness analysis. To account for this univariate and probabilistic sensitivity analyses were performed to explore the impact of parameter uncertainty. Transition probabilities were inserted as beta distributions and utility decrements as gamma distributions [38]. Cost related parameters were

inserted as fixed values when prices were fixed (i.e. GP visits). To measure the impact of the used base line cost and outcome variables these were varied by increasing and decreasing base line inputs by 25% to account for a wide range of uncertainty. Univariate sensitivity analyses on all key input variables were conducted increasing and decreasing each input variable while keeping other variables constant to identify critical parameters driving results. Results of 1-way sensitivity analyses were depicted in a tornado diagram. In addition probabilistic sensitivity analysis was performed to evaluate the uncertainty of the ICER taking into account uncertainty across all variables simultaneously. In this analysis, the base case estimate and a distribution (e.g. normal, beta, gamma, log-normal, fixed) was specified (Table 2). With Monte Carlo sampling 5.000 samples were drawn from these distributions and used as input for the model, so the model was run 5.000 times to evaluate the difference in account with the difference in input. Each iteration produced values for incremental costs, incremental benefits and ICERs. From the 5.000 simulations the probability that the intervention is cost-effective (net monetary benefit > 0, given a willingness to pay of € 80.000) was deduced and the 95% CI.

Table 2. Unit prices of resources used for preterm infants during 1 year trial follow up.

| **Resource** | **Unit cost (€)** | **Source** |
|---|---|---|
| Intervention costs | | |
| Specialist hourly fee | 104 | Hakkaart, 2015 |
| Palivizumab, per unit[§] | 928,60 | GIP databank |
| Pharmacist fee | 6 | FTK |
| | | |
| Direct medical costs | | |
| GP contact, unit | 33 | Hakkaart |
| Hospital admission pediatrics, per day | 627 | Hakkaart |
| Ambulance transfer, urgent* | 613 | Hakkaart |
| PICU admission, per day | 2015 | Hakkaart |
| Wheezing GP contact | 28 | Hakkaart |
| SABA episode, including babyhaler | 21,5 | Medicijnkosten.nl |
| | | |
| Indirect medical costs | | |
| Parental costs | | |
| Transportation (per km) | 0,19 | Hakkaart |
| Work days lost | 278 | Hakkaart |
| | | |

All unit cost are based on 2015 prices. Based on fixed reference prices not included in sensitivity analyses. *Additive to PICU admission cost; [§] price year 2015

*Threshold analyses*

A threshold analysis of lower prophylaxis prices on the ICER was also analysed, to determine the maximum cost of RSV-prophylaxis for which the targeted RSV strategy would have an incremental cost-effectiveness ratio less than the informal threshold of € 80.000/QALY[39]. All analyses were performed with TreeAge Pro and SPSS version 20 (IBM SPSS Statistics, Chicago, IL).

**Results**

*Participants*

The MAKI trial consisted of 429 moderately preterm infants included at birth. Of these 214 infants were randomly assigned to receive palivizumab and 215 infants were assigned to receive placebo. The two groups were well balanced regarding inclusion year, gestational age and birth month and had similar baseline characteristics as described previously (Supplementary Table)[14]. The RISK study consisted of 4.088 moderately preterm infants included at birth with a follow up period of 1 year.

*Costs, health outcomes and cost-effectiveness*

Unit prices and mean use of resources per infant during 1 year trial follow up were evaluated (Table 1-3). During the 1 year follow up the mean total RSV-prophylaxis costs per patient were €4.717 for the RSV prevention group and € 0 for the placebo group. A separate analysis of trial data only produced an ICER of >€1.000.000/QALY when targeted prophylaxis was not considered. The analysis of health outcomes showed that targeted RSV-prophylaxis resulted in 0.0022 QALYs gained (0.931 vs 0.929) at an additional cost of € 472 (€ 758 vs € 286) per patient compared to no prophylaxis. Targeted RSV prevention with palivizumab for moderately preterm infants versus no prophylaxis in the base case produced an ICER of €214.748 per QALY gained.

| Table 3. Mean use of resources | | |
|---|---|---|
| **Resource** | **Palivizumab (n=214)** | **Placebo (n=215)** |
| Intervention costs | | |
| Specialist fee | | |
| Palivizumab prescription (hour) | 0.08[o] | 0 |
| Palivizumab units[§] | 5.08 | 0 |
| Pharmacist fee total | 43.5 | 0 |
| | | |
| Direct medical costs | | |
| Hospital admission, RSV proven (SD) * | 5.8 days (4.8) | 5.8 days (4.8) |
| Ambulance transfer, given PICU admission | 1 | 1 |
| PICU admission (SD) ** | 8.1 days (8.0) | 8.1 days (8.0) |
| Recurrent Wheezing GP contact[#] (SD) | 2.5 (2.2) | 5.3 (5.8) |
| Episodes with SABA prescription[§§] (SD) | 0.12 (0.6) | 0.21 (0.5) |
| | | |
| Indirect medical costs | | |
| Parental costs given hospital admission | | |
| Transportation (km)*** | 189 | 189 |
| Work days lost*** | 2 | 2 |
| | | |

Values are means; § based on Dutch national GIP databank data of actual yearly palivizumab use # = GP reported; §§ GP- or parent reported, corrected for double counting * based on the RSV positive admissions in the RISK study (n=181, hospital laboratory proven, Korsten et al.), the number of RSV positive admissions in the MAKI trial: RSV prophylaxis (n=2, mean duration 5.3 days), placebo (n=11, mean duration 6.6 days). [o] duration for prescription based on personal communication. **based on the RISK study PICU admission duration (Korsten et al.), there were no PICU admission in the RSV prophylaxis group and 1 PICU admission in the placebo group, duration 10.75 days *** not recorded in the MAKI trial, derived from the Miedema et al.

*Sensitivity analyses*

Figure 2 shows that the ICER was most sensitive to the discriminatory power of the prediction rule (range €168.996-246.852/QALY) and the RSV-prophylaxis effectiveness (range €185.637-258.055/QALY). The effect of PICU incidence and the effect of mortality following PICU were limited (range €208.327-217.955/QALY and range € 214.834-219.427/QALY). Furthermore, the effect of the cost of RSV hospitalisation and PICU admission following RSV hospitalisation were limited (range € 208.519-221.674/QALY and range € 213.769-216.620/QALY) (Figure 2). The probabilistic sensitivity analysis showed that the probability of cost effectiveness is 0.5% considering a threshold of €80.000 (Figure 3). The cost effectiveness acceptability curve shows

the performance of targeted RSV prophylaxis compared to standard care at different willingness to pay levels (Figure 4).

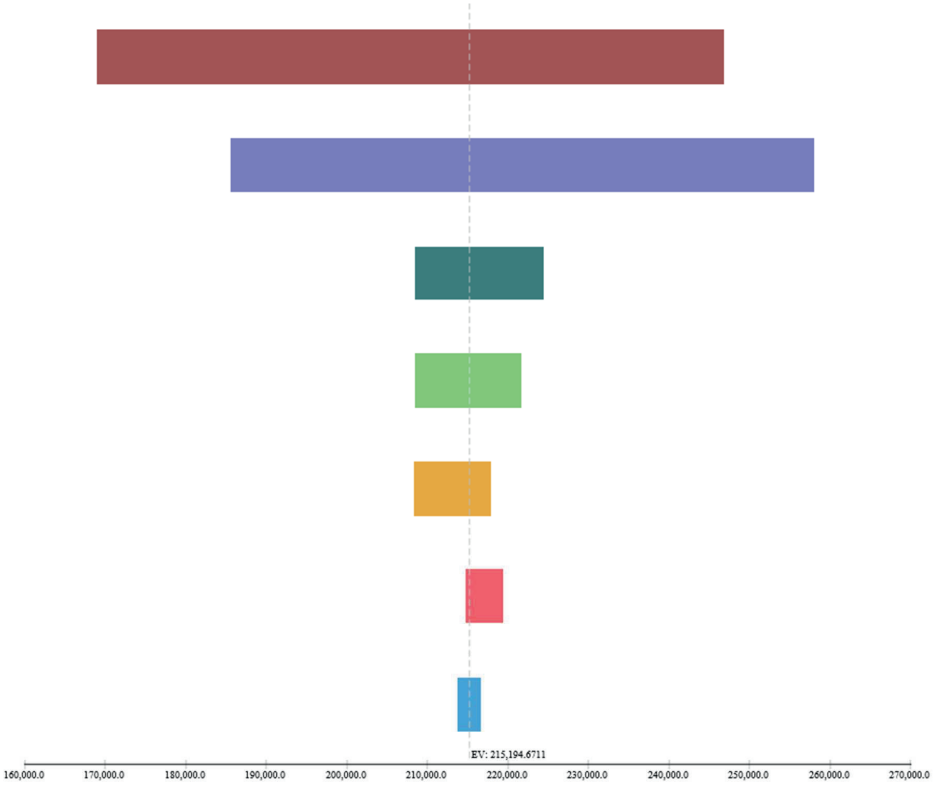



*Figure 2. One way sensitivity analyses, Tornado diagram*
Values are ICERs €/QALY with tornado bars representing the effect of univariate sensitivity analyses. Variables were selected based on level of impact (from top to bottom): high risk probability of the prediction rule, RSV prophylaxis effectiveness in preventing RSV hospitalisations, the RSV hospitalisation incidence in the high risk population, the hospital admission duration, the probability of PICU admission following RSV hospitalisation, the probability of mortality following PICU admission, the PICU admission duration.

*Threshold analysis*

In the scenario analysis to evaluate the effect of lower priced RSV prophylaxis, lowering the price of the treatment with RSV-prophylaxis from €929 to €406 per unit (€2062 per infant per year) assuming future market introduction of a biosimilar anti-RSV humanized monoclonal antibody yields a favourable ICER below the informal threshold of €80.000 per QALY. At a unit cost < €97 (€493 per infant per year) RSV-prophylaxis would become cost saving in this high risk population.

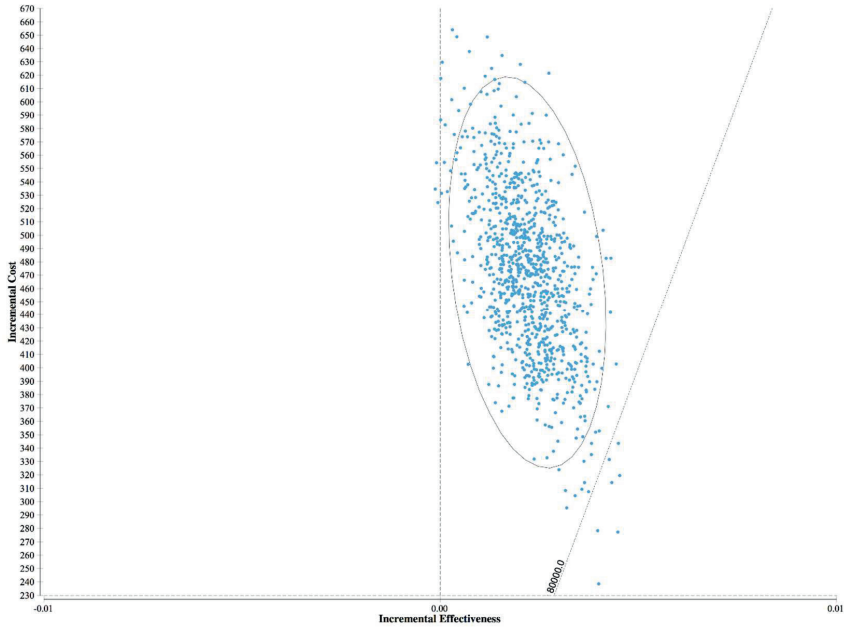



*Figure 3. Incremental cost effectiveness scatter plot on a cost-effectiveness plane showing the statistical uncertainty through 5000 bootstrapped samples*

Results of Probabilistic sensitivity analysis with per infant Incremental cost-effectiveness in a scatterplot for targeted RSV-prophylaxis versus standard care (no RSV prophylaxis) in moderately preterm infants 32-35 weeks gestational age. The reference line represents willingness-to-pay threshold of € 80,000/QALY

**Discussion**

Our results show that targeted RSV prophylaxis results in an incremental cost- effectiveness ratio of €214.748 per QALY gained, and therefore is not a cost effective strategy to prevent severe RSV infection and wheeze in the first year of life. Even targeted RSV-prophylaxis for only 10% of moderately preterm infants with an estimated risk of >10% for RSV hospitalisation the costs are still well above the informal Dutch cost effectiveness threshold €80.000 per QALY gained. We are the first to present targeted cost effectiveness of RSV-prophylaxis compared to no prophylaxis in moderately preterm children based on prospective trial data and a large birth cohort study. The use of RSV-prophylaxis in this high risk population results in a small increase in QALYs against high additional costs. One way and probabilistic sensitivity analyses showed the robustness of our results and impact of individual parameters on the outcome.

Subsequent threshold analyses showed that the current available RSV-prophylaxis, palivizumab, would need a 60% price cut for an acceptable cost effectiveness level at a threshold of €80.000 per QALY. A price cut of >90% would result in a cost saving strategy. Currently a palivizumab biosimilar is under investigation at the Utrecht Centre for Affordable Biotherapeutics but the progress is unknown [40]. Taken together, our study helps to understand acceptable pricing for future RSV preventive interventions, in particular palivizumab biosimilars for otherwise healthy late preterm infants.

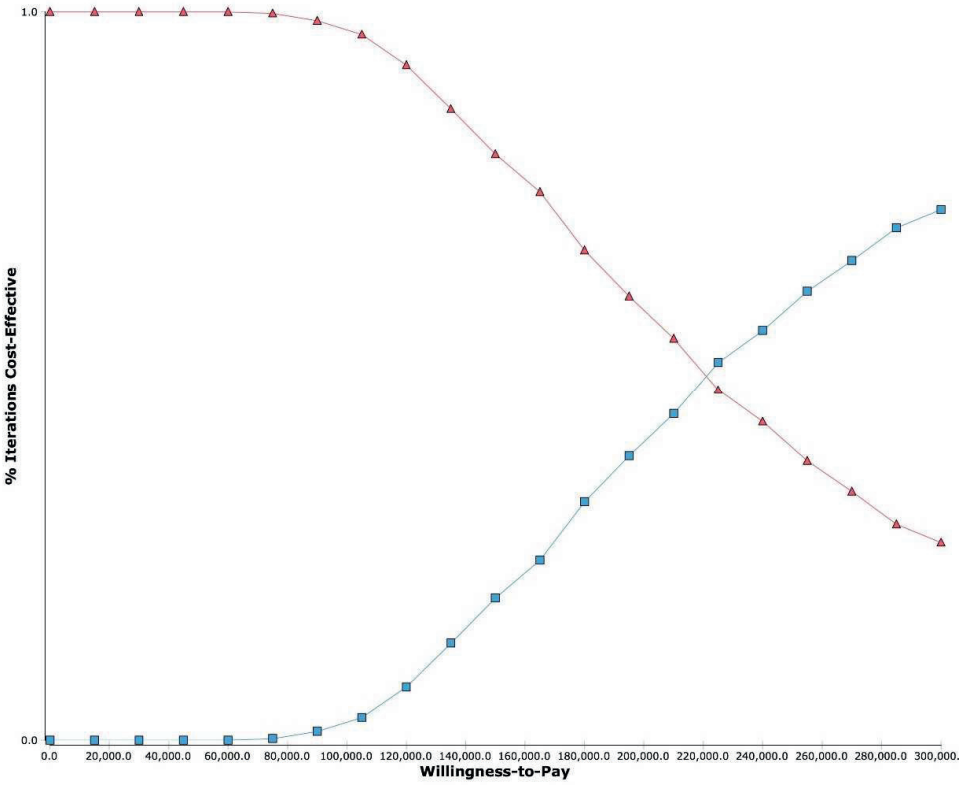



*Figure 4. Cost effectiveness acceptability curve at different willingness to pay levels for RSV prophylaxis based on 5000 iterations.*
Results of Probabilistic sensitivity analysis with per infant Incremental cost-effectiveness in a cost effectiveness acceptability curve of targeted RSV-prophylaxis (blue line) versus standard care (no RSV prophylaxis, red line) in moderately preterm infants 32-35 weeks gestational age.

The major strength of our study is that it is the first cost effectiveness study of RSV prophylaxis in this population based on data from a randomised placebo-controlled trial and a large birth cohort study, which enabled us to include the most reliable baseline probabilities and include all relevant evidence as deemed appropriate by Briggs et al [38]. Some limitations should also be discussed. First, we did not assess all use of resources in our trial. Therefore, we used published data from the Dutch costing manual and published data for resource use. For indirect cost made by parents we included estimates from a Dutch paper better representing our population rather than estimates from a more comprehensive analysis in moderately preterm infants [34,41]. Second, due to the choice for a short time horizon in line with trial follow

up the impact of mortality following severe RSV infection is limited. However, the Dutch RSV mortality study described that RSV related mortality in otherwise healthy preterm infants is minimal. Third, the utility estimates were derived from the literature because with the quality of life estimates from our trial we could not determine utility scores for RSV infection. In our trial we took the TNO-AZL Preschool children Quality of Life (TAPQOL) questionnaire every three months. However, TAPQOL does not report utilities[42]. As a consequence, deriving QALY decreases due to RSV admission or PICU admission from different sources could lead to an effect underestimation because we assumed that not all QALY decreases were additive, for example in case of PICU admission. This will likely not have influenced the results of our study, since the number of PICU admissions are low.

The RSV treatments that are currently in development include 10 vaccines and 11 therapeutic agents in active clinical trials [43]. Maternal vaccination is especially relevant for infants below 6 months of age, as these infants are at high risk for severe disease but are unlikely to benefit from active immunisation. It is our understanding that even with the introduction of a maternal or infant vaccine the use of anti-RSV monoclonal antibodies could still be necessary to protect preterms infants below the age of 3-6 months. The use of a maternal or infant vaccine is highly dependent on level of efficacy and the age at first vaccination and could implicate a time horizon for monoclonal antibody protection before vaccination is possible and effective. Our model could be easily adapted to consider a combination of RSV-prophylaxis with monoclonal antibody and new RSV vaccines.

**Conclusion**

Targeted RSV prophylaxis is not yet cost effective in reducing RSV burden of disease in moderately preterm infants with incremental costs per QALY ratio far exceeding applied threshold values. Our results show that targeted RSV-prophylaxis could become cost-effective if lower priced biosimilar palivizumab or a vaccine becomes available. Compliance with Ethical Statements

*Conflict of interest*

LB reports consulting fees from Janssen, Gilead, Okairos, Mabxience, Alios, AIT, during the conduct of the study; MOB reports consulting fees from AbbVie. All other authors have indicated they have no potential conflicts of interest to disclose.

LB reports grants for investigator initiated studies from MedImmune and from AbbVie, including the MAKI trial from which data for this cost effectiveness study were derived. All other authors have indicated they have no financial relationships relevant to this article to disclose.

*Funding*

This investigator driven study was funded by a grant from the Netherlands Organization for Health Research and Development (NWO-AGIKO grant 920-035-89, to Dr. Blanken). The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

*Informed consent*

Informed consent was obtained from all individual participants included in the study.

**References**


1. Hall CB, Weinberg GA, Iwane MK, et al. The Burden of Respiratory Syncytial Virus Infection in Young Children. *N Engl J Med*. 2009;360(6):588-598.
2. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet*. 2010;375(9725):1545-1555.
3. Smyth RL, Openshaw PJ. Bronchiolitis. *Lancet*. 2006;368(9532):312-322.
4. Geoghegan S, Erviti A, Caballero MT, et al. Mortality due to Respiratory Syncytial Virus. Burden and Risk Factors. *Am J Respir Crit Care Med*. 2017;195(1):96-103.
5. Stein RT, Bont LJ, Zar H, et al. Respiratory syncytial virus hospitalization and mortality: Systematic review and meta-analysis. *Pediatr Pulmonol*. 2017;52(4):556-569.
6. Meijboom MJ, Rozenbaum MH, Benedictus A, et al. Cost-effectiveness of potential infant vaccination against respiratory syncytial virus infection in The Netherlands. *Vaccine*. 2012;30(31):4691-4700.
7. Houben ML, Bont L, Wilbrink B, et al. Clinical Prediction Rule for RSV Bronchiolitis in Healthy Newborns: Prognostic Birth Cohort Study. *Pediatrics*. 2011;127(1):35-41.
8. Bos J, Rietveld E, Moll H, et al. The use of health economics to guide drug development decisions: Determining optimal values for an RSV-vaccine in a model-based scenario-analytic approach. *Vaccine*. 2007;25(39-40):6922-6929.
9. Rietveld E, De Jonge HCC, Polder JJ, et al. Anticipated costs of hospitalization for respiratory syncytial virus infection in young children at risk. *Pediatr Infect Dis J*. 2004;23(6):523-529. http://www.ncbi.nlm.nih.gov/pubmed/15194833. Accessed May 2, 2017.
10. Jansen AGSC, Sanders EAM, Hoes AW, van Loon AM, Hak E. Influenza- and respiratory syncytial virus-associated mortality and hospitalisations. *Eur Respir J*. 2007;30(6):1158-1166.
11. Korsten K, Blanken MO, Nibbelke EE, Moons KGM, Bont L, Dutch RSV Neonatal Network. Prediction model of RSV-hospitalization in late preterm infants: An update and validation study. *Early Hum Dev*. 2016;95:35-40.
12. Anderson EJ, Carbonell-Estrany X, Blanken M, et al. Burden of Severe Respiratory Syncytial Virus Disease Among 33-35 Weeks' Gestational Age Infants Born During Multiple Respiratory Syncytial Virus Seasons. *Pediatr Infect Dis J*. 2017;36(2):160-167.

13. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. *Pediatrics*. 1998;102(3 Pt 1):531-537.
14. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med*. 368(19):1791-1799.
15. Simon A, Ammann RA, Wilkesmann A, et al. Respiratory syncytial virus infection in 406 hospitalized premature infants: results from a prospective German multicentre database. *Eur J Pediatr*. 2007;166(12):1273-1283.
16. Sampalis JS. Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants. *J Pediatr*. 2003;143(5 Suppl):S150-6
17. Prais D, Schonfeld T, Amir J, Israeli Respiratory Syncytial Virus Monitoring Group. Admission to the intensive care unit for respiratory syncytial virus bronchiolitis: a national survey before palivizumab use. *Pediatrics*. 2003;112(3 Pt 1):548-552.
18. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. *Pediatrics*. 2014;134(2):e620-e638.
19. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. *Cochrane database Syst Rev*. 2013;(4):CD006602.
20. Isaacs D. Should respiratory care in preterm infants include prophylaxis against respiratory syncytial virus? The case against. *Paediatr Respir Rev*. 2013;14(2):128-129.
21. Resch B, Resch E, Müller W. Should respiratory care in preterm infants include prophylaxis against respiratory syncytial virus infection? The case in favour. *Paediatr Respir Rev*. 2013;14(2):130-136.
22. Blanken M, Bont L, Rovers M. The cost-effectiveness of palivizumab in the prevention of respiratory syncytial virus bronchiolitis: A systematic review. *Curr Respir Med Rev*. 2011;7(3):203-212.

23. Wang D, Bayliss S, Meads C. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses. *Health Technol Assess*. 2011;15(5):iii-iv, 1-124.
24. GIP / Zorginstituut Nederland. https://www.gipdatabank.nl/databank.asp?tabel=01-basis&item=J06BB16&infoType=g&label=00-totaal&geg=vg.
25. Brand PLP. Respiratory syncytial virus and recurrent wheeze. *N Engl J Med*. 2013;369(8):782. doi:10.1056/NEJMc1307429#SA1.
26. Blanken MO, Rovers MM, Bont L, Dutch RSV Neonatal Network. Respiratory syncytial virus and recurrent wheeze. *N Engl J Med*. 2013;369(8):782-783.
27. Shankar MB, Staples JE, Meltzer MI, Fischer M. Cost effectiveness of a targeted age-based West Nile virus vaccination program. *Vaccine*. April 2017.
28. Debes AK, Gilman RH, Onyango-Makumbi C, Ruff A, Oberhelman R, Dowdy DW. Cost-effectiveness of Diagnostic Algorithms for Tuberculosis in Children Less Than 5 Years of Age. *Pediatr Infect Dis J*. 2017;36(1):36-43.
29. Gregory S, Kuntz K, Sainfort F, Kharbanda A. Cost-Effectiveness of Integrating a Clinical Decision Rule and Staged Imaging Protocol for Diagnosis of Appendicitis. *Value Heal*. 2016;19(1):28-35.
30. van Giessen A, Peters J, Wilcher B, et al. Systematic Review of Health Economic Impact Evaluations of Risk Prediction Models: Stop Developing, Start Evaluating. *Value Health*. 2017;20(4):718-726.
31. Blanken MO, Koffijberg H, Nibbelke EE, Rovers MM, Bont L. Prospective validation of a prognostic model for respiratory syncytial virus bronchiolitis in late preterm infants: a multicenter birth cohort study. *PLoSOne*. 2013;8(3):e59161-.
32. Bindels, PJE; Van de Griendt, EJ; Grol, MH; Van Hensbergen, W; Steenkamer, TA; Uijen, JHJM; Burgers, JS; Geijer, RMM; Tuut M. Dutch general practitioner society (NHG): guideline Asthma in children (3rd revision). https://www.nhg.org/standaarden/volledig/nhg-standaard-astma-bij-kinderen. Published 2014.

33. Hakkaart-van Roijen, L; van der Linden, N; Bouwmans, CAM, Kanters, TA; Tan S. Kostenhandleiding. Methodologie van Kostenonderzoek En Referentieprijzen Voor Economische Evaluaties in de Gezondheidszorg. (Costing Manual. Methods and Reference Prices for Economic Evaluations in Health Care). Diemen
34. Miedema CJ, Kors AW, Tjon ATWE, Kimpen JL. Medical consumption and socioeconomic effects of infection with respiratory syncytial virus in The Netherlands. *Pediatr Infect Dis J*. 20(2):160-163.
35. Greenough A, Alexander J, Burgess S, et al. Health care utilisation of prematurely born, preschool children related to hospitalisation for RSV infection. *Arch Dis Child*. 2004;89(7):673-678.
36. Jones S, Rantell K, Stevens K, et al. Outcome at 6 months after admission for pediatric intensive care: a report of a national study of pediatric intensive care units in the United kingdom. *Pediatrics*. 2006;118(5):2101-2108..
37. Eysink, PED; Blatter BM; van Gool, CH; Gommer, AM; van den Bossche, SNJ; Hoeymans N. *Disease Burden of Unfavorable Work Conditions in the Netherlands*.; 2007. http://www.rivm.nl/bibliotheek/rapporten/270012001.pdf.
38. Briggs, A; Claxton, K; Sculpher M. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press; 2006.
39. Eijsden P van. Fate of new cancer drug is uncertain in Netherlands, as institute deems it too costly. *BMJ*. December 2015:h6778.
40. Utrecht Centre for Affordable Biotherapeutics. https://www.uu.nl/en/organisation/utrecht-centre-of-excellence-for-affordable-biotherapeutics/projects/biosimilar-palivizumab.
41. Leader S, Jacobson P, Marcin J, Vardis R, Sorrentino M, Murray D. A method for identifying the financial burden of hospitalized infants on families. *Value Health*. 5(1):55-59.
42. Fekkes M, Theunissen NC, Brugman E, et al. Development and psychometric evaluation of the TAPQOL: a health-related quality of life instrument for 1-5-year-old children. *Qual Life Res*. 2000;9(8):961-972.
43. Mazur NI, Martinón-Torres F, Baraldi E, et al. Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. *Lancet Respir Med*. 2015;3(11):888-900.

# 9

CHAPTER 9

# General Discussion

**General discussion**

The aim of this thesis was to gain insight into the burden of disease caused by respiratory syncytial virus (RSV) infection in moderate-to-late preterm infants, and to develop strategies to minimize the burden of disease. In this thesis I aimed to determine:

- the effect of RSV prevention on the incidence of wheezing during the first year of life
- the population attributable risks of risk factors for recurrent wheezing in the first year of life
- risk factors for RSV hospitalisation in order to facilitate the development of a risk scoring tool to predict RSV hospitalisation in otherwise healthy moderate-to-late preterm infants
- the cost-effectiveness of targeted RSV prevention in moderate-to-late preterm infants based a risk scoring tool compared to no prophylaxis

**What was known**

- The burden of RSV infection is high in moderate-to-late preterm infants compared to term infants
- RSV infections are either the cause of recurrent wheeze or the first indication of pre-existent pulmonary vulnerability in preterm infants
- Effective RSV prevention is available and registered for this population, but expensive

**What this thesis has contributed**

- RSV hospitalisation incidence is **4-5%** in moderate-to-late preterm infants
- prospective development and validation of a **clinical prediction rule** for RSV hospitalisation
- RSV infection is an important **causal mechanism** in the inception of early wheezing in this population
- Among late preterm infants, RSV immunoprophylaxis is currently **not cost-effective,** even when targeting those with a >10% risk of RSV hospitalisation

In this discussion, I will outline the main findings and then use the results to provide a more general perspective. I will describe the burden of RSV infection in moderate-to-late preterm infants as derived from our collaborative studies, and discuss the current possibilities for RSV prevention in this population, taking into account cost-effectiveness and the potential of targeted RSV prevention.

Finally, specific recommendations to further investigate RSV prevention strategies will be described and different scenarios will be delineated to enhance the feasibility of targeted RSV prevention.

**Main findings**

Our studies indicate that the incidence of RSV hospitalisation incidence in moderate-to-late preterm infants is 4-5% compared to the published literature, and **two- to threefold higher** in high-risk infants based on a risk scoring tool with 3-4 risk factors. RSV infection appears to be an important **causal mechanism** in the inception of early wheezing in this population. Severe RSV infections and subsequent wheezing is preventable in moderate-to-late preterm infants with a targeted RSV prevention strategy using RSV specific monoclonal antibodies (moAb). However, the **cost-effectiveness of this intervention was not favourable** for wide scale use.

**Chapter 2 and 3** delineates that RSV prevention with a monoclonal antibody **in moderate-to-late preterm infants greatly reduces the number of parent-reported wheezing days during the first year of life**, even after the completion of therapy and beyond the RSV season. RSV prevention is associated with a 61% relative reduction in the number of wheezing days, This indicates that RSV infection during infancy is an important mechanism in the pathogenesis of wheezing in this specific population.

**Chapter 4** illustrates that a large proportion of the incidence of recurrent wheezing (RW) can be explained by viral exposure. **A strong relationship exists between RSV bronchiolitis requiring hospitalisation and recurrent wheezing but its contribution to the total incidence of RW is relatively modest compared to other risk factors such as day care attendance that are associated with viral exposure.**

**Chapter 5 and 6** outlines the derivation and validation of a Dutch risk-scoring tool to **identify a subgroup of moderate-to-late preterm infants with a ten-fold higher risk of RSV hospitalisation than the reference group of term infants**. Furthermore, in an international collaboration we conducted a meta-analysis of multiple published risk-scoring tools, including the Dutch risk-scoring tool, to provide a validated risk-scoring tool applicable to the Northern Hemisphere. This initiative provides the basis for country specific cost-effectiveness analyses for current and future RSV prevention strategies.

**Chapter 7 and 8** indicates that **targeted RSV prevention** taking into account not only hospitalisations but also wheezing in a subgroup of infants at high-risk for RSV hospitalisation was **not cost-effective in reducing the RSV burden in moderate-to-late preterm infants**.

Although the burden of RSV infection is high in moderate-to-late preterm infants, the cost of RSV prevention with monoclonal antibodies must decline before wide scale use in high-risk moderate-to-late preterm infants can be justified.

**Implications for current RSV prevention practice**

Our group of investigators were the first to describe a causal mechanism between RSV infection and early wheezing and we developed a validated risk-scoring tool to facilitate targeted RSV prevention. We calculated that the current RSV prevention possibilities are not sufficient to provide cost-effective disease reduction strategies.

Cost-effectiveness analyses have become an important element of current RSV prevention policy because healthcare budget reductions are more than ever necessary to confine rising health care costs. In 2014 the American Academy of Pediatrics (AAP) published its most recent guidelines to assist in the identification of infants most likely to benefit from RSV prophylaxis[1]. This guideline recommends palivizumab prophylaxis for infants born before 29 weeks and 0 days and selected high-risk groups, including children with bronchopulmonary dysplasia and hemodynamically significant heart disease. Risk factors for severe RSV disease were considered unimportant. The strength and quality of the evidence for this new guideline is limited and mainly guided by the New Vaccine Surveillance Network Study in which 559 hospitalisations in the period 2000-2004 were analysed, including 12 hospitalised infants born before 29 weeks gestational age [2]. This sparked some discussion and several publications both criticizing the new guideline as a health care budget measure, but others also supporting the new guideline in describing no difference in RSV-related hospitalisation and burden of illness before and after the new guideline [3–8]. Notwithstanding all discussion the guideline is here to stay. In November 2017, The Committee on Infectious Diseases and the Subcommittee on Bronchiolitis of the AAP again considered all available data regarding palivizumab, and both groups reaffirmed the recommendations in the 2014 RSV policy statement and technical report. The impact of the AAP guidelines is considerable and the downscaled RSV prevention guideline is today replicated in several countries. Currently the Neonatology subcommittee of the Dutch Society of Pediatrics is debating the extent of the current Dutch RSV prevention guidelines.

The debate on the guideline for RSV immunoprophylaxis is understandable because widespread palivizumab prophylaxis is hindered by high cost of the therapy and inconvenient

monthly intramuscular dosing. In 2017, the annual cost of the current RSV palivizumab prophylaxis program was € 12.8 million in the Netherlands (online Gipdatabank.nl). These costs were incurred by 2.797 infants who received palivizumab and pertained to one of the reimbursement categories.

This is € 3 million more than the total cost per year for a widely used drug like Nexium (esomeprazol) for which there are over 200.000 users in the Netherlands, and 50% more than the total cost for Ventolin (salbutamol), which amounts to € 7.9 million for more than 800.000 users[9]. In the light of these comparisons, some consideration is required before expanding the indications for palivizumab to more infants at high cost. It is important to consider that preterm infants are a highly vulnerable population. The allocation of our health care budget demands a choice between prioritizing certain groups of vulnerable patients or choosing to treat every patient or individual as equal. Should we invest in a curative treatment to gain another Quality Adjusted Live Year (QALY) for an elderly 80-year old man or should we invest in a preventive treatment to protect the health of a 3-month old moderate-to-late preterm infant? A QALY in itself is blind to who loses or gains the QALY and does not take into account health condition, severity of disease or personal characteristics like age or societal role. This can be countered by government policy regulations or by QALY weighting favouring for example children or young adults who are productive and have the care for young children compared to the very old. The impact of economic productivity on health economic decisions is another difficult debate for which policy makers and researchers have no clear answer.

A gap exists between the current practice of completely excluding RSV prevention in moderate-to-late preterms and the overall motivation to reduce the RSV burden in this population. This gap could potentially be bridged with the identification of a subgroup of high-risk moderate-to-late preterm infants. I proposed the use of a risk-scoring tool to guide targeted RSV prevention and analyse the cost-effectiveness of this approach. Although sensible in a time of health care budget constraints, targeted prevention remains rare but is an accepted approach [10–13].

Even when RSV-prophylaxis is targeted at only 10% of moderate-to-late preterm infants with an estimated risk of >10% for RSV hospitalisation, this results in an incremental cost-effectiveness ratio of >€200.000 per QALY gained. This is still well above the informal Dutch cost-effectiveness threshold of €80.000 per QALY gained. The reduction of RSV related

wheezing through prophylaxis adds little to the cost-effectiveness because the total cost of wheezing is low in terms of medication use and hospitalisations and the associated QALY gained is low if the type of wheezing does not translate into lifelong asthma.

I estimated that the current available RSV-prophylaxis, palivizumab, would need a 60% price reduction for an acceptable cost-effectiveness level at a threshold of €80.000 per QALY. A price reduction of >90% would result in a cost saving strategy. Recently, one important step was taken towards affordable RSV prevention in the form of a Ministry negotiated price reduction of Synagis (palivizumab) of approximately 30% in the Netherlands [14]. In itself, this measure will not be enough to guide the decision to extend palivizumab coverage to high risk moderate-to-late preterm infants but it is an important first step.

I hypothesized in the discussion of our cost-effectiveness analysis, that including long-term asthma diagnosis could potentially influence the outcome of the analysis. During the execution of the research described in this thesis we were limited to 1-year follow up data. The 6-year follow up study of our trial was essential to explicate the relationship of RSV infection and the diagnosis of asthma at 6 years of age. My colleague Nienke Scheltema et al. described a decreasing protective effect on wheezing up to the age of 6 years with no relationship with the diagnosis of asthma at school-age [15]. In summary, the major burden of RSV infection is in the first year of life with a diminishing effect through the course of the first 6 years of life. Therefore, increasing the cost-effectiveness time horizon would not include more health care costs avoided and subsequently not contribute to a more beneficial incremental cost-effectiveness ratio.

**Future RSV prevention**

Affordable RSV prevention should be sought in novel RSV preventive interventions, like new extended half-life moAbs, palivizumab biosimilars or an RSV vaccine. Following my description of the burden of disease of RSV infection in moderate-to-late preterm infants and the options for prevention, there is still a significant need for a product equally or potentially more effective than palivizumab. Ideally, this treatment would have an improved cost-benefit profile and a more convenient or less frequent administration to justify use in a larger population of at-risk infants. The RSV treatments that are currently in development include more than 20 vaccines and therapeutic agents in active clinical trials and an equal number in the preclinical stage (PATH snapshot) (Figure 1)[16].

Another approach is currently under development at the University Medical Center Utrecht. Researchers Löwensteyn and Mazur from the Bont RSV Research Group have developed nasal drops based on commercial palivizumab to determine its safety and efficacy in the prevention of RSV infection [17]. The phase 1/2a-b trials received ethical approval and are currently ongoing. Intranasal palivizumab has the potential to be a low cost option compared to intramuscular palivizumab, if it is equally effective at low doses, targeting the local nasal mucosa. A potential drawback is the possible need for frequent (daily) doses.

Regarding new extended half-life moAbs, Zhu et al. published promising preliminary results on an extended half-life RSV specific moAb, MEDI8897 [18]. They suggest through a modeling exercise based on the known pharmacokinetics of palivizumab that a single administration of MEDI8897 at an appropriate dose will result in serum levels that correlate with near complete protection against RSV in cotton rats. The recent publication of the 1b/2a dose-escalation study in healthy preterm infants described a favorable safety profile and a 5 month RSV protection profile based on serum concentrations [19]. On December 20th, 2018 MedImmune reported that the phase 2b trial of MEDI8897, also known as nirsevimab, in healthy infants of 29 to 34 weeks gestational age was completed [20]. Results are reportedly promising because on February 5th, 2019 MedImmune was granted PRIME eligibility by the EMA based on positive primary analyses of the phase 2b trial [21]. PRIME is a scheme to support the development of medicines that target an unmet need and is focused on optimizing development plans and speed up evaluation.

Some reservations on the expectations regarding MEDI8897 are necessary, especially in light of the non-approval of motavizumab by the Federal Drug Agency in 2010. The signs seemed to be all positive for this "ultra-potent, affinity-matured, humanized moAb derived from palivizumab" [22,23]. However, clinical trials showed that motavizumab was associated with adverse skin reactions. Nineteen motavizumab patients had "high grade hypersensitivity" events and 3 cases of anaphylaxis, compared with no severe allergic reactions in the palivizumab group, which made the FDA conclude that motavizumab didn't offer any advantages over palivizumab and that it may be more dangerous [23,24]. MEDI8897 however could potentially be cost-saving in high-risk moderate-to-late preterm infants at a "vaccine price" of **€ 500,** as estimated in our cost-effectiveness study for palivizumab, in case of a single dose providing season long protection. For this estimation we assume a RSV hospitalisation rate of ≥10% and an efficacy of 80%. Total cost for season long protection will need to be

lower if either the hospitalisation rate or the efficacy is lower. Taking into account research and development (R&D) costs, potentially including R&D of the failed motavizumab, and the relative high production cost of monoclonal antibodies, I find it hard to expect a favorable cost-effectiveness for the product. Recognizing that R&D costs are fixed costs and with the inclusion of "lost" R&D cost due to the failure of motavizumab, and production costs which are relatively fixed because monoclonal antibodies are manufactured in low-yield, time-consuming mammalian cells, it is likely that the dose price will be several fold higher.

Another more affordable approach would be the introduction of a palivizumab biosimilar. Biosimilars are highly similar but not equal to the reference biological medicine, in this case, the monoclonal antibody palivizumab. Biological medicines are isolated from a variety of natural sources, human, animal, or microorganism, and may be produced by biotechnological methods and other cutting-edge technologies. Total similarity between a biological and a biosimilar is unattainable because of the natural variability inherent in the production process of biological medicines. For their development, the European Medicines Agency (EMA) strives to avoid unnecessary repetition of clinical trials already conducted on the reference drug. Instead, companies and researchers are required to demonstrate that their biological medicine is "highly similar" to the reference drug. Furthermore, testing should prove **no clinically meaningful differences** between the biosimilar and the reference medicine in terms of safety, quality and efficacy [25]. Currently a palivizumab biosimilar, named lunamab, is under investigation in a collaborative project involving the World Health Organization and local manufacturers (mAbXience, Libbs, Medigen and SPIMACO) in low income countries, supported by the Utrecht Centre for Affordable Biotherapeutics (UCAB) [26]. The development process relating to chemistry, manufacturing and control of the study drug for the clinical program, whereby the drug will first be tested in healthy adults in a phase I trial, is expected to evolve over another year (update N. Dorrestijn/UCAB, personal communication). In the development process a pricing study was performed based on published RSV incidence data from Brasil to determine the benchmark acquisition cost for an acceptable level of cost-effectiveness [27]. This study concluded that a unit price in the range of $ 119-149 would result in the cost-neutral implementation of a palivizumab biosimilar targeted at preterm infants ≤ 36 weeks gestational age[27].

Regarding the pricing of a palivizumab biosimilar, I estimated that with the currently available palivizumab product at a unit price of **€ 100 and 5 monthly doses, a cost saving strategy could**

**be realized** for high risk moderate-to-late preterm infants at a cost-effectiveness threshold of €80.000 per QALY. This price drop seems unlikely because price reductions are expected to be in the range of 20-30%, as exemplified by infliximab (Remicade) biosimilars Remsima, Inflectra and Flixabi. This contrast is substantial when compared to the 80+ percent reduction that occurs when generic versions of typical medicines are marketed. However, recent developments are promising as indicated by the price developments involving Humira (adalimumab), whereby the distributor AbbVie is reportedly prepared to offer discounts of up to 80% in the Nordic tender market in a battle with several adalimumab biosimilars [28].

In contrast to the next RSV specific monoclonal antibody or biosimilar, a RSV vaccine could prove to be more effective and less costly, whereby implementation in a wider population of preterm or even term infants could be considered. Below is a snapshot of current RSV vaccines and monoclonal antibodies in various stages of development from preclinical animal studies to different phases of evolving clinical trials. The vaccine in the most advanced development stage is a maternal nanoparticle vaccine targeting the RSV F surface protein developed by Novavax (August 2017).

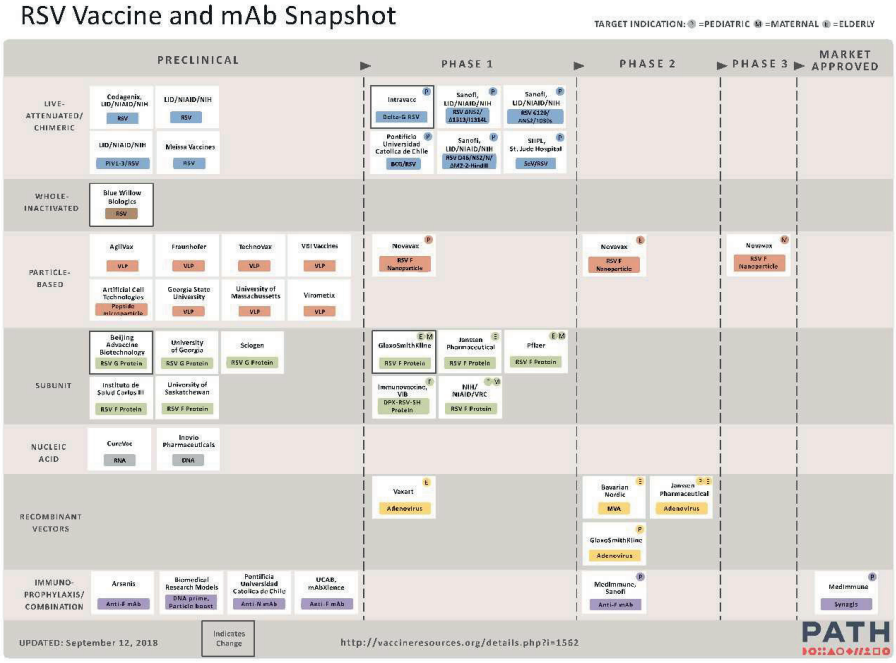



*Figure 1. Current RSV vaccines and monoclonal antibodies in various stages of development.*

Maternal vaccination is especially relevant for infants less than 6 months of age, as these infants are at high risk for severe RSV infection but are less likely to benefit from active immunization. However, even with the introduction of a maternal or infant vaccine the use of anti-RSV monoclonal antibodies may still be necessary to protect preterm infants less than 3-6 months of age. A recently developed mathematical model to predict the percentage of children with life-threatening RSV infection during the first year of life that may be prevented by maternal vaccination, showed that preterm infants were predicted to benefit less from a maternal RSV vaccine than term infants [29]. The use of a maternal vaccine is highly dependent on the timing of maternal vaccination and the subsequent level of efficacy based on progressive antibody transfer from the mother to fetus [30–33]. For infants, the age at first vaccination of a live vaccine will be a delicate balance between safety and efficacy but potentially feasible because preterm infants of all gestational ages currently are vaccinated in hospital starting at the age of 8 weeks. In addition, if vaccines are used in older children to reduce RSV transmission to younger and more vulnerable infants there is some evidence that a significant reduction of RSV infection in the non-vaccinated young infants can be expected [34]. The use of maternal or infant vaccines alone, dependent on the time of administration, may have implications for a continuing demand for monoclonal antibody protection in preterm infants if sub-optimal efficacy is demonstrated following maternal vaccination and if infant vaccination is unsafe or ineffective.

**Cost-effectiveness analysis**

Cost-effectiveness analyses will be pivotal to determine the costs and benefits of new moAbs or vaccines in target populations based on a broad societal perspective, which takes into account direct medical costs and effects but also indirect costs like loss of productivity experienced by parents. Several modelling studies have been performed to estimate the impact and cost-effectiveness of a future RSV vaccine [29,35–37]. In the study by Cromer et al. vaccine efficacy ranged from 50% to 100% in different scenarios and age at first vaccination between 2-4 months. Assuming complete disease elimination in children younger than 5 years, the authors concluded that the maximum price payable for the full purchase and administration of an RSV-immunization program would be £244 [36].

Although the future regarding RSV vaccines sounds promising, I expect that at least part of the preterm birth cohort will still require passive immunization with monoclonal antibodies

before active vaccination is possible. Based on this assumption, our current cost-effectiveness model can be adapted to consider a combination of RSV-prophylaxis with a monoclonal antibody and a new maternal or infant RSV vaccine. I propose, a RSV vaccination strategy in which term infants will be protected by either a maternal or an infant vaccine and preterm infants will be protected by an extended half-life monoclonal antibody or a biosimilar palivizumab agent. The total term birth cohort at present consists of approximately 160.000 infants and the preterm birth cohort of approximately 12.000 [38,39](2016). If the total seasonal cost of an extended half-life monoclonal antibody or 5 doses of biosimilar does not exceed € 500 including administration costs, then the preterm birth cohort could be protected with a total cost of 12.000 x €500 = €6 million, which is less than half of the current total palivizumab program cost that equals €12.8 million [9]. The remaining €6.5 million could then be used for the term birth cohort at €6.5 million / 160.000 = €40 per maternal vaccination or €20 for 2 consecutive infant vaccinations. This seems feasible, recognizing that the influenza vaccine costs about €11 , and administrative costs are approximately € 5-6 in the Netherlands [40](Influvac).

**Budget Impact**

Eventually the reimbursement decision of a new RSV prevention program with a vaccine and/or a monoclonal antibody will also depend on a budget impact analysis (BIA). A BIA model addresses the expected changes in expenditure of the available health care budget after the adoption of a new intervention. In the case of RSV prevention this also accounts for immunoprophylaxis/vaccination strategies already in use [41]. A budget impact model will encompass the incidence and prevalence of RSV infections, resource utilization, the treatment regimen, the proposed target population, market penetration and expected off-label use or indication expansion. With a BIA the likely financial consequences of a new preventive RSV treatment (regimen) compared to existing treatments and the effect on the health care budget can be estimated. This outcome is normally not a single estimate but a range of values based on model input variables, scenario analyses with different assumptions regarding target population(s) or treatment regimen(s) and also choices regarding adoption of a new treatment alongside an existing treatment, as could potentially be the case in RSV prevention.

The current budget for the national immunization program in the Netherlands is approximately €83.5 million (2016) with an acceptance threshold for new vaccines set at

€20.000 to €80.000 per quality adjusted life year gained [42]. A new RSV prevention program could be acceptable if it approaches this threshold, and is probably closer to € 20.000 than € 80.000. However, the use of thresholds is disputed, and alternative fixed budget, fixed trade off, and flexible trade off approaches have been proposed, to assess the value of a new intervention or treatment strategy. In the end the question remains as to how we want to spend our health care budget and if palivizumab or one of its moAb successors, or a biosimilar or a new RSV vaccine is the best preventive strategy to implement and at what cost?

**Conclusion and Recommendations**

In conclusion, RSV infection causes a high burden of disease in moderate-to-late preterm infants, through direct morbidity during hospitalisation and RSV related wheezing. RSV-related hospitalisation is two- to three-fold higher in a subgroup with specific risk factors compared to the overall cohort of moderate-to-late preterm infants. I developed a model with my co-investigators, to assess the cost-effectiveness of targeted RSV-prophylaxis compared to no prophylaxis, which can easily be adapted to guide the implementation of future RSV vaccines or biosimilars.

A new RSV prevention strategy should ideally be suitable for both preterm and term infants. Current promising interventions include an inexpensive, single-dose, extended half-life moAb, a less costly biosimilar than palivizumab and a widely adopted, effective maternal vaccine. Success with this proposed initiative is possible by lobbying pharmaceutical companies and the government for continued research funding and embarking on a healthy discussion on acceptable pricing. Successful implementation of the chosen strategy also requires solid endorsement of the intervention by the Neonatology subcommittee of the Dutch Society of Pediatrics. Hopefully, collaborative research and engagement with key stakeholders on the importance of RSV prevention will lead to a reduced RSV burden in the near future.

**References**


1. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. *Pediatrics*. 2014;134(2):e620-e638.
2. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory Syncytial Virus-Associated Hospitalizations Among Children Less Than 24 Months of Age. *Pediatrics*. 2013;132(2):e341-e348.
3. McLaurin KK, Chatterjee A, Makari D. Modeling the Potential Impact of the 2014 American Academy of Pediatrics Respiratory Syncytial Virus Prophylaxis Guidance on Preterm Infant RSV Outcomes. *Infect Dis Ther*. 2015;4(4):503-511.
4. Hasegawa K, Mansbach JM, Piedra PA, et al. Eligibility for palivizumab prophylaxis in a cohort of children with severe bronchiolitis. *Pediatr Int*. 2015;57(5):1031-1034.
5. Anderson EJ, Carbonell-Estrany X, Blanken M, et al. Burden of severe respiratory syncytial virus disease among 33-35 weeks' gestational age infants born during multiple respiratory syncytial virus seasons. *Pediatr Infect Dis J*. 2017;36(2).
6. Rajah B, Sánchez PJ, Garcia-Maurino C, Leber A, Ramilo O, Mejias A. Impact of the Updated Guidance for Palivizumab Prophylaxis against Respiratory Syncytial Virus Infection: A Single Center Experience. *J Pediatr*. 2017;181:183-188.e1.
7. Goldstein M, Krilov L, Fergie J, et al. Respiratory Syncytial Virus Hospitalizations among U.S. Preterm Infants Compared with Term Infants Before and After the 2014 American Academy of Pediatrics Guidance on Immunoprophylaxis: 2012–2016. *Am J Perinatol*. 2018;35(14):1433-1442.
8. Belleudi V, Trotta F, Pinnarelli L, Davoli M, Addis A. Neonatal outcomes following new reimbursement limitations on palivizumab in Italy. *Arch Dis Child*. 2018;103(12):1163-1167.
9. Zorginstituut Nederland / GIPdatabank. https://www.gipdatabank.nl/. Accessed January 28, 2019.
10. Shankar MB, Staples JE, Meltzer MI, Fischer M. Cost effectiveness of a targeted age-based West Nile virus vaccination program. *Vaccine*. 2017;35(23):3143-3151.

11. Debes AK, Gilman RH, Onyango-Makumbi C, Ruff A, Oberhelman R, Dowdy DW. Cost-effectiveness of Diagnostic Algorithms for Tuberculosis in Children Less Than 5 Years of Age. *Pediatr Infect Dis J*. 2017;36(1):36-43.
12. Gregory S, Kuntz K, Sainfort F, Kharbanda A. Cost-Effectiveness of Integrating a Clinical Decision Rule and Staged Imaging Protocol for Diagnosis of Appendicitis. *Value Heal*. 2016;19(1):28-35.
13. van Giessen A, Peters J, Wilcher B, et al. Systematic Review of Health Economic Impact Evaluations of Risk Prediction Models: Stop Developing, Start Evaluating. *Value Heal*. 2017;20(4):718-726.
14. *Staatscourant 2018 Nr. 71139. Kennisgeving van de Minister Voor Medische Zorg van de Ontwerpregeling Tot Wijziging van de Bijlage Bij de Regeling Maximumprijzen Geneesmiddelen*.; 2018.
15. Scheltema NM, Nibbelke EE, Pouw J, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. *Lancet Respir Med*. 2018;6(4).
16. PATH. Respiratory syncytial virus. https://www.path.org/publications/files/CVIA_RSV_snapshot_fs.pdf. Accessed 06 January 2018.
17. University Medical Center Utrecht. Effect of intranasal administration of palivizumab on respiratory syncytial virus-associated infection - a randomized clinical trial. Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-002742-37/NL. Accessed February 5, 2019.
18. Zhu Q, McLellan JS, Kallewaard NL, et al. A highly potent extended half-life antibody as a potential RSV vaccine surrogate for all infants. *Sci Transl Med*. 2017;9(388):eaaj1928.
19. Domachowske JB, Khan AA, Esser MT, et al. Safety, Tolerability, and Pharmacokinetics of MEDI8897, an Extended Half-Life Single-Dose Respiratory Syncytial Virus Prefusion F-Targeting Monoclonal Antibody Administered as a Single Dose to Healthy Preterm Infants. *Pediatr Infect Dis J*. 2018;37(9):1.

20. A Study to Evaluate the Safety and Efficacy of MEDI8897 for the prevention of Medically Attended RSV LRTI in Healthy Preterm Infants (MEDI8897 Ph2b). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/record/NCT02878330. Accessed February 5, 2019.
21. EMA grants PRIME eligibility for potential next-generation RSV medicine MEDI8897. https://www.astrazeneca.com/media-centre/press-releases/2019/ema-grants-prime-eligibility-for-potential-next-generation-rsv-medicine-medi8897-05022019.html. Accessed February 6, 2019.
22. Wu H, Pfarr DS, Johnson S, et al. Development of motavizumab, an ultra-potent antibody for the prevention of respiratory syncytial virus infection in the upper and lower respiratory tract. *J Mol Biol*. 2007;368(3):652-665.
23. Carbonell-Estrany X, Simões EAF, Dagan R, et al. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. *Pediatrics*. 2010;125(1):e35-51.
24. Abarca K, Jung E, Fernández P, et al. Safety, Tolerability, Pharmacokinetics, and Immunogenicity of Motavizumab, a Humanized, Enhanced-Potency Monoclonal Antibody for the Prevention of Respiratory Syncytial Virus Infection in At-Risk Children. *Pediatr Infect Dis J*. 2009;28(4):267-272.
25. European Medicines Agency: scientific guidelines on biosimilar medicinal products. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar. Accessed January 28, 2019.
26. Utrecht Centre for Affordable Biotherapeutics. https://www.uu.nl/en/news/first-consortium-of-local-manufacturers-to-make-affordable-biosimilars-available-for-low-income. Accessed January 28, 2019.
27. Fiselier, S.L.; Hollants B. RSV-prophylaxis with a palivizumab biosimilar in Brazil, a multi-scenario cost-effectiveness study for a palivizumab biosimilar against RSV-infection in preterm infants in Brazil. Thesis. 2018.
28. Brennan Z. AbbVie Sees 80% Discounts in Nordic Market With New Humira Biosimilars. Regulatory Focus. https://www.raps.org/news-and-articles/news-articles/2018/11/abbvie-sees-80-discounts-in-nordic-market-with-ne%0A. Published 2018.

29. Scheltema NM, Kavelaars XM, Thorburn K, et al. Potential impact of maternal vaccination on life-threatening respiratory syncytial virus infection during infancy. *Vaccine*. 2018;36(31):4693-4700.
30. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol*. 1996;36(5):248-255. http://www.ncbi.nlm.nih.gov/pubmed/8955500. Accessed January 28, 2019.
31. Chu HY, Tielsch J, Katz J, et al. Transplacental transfer of maternal respiratory syncytial virus (RSV) antibody and protection against RSV disease in infants in rural Nepal. *J Clin Virol*. 2017;95:90-95.
32. Chu HY, Englund JA. Maternal Immunization. *Clin Infect Dis*. 2014;59(4):560-568. doi:10.1093/cid/ciu327.
33. Vojtek I, Dieussaert I, Doherty TM, et al. Maternal immunization: where are we now and how to move forward? *Ann Med*. 2018;50(3):193-208.
34. Poletti P, Merler S, Ajelli M, et al. Evaluating vaccination strategies for reducing infant respiratory syncytial virus infection in low-income settings. *BMC Med*. 2015;13(1):49.
35. Meijboom MJ, Rozenbaum MH, Benedictus A, et al. Cost-effectiveness of potential infant vaccination against respiratory syncytial virus infection in The Netherlands. *Vaccine*. 2012;30(31):4691-4700.
36. Cromer D, van Hoek AJ, Newall AT, Pollard AJ, Jit M. Burden of paediatric respiratory syncytial virus disease and potential effect of different immunisation strategies: a modelling and cost-effectiveness analysis for England. *Lancet Public Heal*. 2017;2(8):e367-e374.
37. Hogan AB, Campbell PT, Blyth CC, et al. Potential impact of a maternal vaccine for RSV: A mathematical modelling study. *Vaccine*. 2017;35(45):6172-6179.
38. Centraal Bureau voor de Statistiek. https://statline.cbs.nl/StatWeb/publication/?VW=T&DM=SLNL&PA=37422ned&D1=0,4-5,7,9,11,13,17,26,35,40-41&D2=0,10,20,30,40,(l-4)-l&HD=090218-0953&HDR=G1&STB=T. Accessed January 28, 2019.
39. Perinatale Registratie. https://www.perined.nl/. Accessed January 28, 2019.

40. Zorginstituut Nederland / www.medicijnkosten.nl. https://www.medicijnkosten.nl/databank?zoekterm=influenzavaccin&toedieningsvorm=SUSPENSIE&ddd_per_artikel=0&hoeveelheid=1. Accessed January 28, 2019.
41. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Heal*. 2014;17(1):5-14..
42. van Lier, E.A.; Geraerdts, J.L.E.; Oomen P.J.; Giesbers H.; van Vliet, J.A.; Drijfhout, I.A.; Zonnenberg-Hoff, I.F; de Melker HE. *Rijksinstituut Voor Volksgezondheid En Milieu (RIVM): Vaccinatiegraad En Jaarverslag Rijksvaccinatieprogramma Nederland 2016*.; 2017. https://www.rivm.nl/bibliotheek/rapporten/2017-0010.pdf.

# 10

CHAPTER 10

# Nederlandse samenvatting

**Nederlandse samenvatting**

Het doel van dit proefschrift was om inzicht te krijgen in de ziektelast veroorzaakt door infecties door het respiratoir syncytieel virus (RSV) bij "laat premature zuigelingen", een omschrijving van de groep kinderen die geboren is na 32 weken maar voor 36 weken zwangerschapsduur, dus 8 tot 4 weken te vroeg. Aanvullend was het doel om strategieën te ontwikkelen om de ziektelast door RSV in deze populatie te verminderen.

De onderzoeken die in dit proefschrift beschreven worden omvatten:

- het effect van RSV preventie op de incidentie van piepende ademhaling tijdens het eerste levensjaar
- de population attributable risk, een onderzoeksmaat die het relatieve risico combineert met de incidentie van risicofactoren voor terugkerend piepen in het eerste levensjaar
- risicofactoren voor ziekenhuisopname met een RSV infectie bepalen met als doel een risicoscore-instrument te ontwikkelen om RSV ziekenhuisopname te voorspellen in gezonde, laat premature zuigelingen
- de kosteneffectiviteit van gerichte RSV preventie bij laat premature zuigelingen op basis van een risicoscore-instrument vergeleken met geen profylaxe

In deze samenvatting zal ik de belangrijkste bevindingen schetsen en vervolgens de resultaten gebruiken om een meer algemeen perspectief te bieden. Ik zal de ziektelast van RSV-infectie in laat premature zuigelingen beschrijven op basis van mijn onderzoeken en de huidige mogelijkheden voor RSV preventie in deze populatie bespreken, rekening houdend met de kosteneffectiviteit en het potentieel van gerichte RSV preventie.

Ik zal afsluiten met specifieke aanbevelingen voor verder onderzoek naar RSV preventie.

**Voornaamste bevindingen**

Onze studies tonen aan dat de incidentie van ziekenhuisopname vanwege RSV infectie bij laat premature zuigelingen 4-5% is, en twee- tot driemaal hoger bij hoog-risico zuigelingen op basis van een risicoscore-instrument met 3-4 risicofactoren. RSV-infectie lijkt een belangrijke factor te zijn bij het ontstaan van een vroege piepende ademhaling bij deze kinderen. Ernstige RSV-infecties en daaropvolgende piepende ademhaling zijn te voorkomen bij laat premature zuigelingen met een gerichte RSV preventie met behulp van RSV-specifieke monoklonale

antilichamen (moAb). De kosteneffectiviteit van deze interventie is echter niet gunstig voor grootschalig gebruik.

**Hoofdstuk 2 en 3** beschrijven dat RSV preventie met een monoklonaal antilichaam bij laat premature zuigelingen het aantal door ouders gerapporteerde dagen met piepende ademhaling in het eerste levensjaar sterk vermindert, zelfs na het einde van de behandeling en na het RSV-seizoen, lopend van 1 oktober tot 1 april. RSV preventie gaat gepaard met een relatieve vermindering van 61% van het aantal dagen met een piepende ademhaling. Dit geeft aan dat RSV-infectie tijdens de kindertijd een belangrijk mechanisme is in het ontstaan van piepende ademhaling bij deze specifieke populatie.

**Hoofdstuk 4** illustreert dat een groot deel van de incidentie van recurrent wheezing (RW) kan worden verklaard door blootstelling aan virussen. Er bestaat een sterke relatie tussen RSV-bronchiolitis ziekenhuisopname en terugkerende piepende ademhaling, maar de bijdrage aan de totale incidentie van RW is relatief bescheiden in vergelijking met andere risicofactoren, zoals dagopvang, die geassocieerd zijn met virale blootstelling.

**Hoofdstuk 5 en 6** schetst de ontwikkeling en validatie van een Nederlands risicoscore-instrument om een subgroep van laat premature zuigelingen te vinden met een tien keer hoger risico op ziekenhuisopname vanwege RSV infectie dan de referentiegroep van voldragen zuigelingen. Verder hebben we in een internationale samenwerking meerdere gepubliceerde risicoscore-instrumenten, waaronder het Nederlandse instrument, met elkaar vergeleken en de date gezamenlijk geanalyseerd om een gevalideerd risicoscore-instrument te bieden dat van toepassing is op het noordelijk halfrond. Dit initiatief biedt de basis voor landenspecifieke kosteneffectiviteitsanalyses voor huidige en toekomstige RSV preventiestrategieën.

**Hoofdstuk 7 en 8** beschrijven dat gerichte RSV preventie niet kosteneffectief was in het verminderen van de RSV belasting bij laat premature zuigelingen. Hierbij wordt niet alleen rekening gehouden met ziekenhuisopnames, maar ook met piepende ademhaling in een subgroep van zuigelingen met een hoog risico op ziekenhuisopname vanwege een RSV-infectie. Hoewel de belasting van RSV-infectie groot is bij laat premature kinderen, moeten de kosten van RSV preventie met monoklonale antilichamen afnemen voordat grootschalig gebruik bij hoog-risico laat premature zuigelingen kan worden gerechtvaardigd.

**Implicaties voor de huidige RSV preventie**

Onze onderzoekersgroep was de eerste om een oorzakelijk verband te beschrijven tussen RSV-infectie en vroege piepende ademhalingsklachten en we ontwikkelden een gevalideerde risicoscore-instrument om gerichte RSV preventie mogelijk te maken. We berekenden dat de huidige RSV preventiemogelijkheden niet voldoende zijn om kosteneffectieve strategieën te bieden voor het verminderen van de RSV ziektelast.

Kosteneffectiviteitsanalyses zijn een belangrijk onderdeel geworden van het huidige RSV preventiebeleid omdat beperkingen van het gezondheidszorgbudget meer dan ooit nodig zijn vanwege de stijgende kosten voor de gezondheidszorg. In 2014 heeft de American Academy of Pediatrics (AAP) haar meest recente richtlijnen gepubliceerd waarin de groepen zuigelingen worden geïdentificeerd die recht hebben op RSV-profylaxe[1]. Deze richtlijn beveelt palivizumab-profylaxe aan voor zuigelingen geboren vóór 29 weken en 0 dagen en geselecteerde hoog-risicogroepen, waaronder kinderen met bronchopulmonale dysplasie en hemodynamisch significante hartaandoeningen. Risicofactoren voor ernstige RSV ziekte werden als onbelangrijk beschouwd. De onderbouwing en de kwaliteit van het bewijs voor deze nieuwe richtlijn is beperkt en wordt voornamelijk bepaald door de New Vaccine Surveillance Network Study, waarin 559 ziekenhuisopnames in de periode 2000-2004 werden geanalyseerd, waaronder 12 opgenomen zuigelingen geboren vóór 29 weken zwangerschapsduur [2]. Deze herziening leidde tot enige discussie en verschillende publicaties waarin de nieuwe richtlijn als een maatregel voor het reduceren van gezondheidszorg kosten werd afgedaan. Daartegenover stonden publicaties die de nieuwe richtlijn ondersteunen doordat ze geen verschil in RSV-gerelateerde ziekenhuisopnames en ziektelast vóór en na de nieuwe richtlijn beschreven [3-8]. Ondanks alle discussies zal de richtlijn niet snel veranderen. In november 2017 hebben de Commissie infectieziekten en de Subcommissie Bronchiolitis van de AAP opnieuw alle beschikbare gegevens met betrekking tot palivizumab besproken en beide groepen hebben de aanbevelingen in de RSV-beleidsverklaring en het technisch rapport van 2014 opnieuw bevestigd. De impact van de AAP-richtlijnen is aanzienlijk en deze meer beperkte RSV preventierichtlijn is tegenwoordig in meerdere landen overgenomen. Momenteel bespreekt de subcommissie Neonatologie van de Nederlandse Vereniging voor Kindergeneeskunde de reikwijdte van de huidige Nederlandse RSV preventierichtlijnen.

Het debat over de richtlijn voor RSV-immunoprofylaxe is begrijpelijk omdat wijdverspreide palivizumab-profylaxe wordt belemmerd door hoge kosten van de therapie en onhandige

maandelijkse intramusculaire toediening. In 2017 bedroegen de jaarlijkse kosten van het huidige profylaxeprogramma van RSV palivizumab € 12,8 miljoen in Nederland (online Gipdatabank.nl). Deze kosten werden gemaakt door 2.797 zuigelingen die palivizumab kregen en behoorden tot een van de categorieën van kinderen voor wie palivizumab vergoed wordt. Dit is € 3 miljoen meer dan de totale kosten per jaar voor een veel gebruikt geneesmiddel zoals Nexium (esomeprazol) waarvoor er meer dan 200.000 gebruikers in Nederland zijn en 50% meer dan de totale kosten voor Ventolin (salbutamol), waarvoor de totale kosten € 7,9 miljoen zijn voor meer dan 800.000 gebruikers [9]. In het licht van deze vergelijkingen moet er een zorgvuldige afweging gemaakt worden voordat de indicatie voor palivizumab tegen hogere kosten wordt uitgebreid. Het is belangrijk mee te laten wegen dat premature zuigelingen een zeer kwetsbare populatie is. De toewijzing van ons budget voor gezondheidszorg vereist een keuze tussen enerzijds bepaalde groepen kwetsbare patiënten en anderzijds de behandeling voor elke patiënt als gelijkwaardig beschouwen. Moeten we investeren in een genezende behandeling om nog een (deel van een) Quality Adjusted Live Year (QALY), gedefinieerd als een jaar in volledige gezondheid, te winnen voor een 80-jarige man of moeten we investeren in een preventieve behandeling om de gezondheid te beschermen van een 3 maanden oude, laat premature zuigeling? Een QALY is op zichzelf blind voor wie de QALY verliest of wint en houdt geen rekening met de gezondheidstoestand, de ernst van de ziekte of persoonlijke kenmerken zoals leeftijd of maatschappelijke rol zoals ouder van jonge kinderen zijn of mantelzorger. Dit kan worden gestuurd door overheidsbeleid of door QALY-weging ten gunste van bijvoorbeeld kinderen of jonge volwassenen die productief zijn en de zorg voor jonge kinderen hebben in vergelijking met ouderen. De impact van economische productiviteit op gezondheid-economische beslissingen is een ander moeilijk debat waarvoor beleidsmakers en onderzoekers geen duidelijk antwoord hebben.

Er bestaat een kloof tussen de huidige praktijk van geen RSV preventie voor laat premature zuigelingen en de algehele motivatie om de RSV-belasting in deze populatie te verminderen. Deze kloof kan mogelijk worden overbrugd met de identificatie van een subgroep van laat premature zuigelingen met een hoog risico. Ik stel voor om een risicoscore-instrument te gebruiken om gerichte RSV preventie te sturen en de kosteneffectiviteit van deze aanpak te analyseren. Hoewel wenselijk in een tijd van budgettaire beperkingen in de gezondheidszorg, blijft gerichte preventie weliswaar een zeldzame maar geaccepteerde aanpak [10-13].

Zelfs als RSV-profylaxe gericht aan slechts 10% van de laat premature zuigelingen met een geschat risico van >10% voor ziekenhuisopname vanwege RSV-infectie wordt gegeven, resulteert dit in een incrementele kosten-batenverhouding van >€ 200.000 per gewonnen QALY. Dit is nog steeds ruim boven de informele Nederlandse drempel voor kosteneffectiviteit van € 80.000 per gewonnen QALY. De vermindering van RSV-gerelateerde piepende ademhaling door profylaxe voegt weinig toe aan de kosteneffectiviteit omdat de totale kosten van piepende ademhaling laag zijn wat betreft medicatiegebruik en ziekenhuisopnamen. Bovendien is de hiermee gewonnen hoeveelheid QALY's laag als piepende ademhaling zich niet ontwikkelt tot levenslange astma.

Op basis van mijn berekening zou er een prijsverlaging van 60% moeten komen van de huidige beschikbare RSV-profylaxe, palivizumab, voor een aanvaardbaar kosteneffectiviteitsniveau uitgaande van een drempel van € 80.000 per QALY. Een prijsdaling van> 90% zou resulteren in een kostenbesparende strategie. Onlangs is een belangrijke stap gezet in de richting van meer betaalbare RSV preventie in de vorm van een door het ministerie onderhandelde prijsverlaging van Synagis (palivizumab) van ongeveer 30% in Nederland [14]. Op zich is deze maatregel niet voldoende om hierop de vergoeding van palivizumab uit te breiden naar laat premature zuigelingen met een hoog risico, maar het is een belangrijke eerste stap.

In mijn artikel over de kosteneffectiviteit van RSV preventie beschreef ik dat het eventueel voorkomen van astma diagnoses de uitkomst van de analyse zou kunnen beïnvloeden. Tijdens de uitvoering van het onderzoek beschreven in dit proefschrift waren we beperkt tot 1 jaar follow-up data. De 6-jaar durende vervolgstudie van onze studie was essentieel om de relatie van RSV-infectie en de diagnose van astma op 6-jarige leeftijd te verhelderen. Mijn collega Nienke Scheltema et al. beschreven een afnemend beschermend effect op piepende ademhaling tot de leeftijd van 6 jaar zonder verband met de diagnose van astma op schoolleeftijd [15]. Samenvattend wordt de belangrijkste ziektelast van RSV-infectie in het eerste jaar van het leven gezien waarna de ziektelast afneemt in de loop van de eerste 6 jaar van het leven. Daarom zou het vergroten van de tijdshorizon van de kosteneffectiviteit analyses niet meer kosten voor de gezondheidszorg omvatten en daarmee niet bijdragen aan een gunstiger kosten-batenverhouding.

**Toekomstige RSV preventie**

Betaalbare RSV preventie moet worden gezocht in nieuwe methodes voor RSV preventie, zoals nieuwe moAbs met verlengde halfwaardetijd, waardoor ze langer werken en minder vaak toegediend hoeven te worden; palivizumab biosimilars, die potentieel goedkoper zijn; of een RSV-vaccin. Naar aanleiding van mijn beschrijving van de ziektelast van RSV-infectie bij laat premature zuigelingen en de opties voor preventie, is er nog steeds een grote behoefte aan een relatief goedkoop product dat net zo effectief of zelfs effectiever is dan palivizumab. Idealiter zou deze behandeling een verbeterd kosten-batenprofiel en een minder belastende of minder frequente toediening hebben om gebruik bij een grotere populatie van zuigelingen te rechtvaardigen. De RSV-behandelingen die momenteel worden ontwikkeld, omvatten meer dan 20 vaccins en therapeutische middelen in actieve klinische onderzoeken en een gelijk aantal in de preklinische fase (PATH-momentopname) (figuur 1) [16].

Een andere aanpak wordt momenteel onderzocht in het Universitair Medisch Centrum Utrecht. Onderzoekers Löwensteyn en Mazur van de RSV Research Group hebben neusdruppels ontwikkeld op basis van commercieel palivizumab om de veiligheid en werkzaamheid ervan in de preventie van RSV-infectie te bepalen [17]. De fase 1 / 2a-b-onderzoeken kregen ethische goedkeuring en zijn momenteel actief. Intranasale palivizumab heeft de potentie om een goedkope optie te zijn in vergelijking met intramusculaire palivizumab, als het even effectief is bij lage doses, gericht op het lokale neusslijmvlies. Een mogelijk nadeel is de mogelijke noodzaak van frequente (dagelijkse) doses.

Met betrekking tot nieuwe verlengde halfwaardetijd moAbs hebben Zhu et al. veelbelovende voorlopige resultaten op een verlengde halfwaardetijd RSV-specifieke moAb, MEDI8897, gepubliceerd [18]. Ze suggereren door middel van modellering op basis van de bekende werking van palivizumab in het lichaam dat een enkele toediening van MEDI8897 bij een geschikte dosis zal leiden tot bloedspiegels die correleren met bijna complete bescherming tegen RSV bij katoenratten. De recente publicatie van de 1b / 2a dosis-escalatiestudie bij gezonde te vroeg geboren zuigelingen beschrijft een gunstig veiligheidsprofiel en een 5-maanden durend RSV-beschermingsprofiel op basis van serumconcentraties [19]. Op 20 december 2018 meldde MedImmune dat de fase 2b-studie van MEDI8897, ook bekend als nirsevimab, bij gezonde zuigelingen van 29 tot 34 weken zwangerschapsduur is voltooid [20]. De resultaten zijn naar verluidt veelbelovend omdat op 5 februari 2019 MedImmune door het European Medicines Agency (EMA) in aanmerking kwam voor het PRIME programma op basis van positieve

primaire analyses van de fase 2b trial [21]. PRIME is een programma ter ondersteuning van de ontwikkeling van geneesmiddelen die gericht zijn op een onvervulde behoefte en is gericht op het optimaliseren van ontwikkelingsplannen en het versnellen van de evaluatie voor toepassing.

Enige bedenkingen ten aanzien van de verwachtingen van MEDI8897 zijn noodzakelijk, vooral in het licht van de niet-goedkeuring van motavizumab door het Federal Drugs Agency (FDA), de Amerikaanse EMA, in 2010. De tekenen leken allemaal positief te zijn voor dit "ultra-krachtige, hoge affiniteit, gehumaniseerde moAb afgeleid van palivizumab" [22,23]. Klinische onderzoeken hebben echter aangetoond dat motavizumab werd geassocieerd met ongunstige huidreacties. Negentien motavizumab-patiënten hadden "hooggradige overgevoeligheidsreacties" en 3 gevallen van anafylaxie, vergeleken met geen ernstige allergische reacties in de palivizumab-groep, waardoor de FDA concludeerde dat motavizumab geen voordelen ten opzichte van palivizumab bood en dat het mogelijk gevaarlijker is [23,24]. MEDI8897 kan echter potentieel kostenbesparend zijn bij hoog-risico laat premature zuigelingen tegen een "vaccinprijs" van €500, zoals geschat in ons kosteneffectiviteitsonderzoek voor palivizumab, uitgaande van een enkele dosis die seizoenlange bescherming biedt . Voor deze schatting gaan we uit van een met hoog-risico geassocieerde RSV-hospitalisatiegraad van ≥10% en een effectiviteit van 80%. De totale kosten voor seizoenlange bescherming moeten lager zijn als de incidentie van ziekenhuisopnames in de doelgroep of de werkzaamheid lager is. Rekening houdend met kosten voor onderzoek en ontwikkeling (R&D), mogelijk met inbegrip van R&D van het mislukte motavizumab en de relatief hoge productiekosten van monoklonale antilichamen, vind ik het moeilijk om een gunstige kosteneffectiviteit voor het product te verwachten. Omdat R&D-kosten relatief vaste kosten zijn mogelijk vermeerderd met de "verloren" motavizumab R&D-kosten en omdat productiekosten relatief hoog zijn omdat monoklonale antilichamen worden vervaardigd in zoogdiercellen met een laag rendement en tijdrovend proces, is het waarschijnlijker dat de dosisprijs een aantal maal hoger zal zijn.

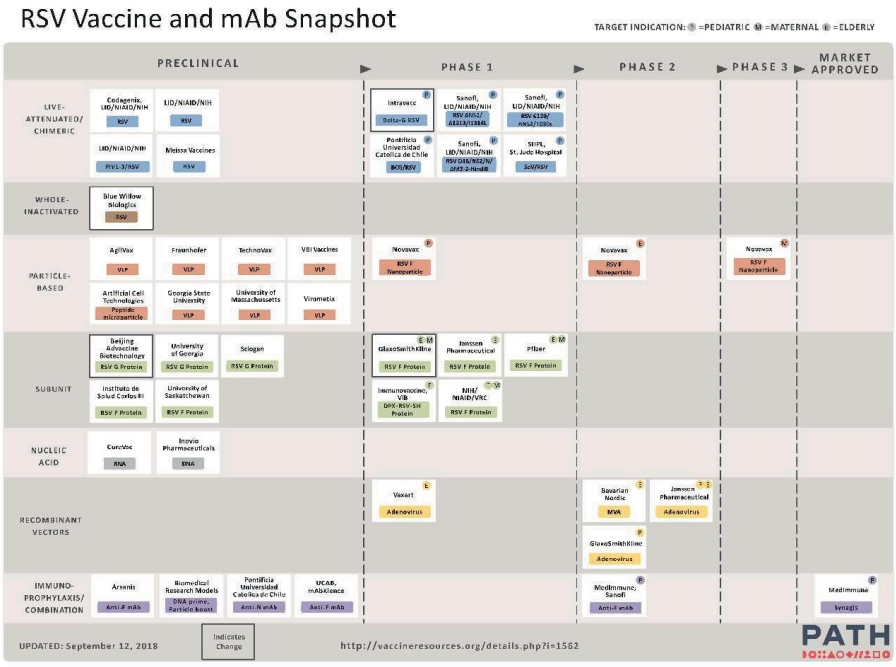
Een andere, meer betaalbare benadering zou de introductie van een palivizumab biosimilar zijn. Biosimilars zijn zeer vergelijkbaar, maar niet gelijk aan de originele biologicals, in dit geval het monoklonale antilichaam palivizumab. Biologicals zijn geïsoleerd uit een verscheidenheid aan natuurlijke bronnen, van mensen, dieren of micro-organismen en kunnen worden geproduceerd door biotechnologische methoden en andere geavanceerde technologieën.

Een biological en een biosimilar komen nooit volledig overeen vanwege de natuurlijke variabiliteit die inherent is aan het productieproces van biologische geneesmiddelen. Voor hun ontwikkeling streeft het Europees Geneesmiddelenbureau (EMA) naar het voorkomen van onnodige herhaling van reeds uitgevoerde klinische proeven met het referentiegeneesmiddel, i.e. biological. In plaats daarvan moeten bedrijven en onderzoekers aantonen dat hun biologische geneesmiddel "sterk gelijk" is aan het referentiegeneesmiddel. Bovendien moeten testen geen klinisch relevante verschillen aantonen tussen de biosimilar en het referentiegeneesmiddel op het gebied van van veiligheid, kwaliteit en werkzaamheid [25]. Momenteel wordt een palivizumab biosimilar, genaamd lunamab, onderzocht in een samenwerkingsproject waarbij de Wereldgezondheidsorganisatie (WHO) en lokale fabrikanten betrokken zijn ( mAbXience, Libbs, Medigen en SPIMACO) in landen met lage inkomens, ondersteund door het Utrecht Centre for Affordable Biotherapeutics (UCAB) [26]. Het ontwikkelingsproces met betrekking tot chemische aspecten, productie en controle van het studiegeneesmiddel voor het klinische programma, waarbij het medicijn eerst in gezonde volwassenen in een fase I-onderzoek zal worden getest, zal naar verwachting over een jaar kunnen beginnen (update N. Dorrestijn / UCAB, persoonlijke communicatie). In het ontwikkelingsproces werd een prijsonderzoek uitgevoerd op basis van gepubliceerde RSV-incidentiegegevens uit Brazilië om een benchmark prijs vast te kunnen stellen voor een aanvaardbaar kosteneffectiviteitsniveau. Deze studie concludeerde dat een eenheidsprijs in het bereik van $ 119-149 zou resulteren in de kostenneutrale implementatie van een palivizumab biosimilar gericht op premature zuigelingen ≤ 36 weken zwangerschapsduur [27].

Wat betreft de prijsbepaling van een palivizumab biosimilar, schatte ik dat met het momenteel beschikbare palivizumab-product voor een eenheidsprijs van € 100 en 5 maandelijkse doses, een kostenbesparende strategie zou kunnen worden gerealiseerd voor hoog-risico laat premature zuigelingen tegen een kosteneffectiviteit drempel van € 80.000 per QALY. Deze prijsdaling lijkt onwaarschijnlijk omdat de prijsverlagingen naar verwachting eerder tussen de 20-30% zal liggen, zoals geïllustreerd door infliximab (Remicade) biosimilars Remsima, Inflectra en Flixabi. Dit contrast is aanzienlijk in vergelijking met de 80% korting die optreedt wanneer generieke versies van non-biological geneesmiddelen op de markt worden gebracht. Recente ontwikkelingen zijn echter veelbelovend, zoals blijkt uit de prijsontwikkelingen van biological Humira (adalimumab), waarbij de distributeur AbbVie naar

verluidt bereid is kortingen tot 80% te bieden op de Noordse tendermarkt in een gevecht met verschillende adalimumab-biosimilars [28].

In tegenstelling tot het volgende RSV-specifieke monoklonale antilichaam of biosimilar, zou een RSV-vaccin effectiever en minder duur kunnen blijken, waarbij toepassing in een grotere populatie premature of zelfs voldragen zuigelingen zou kunnen worden overwogen. Hieronder vindt u een momentopname van de huidige RSV-vaccins en monoklonale antilichamen in verschillende stadia van ontwikkeling van preklinische dierstudies tot verschillende fasen van klinische onderzoeken. Het vaccin in de meest geavanceerde ontwikkelingsfase is een vaccin voor de moeders van nanodeeltjes dat zich richt op het RSV F-oppervlakte-eiwit dat Novavax (augustus 2017) heeft ontwikkeld.




*Figuur 1. Huidige RSV-vaccins en monoklonale antilichamen in verschillende stadia van ontwikkeling.*

Maternale vaccinatie, waarbij de moeder een vaccinatie krijgt ten bate van haar nog ongeboren kind, is vooral relevant voor zuigelingen jonger dan 6 maanden, omdat deze kinderen een hoog risico lopen op ernstige RSV-infectie, maar minder kans hebben op actieve immunisatie. Zelfs met de introductie van een vaccin voor moeders of kinderen kan het gebruik van anti-RSV monoklonale antilichamen echter nog steeds nodig zijn om te vroeg geboren kinderen jonger dan 3-6 maanden te beschermen. Een recent ontwikkeld wiskundig model om het percentage kinderen met levensbedreigende RSV-infectie tijdens het eerste levensjaar te voorspellen, dat kan worden voorkomen door maternale vaccinatie, toonde aan dat premature zuigelingen naar verwachting minder baat zouden hebben bij een maternaal RSV-vaccin dan bij voldragen zuigelingen [29]. Het gebruik van een maternaal vaccin is in hoge mate afhankelijk van de timing van maternale vaccinatie en het daaropvolgende niveau van werkzaamheid op basis van antilichaamoverdracht van de moeder naar de foetus [30-33]. Voor zuigelingen is de leeftijd bij de eerste vaccinatie met een levend vaccin een delicate balans tussen veiligheid en werkzaamheid, maar het is mogelijk haalbaar gezien het feit dat te vroeg geboren zuigelingen van alle zwangerschapsduur op dit moment al worden gevaccineerd in het ziekenhuis vanaf de leeftijd van 8 weken. Als er bovendien vaccins worden gebruikt bij oudere kinderen om de RSV-overdracht te verminderen naar jongere en meer kwetsbare zuigelingen, is er enig bewijs dat een significante vermindering van RSV-infectie bij niet-gevaccineerde jonge kinderen kan worden verwacht [34]. Het gebruik van vaccins voor moeders of jonge kinderen alleen, afhankelijk van het tijdstip van toediening, kan als gevolg hebben dat er een aanhoudende vraag naar bescherming van monoklonale antilichamen bij premature zuigelingen blijft. Dit geldt vooral als suboptimale werkzaamheid wordt aangetoond na vaccinatie van de moeder en als vaccinatie van zuigelingen onveilig of niet effectief is.

**Kosteneffectiviteit**

Kosteneffectiviteitsanalyses zullen van cruciaal belang zijn om de kosten en baten van nieuwe moAbs of vaccins in doelpopulaties te bepalen op basis van een breed maatschappelijk perspectief, waarbij rekening wordt gehouden met directe medische kosten en effecten, maar ook indirecte kosten zoals verlies van productiviteit ervaren door ouders. Er zijn verschillende modelstudies uitgevoerd om de impact en de kosteneffectiviteit van een toekomstig RSV-vaccin te schatten [29,35-37]. In het onderzoek van Cromer et al. varieerde de werkzaamheid van

het vaccin van 50% tot 100% in verschillende scenario's en de leeftijd bij de eerste vaccinatie tussen 2-4 maanden. Uitgaande van volledige uitbanning van de ziekte bij kinderen jonger dan 5 jaar, concludeerden de auteurs dat de maximale prijs voor de volledige aankoop en toediening van een RSV-immunisatieprogramma £ 244 per kind zou zijn[36].

Hoewel de toekomst met betrekking tot RSV-vaccins veelbelovend klinkt, verwacht ik dat ten minste een deel van het prematuren cohort nog steeds een passieve immunisatie met monoklonale antilichamen nodig heeft voordat actieve vaccinatie mogelijk is. Op basis van deze aanname kan ons huidige kosteneffectiviteitsmodel worden aangepast om een combinatie van RSV-profylaxe met een monoklonaal antilichaam en een nieuw moeder- of kind RSV-vaccin te overwegen. Ik stel voor, een RSV-vaccinatiestrategie waarbij voldragen zuigelingen beschermd worden door een vaccin voor moeders of zuigelingen en waarbij premature zuigelingen worden beschermd door een verlengd monoklonaal antilichaam met halfwaardetijd of een biosimilar palivizumab-middel. Het actuele totale geboortecohort bestaat momenteel uit ongeveer 160.000 zuigelingen en het prematuren geboortecohort uit ongeveer 12.000 kinderen (2016) [38,39]. Als de totale seizoensgebonden kosten van een monoklonaal antilichaam met verlengde halfwaardetijd of 5 doses biosimilar niet meer bedragen dan € 500, inclusief administratiekosten, kan het vroeggeboortecohort worden beschermd met een totale kostprijs van 12.000 x € 500 = € 6 miljoen, minder dan de helft van de huidige totale palivizumab-programmakosten welke momenteel € 12,8 miljoen bedraagt [9]. De resterende € 6,5 miljoen kan vervolgens worden gebruikt voor het à terme geboortecohort, € 6,5 miljoen / 160.000 = € 40 per maternale vaccinatie of € 20 voor 2 opeenvolgende zuigelingenvaccinaties. Dit lijkt haalbaar, gebaseerd op het gegeven dat het griepvaccin ongeveer € 11 kost en de administratieve kosten ongeveer € 5-6 in Nederland zijn (Influvac) [40].

**Budgetimpact**

Uiteindelijk zal de beslissing over de vergoeding van een nieuw RSV preventieprogramma met een vaccin en / of een monoklonaal antilichaam ook afhangen van een budgetimpactanalyse (BIA). Een BIA-model behandelt de verwachte wijzigingen in de uitgaven van het beschikbare budget voor de gezondheidszorg na de goedkeuring van een nieuwe interventie. In het geval van RSV preventie houdt dit ook rekening met immunoprofylaxe / vaccinatiestrategieën die al in gebruik zijn [41]. Een budgetimpactmodel zal de incidentie en prevalentie van RSV-infecties,

het gebruik van zorgkosten, het behandelingsregime, de voorgestelde doelpopulatie, marktpenetratie en het verwachte off-label gebruik of indicatie uitbreiding omvatten. Met een BIA kunnen de te verwachten financiële gevolgen van een nieuwe preventieve RSV-behandeling (regime) in vergelijking met bestaande behandelingen en het effect op het budget voor de gezondheidszorg worden geschat. Dit resultaat is normaal gesproken geen enkele schatting, maar een reeks waarden op basis van modellering met verschillende input variabelen, scenarioanalyses met verschillende aannames met betrekking tot de doelpopulatie(s) of behandelingsschema(s) en ook keuzes met betrekking tot de goedkeuring van een nieuwe behandeling naast een bestaande behandeling, zoals mogelijk het geval kan zijn bij RSV preventie.

Het huidige budget voor het nationale immunisatieprogramma in Nederland is ongeveer € 83,5 miljoen (2016) met een acceptatiedrempel voor nieuwe vaccins vastgesteld op tussen de € 20.000 tot € 80.000 per quality adjusted life year [42]. Een nieuw RSV preventieprogramma zou acceptabel kunnen zijn als het deze drempel benadert en ligt waarschijnlijk dichter bij € 20.000 dan € 80.000. Het gebruik van thresholds/drempels wordt echter betwist en er zijn alternatieve benaderingen (fixed budget, fixed trade off, and flexible trade off) voorgesteld om de waarde van een nieuwe interventie- of behandelingsstrategie te beoordelen. Uiteindelijk blijft de vraag hoe we ons budget voor de gezondheidszorg willen besteden: is palivizumab, een van zijn monoklonale opvolgers, een biosimilar of een nieuw RSV-vaccin de beste preventieve strategie om te implementeren en tegen welke kosten?

**Conclusie en aanbevelingen**

RSV-infectie veroorzaakt een hoge ziektelast bij laat premature zuigelingen, door directe morbiditeit tijdens ziekenhuisopname en RSV-gerelateerde piepende ademhaling. Het risico op RSV-gerelateerde ziekenhuisopname is twee tot drie keer hoger in een subgroep met specifieke risicofactoren in vergelijking met het totale cohort van laat premature zuigelingen. Ik heb met mijn co-onderzoekers een model ontwikkeld om de kosteneffectiviteit van gerichte RSV-profylaxe te beoordelen in vergelijking met geen profylaxe, die gemakkelijk kan worden aangepast om de implementatie van toekomstige RSV-vaccins of biosimilars te begeleiden.

Een nieuwe RSV preventiestrategie zou idealiter geschikt moeten zijn voor zowel premature als voldragen zuigelingen. Huidige veelbelovende interventies omvatten een goedkope, single-dose, verlengde halfwaardetijd moAb, een minder dure biosimilar dan palivizumab en

een algemeen toegepast, effectief maternaal vaccin. Het succes van deze (combinatie)therapieën is afhankelijk van de lobby bij farmaceutische bedrijven en de overheid voor voortdurende onderzoeksfinanciering en het aangaan van een gezonde discussie over acceptabele prijzen. Een succesvolle implementatie van de gekozen strategie vereist ook goedkeuring van de interventie door het subcomité Neonatologie van de Nederlandse Vereniging voor Kindergeneeskunde. Hopelijk zal gezamenlijk onderzoek en engagement met de belangrijkste belanghebbenden over het belang van RSV preventie in de nabije toekomst leiden tot een verlaagde RSV-last.

**Referenties**


1. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. *Pediatrics*. 2014;134(2):e620-e638.
2. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory Syncytial Virus-Associated Hospitalizations Among Children Less Than 24 Months of Age. *Pediatrics*. 2013;132(2):e341-e348.
3. McLaurin KK, Chatterjee A, Makari D. Modeling the Potential Impact of the 2014 American Academy of Pediatrics Respiratory Syncytial Virus Prophylaxis Guidance on Preterm Infant RSV Outcomes. *Infect Dis Ther*. 2015;4(4):503-511.
4. Hasegawa K, Mansbach JM, Piedra PA, et al. Eligibility for palivizumab prophylaxis in a cohort of children with severe bronchiolitis. *Pediatr Int*. 2015;57(5):1031-1034.
5. Anderson EJ, Carbonell-Estrany X, Blanken M, et al. Burden of severe respiratory syncytial virus disease among 33-35 weeks' gestational age infants born during multiple respiratory syncytial virus seasons. *Pediatr Infect Dis J*. 2017;36(2).
6. Rajah B, Sánchez PJ, Garcia-Maurino C, Leber A, Ramilo O, Mejias A. Impact of the Updated Guidance for Palivizumab Prophylaxis against Respiratory Syncytial Virus Infection: A Single Center Experience. *J Pediatr*. 2017;181:183-188.e1.
7. Goldstein M, Krilov L, Fergie J, et al. Respiratory Syncytial Virus Hospitalizations among U.S. Preterm Infants Compared with Term Infants Before and After the 2014 American Academy of Pediatrics Guidance on Immunoprophylaxis: 2012–2016. *Am J Perinatol*. 2018;35(14):1433-1442.
8. Belleudi V, Trotta F, Pinnarelli L, Davoli M, Addis A. Neonatal outcomes following new reimbursement limitations on palivizumab in Italy. *Arch Dis Child*. 2018;103(12):1163-1167.
9. Zorginstituut Nederland / GIPdatabank. https://www.gipdatabank.nl/. Accessed January 28, 2019.
10. Shankar MB, Staples JE, Meltzer MI, Fischer M. Cost effectiveness of a targeted age-based West Nile virus vaccination program. *Vaccine*. 2017;35(23):3143-3151.

11. Debes AK, Gilman RH, Onyango-Makumbi C, Ruff A, Oberhelman R, Dowdy DW. Cost-effectiveness of Diagnostic Algorithms for Tuberculosis in Children Less Than 5 Years of Age. *Pediatr Infect Dis J*. 2017;36(1):36-43.
12. Gregory S, Kuntz K, Sainfort F, Kharbanda A. Cost-Effectiveness of Integrating a Clinical Decision Rule and Staged Imaging Protocol for Diagnosis of Appendicitis. *Value Heal*. 2016;19(1):28-35.
13. van Giessen A, Peters J, Wilcher B, et al. Systematic Review of Health Economic Impact Evaluations of Risk Prediction Models: Stop Developing, Start Evaluating. *Value Heal*. 2017;20(4):718-726.
14. *Staatscourant 2018 Nr. 71139. Kennisgeving van de Minister Voor Medische Zorg van de Ontwerpregeling Tot Wijziging van de Bijlage Bij de Regeling Maximumprijzen Geneesmiddelen*.; 2018.
15. Scheltema NM, Nibbelke EE, Pouw J, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. *Lancet Respir Med*. 2018;6(4).
16. PATH. Respiratory syncytial virus. https://www.path.org/publications/files/CVIA_RSV_snapshot_fs.pdf. Accessed 06 January 2018.
17. University Medical Center Utrecht. Effect of intranasal administration of palivizumab on respiratory syncytial virus-associated infection - a randomized clinical trial. Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-002742-37/NL. Accessed February 5, 2019.
18. Zhu Q, McLellan JS, Kallewaard NL, et al. A highly potent extended half-life antibody as a potential RSV vaccine surrogate for all infants. *Sci Transl Med*. 2017;9(388):eaaj1928.
19. Domachowske JB, Khan AA, Esser MT, et al. Safety, Tolerability, and Pharmacokinetics of MEDI8897, an Extended Half-Life Single-Dose Respiratory Syncytial Virus Prefusion F-Targeting Monoclonal Antibody Administered as a Single Dose to Healthy Preterm Infants. *Pediatr Infect Dis J*. 2018;37(9):1.

20. A Study to Evaluate the Safety and Efficacy of MEDI8897 for the prevention of Medically Attended RSV LRTI in Healthy Preterm Infants (MEDI8897 Ph2b). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/record/NCT02878330. Accessed February 5, 2019.
21. EMA grants PRIME eligibility for potential next-generation RSV medicine MEDI8897. https://www.astrazeneca.com/media-centre/press-releases/2019/ema-grants-prime-eligibility-for-potential-next-generation-rsv-medicine-medi8897-05022019.html. Accessed February 6, 2019.
22. Wu H, Pfarr DS, Johnson S, et al. Development of motavizumab, an ultra-potent antibody for the prevention of respiratory syncytial virus infection in the upper and lower respiratory tract. *J Mol Biol*. 2007;368(3):652-665.
23. Carbonell-Estrany X, Simões EAF, Dagan R, et al. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. *Pediatrics*. 2010;125(1):e35-51. doi:10.1542/peds.2008-1036.
24. Abarca K, Jung E, Fernández P, et al. Safety, Tolerability, Pharmacokinetics, and Immunogenicity of Motavizumab, a Humanized, Enhanced-Potency Monoclonal Antibody for the Prevention of Respiratory Syncytial Virus Infection in At-Risk Children. *Pediatr Infect Dis J*. 2009;28(4):267-272.
25. European Medicines Agency: scientific guidelines on biosimilar medicinal products. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar. Accessed January 28, 2019.
26. Utrecht Centre for Affordable Biotherapeutics. https://www.uu.nl/en/news/first-consortium-of-local-manufacturers-to-make-affordable-biosimilars-available-for-low-income. Accessed January 28, 2019.
27. Fiselier, S.L.; Hollants B. RSV-prophylaxis with a palivizumab biosimilar in Brazil, a multi-scenario cost-effectiveness study for a palivizumab biosimilar against RSV-infection in preterm infants in Brazil. Thesis. 2018.
28. Brennan Z. AbbVie Sees 80% Discounts in Nordic Market With New Humira Biosimilars. Regulatory Focus. https://www.raps.org/news-and-articles/news-articles/2018/11/abbvie-sees-80-discounts-in-nordic-market-with-ne%0A. Published 2018.

29. Scheltema NM, Kavelaars XM, Thorburn K, et al. Potential impact of maternal vaccination on life-threatening respiratory syncytial virus infection during infancy. *Vaccine*. 2018;36(31):4693-4700..
30. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol*. 1996;36(5):248-255. http://www.ncbi.nlm.nih.gov/pubmed/8955500. Accessed January 28, 2019.
31. Chu HY, Tielsch J, Katz J, et al. Transplacental transfer of maternal respiratory syncytial virus (RSV) antibody and protection against RSV disease in infants in rural Nepal. *J Clin Virol*. 2017;95:90-95..
32. Chu HY, Englund JA. Maternal Immunization. *Clin Infect Dis*. 2014;59(4):560-568. doi:10.1093/cid/ciu327.
33. Vojtek I, Dieussaert I, Doherty TM, et al. Maternal immunization: where are we now and how to move forward? *Ann Med*. 2018;50(3):193-208.
34. Poletti P, Merler S, Ajelli M, et al. Evaluating vaccination strategies for reducing infant respiratory syncytial virus infection in low-income settings. *BMC Med*. 2015;13(1):49.
35. Meijboom MJ, Rozenbaum MH, Benedictus A, et al. Cost-effectiveness of potential infant vaccination against respiratory syncytial virus infection in The Netherlands. *Vaccine*. 2012;30(31):4691-4700.
36. Cromer D, van Hoek AJ, Newall AT, Pollard AJ, Jit M. Burden of paediatric respiratory syncytial virus disease and potential effect of different immunisation strategies: a modelling and cost-effectiveness analysis for England. *Lancet Public Heal*. 2017;2(8):e367-e374.
37. Hogan AB, Campbell PT, Blyth CC, et al. Potential impact of a maternal vaccine for RSV: A mathematical modelling study. *Vaccine*. 2017;35(45):6172-6179.
38. Centraal Bureau voor de Statistiek. https://statline.cbs.nl/StatWeb/publication/?VW=T&DM=SLNL&PA=37422ned&D1=0,4-5,7,9,11,13,17,26,35,40-41&D2=0,10,20,30,40,(l-4)-l&HD=090218-0953&HDR=G1&STB=T. Accessed January 28, 2019.
39. Perinatale Registratie. https://www.perined.nl/. Accessed January 28, 2019.

40. Zorginstituut Nederland / www.medicijnkosten.nl. https://www.medicijnkosten.nl/databank?zoekterm=influenzavaccin&toedieningsvorm=SUSPENSIE&ddd_per_artikel=0&hoeveelheid=1. Accessed January 28, 2019.
41. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Heal*. 2014;17(1):5-14.
42. van Lier, E.A.; Geraerdts, J.L.E.; Oomen P.J.; Giesbers H.; van Vliet, J.A.; Drijfhout, I.A.; Zonnenberg-Hoff, I.F; de Melker HE. *Rijksinstituut Voor Volksgezondheid En Milieu (RIVM): Vaccinatiegraad En Jaarverslag Rijksvaccinatieprogramma Nederland 2016*.; 2017. https://www.rivm.nl/bibliotheek/rapporten/2017-0010.pdf.

# 11

CHAPTER 11

Dankwoord
List of publications
Curicculum vitae

**Dankwoord**

Beste pasgeborenen en ouders, zonder jullie was dit proefschrift er niet gekomen. Jullie bereidwilligheid om mee te doen aan de onderzoeken was bijzonder en essentieel om de onderzoeken naar RSV infecties zoals beschreven in dit proefschrift mogelijk te maken. Met veel plezier hebben we kennis met jullie gemaakt in de verschillende ziekenhuizen en zochten we jullie thuis steeds weer op. Dank voor alles.

Beste kinderartsen van het RSV Neonatal Network, maar ook alle arts-assistenten, verpleegkundigen en secretaresses van de kinderafdelingen die deelgenomen hebben aan de RISK en de MAKI studie, jullie hebben met enthousiasme de deur voor ons geopend en samen onze onderzoeken tot een succes gemaakt.

En verder schieten woorden tekort voor:
Louis, Maroeska, Jan, Lieke, Wendy, Loes, Pauline, Margreet, alle andere toppers en medepromovendi van de RSV-onderzoekgroep, alle co-auteurs en internationale collaborators, Jorit, Jorine, Mariëlle, Saskia, Niek, Koos, Annemiek, Leanne, Katrien, Loek, het Synacare team, alle lieve en zeer gewaardeerde kamergenootjes, mijn fijne collega's van het WKZ en in het bijzonder de Neonatologie, mijn ouders en schoonouders, broers, zwager, schoonzussen en al mijn fijne vrienden.

Lieve Eef, Guusje, Bram en Just

# Bedankt!

Maarten, mei 2019

**List of publications**

This thesis

- Blanken M, Rovers M, Sanders EA, Bont L. Ethical considerations and rationale of the MAKI trial: A multicenter double-blind randomized placebo-controlled trial into the preventive effect of palivizumab on recurrent wheezing associated with respiratory syncytial virus infection in children with a gestational age of 33-35 weeks. Contemporary Clinical Trials. Nov. 2012; 33(6): 1287-92.

- Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra P, Meijer A, Kimpen JJL, Bont L, Dutch RSV Neonatal Network. Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants. N Engl J Med. 2013 May 9;368(19):1791-9

- Blanken MO, Korsten K, Achten NB, Tamminga S, Nibbelke EE, Sanders EA, Smit HA, Groenwold RH, Bont L; Dutch RSV Neonatal Network. Population-Attributable Risk of Risk Factors for Recurrent Wheezing in Moderate Preterm Infants During the First Year of Life. Paediatr Perinat Epidemiol. 2016 Jul;30(4):376-85

- Blanken MO, Koffijberg H, Nibbelke EE, Rovers MM, Bont L, Dutch RSV Neonatal Network.(2013) Prospective Validation of a Prognostic Model for Respiratory Syncytial Virus Bronchiolitis in Late Preterm Infants: A Multicenter Birth Cohort Study. PLoS One. 2013;8(3):e59161

- Blanken MO, Paes B, Anderson EJ, Lanari M, Sheridan-Pereira M, Buchan S, Fullarton JR, Grubb E, Notario G, Rodgers-Gray BS, Carbonell-Estrany X. Risk scoring tool to predict respiratory syncytial virus hospitalisation in premature infants. Pediatr Pulmonol. 2018 May;53(5):605-612

- Blanken MO, Bont L, Rovers M. The cost-effectiveness of palivizumab in the prevention of respiratory syncytial virus bronchiolitis; a systematic review. Current Respiratory Medicine Reviews. Jun. 2011; 7(3): 203-212 and MSc thesis Health Economics, Policy and Law, Erasmus University (2012)

- Blanken MO, Frederix GW, Nibbelke EE, Koffijberg H, Sanders EAM, Rovers MM, Bont L; Dutch RSV Neonatal Network. Cost-effectiveness of rule-based immunoprophylaxis against respiratory syncytial virus infections in preterm infants. Eur J Pediatr. 2018 Jan;177(1):133-144


Other publications


- Korsten K, Blanken MO, Buiteman BJM, Nibbelke EE, Naaktgeboren CA, Bont LJ, Wildenbeest JG. RSV hospitalization in infancy increases the risk of current wheeze at age 6 in late preterm born children without atopic predisposition. Eur J Pediatr. 2019 Apr;178(4):455-462

- Scheltema NM, Nibbelke EE, Pouw J, Blanken MO, Rovers MM, Naaktgeboren CA, Mazur NI, Wildenbeest JG, van der Ent CK, Bont LJ. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. Lancet Respir Med. 2018 Apr;6(4):257-264

- Achten NB, Wu P, Bont L, Blanken MO, Gebretsadik T, Chappell JD, Wang L, Yu C, Larkin EK, Carroll KN, Anderson LJ, Moore ML, Sloan CD, Hartert TV. Interference Between Respiratory Syncytial Virus and Human Rhinovirus Infection in Infancy. J Infect Dis. 2017 Apr 1;215(7):1102-1106

- Anderson EJ, Carbonell-Estrany X, Blanken M, Lanari M, Sheridan-Pereira M, Rodgers-Gray B, Fullarton J, Rouffiac E, Vo P, Notario G, Campbell F, Paes B. Burden of Severe Respiratory Syncytial Virus Disease Among 33-35 Week Gestational Age Infants Born During Multiple Respiratory Syncytial Virus Seasons. Pediatr Infect Dis J. 2017 Feb;36(2):160-167.

- Korsten K, Blanken MO, Nibbelke EE, Moons KG, Bont L; Dutch RSV Neonatal Network. Prediction model of RSV-hospitalization in late preterm infants: An update and validation study. Early Hum Dev. 2016 Apr;95:35-40

- Sheridan-Pereira M, Murphy J, Sloan J, Crispino G, Leahy A, Corcoran JD, Dempsey E, Elnazir B, Gavin P, Sharif F, Gul R, Satas S, Murphy J, Gormally S, Shanaa I, Waldron D, Mc Mahon P, Carson J, Blanken M, Bont L, Paes B. Respiratory Syncytial Virus Preterm (32-36 Completed Weeks of Gestation) Risk Estimation Measure for RSV Hospitalization in Ireland: A Prospective Study. Pediatr Infect Dis J. 2016 Jan;35(1):19-24

- Achten NB, Korsten K, Blanken MO, Nibbelke EE, Bont L. Cesarean section and hospitalization for respiratory syncytial virus infection. Pediatr Infect Dis J. 2015 Feb;34(2):227.

- Blanken MO, Rovers MM, Bont L, Dutch RSV Neonatal Network. Respiratory Syncytial Virus and Recurrent Wheeze. N Engl J Med. 2013 Aug 22;369(8):782-3

- Bont L, Blanken MO. Viral respiratory burden in moderate-to-late preterms: the viral burden. Early Human Development. Supplement. Early Hum Dev. 2013 Jun;89 Suppl 1:S37-9.

- Belderbos ME, van Bleek GM, Levy O, Blanken MO, Houben ML, Schuijff L, Kimpen JL, Bont L. Skewed pattern of Toll-like receptor 4-mediated cytokine production in human neonatal blood: Low LPS-induced IL-12p70 and high IL-10 persist throughout the first month of life. Clin Immunol. Nov. 2009; 133(2): 228-37.

- Tijdink JM, Blanken MO, Bont L. Nieuwe inzichten in epidemiologie en pathogenese van infecties met respiratoir syncytieel virus. Tijdschrift voor Infectieziekten 2007;2:137-142

**Curriculum vitae**

Maarten Blanken werd geboren op 18 mei 1981 te Groningen. Zijn jeugd bracht hij door in Roden en zijn middelbare school doorliep hij aan het Willem Lodewijk Gymnasium in Groningen waar hij in 1999 zijn eindexamen behaalde (Bèta / Geschiedenis / Latijn).
In 1999 ging hij studeren in Groningen, door 3x uitloten voor Geneeskunde heeft hij eerstejaarsvakken gevolgd van de studies Biologie (1999), Geschiedenis (1999), Psychologie (1999), HBO-verpleegkunde (2000, propedeutisch examen) en Rechten (2001).

In 2001 startte hij in de 3e week van september, na een naplaatsing en mede dankzij een driehoeksruil van zijn initiële startplek in Maastricht, met de studie Geneeskunde in Groningen. Hij volgde van 2004 tot 2006 zijn co-schappen in het Tjongerschans ziekenhuis in Heerenveen. Voor zijn afstudeeronderzoek maakte hij de overstap naar het Wilhelmina Kinderziekenhuis in Utrecht om te werken bij de RSV Onderzoeksgroep (Prof. Dr. L. Bont). In 2007 startte hij als arts-assistent niet in opleiding in het Wilhelmina Kinderziekenhuis op achtereenvolgens de afdeling Kindernefrologie (hemodialyse-afdeling Hommel) en op de Neonatale Intensive Care Unit.

In 2008 volgde een start als arts-onderzoeker met het opzetten van de MAKI trial en de RISK studie wat leidde tot dit proefschrift. Hij werd begeleid door Prof. Dr. Louis Bont en Prof. Dr. Maroeska Rovers en in de beginfase van het onderzoek ook door Prof. Dr. Jan Kimpen en Prof. Dr. Lieke Sanders.
Gedurende zijn promotie volgde hij van 2011 tot 2012 het interdisciplinaire trainingsprogramma TULIPS (Training Upcoming Leaders in Paediatric Science") ter voorbereiding van een onderzoekscarrière in de Kindergeneeskunde en van 2010 tot 2012 verbreedde hij zijn basis verder met de opleiding tot health economist (MSc HEPL, Erasmus Universiteit Rotterdam).

In 2011 verwierf hij een AGIKO stipendium van ZonMw voor het onderzoek: "Respiratory syncytial virus (RSV) bronchiolitis in preterm infants 32-35 weeks gestational age: towards reducting the burden of disease", waarvan de resultaten onderdeel werden van dit proefschrift.

Als onderdeel van het AGIKO traject was hij van 2012 tot 2013 als Research Fellow werkzaam in het Hospital for Sick Children, Toronto, Canada (supervisor: Dr. W. Ungar; Early Investigators Exchange Programme Grant).

Daarna volgde in 2013 de opleiding tot kinderarts, eerst in het Meander Medisch Centrum in Amersfoort (opleider: Dr. P. Hogeman) en vervolgens in het WKZ (opleider: Prof. Dr. J. Frenkel). Aansluitend werd hij in 2018 aangenomen als fellow Neonatologie in het UMC/WKZ (opleider: Dr. W. de Vries / Dr. F. Groenendaal)

In de toekomst hoopt hij zijn werk als kinderarts op de Neonatale Intensive Care te blijven combineren met management en gezondheidseconomisch onderzoek voor het verbeteren van de zorg voor premature en ernstig zieke kinderen.

Maarten Blanken is sinds het begin van zijn studententijd verliefd op Evelien Verweij. Samen hebben zij 3 kinderen: Guusje (2011), Bram (2014) en Just (2015) en wonen in Zeist.