

Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial



Nienke M Scheltema, Elisabeth E Nibbelke, Juliette Pouw, Maarten O Blanken, Maroeska M Rovers, Christiana A Naaktgeboren, Natalie I Mazur, Joanne G Wildenbeest, Cornelis K van der Ent, Louis J Bont

Summary

Background Respiratory syncytial virus (RSV) infection is associated with subsequent wheeze and asthma. We previously reported on the causal relationship between prevention of RSV infection during infancy and reduced frequency of subsequent wheeze using a double-blind, randomised, placebo-controlled trial (MAKI). We continued follow-up and analysed the effect of RSV prevention during infancy on asthma and lung function at age 6 years.

Methods We studied 429 infants born at 32–35 weeks of gestation between 2008–10 who had randomly received either palivizumab for RSV immunoprophylaxis or placebo during the RSV season of their first year of life. After the first year of follow-up, single, assessor-blind follow-up of children continued until they were aged 6 years. Primary outcomes were parent-reported current asthma and forced expiratory volume in 0.5 s (FEV_{0.5}). The trial is registered in the ISRCTN registry, number ISRCTN73641710.

Findings 395 (92%) of 429 participants completed this 6-year follow-up study. Parent-reported current asthma was reported in 28 (14.1%) of 199 children in the RSV prevention group and 47 (24.0%) of 196 children in the placebo group (absolute risk reduction [ARR] 9.9%, 95% CI 2.2 to 17.6). The difference in current asthma, which was a composite endpoint, was due to a difference in infrequent wheeze (one to three episodes in the past year; 12 [6.0%] of 199 vs 26 [13.4%] of 194, ARR 7.4%, 95% CI 1.5 to 13.2). FEV_{0.5} percentage predicted values were similar between the RSV prevention group (89.1% [SD 10.6]) and placebo group (90.1% [11.1]), with a mean difference of 1.0 (95% CI –1.3 to 3.3). The proportion of children with current physician-diagnosed asthma was similar between the RSV prevention group (19 [10.3%] of 185) and placebo group (18 [9.9%] of 182), with an ARR of –0.4 (95% CI –6.5 to 5.8).

Interpretation In otherwise healthy preterm infants, this single-blind, randomised, placebo-controlled trial showed that RSV prevention did not have a major effect on current asthma or lung function at age 6 years. Future research will inform on the effect of RSV prevention on asthma at school age in the general population.

Funding AbbVie.

Introduction

Respiratory syncytial virus (RSV) infection is a notable cause of morbidity and mortality in young children,^{1,2} and RSV-related lower respiratory tract infection has been associated with subsequent wheeze and asthma at school age.^{3–10} With more than 358 million people affected by asthma in 2015, it is one of the most common chronic diseases globally and creates substantial disability in children.¹¹

The nature of the relationship between RSV infection during infancy and asthma in later childhood is unclear. Some observational cohort studies have shown an increased risk of asthma after RSV infection during infancy,^{3–8,10} but others have shown no clear relationship.^{12–14} However, these studies were not designed to provide evidence for causality. A recent observational case-control study that followed preterm children from Japan up to the age of 6 years showed that RSV prophylaxis reduced the incidence of recurrent wheezing, but not of atopic asthma.⁷ A randomised trial done in healthy term infants in the USA studied the effect of RSV prevention by motavizumab on severe RSV infection and medically attended wheezing up to age 3 years, but did not examine

long-term asthma development.¹⁵ To date, no randomised clinical trial using RSV prophylaxis has assessed the causal link between RSV infection during infancy and subsequent development of asthma or abnormal lung function.

We previously reported 1-year follow-up results of a multicentre, double-blind, randomised, placebo-controlled trial (MAKI) assessing the causal link between RSV infection during infancy and recurrent wheeze.¹⁶ We showed that, compared with placebo, RSV prevention by the monoclonal antibody palivizumab reduced the total number of wheezing days in the first year of life by 61% in otherwise healthy preterm infants. Single, assessor-blind follow-up of trial participants continued. In this study we assessed the effect of RSV prevention during infancy on asthma and lung function at age 6 years in the same patient population, in line with WHO and SAGE recommendations.^{17,18}

Methods

Study design and participants

In the MAKI trial, we enrolled otherwise healthy preterm infants, born at 32 weeks and 1 day to 35 weeks and 6 days

Lancet Respir Med 2018;
6: 257–64

Published Online
February 27, 2018
[http://dx.doi.org/10.1016/S2213-2600\(18\)30055-9](http://dx.doi.org/10.1016/S2213-2600(18)30055-9)

See [Comment](#) page 232

Department of Pediatric Infectious Diseases and Immunology, Wilhelmina Children's Hospital (N M Scheltema MD, E E Nibbelke MSc, M O Blanken MD, N I Mazur MD, J G Wildenbeest MD, Prof L J Bont MD), Department of Pediatric Pulmonology, Wilhelmina Children's Hospital (Prof C K van der Ent MD), Laboratory of Translational Immunology (Prof L J Bont), University Medical Center Utrecht, Utrecht, Netherlands; Department of Internal Medicine, St Antonius Hospital, Nieuwegein, Netherlands (J Pouw MD); Department of Operating Rooms and Department of Epidemiology, Biostatistics and HTA, Radboud University Medical Center, Nijmegen, Netherlands (Prof M M Rovers PhD); and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands (C A Naaktgeboren PhD)

Correspondence to:
Prof Louis J Bont, Department of Pediatric Infectious Diseases and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands
l.bont@umcutrecht.nl

Research in context

Evidence before this study

Respiratory syncytial virus (RSV) infection during infancy has been associated with asthma in later childhood. However, the nature of the relationship between RSV infection and asthma is unclear. We searched PubMed for clinical trials that assessed the link between RSV prevention and subsequent development of asthma. We searched for articles published in English up to Aug 11, 2017, using search terms related to RSV infection and prevention, wheeze, and asthma. We found one randomised trial from the USA showing no effect of RSV prevention by motavizumab on medically attended wheezing up to age 3 years in native American children. One observational case-control study from Japan showed that RSV prevention by palivizumab in otherwise healthy preterm children reduced subsequent physician-diagnosed recurrent wheezing up to age 6 years.

Added value of this study

We have previously reported on the causal relationship between RSV infection and recurrent wheeze in otherwise

healthy preterm infants using a double-blind, randomised, placebo-controlled trial. We continued single, assessor-blind follow-up of trial participants and analysed the effect of RSV prevention during infancy on asthma and lung function at age 6 years. We found that RSV prevention in otherwise healthy preterm infants reduced the risk of parent-reported asthma at age 6 years, which was mainly explained by differences in proportions of participants with infrequent wheeze. RSV prevention did not affect the risk of physician-diagnosed asthma or results of lung function tests at age 6 years.

Implications of all the available evidence

To the best of our knowledge, this is the first study designed to establish the causal relationship between RSV infection during infancy and asthma up to school age in otherwise healthy preterm infants. RSV prevention did not have a major effect on current asthma or lung function at age 6 years, which might have implications for future RSV preventive interventions in terms of cost-effectiveness.

of gestation.¹⁶ Infants were younger than 6 months at the start of the RSV season and were randomly assigned in a 1:1 ratio to receive palivizumab for RSV immunoprophylaxis or placebo. Randomisation was stratified according to gestational age and masking was secured by an independent pharmacist who had generated a permuted-block randomisation list. Parents recorded airway symptoms and airway-related physician attendance or medication use in a daily log until the first birthday of their infant. Details about the study design and study protocol have been previously described (ISRCTN73641710).¹⁶

In this study, children were followed up until age 6 years. To ensure continued study participation, parents received regular newsletters. Parents were invited to complete a questionnaire on respiratory symptoms when their child was aged 3 years and to participate in this follow-up study when their child was aged 6 years. Study assessments were done at the paediatric lung function laboratory of the University Medical Center Utrecht or at the child's home by the same research team and equipment, if preferred by parents. The study team was re-masked after the first year of follow-up. Thus, study assessments were conducted by researchers who were unaware of the child's assigned treatment group. The randomisation code was kept by an independent physician until 6-year follow-up was completed. Parents who had been unmasked in 2011 were instructed not to reveal treatment allocation to the researchers at follow-up.

Parents provided separate written informed consent for their child to participate in the follow-up study. The institutional review board at the University Medical Center Utrecht approved the study, which was part of an amended protocol. The study was conducted according

to the principles of the Declaration of Helsinki (2000) and to Good Clinical Practice guidelines, including yearly monitoring.

Procedures

Following a recent recommendation from a US Food and Drug Administration (FDA)–National Institutes of Health (NIH) workshop on RSV vaccine development,¹⁹ we measured patient-reported outcomes with a parent-completed asthma questionnaire and lung function to show effectiveness of RSV prevention in preventing asthma. Using a patient-reported outcome for asthma was also suggested by an academic expert group, concluding that parent-reported questionnaires are commonly used in seminal studies and are feasible for longitudinal studies.²⁰

At age 3 years, a trial-specific questionnaire on respiratory health was completed by parents, including questions about wheeze since the child's first birthday and current use of airway medication (bronchodilators or inhaled corticosteroids). Data collected at age 3 years were analysed together with data collected at age 6 years after the research team had been unmasked.

At age 6 years, the International Study of Asthma and Allergies in Childhood questionnaire²¹ was done, supplemented with trial-specific questionnaires on respiratory health. We contacted general practitioners of trial participants to obtain patient information on medically attended asthma symptoms. From this information, we assessed the presence of current physician-diagnosed asthma. All respiratory function assessments were done according to the American Thoracic Society–European Respiratory Society guidelines²² and spirometry results were converted to percentage predicted values using

Dutch normative values adjusted for sex, age, and height.²³ In addition to spirometry, the fraction of exhaled nitric oxide was measured in exhaled breath and the resistance of the respiratory system was assessed by the interrupter technique (Rint).²² Median resistance of the respiratory system was calculated from at least eight acceptable interruptions (appendix).

Serum total IgE concentration and allergen-specific IgE for house dust mite, birch, mugwort, timothy, *Aspergillus fumigatus*, dog, and cat were measured using ImmunoCAP tests (Thermo Fisher Scientific, Uppsala, Sweden).

Outcomes

The first primary outcome was current asthma, defined as parent-reported wheeze in the past 12 months or use of asthma medication in the past 12 months, or both (appendix). Parent-reported wheeze in the past 12 months was categorised into infrequent (one to three episodes) or frequent (more than three episodes). The second primary outcome was forced expiratory volume in 0.5 s (FEV_{0.5}), assessed by spirometry. FEV_{0.5} was chosen instead of FEV₁ as the primary outcome because of the young age of study participants.²² All outcomes were at age 6 years unless otherwise specified.

Secondary outcomes were FEV₁, forced vital capacity (FVC), forced expiratory flow between 25% and 75% of vital capacity (FEF₂₅₋₇₅), FEV_{0.5}:FVC ratio, FEV₁:FVC ratio, FEV_{0.5} and FEV₁ after administration of a bronchodilator, fraction of exhaled nitric oxide, and resistance of the respiratory system.

Secondary questionnaire-based outcomes were wheeze at ages 1–3 years, use of asthma medication at age 3 years, nocturnal cough in the past 12 months, use of oral corticosteroids for respiratory symptoms ever, medically attended respiratory infection in the past 12 months (otitis, upper respiratory tract infection, pharyngitis, pseudocroup, or lower respiratory tract infection), eczema, allergic rhinitis, and food allergy. Eczema was defined as a positive response to the question “Has your child ever experienced eczema?” Allergic rhinitis was defined as a positive response to the question “Has your child ever experienced hay fever?”

Secondary laboratory-based outcomes were total IgE and allergic sensitisation defined as an allergen-specific IgE concentration of at least 0.35 kU per L for at least one of the tested allergens.

Current physician-diagnosed asthma was a post-hoc endpoint, defined as physician-diagnosed asthma or bronchial hyper-reactivity in the past 12 months. We used this composite endpoint because it is common clinical practice in the Netherlands to postpone asthma diagnosis until age 7 years or older.

Statistical analysis

All analyses were done on an intention-to-treat basis. The primary and secondary outcomes were prespecified, and a detailed description of the analyses is in the appendix.

Current physician-diagnosed asthma was defined post-hoc. Post-hoc subgroup analyses were done to assess the influence of atopic status, intertester variability, differences over study duration (2014–16), and study site (home visit or research centre). Study groups were compared by calculating absolute risk reductions (ARR), relative risk reductions, or mean differences with 95% CI. If applicable, between-group differences were assessed using the χ^2 test, Fisher's exact, *t* test, or Mann-Whitney U test. MAKI was powered to establish a clinically relevant difference in current asthma of 9% or more and a clinically relevant difference in FEV_{0.5} percentage predicted of 7% or more. Complete case analysis was done if less than 10% of data were missing. Otherwise, we did multiple imputation and compared results of complete case analysis with results from the multiple imputation. Approximately 100 baseline characteristics and relevant outcome variables were used for imputation. Statistical analyses were done with SPSS statistical software, version 22.0, except for multiple imputation, which was done with R, version 3.1.1 using the mice package (appendix).

See Online for appendix

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. NMS and LJB had full access to all data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

429 infants were recruited to the original study between April and December of each year between 2008 and 2010, and assigned to receive either palivizumab (*n*=214) or placebo (*n*=215). Baseline characteristics at randomisation have been published previously and were well balanced between study groups.¹⁶ 199 participants in the palivizumab group and 196 participants in the placebo group were included in the follow-up at age 6 years (figure 1). 342 (87%) of these 395 children successfully completed spirometry. 103 (26%) of 395 participants had their study measurements taken at home. Mean age at 6 years follow-up was similar between the groups (5.8 years [SD 0.3] vs 5.9 years [0.3]; appendix).

The proportion of children with current parent-reported asthma was lower in the RSV prevention group (28 [14.1%] of 199) than in the placebo group (47 [24.0%] of 196 participants; ARR 9.9% [95% CI 2.2 to 17.6]; table 1). Current asthma was a composite outcome of wheeze and use of asthma medication in the past 12 months. Fewer children reported wheeze in the RSV prevention group (23 [11.6%] of 199) than in the placebo group (39 [19.9%] of 196; ARR 8.3% [95% CI 1.2 to 15.5]), while similar proportions of participants used asthma medication (18 [9.0%] of 199 in the RSV prevention group vs 25 [12.8%] of 195 in the placebo

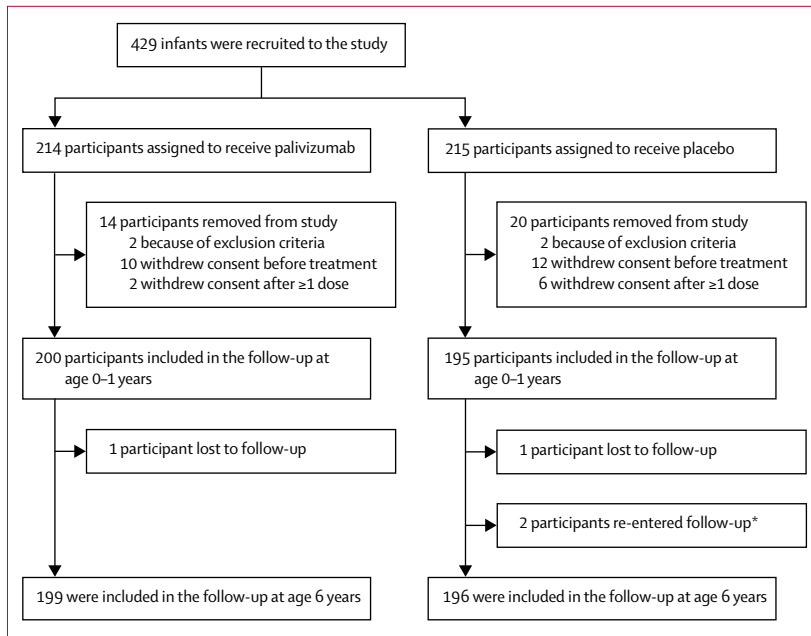


Figure 1: Study population flow chart

*Both children who re-entered the study had received placebo and their parents withdrew consent after one and three injections respectively, but gave consent for all other study assessments.

	RSV prevention (n=199)	Placebo (n=196)	Absolute risk reduction (95% CI)	Relative risk reduction (95% CI)	Mean difference (95% CI)
Current asthma	28 (14.1%)	47 (24.0%)	9.9 (2.2 to 17.6)	41.3 (10.3 to 61.6)	..
FEV _{0.5} percentage predicted*	89.1 (10.6)	90.1 (11.1)	..	..	1.0 (-1.3 to 3.3)

Data are n (%) or mean (SD). Absolute and relative risk reduction given in percentage points. RSV=respiratory syncytial virus. FEV_{0.5}=forced expiratory volume in 0.5 s. *Data available for 342 children.

Table 1: Current asthma and FEV_{0.5} at age 6 years according to treatment group

group; ARR 3.8% [95% CI -2.4 to 9.9]; table 2). Of the participants who reported wheeze in the past 12 months, 12 (52.2%) of the 23 participants in the RSV prevention group and 26 (70.3%) of 37 participants in the placebo group reported that the wheeze was infrequent (one to three reported episodes in the past year). FEV_{0.5} percentage predicted values were similar between the RSV prevention group (89.1 [SD 10.6%]) and placebo group (90.1 [11.1%]), although less than 100% of predicted (table 1, figure 2). When multiple imputation was used to address incomplete data, primary outcome results were similar to those without imputation (appendix).

At follow-up at age 3 years, 36 (19.7%) of 183 children in the RSV prevention group had had wheeze since their first birthday, compared with 54 (28.9%) of 187 children in the placebo group (ARR 9.2% [95% CI 0.5-17.9]; table 2). The proportion of children who developed wheeze after the first year of life was low and similar between children receiving RSV prevention (12 [6.0%] of 199) and placebo (13 [6.6%] of 196; data

not shown). Data from physicians showed a similar frequency of physician-diagnosed asthma in the past 12 months between the groups (19 [10.3%] of 185 in the RSV prevention group vs 18 [9.9%] of 182 in the placebo group). No difference was found between the proportions of children with eczema, allergic rhinitis, or food allergy in the RSV prevention and placebo group (table 2). Children in the RSV prevention group had lower median total IgE values (45.0 kU per litre [IQR 18.0-136.0]) than children in the placebo group (68.0 kU per litre [28.5-182.5]; $p=0.04$), but the proportions of children with allergic sensitisation to the specific aeroallergens were all similar between the two groups (appendix).

Lung function results were similar between the RSV prevention and placebo groups. As expected in this population of preterm infants, FEV₁, FEV₂₅₋₇₅, FEV_{0.5}:FVC ratio, and FEV₁:FVC ratio were less than 100% of predicted, but similar between the RSV prevention and placebo groups (table 3). Reversibility expressed as change in percentage predicted FEV_{0.5} or FEV₁, fraction of exhaled nitric oxide, and resistance of the respiratory system were similar between the RSV prevention and placebo groups. FEV_{0.5} and other lung function results were also similar after administration of a bronchodilator (FEV_{0.5} percentage predicted 97.2% and 97.6% in the RSV prevention and placebo group respectively).

In the post-hoc subgroup analysis of children with and without atopy, the prevalence of parent-reported current asthma at age 6 years was higher in the placebo group than the RSV prevention group regardless of atopic status, although this difference was not significant for all statuses (appendix). Stratification by follow-up study year (2014-16) or location of study measurements (research centre vs home visit) did not change primary outcome results (data not shown). None of the post-hoc analyses revealed subgroup-specific lung function differences between children in the RSV prevention and placebo group. Analysis of lung function showed that mean FEV_{0.5} percentage predicted was lower in the 65 children with parent-reported current asthma (86.1% [SD 12.1]) than in the 277 children without current asthma (90.4% [10.4]; mean difference 4.2 [95% CI 1.3 to 7.2]); appendix). Similarly, FEV_{0.5} percentage predicted was lower in the 32 children with current physician-diagnosed asthma (85.1% [SD 15.0]) than in the 288 without (90.0% [10.4]; mean difference 4.9 [95% CI -0.6 to 10.4]). Current asthma at age 6 years was slightly more prevalent in children with RSV-related hospital admission during the first year of life (five [45.5%] of 11 children) than in children who were not admitted to hospital (70 [18.2%] of 384; ARR 27.2% [95% CI -2.5 to 56.9%]); whereas FEV_{0.5} percentage predicted at age 6 years was slightly lower in patients who had been admitted to hospital (n=10; 85.5% [SD 15.4]) than in those who had not (n=332; 89.7% [10.7]; mean difference 4.2% [95% CI -6.8 to 15.2]; data not shown).

	RSV prevention	Placebo	Absolute risk reduction (95% CI)	Relative risk reduction (95% CI)
Follow-up at age 3 years				
Wheeze at ages 1–3 years	36 (19.7%) of 183	54 (28.9%) of 187	9.2 (0.5 to 17.9)	31.9 (1.5 to 52.9)
Current use of asthma medication	14 (7.6%) of 184	23 (12.2%) of 188	4.6 (–1.4 to 10.7)	37.8 (–17.1 to 67.0)
Follow-up at age 6 years				
Wheeze in the past 12 months*	23 (11.6%) of 199	39 (19.9%) of 196	8.3 (1.2 to 15.5)	41.9 (6.5 to 63.9)
Infrequent wheeze (1–3 episodes)	12 (6.0%) of 199	26 (13.4%) of 194	7.4 (1.5 to 13.2)	55.0 (13.4 to 76.6)
Frequent wheeze (>3 episodes)	11 (5.5%) of 199	11 (5.7%) of 194	0.1 (–4.4 to 4.7)	2.5 (–119.6 to 56.7)
Use of asthma medication in the past 12 months*	18 (9.0%) of 199	25 (12.8%) of 195	3.8 (–2.4 to 9.9)	29.5 (–25.1 to 60.2)
Nocturnal cough in the past 12 months	53 (26.6%) of 199	57 (29.2%) of 195	2.6 (–6.3 to 11.5)	8.9 (–25.2 to 33.7)
Use of oral corticosteroids for respiratory symptoms ever	4 (2.0%) of 199	8 (4.1%) of 195	2.1 (–1.3 to 5.5)	51.0 (–60.1 to 85.0)
Medically attended respiratory infection in the past 12 months	87 (43.7%) of 199	83 (42.6%) of 195	–1.2 (–10.9 to 8.6)	–2.7 (–28.9 to 18.1)
Eczema	68 (34.2%) of 199	66 (33.8%) of 195	–0.3 (–9.7 to 9.0)	–1.0 (–32.9 to 23.3)
Allergic rhinitis	22 (11.1%) of 199	17 (8.7%) of 195	–2.3 (–8.2 to 3.5)	–26.8 (–131.4 to 30.5)
Food allergy	20 (10.1%) of 199	14 (7.2%) of 195	–2.9 (–8.4 to 2.7)	–40.0 (–169.2 to 27.2)
Physician-diagnosed asthma in the past 12 months	19 (10.3%) of 185	18 (9.9%) of 182	–0.4 (–6.5 to 5.8)	–3.8 (–91.4 to 43.7)
Total IgE, kU per L†	45.0 (18.0–136.0)	68.0 (28.5–182.5)‡	..	..
Specific IgE ≥0.35 kU per L against any aeroallergen	38 (27.3%) of 139	27 (25.7%) of 105	–1.6 (–12.8 to 9.5)	–6.3 (–62.3 to 30.4)

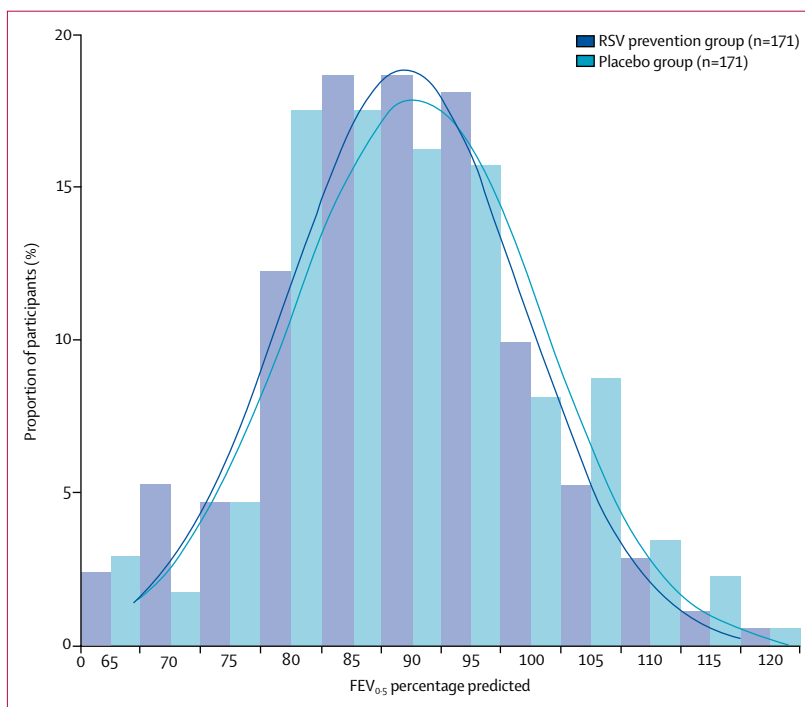
Data are n (%) of N or median (IQR). Absolute and relative risk reduction given in percentage points. RSV=respiratory syncytial virus. *Used for primary outcome. †Data available for 240 participants. ‡Between-group difference tested with Mann-Whitney U test; p=0.04.

Table 2: Secondary outcome results

Discussion

In this RSV prevention trial assessing the causal link between RSV infection and asthma, we found that RSV prevention in otherwise healthy preterm infants reduced the risk of parent-reported asthma at age 6 years, which was mostly explained by differences in infrequent wheeze. Furthermore, at age 6 years, no difference was noted in physician-diagnosed asthma in the past year or in lung function.

Only a few asthma prevention trials have been able to follow children up to an age at which pulmonary function testing is possible.^{24–27} Most studies investigated inhaled or systemic glucocorticosteroids or mast cell stabilisers in high-risk populations. MAKI is the first randomised RSV prevention trial with pulmonary function testing in participants of any age. We showed that RSV prevention was associated with a decrease in parent-reported wheeze at 6 years of age. Similar results have been reported by others,²⁸ including a case-control study from Japan showing that palivizumab prophylaxis during infancy was associated with a reduction of parent-reported recurrent wheeze up to age 6 years.⁷ However, our study showed no effect of RSV prevention on current physician-diagnosed asthma at age 6 years. A randomised controlled trial in term native American infants using motavizumab for RSV prophylaxis also showed no effect of RSV prevention on medically attended wheeze up to age 3 years.^{15,29,30} Two possible explanations exist for the

Figure 2: FEV_{0.5} percentage predicted at age 6 years

FEV_{0.5}=forced expiratory volume in 0.5 seconds. RSV=respiratory syncytial virus.

	Number of patients with available data	RSV prevention group	Placebo group	Mean difference (95% CI)
FEV ₁ percentage predicted	342	91.5 (9.3)	92.3 (9.8)	0.8 (-1.2 to 2.9)
FVC percentage predicted	342	97.9 (10.9)	98.2 (10.1)	0.4 (-1.9 to 2.6)
FEF ₂₅₋₇₅ percentage predicted	342	96.3 (22.7)	98.0 (22.9)	1.7 (-3.2 to 6.5)
FEV _{0.5} :FVC ratio percentage predicted	342	91.4 (10.3)	91.7 (9.3)	0.2 (-1.9 to 2.3)
FEV ₁ :FVC ratio percentage predicted	342	93.2 (7.2)	93.3 (6.4)	0.1 (-1.3 to 1.6)
FEV _{0.5} percentage change after bronchodilator	290	8.1 (5.8)	7.6 (5.7)	-0.5 (-1.8 to 0.8)
FEV ₁ percentage change after bronchodilator	290	4.8 (5.0)	4.3 (4.9)	-0.5 (-1.6 to 0.7)
Fraction of exhaled nitric oxide, ppb	306	8.0 (6.0–12.0)	7.0 (6.0–10.0)*	..
Resistance of the respiratory system, kPa L ⁻¹ sec	313	0.84 (0.74–0.97)	0.82 (0.70–0.95)†	..

Data are mean (SD) or median (IQR). RSV=respiratory syncytial virus. FVC=forced vital capacity. FEF₂₅₋₇₅=forced expiratory flow between 25% and 75% of vital capacity. FEV_{0.5}=forced expiratory volume in 0.5 s. *Between-group difference tested with Mann-Whitney U test; p=0.13. †Between-group difference tested with Mann-Whitney U test; p=0.33.

Table 3: Secondary outcome lung function results at age 6 years

differences we observed between parent-reported and physician-diagnosed asthma. First, information bias (reporter) might have occurred because parents were informed of treatment allocation, and because the occurrence of asthma symptoms earlier in life might have influenced recognition and reporting of asthma at age 6 years. Second, asthma symptoms might have not been severe enough to warrant a doctor's visit. Altogether, this has led us to conclude that RSV prevention does not reduce clinically relevant asthma symptoms at age 6 years.

Overall spirometry results showed decreased lung function compared with reference values, which is in line with previous studies showing that childhood lung function is reduced in preterm children, even those who are only mildly preterm and otherwise healthy.^{28,31,32} Although the correlation between asthma and lung function is generally poor,³³ other studies have shown reduced lung function values in children with asthma,^{34–36} which is in line with the lower FEV_{0.5} values seen in children with current asthma in our trial regardless of treatment group.

Our study has some strengths and limitations. The major strengths of our study are the randomised design, which precludes bias from selection or confounding, the proportion of trial participants who responded, and the lung function testing. Some potential limitations should also be discussed. First, follow-up of study participants occurred single-blind after the first year of life and might have resulted in reporting bias by parents. Second, we used a patient-reported outcome as recommended for RSV prevention trials during a recent FDA–NIH workshop, which might have been sensitive to reporting bias by parents as well.¹⁹ For example, the presence or absence of asthma symptoms during infancy might have influenced recognition and the threshold of labelling respiratory symptoms as wheeze or asthma in later childhood. Together, this might have led to an

overestimation or underestimation of asthma prevalence. We aimed to minimise inconsistent reporting by having the same team of researchers who were unaware of treatment allocation taking the questionnaire and by studying objective outcomes such as lung function. Third, this trial was conducted in healthy preterm infants in a high-income setting and our results cannot be generalised to term infants or to lower-income regions. Fourth, our study has not been powered to detect smaller, but clinically relevant effects of RSV prevention on different asthma phenotypes. Fifth, our study might be hampered by missing lung function data, which might have resulted in reduced power to detect differences in lung function, especially for subgroup analyses. However, the proportion of successful lung function data (87%) in our study was similar to what was observed in other trials (83–84%).^{37,38} Sixth, lung function was assessed only when children were free of respiratory symptoms and during spring or summer, which might have resulted in an underestimation of lung function deficits. The use of a bronchial challenge test might have increased sensitivity to detect airway reversibility, but was considered infeasible in our cohort of young children. Seventh, the prevalence of current physician-diagnosed asthma in this study might be underestimated; physician-attended asthma symptoms in children who attended another physician or hospital than mentioned by parents could have been missed. However, information about these medical events is usually reported to the patient's general practitioner in the Netherlands. Eighth, RSV prevention by other immunisation strategies than palivizumab immunoprophylaxis, such as maternal vaccination or active immunisation by a child vaccine, might have different effects on subsequent wheeze and asthma development. Results of this study therefore cannot be extrapolated to the general population. Ninth, our study has not been designed to measure cost-effectiveness of RSV prevention and results are therefore

not directly applicable to cost-effectiveness analyses of future RSV preventive strategies. Finally, we did not account for multiple testing with regard to the current asthma and lung function outcomes. Bonferroni correction would not have changed our results.

Reflection on lessons learnt from this asthma prevention trial shows the essential value of objective outcome measures. We would therefore consider combining subjective outcomes, such as physician-confirmed asthma symptoms and patient-reported outcomes, with objective lung function measurements, which can only be measured reliably in children aged at least 6 years.

In conclusion, our study was designed to establish the causal relationship between RSV infection during infancy and asthma up to the age of 6 years in otherwise healthy preterm infants. RSV prevention did not have a major effect on current asthma or lung function at age 6 years. RSV prevention only reduced the risk of parent-reported infrequent wheeze at age 6 years, while the risk of physician-diagnosed asthma did not decrease. Future RSV vaccine studies will inform on whether RSV prevention is related to the risk of asthma at school age in the general population.

Contributors

NMS, MOB, MMR, and LJB designed the study. NMS, EEN, JP, and NIM collected data. NMS, MMR, CAN, CKvDE, and LJB analysed and interpreted data. All authors contributed to the writing of the manuscript.

Declaration of interests

MOB reports consulting fees from AbbVie paid to his institution, and a personal grant from the Netherlands organisation for Health Research and Development (NWO AGIKO 920-035-89) paid to his institution. CKvDE reports grants from Gilead, Galapagos, and Vertex Pharmaceuticals, and advisory board fees paid to his institution from ProQR and Teva. LJB reports grants from AbbVie during the conduct of the study and grants from MedImmune, Janssen, MeMed, and the Bill & Melinda Gates Foundation. All other authors declare no competing interests.

Acknowledgments

We thank the children and families of the MAKI trial for their commitment and participation. We thank all members of the MAKI research team for their efforts, including the staff of the paediatric lung function laboratory of the University Medical Center Utrecht. We thank Dr Bert Arets for his role as an independent physician.

References

- Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med* 2009; **360**: 588–98.
- Shi T, McAllister DA, O'Brien KL, 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**: 946–58.
- 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**: 541–45.
- 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**: 1045–52.
- Henderson J, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, 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**: 386–92.
- Bacharier LB, Cohen R, Schweiger T, et al. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. *J Allergy Clin Immunol* 2012; **130**: 91–100.e3.
- Mochizuki H, Kusuda S, Okada K, Yoshihara S, Furuya H, Simões EAF. Palivizumab prophylaxis in preterm infants and subsequent recurrent wheezing: 6-year follow-up study. *Am J Respir Crit Care Med* 2017; **196**: 29–38.
- Carbonell-Estrany X, Pérez-Yarza EG, García LS, Cabañas JMG, Bòria EV, Atienza BB. Long-term burden and respiratory effects of respiratory syncytial virus hospitalization in preterm infants—The SPRING study. *PLoS One* 2015; **10**: 1–16.
- Rubner FJ, Jackson DJ, Evans MD, et al. Early life rhinovirus wheezing, allergic sensitization, and asthma risk at adolescence. *J Allergy Clin Immunol* 2017; **139**: 501–07.
- Zomer-Kooijker K, Van Der Ent CK, Ermers MJJ, Uiterwaal CSPM, Rovers MM, Bont LJ. Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection. *PLoS One* 2014; **9**: e87162.
- Vos T, Allen C, Arora M, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**: 1545–602.
- 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**: 131–37.
- Carroll KN, Gebretsadik T, Escobar GJ, et al. Respiratory syncytial virus immunoprophylaxis in high-risk infants and development of childhood asthma. *J Allergy Clin Immunol* 2017; **139**: 66–71.e3.
- Korppi M, Piippo-Savolainen E, Korhonen K, Remes S. Respiratory morbidity 20 years after RSV infection in infancy. *Pediatr Pulmonol* 2004; **38**: 155–60.
- O'Brien KL, Chandran A, Weatherholtz R, et al. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. *Lancet Infect Dis* 2015; **15**: 1398–408.
- Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med* 2013; **368**: 1791–99.
- WHO. WHO preferred product characteristics for respiratory syncytial virus (RSV) vaccines. World Health Organization: Geneva, 2017. <http://apps.who.int/iris/bitstream/10665/258705/1/WHO-IVB-17-11-eng.pdf?ua=1>.
- WHO. Weekly epidemiological record. *Wkly Epidemiol Rec* 2016; **21**: 265–84.
- Roberts JN, Graham BS, Karron RA, et al. Challenges and opportunities in RSV vaccine development: meeting report from FDA/NIH workshop. *Vaccine* 2016; **34**: 4843–49.
- Simões EAF, Carbonell-Estrany X, Guilbert T, et al. Clinical endpoints for respiratory syncytial virus prophylaxis trials in infants and children in high-income and middle-income countries. *Pediatr Infect Dis J* 2015; **34**: 1086–92.
- Asher MI, Keil U, Anderson HR, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; **8**: 483–91.
- Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med* 2007; **175**: 1304–45.
- Koopman M, Zanen P, Kruitwagen CL, van der Ent CK, Arets HG. Reference values for paediatric pulmonary function testing: the Utrecht dataset. *Respir Med* 2011; **105**: 15–23.
- Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; **354**: 1985–97.
- Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006; **354**: 1998–2005.
- Kotaniemi-Syrjänen A, Reijonen TM, Korhonen K, Korppi M. Sodium cromoglycate therapy in wheezing infants: preliminary evidence of beneficial outcome at early school age. *Pediatr Int* 2005; **47**: 627–34.

- 27 Lukkariinen M, Lukkariinen H, Lehtinen P, Vuorinen T, Ruuskanen O, Jartti T. Prednisolone reduces recurrent wheezing after first rhinovirus wheeze: a 7-year follow-up. *Pediatr Allergy Immunol* 2013; **24**: 237–43.
- 28 Prais D, Kaplan E, Klinger G, et al. Short-and long-term pulmonary outcome of palivizumab in children born extremely prematurely. *Chest* 2016; **149**: 801–08.
- 29 Simões EAF. Motavizumab, RSV, and subsequent wheezing. *Lancet Infect Dis* 2016; **16**: 639–40.
- 30 O'Brien KL, Driscoll AJ, Santosham M, Hammitt LL, Karron RA. Motavizumab, RSV, and subsequent wheezing – authors' reply. *Lancet Infect Dis* 2016; **16**: 1329–30.
- 31 Edwards MO, Kotecha SJ, Lowe J, Watkins WJ, Henderson AJ, Kotecha S. Effect of preterm birth on exercise capacity: a systematic review and meta-analysis. *Pediatr Pulmonol* 2015; **50**: 293–301.
- 32 den Dekker HT, Sonnenschein-van der Voort AMM, De Jongste JC, et al. Early growth characteristics and the risk of reduced lung function and asthma: a meta-analysis of 25,000 children. *J Allergy Clin Immunol* 2016; **137**: 1026–35.
- 33 Fleming L, Murray C, Bansal AT, et al. The burden of severe asthma in childhood and adolescence: Results from the paediatric U-BIOPRED cohorts. *Eur Respir J* 2015; **46**: 1322–33.
- 34 Bisgaard H, Jensen SM, Bønnelykke K. Interaction between asthma and lung function growth in early life. *Am J Respir Crit Care Med* 2012; **185**: 1183–89.
- 35 Busi LE, Restuccia S, Tourres R, Sly PD. Assessing bronchodilator response in preschool children using spirometry. *Thorax* 2017; **72**: 367–72.
- 36 Guilbert TW, Singh AM, Danov Z, et al. Decreased lung function after preschool wheezing rhinovirus illnesses in children at risk to develop asthma. *J Allergy Clin Immunol* 2011; **128**: 510–32.
- 37 Bisgaard H, Stokholm J, Chawes BL, et al. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med* 2016; **375**: 2530–39.
- 38 Doyle LW, Carse E, Adams A-M, Ranganathan S, Opie G, Cheong JLY. Ventilation in extremely preterm infants and respiratory function at 8 years. *N Engl J Med* 2017; **377**: 329–37.