**REspiratory Syncytial virus Consortium in EUrope (RESCEU) Birth Cohort Study: Defining the burden of infant Respiratory Syncytial Virus disease in Europe.**

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**Abstract**

***Introduction***

Respiratory syncytial virus (RSV) causes significant morbidity and mortality in infants worldwide. Although prematurity and cardiopulmonary disease are risk factors for severe disease, the majority of infants hospitalized with RSV are previously healthy. Various vaccines and therapeutics are under development and expected to be available in the near future. To inform the use of these new vaccines and therapeutics, it is necessary to determine the burden of RSV disease in Europe to gain better insight into the full spectrum of disease severity in young children and the associated societal and healthcare costs, including primary care costs. We will prospectively follow-up a birth cohort to obtain incidence data on RSV acute respiratory tract infection (ARTI), medically attended (MA) RSV ARTI and RSV associated hospitalization.

***Methods***

Multicenter prospective, observational study of a birth cohort consisting of 10,000 healthy infants, recruited from the general population during 3 consecutive years and followed up for at least 1 year. RSV associated hospitalization will be determined by questionnaires and hospital chart reviews. A nested cohort of 1000 infants will be actively followed up during the RSV season(s) in their first year of life with weekly contact to elicit any respiratory symptoms. In case of ARTI, a respiratory sample will be collected for RSV molecular diagnosis. Additional samples will be taken at birth and in a subgroup who develop RSV ARTI.

***Results***

The primary outcome is the incidence rate of RSV-associated hospitalization in the first year of life. In the active cohort the primary outcome is RSV associated ARTI and MA-ARTI.

***Conclusion***

With this study we aim to provide key information to fill the gaps in knowledge about the burden of RSV disease in healthy infants to inform regulators, governments and other stakeholders responsible for policy decisions should a vaccine or treatment against RSV become available.

ClinicalTrials.gov registration number: NCT03627572

Key words: respiratory syncytial virus, infant, birth cohort, disease severity, hospitalization, Europe.

**Introduction**

Human respiratory syncytial virus (RSV) causes severe disease in individuals at the extremes of the age spectrum and in high risk groups. It was estimated that in 2015 RSV was associated with 33.1 million acute lower respiratory tract infections, 3.2 million RSV-related hospital admissions, and an overall mortality of 118.200 in children under the age of five years worldwide [1]. These estimates were based on few data and there is a substantial gap in knowledge on morbidity and associated healthcare and societal costs in Europe. Although prematurity and cardiorespiratory comorbidity are well-known risk factors for severe disease in young children, the majority of children admitted to pediatric intensive care units because of severe RSV acute respiratory tract infections (ARTIs) are previously healthy infants [2-4]. Data about RSV incidence and burden of disease in healthy children are scarce, since most studies are performed only in high risk groups. Moreover, RSV infection in childhood is associated with subsequent wheezing and asthma [5-7], and these long‐term sequelae pose a substantial additional burden on the healthcare system.

Treatment and prophylaxis options are limited. Ribavirin has been used as treatment but is not routinely recommended in light of limited evidence of benefit [8], hence only supportive care is available for infants with severe RSV infection. Passive prophylaxis with RSV specific antibodies (palivizumab) is only available for high risk groups (prematurely born infants and infants with significant cardiac and/or respiratory comorbidity).

Various new RSV vaccines and therapeutics are expected to be available in the near future [9]. To properly evaluate the implementation of these new vaccines and therapeutics, it is necessary to determine the burden of RSV disease in Europe to gain better insight into disease severity in young children and the associated societal and healthcare costs. There is a parallel need to assemble clinical resources to identify the correlates of severe RSV disease for clinical management, classification of disease severity in clinical trials and identification of biomarkers for severe disease, which are currently lacking [10].

For this purpose, the RESCEU (Respiratory Syncytial virus Consortium in Europe) consortium has been established. RESCEU will perform the largest prospective multi‐center study in healthy children to provide accurate data on RSV disease incidence and sequelae (long‐term airway morbidity, including asthma) and economic consequences of RSV infection. We will prospectively follow-up a birth cohort of 10,000 healthy children during at least one year to obtain incidence data on RSV ARTI, medically attended (MA) RSV ARTI and hospitalization due to RSV.

**Methods**

***Objectives***

The primary objective of the RESCEU birth cohort study is to determine the incidence of RSV infection-associated ARTI, RSV associated MA ARTI and RSV-related hospitalization during the first year of life (figure 1).

Figure 1. Visual representation of study cohorts and endpoints.



Abbreviations: N, number of participants; ; RSV, respiratory syncytial virus; ARTI, acute respiratory tract infection; MA-ARTI: Medically Attended ARTI.

In addition the following secondary objectives will be assessed:

1. To estimate how RSV infection of different severity relates to wheeze up to 3 years of age.
2. To determine the rate of all-cause medically attended (inpatient or outpatient) ARTI.
3. To determine mortality (RSV associated and all-cause) through all RSV seasons of follow up.
4. To determine health care costs, health care resource use, interruption of normal activities, and Health Related Quality of Life (HRQoL) in RSV-associated and all-cause medically attended (inpatient or outpatient) ARTI patients and their families.
5. To determine the incidence of RSV-related secondary bacterial respiratory tract infections, defined as doctor’s diagnosis of a bacterial respiratory tract infection, within 21 days after onset of RSV infection and their association with antibiotic use in hospitalized RSV ARTI patients and non-hospitalized RSV ARTI patients.
6. To collect clinical samples for biomarker analysis from a subset of infants in the active cohort.
7. To determine the incidence rate of other respiratory pathogens associated with all medically attended (inpatient or outpatient) ARTI.
8. To determine the proportion of viral ARTI attributable to RSV.
9. To determine important risk factors for RSV infection (by severity and healthcare utilization).

***Study design***

A multi-country, multicenter, prospective, observational cohort study.

***Study period***

Continuous recruitment will take place between July 2017 and December 2019 (active cohort) or April 2020 (all) in order to create a cohort with evenly distributed dates of birth over the year and to include several RSV seasons. All participants will at least be followed up to the age of one year. Participants of the active cohort will be actively followed up during the 2017-2018, 2018-2019 and 2019-2020 RSV seasons.

***Study population***

Birth cohort consisting of 10,000 healthy infants, recruited from the general population. Infants are recruited from maternity wards during the first days after birth in the following five participating centers: Spaarne Gasthuis, Haarlem, the Netherlands; Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain; participating hospitals in the Thames Valley and South Midlands Clinical Research Network (Oxford) United Kingdom; Royal Hospital for Sick Children, Edinburgh, United Kingdom; and Turku University Hospital, Turku, Finland.

*Inclusion criteria*

Healthy children with a gestational age of at least 37+0 weeks, born in the catchment area of participating centers. Children with perinatal problems, including mild to moderate asphyxia, respiratory distress or suspected early onset neonatal infection will be included and are distinguished and analyzed separately at end of study. Parents or legal guardians will be able to communicate in the local language.

*Exclusion criteria*

Children with a clinically significant medical illness including cardiovascular, respiratory, renal, gastrointestinal, haematologic, neurological, endocrine, immunological, musculoskeletal, oncological or congenital disorders will be excluded from study participation. Any acute severe medical condition present at the time of sampling in the first week of life (e.g. sepsis, severe asphyxia, for which the child is admitted to the hospital) is defined as an exclusion criterium for participation in the active birth cohort. Other exclusion criteria are receipt of maternal RSV vaccine during pregnancy and being in social care.

***Recruitment and informed consent procedure***

Recruitment will take place during the peri-natal period by distribution of information letters and direct contact by study investigators. The investigator will explain the nature of the study and will inform the parents/legal guardian(s) of the infant that participation is voluntary and that they can withdraw from the study at any time. Written informed consent will be obtained from parent(s)/legal guardian(s) of each subject prior to any study procedure.

***Study procedures***

*All participants*

Parents of all infants who provide consent to participate in the study will be asked to fill out a questionnaire at inclusion and at the age of 1 year. The information collected at baseline will contain details about pregnancy, perinatal course and potential risk factors for RSV hospitalization and long-term wheeze and asthma. In the first year questionnaire parents will be asked amongst others if their child was hospitalized because of an ARTI, in which case the study team will review the hospitalization chart for admission details and the results of RSV testing. All participating centers perform RSV testing as standard of care in infants hospitalized with ARTI or will monitor admissions for ARTIs to test children from the RESCEU cohort for RSV.

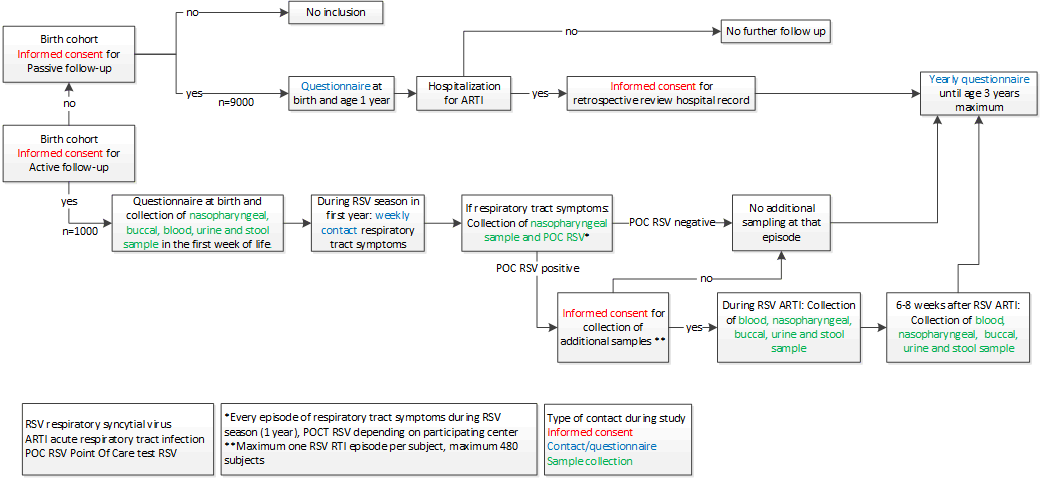
*Active cohort*

Within the birth cohort a nested cohort of 1,000 infants will be actively followed up during the first year of life (active cohort). In addition to the baseline and 1 year questionnaire, samples will be collected in the first week of life (figure 2, suppl table 1). These infants will be actively followed up during RSV season(s) in their first year of life (1 October to 1 May, or longer if RSV is still circulating) by weekly contact enquiring about respiratory symptoms. An ARTI is defined as the presence of any of the following symptoms for at least one day; runny or blocked nose, coughing, wheezing or dyspnea. In case of ARTI, a member of the study team will visit the infant within 72 hours after notification of the study team and take a nasal swab for RSV PCR. If the infant develops an ARTI parents will also be asked to fill out a diary for 14 days about severity of symptoms, quality of life, health care usage and parental absenteeism from work. The adapted parental version of the ReSVinet scale will be used to determine symptom severity [11].

*Biomarker sub-study*

Three of the five centers (Spaarne Gasthuis Haarlem/Hoofddorp, Hospital Clínico Universitario de Santiago and participating hospitals in the Thames Valley (Oxford region)) are also participating in the biomarker sub-study. The aim of the biomarker sub-study is to find markers for disease severity of RSV infection. In these centers an RSV point of care test (POCT) will be performed directly on the collected nasal swab from infants in the active cohort at the moment of an ARTI. If the RSV POCT is positive, additional samples will be collected at the moment of infection and 6-8 weeks later (figure 2, suppl table 1).

Figure 2. Overview of study design and main procedures of the birth cohort study.

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*Evaluation of long-term sequelae*

To evaluate long-term sequelae, parents of all infants participating in the active cohort and of all infants hospitalized because of an ARTI will receive a questionnaire at the age of 2 and 3 years about long-term sequelae and quality of life.

***RSV testing***

*Sample collection ARTI (active cohort)*

All ARTI samples will be collected by a trained member of the study team by taking a nasal flocked swab (FLOQSwab™, Copan diagnostics), which will be directly stored in viral transport medium (MicroTest™ M4RT® (Remel, 3 ml)). Collected samples will be tested for RSV by POCT directly and/or stored in aliquots at −80 °C.

*RSV POCT*

RSV POCT will be done at Spaarne Gasthuis Haarlem, Hospital Clínico Universitario de Santiago and participating hospitals in the Thames Valley (Oxford region). The Alere™ i RSV assay (Alere Inc., Waltham, MA, USA)[17] will be used as the RSV POCT. Staff will get hands-on-training on participant sampling and how to perform the Alere™ i RSV POCT according to the manufacturer’s instruction. In short, 200 μl of the viral transport medium mixed with the swab will be aspirated with the included transfer pipette and added to the sample receiver liquid (elution buffer) and mixed for 10 seconds. After initiating the test, results will be displayed within 15 minutes as either RSV positive or negative. The remaining sample will be stored in aliquots at −80 °C.

*RSV PCR*

After active surveillance has finished, RSV quantitative reverse transcription polymerase chain reaction (RT-qPCR) will be performed on all ARTI samples collected during the study.

***Outcomes***

The primary outcome is the incidence rate of RSV-associated ARTI leading to hospitalization in the first year of life. In the active cohort the primary outcome is RSV associated ARTI and MA RSV infection defined as any medical care for RSV infection.

*Secondary endpoints*

1. Parent reported wheeze and doctor’s diagnosis of wheeze by routine care.
2. Incidence of all-cause medically attended (inpatient or outpatient) ARTI.
3. Mortality through all RSV seasons of follow up including RSV-associated deaths and all cause deaths.
4. Health care utilization for RSV-associated and all-cause medically attended (inpatient or outpatient) ARTI or respiratory events.
5. Incidence of RSV-associated secondary bacterial pneumonia and associated antibiotic consumption events within 21 days after onset of RSV-related symptoms.
6. Biomarkers of risk, severity of disease and long-term outcome of RSV infection.
7. Incidence of other respiratory pathogens associated with all medically attended (inpatient or outpatient) ARTI.
8. Proportion of viral infections attributable to RSV.
9. Risk factors for RSV.

***Ethical considerations***

The study will be conducted according to the principles of the Declaration of Helsinki (www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other relevant guidelines, regulations and Acts. The study was approved by the Institutional Review Board (IRB) of the University Medical Center Utrecht, NHS National Research Ethics Service Oxfordshire Committee A (ref. 17/SC/0335) and South East Scotland Research Ethics Committee (Ref 17/SS/0086), the Ethics Committee of the Hospital District of Southwest Finland, and Hospital Clínico Universitario de Santiago de Compostela. The protocol and patient information have also been reviewed by a member of the RESCEU Patient Advisory Board (PAB).

***Statistical methods***

## *Sample size calculation*

For the primary analysis the ratio between cases of RSV-related hospitalizations in the first year of life and total number of children in the study will be calculated (full birth cohort). In addition, the ratio between the cases of MA RSV ARTI and the number of children undergoing active surveillance will be calculated (active cohort).

For sample size calculation a yearly incidence of hospitalization of 0,7% was assumed based on previous literature [4, 12]. A sample size of 8700 will produce a two-sided 95% confidence interval with a half width of 0.002 (Confidence interval formula: Exact, Clopper-Pearson). Accounting for a 10% loss to follow up, 10,000 children will be included in the full birth cohort (Table 1).

Table 1. Expected incidence of RSV-hospitalization and MA-RSV.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Sites | Outcome | Infants | RSV seasons | Expected  Incidence (%)/year | CI Half-Width (%) |
| Healthy baby, GA at least 37+0 (full cohort) | NL, UK, SP, FI | RSV-hospitalization | 10,0  00 | 1 | 0,7 (4, 12) | 0,5-1,3 |
| Healthy baby, GA at least 37+0  (active cohort) | NL, UK, SP, FI | MA RSV | 1,000 | 1 | 10 (4, 12, 13) | 8,0-12,0 |

Abbreviations: CI, Confidence Interval; GA, Gestational Age; NL, Netherlands; UK, United Kingdom; SP, Spain; FI, Finland; MA RSV, Medically Attended RSV.

*Statistical analysis*

Descriptive statistics will be used to describe the incidence rate of RSV associated hospitalization, MA RSV ARTI and non-MA RSV ARTI in the birth cohort. Baseline characteristics of the passive and active cohort will be compared. Demographic parameters, clinical parameters and outcome and laboratory test results will be displayed as categorical data with percentages or as continuous variables with mean (+/-SD) and/or median (interquartile range). Comparisons between groups will be performed using chi-square for categorical variables, Student-t-test for normally distributed continuous variables or Mann-Whitney U test for not normally distributed continuous variables. Multivariate regression analysis will be performed to analyse multiple risk factors for RSV disease. Statistical analyses will be performed using SPSS version 20 or a more recent version or with R statistical software version 3.5.1 or higher.

***Dissemination and publication***

Results of this study will be disclosed unreservedly.

**Discussion**

Various studies have evaluated the burden of RSV disease in infants. The study by Hall *et al.* showed that RSV causes substantial morbidity in children under the age of five years in the United States. Disease burden was highest in infants under the age of 6 months with an annual hospitalization rate of 1.7%. Most children admitted with RSV were previously healthy [4]. In a recent systematic review, Shi *et al.* collected data from all published and unpublished population based studies about RSV infection in infants under five years of age of the last 20 years to estimate the total RSV associated disease burden world-wide. They estimated that worldwide 1.4 million RSV related hospitalizations and 27.300 in hospital deaths occurred in infants under the age of 6 months, accounting for 45% of the total number of hospitalizations and deaths in children under the age of 5 years [1]. Although they were able to collect substantially more data compared to their previous systematic review [13], the uncertainty range of their estimations remained substantial, leading to the conclusion that more detailed data about RSV disease burden are needed. This is especially important for future introduction of RSV vaccines, because policymakers will need this information to decide whether to introduce these vaccines and to evaluate the effect on morbidity and mortality after introduction. One way to obtain more detailed data about burden of RSV disease and associated socioeconomic impact is by means of a prospective birth cohort study. Only a few prospective birth cohort studies were performed to evaluate the burden of RSV infection in healthy infants [12, 14-16]. These studies were all relatively small single center studies. In addition, in part of the studies home swabbing by the parents was used. With the current cohort study we aim to provide accurate data about RSV related hospitalization as well as the burden of RSV disease in Europe.

The development of an RSV vaccine has been identified as a priority by the World Health Organization [17]. To date, more than forty vaccines against RSV are in development, varying from pre-clinical to phase 3 [18]. Since the main population at risk for severe disease are infants in the first months of life, who are too young to be protected by active immunization, other strategies have been developed [19]. One strategy is maternal vaccination, which aims to protect infants from birth through the first 3-6 months of life by transfer of protective maternal antibodies during the second half of pregnancy. Maternal vaccination against pertussis has already proven that this strategy is very effective in preventing disease in young infants [20]. Results of a recent phase 3 trial of maternal vaccination with a RSV F-protein nanoparticle vaccine (PREPARE trial) showed protection against severe RSV in infants younger than 90 days, but the study did not reach its primary endpoint [21].

Another strategy is to administer monoclonal antibodies against RSV to young infants during the RSV season. To date, palivizumab is the only market approved monoclonal antibody, but is registered for high-risk infants. Due to the high costs, palivizumab is only affordable for high risk infants in developed countries. In addition, monthly intramuscular injections are necessary. A promising candidate is Medi8897, an extended half-life monoclonal antibody against RSV F. In a recent phase 2b trial in preterm infants of a gestational age of 29-35 weeks a 78% reduction in the incidence of RSV related hospitalization and a 70% reduction in the incidence of medically attended RSV was seen [22]. Since the development of an RSV vaccine has been prioritized not only by the WHO, but also by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), promising candidates in later stages of development could expect support and accelerated evaluation from these organizations in order to obtain faster market approval.

With this in mind, expectations are that within 5 years an approved product for prevention of RSV for all infants will be on the market. Subsequently governments will have to decide whether this new vaccine would be eligible to be implemented into their national immunization schedule. Information about RSV incidence and associated burden on health care use as well as economic and societal impact and long-term sequelae in the population is imperative to evaluate the possible benefit of introducing a new vaccine into a national immunization programme. With this study we aim to provide this key information to fill the gaps in knowledge about the burden of RSV disease in healthy infants and help regulators, governments and other stakeholders with decision making.

## Study group members

The RESCEU investigators are as follows: Joanne Wildenbeest; Roy Zuurbier; Koos Korsten; Marlies van Houten; Marie Billard; Nicole Derksen-Lazet; Louis Bont (University Medical Center Utrecht); Simon Drysdale; Matthew Snape; Hannah Robinson; Andrew Pollard (University of Oxford); Federico Martinón-Torres; Carmen Rodríguez-Tenreiro Sánchez; Alberto Gómez-Carballa; (Servicio Galego de Saude); Terho Heikkinen (University of Turku and Turku University Hospital); Steve Cunningham, Harish Nair, Harry Campbell, (University of Edinburgh); Amanda Leach (GlaxoSmithKline); Peter Openshaw (Imperial College London); Philippe Beutels (Universiteit Antwerpen); Eva Molero (Synapse); Adam Meijer, Elisabeth Sanders (National Institute for Public Health and the Environment); Thea Kølsen Fischer (Statens Serum Institut); Maarten van den Berge (Academisch Ziekenhuis Groningen); Carlo Giaquinto (PENTA Foundation); Mark Esser (AstraZeneca); Charles Knirsch (Pfizer); Scott Gallichan, (Sanofi Pasteur); Jeroen Aerssens (Janssen); and Brian Rosen (Novavax).

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We thank all the participating infants and their families, and all the members of the research teams.

## NOTES

## Conflict of interests

LJB has regular interaction with pharmaceutical and other industrial partners. He has not received personal fees or other personal benefits. UMCU has received major funding (>€100,000 per industrial partner) for investigator initiated studies from AbbVie, MedImmune, Janssen, the Bill and Melinda Gates Foundation, Nutricia (Danone) and MeMed Diagnostics. UMCU has received major cash or in kind funding as part of the public private partnership IMI-funded RESCEU project from GSK, Novavax, Janssen, AstraZeneca, Pfizer and Sanofi. UMCU has received major funding by Julius Clinical for participating in the INFORM study sponsored by MedImmune. UMCU has received minor funding for participation in trials by Regeneron and Janssen from 2015-2017 (total annual estimate less than €20,000). UMCU received minor funding for consultation and invited lectures by AbbVie, MedImmune, Ablynx, Bavaria Nordic, MabXience, Novavax, Pfizer, Janssen (total annual estimate less than €20,000). Dr. Bont is the founding chairman of the ReSViNET Foundation.

F. M-T. has received honoraria from GSK, Pfizer, Sanofi Pasteur, Merck Sharp & Dohme, Seqirus, and Janssen for taking part in advisory boards and expert meetings, and for acting as speaker in congresses outside the scope of the submitted work. F. M-T. has also acted as principal investigator in RCTs of the above-mentioned companies as well as Ablynx, Regeneron, Roche, Abbot, Novavax, and Medimmune, with honoraria paid to his institution. F.M-T. research activities received support from the Instituto de Salud Carlos III (Proyecto de Investigación en Salud, Acción Estratégica en Salud): project ReSVinext ISCIII/PI16/01569/Cofinanciado FEDER; Consellería de Sanidade, Xunta de Galicia (RHI07/2-intensificación actividad investigadora, PS09749 and 10PXIB918184PR), Instituto de Salud Carlos III (Intensificación de la actividad investigadora 2007–2012, PI16/01569), Fondo de Investigación Sanitaria (FIS; PI070069/PI1000540) del plan nacional de I+D+I and ‘fondos FEDER’, and 2016-PG071 Consolidación e Estructuración REDES 2016GI-1344 G3VIP (Grupo Gallego de Genética Vacunas Infecciones y Pediatría, ED341D R2016/021.

MDS acts on behalf of the University of Oxford as an Investigator on studies sponsored and/or funded by vaccine manufacturers including Novavax, Glaxosmithkline, Janssen, Medimmune, MCM and Pfizer. He receives no personal financial benefit for this work.

AJP is Chair of UK Dept. Health and Social Care’s (DHSC) Joint Committee on Vaccination & Immunisation (JCVI) & the European Medicines Agency (EMA) scientific advisory group, on vaccines and is a member of the WHO’s SAGE. AJP is an NIHR Senior Investigator. The views expressed in this article do not necessarily represent the views of DHSC, JCVI, NIHR or WHO..

SC provides consultancy with fees paid to the University of Edinburgh for Ablynx (Sanofi), Janssen, Pulmocide, ReViral. In addition, SC is a PI for studies relating to RSV therapeutics for MedImmune.

SBD acts on behalf of St George’s, University of London as an Investigator on studies sponsored and/or funded by vaccine manufacturers including Janssen and Medimmune. He receives no personal financial benefit for this work.

TH has received honoraria from Janssen and Sanofi Pasteur for participation in ad hoc advisory board meetings and independent data monitoring committees. Turku University Hospital (a secondary employer of TH) has received a grant from Janssen for RSV epidemiologic studies unrelated to this protocol.

Amanda Leach is an employee of GlaxoSmithKline and holds shares in the company.

All remaining authors declare no competing interests.

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Supplementary table 1. Sample collection in the active cohort and biomarker sub-study.

|  |  |  |  |
| --- | --- | --- | --- |
| Moment of sampling | Sample | Volume | Analysis |
| In the first week after birth (day 5 +/- 2) | Serum (capillary/venous) | Max 1.8 ml | RSV serology  Proteome\* |
|  | Paxgene (capillary/venous) | 0.2- 0.5 ml | Transcriptome\* |
|  | Whole blood (only if venous) | Max 1 ml | Cellular immunology\* |
|  | Nasopharyngeal swab | n/a | Airway microbiome  Airway transcriptome |
|  | Buccal swab | n/a | DNA/GWAS |
|  | Stool | 5-10 ml (min 2 ml) | Microbiome |
|  | Urine | 3 ml | Metabolomics |
| ARTI | Nasal swab | n/a | RSV POCT (qualitative)  RSV RT-PCR# (quantitative) |
| Biomarker substudy: RSV ARTI and convalescence (6-8 weeks later) | Serum (venous) | 1-2 ml | RSV serology  Proteome\* |
|  | Paxgene (venous) | 0.2-0.5 ml | Transcriptome\* |
|  | Whole blood (venous) | 1-2 ml | Cellular immunology\* |
|  | Stool | 5-10 ml (min 2 ml) | Microbiome |
|  | Nasopharyngeal swab |  | Airway microbiome  Airway transcriptome |
|  | Urine | 3 ml | Metabolomics |
|  | Buccal swab | n/a | DNA/GWAS |

\* and additional RSV-related biomarkers

# and multiplex RT-PCR respiratory viruses in case of RSV ARTI

Abbreviations: RSV, respiratory syncytial virus; n/a, not applicable; DNA, deoxyribonucleic acid; GWAS, genome-wide association study; ARTI, acute respiratory tract infection; POCT, Point of care test; RT-PCR, reverse transcription polymerase chain reaction