REspiratory Syncytial virus Consortium in EUrope (RESCEU) study: Defining the burden of disease of Respiratory Syncytial Virus in Europe.

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To determine the burden of disease due to RSV in young term born infants.The active cohort study is expanded to other family members during the COVID-19 pandemic to gain insight in COVID-19 related burden to families. In addition we would like to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Viral infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON52977

Source
ToetsingOnline

Brief title
Burden of disease of RSV

Condition

- Viral infectious disorders
- Respiratory tract infections

Synonym
COVID-19, RSV-bronchiolitis, RSV-infection, SARS-CoV-2

Research involving
Human

Sponsors and support

Primary sponsor: University Medical Center Utrecht
Source(s) of monetary or material Support: Inovative Medicine Initiative (IMI) gefinancieerd door het H2020 framework van de Europese Unie. COVID-19 gerelateerd gedeelte: ZonMW

Intervention

Keyword: Burden of disease, Infant, Respiratory Syncytial Virus, Respiratory Tract Symptoms

Outcome measures

Primary outcome

- The primary outcome is to determine the incidence of RSV infection-associated ARTI, RSV associated medically attended ARTI (MA-ARTI) (active cohort) and RSV-related hospitalization (all) during the first year of life.

Secondary outcome

Secundary outcome measures are:

- To estimate how RSV infection of different severity relates to wheeze up to age 3 years. The incidence and severity of wheeze will be determined by annual questionnaires at age 1 year, 2 years and 3 years (active cohort and all children hospitalized for RSV ARTI)

- To determine the rate of all-cause medically attended (inpatient or outpatient) ARTI.

- To determine mortality (RSV associated and all-cause) through all RSV seasons of follow up

- 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.

- To determine the incidence of RSV-related secondary bacterial respiratory tract infections within 21 days after onset of RSV infection and their association with antibiotic use in hospitalized RSV ARTI patients (all children) and non-hospitalized RSV ARTI patients (active cohort).
- To collect clinical samples for biomarker analysis from a subset of infants in the active cohort.
- To determine the incidence rate of other respiratory pathogens (influenza, rhinovirus, etc.) associated with all medically attended (inpatient or outpatient) ARTI.
- To determine the proportion of viral ARTI attributable to RSV.
- To determine important risk factors for RSV infection (by severity and healthcare utilization)

COVID-19 related part:

- The incidence of overall, asymptomatic, mild and medically attended SARS-CoV-2 infection in children and their parents.
- Transmission patterns of SARS-CoV-2 within households with young children
- Risk of transmission of asymptomatic SARS-CoV-2 infection to members of the same Household.
- Description of symptom severity of SARS-CoV-2 in children.
- Detection rate of SARS-CoV-2 in feces and saliva.

CoKids Follow-up Study:

- The incidence of different SARS-CoV-2 variants in children and their family members with a symptomatic infection.
- Transmission patterns of the various SARS-CoV-2 strains within households with young children.
- Difference in symptom severity between the various SARS-CoV-2 strains.
- Description of the occurrence of re-infection(s) with the new variants of SARS-CoV-2.
- Long term effects associated with an infection by the different SARS-CoV-2 strains

Related to the protective behaviours substudy:

- The use of protective behaviours in RESCEU birth cohort study participants.
- The influence of parents perceived risk for their children on their use of protective behaviours against respiratory infections.
- Differences in parents perceived risk for their children to get RSV, COVID-19, Influenza virus and common cold.

Extension to six years of age part:

- To compare the incidence of asthma after RSV hospitalization with the incidence of asthma after milder RSV infection.
- To compare the incidence of asthma after RSV hospitalization with the incidence of asthma after hospitalization due to other viral infections.
- Determine the risk factors for persistent wheezing at the age of 3 and 6

years.

Study description

Background summary

The REspiratory Syncitial virus Consortium in EUrope (RESCEU) is an Innovative Medicine Initiative (IMI) effort funded by the EU under the H2020 framework to define and understand the burden of disease caused by human respiratory syncytial virus (RSV) infection. RSV causes severe disease in young infants. It was estimated that RSV was associated with 34 million cases of acute respiratory tract infection (ARTI), 3.4 million ARTI hospitalizations and 55,000 to 199,000 deaths in children <5 years in 2005 worldwide. These estimates were based on limited data and there is a substantial gap in knowledge on morbidity and associated healthcare and social costs in Europe. New vaccines and therapeutics against RSV are in development and will soon be available on the European market. RESCEU will deliver knowledge of the incidence and burden of disease RSV in young children and older adults in Europe, which is essential for stakeholders (governments, etc) to take decisions about prophylaxis and treatment.

Since January 2020 the novel coronavirus SARS-CoV-2 has spread through the world with an unprecedented morbidity and mortality especially in older adults. Children seems less affected by this virus. Data about burden of disease and the role of children in transmission of the virus are currently lacking. This information is important for decisionmakers regarding measures to control the spread of SARS-CoV-2, e.g. is it necessary to close schools and daycare centers or can they open again.

In addition various new variants of SARS-CoV-2 have emerged. It is not yet clear what the role of these new variants is in transmission and disease burden within families.
There is more and more evidence that SARS-CoV-2 causes long-term symptoms but the incidence and severity of symptoms is not yet clear, especially in children.

As part of the efforts to control the spread of SARS-CoV-2, governments have recommended a number of protective behaviours to prevent the spread of SARS-CoV-2. This has also led to changes in epidemiology of other viruses like RSV, with an absent winter peak last winter. The question is what the role is of protective behaviour and how much it is influenced by perceived risks.

RSV infection is known to be associated with recurrent wheezing in the first year of life. It is still unclear whether RSV infection at a young age is associated with the development of asthma at school age and the mechanisms of

this possible association.

Study objective

To determine the burden of disease due to RSV in young term born infants.

The active cohort study is expanded to other family members during the COVID-19 pandemic to gain insight in COVID-19 related burden to families. In addition we would like to evaluate the role of new SARS-CoV-2 strains in spreading and burden within families with young children.

By extending follow-up to school age (6 years), we expect to gain important information on the association between RSV infection in the first year of life and the subsequent development of asthma.

Study design

Prospective epidemiological, observational, multi-country, multicenter, cohort study.

Study burden and risks

Because the total study population is split in two seperate birth cohorts with specific study procedures, they are explained separate below:

Passive birth cohort (N=9000)
Parents will be asked to fill out a questionnaire at inclusion and at age one year. In case of a hospitalization for respiratory infection within the first year, data of this specific hospital admission will be collected retrospectively after consent. If no hospitalization occurs within the first year, follow-up ends at one year.
Only children who were admitted to the hospital for ARTI during the first year of life will be followed up to the age of maximum 3 years by yearly questionnaires.These questionnaires focus on long-term respiratory symptoms following a RSV associated hospitalization.

During 2021 participants will be invited online to participate to the protective behaviours sub-study. Parents who agree to participate will be asked to complete two times the same online questionnaire 3-4 months apart. The questionnaires seek information on parents perceived risk of COVID-19, RSV infections, influenza infections and common cold for their child enrolled in the RESCEU birth cohort study, as well as perceived efficacy and past and current use of protective behaviours against respiratory infections.

Active birth cohort (N=1000)
Parents are asked to fill in a baseline questionnaire at inclusion and yearly

questionnaires until the age of 3 years. In addition, a blood sample, a nasopharyngeal swab, nasal mucosal lining fluid , a buccal swab, and stool and urine samples will be collected in the first week after birth. Taking a nasopharyngeal swab, nasal mucosal lining fluid and a buccal swab can give a brief moment of discomfort at the moment of sampling.
During the RSV season (October - May) within the first year of life parents will be contacted weekly (by telephone or email and/or by (daily) telephone app) to monitor respiratory symptoms of their child. Parents are asked to contact the study team if the infant experiences an ARTI. The study team will visit the infant within 72 hours at home and take 1 nasopharyngeal swab to perform a point of care (POC) test for RSV and RT-PCR (and additional analyses if RSV is positive). If RSV is positive, informed consent will be asked for participation in the biomarker sub-study (n=480, maximum). If included in the biomarker sub-study, the following additional sampling procedures will be performed by the study team at the moment of infection and 6-8 weeks after infection: A venous puncture (max 4 ml blood), stool and urine samples, a buccal swab, a nasopharyngeal swab and nasal mucosal lining fluid will be collected.

During the acute respiratory tract infection, parents are asked to complete a daily diary on respiratory symptoms and quality of life (parental and their child) for as long as the respiratory episode is present. After a respiratory episode, parents are asked to complete a more extensive questionnaire on respiratory symptoms, health care use and quality of life.

Possible benefit:
There is no clear direct clinical benefit for the subjects participating in this proposed study. However, the results of this study aim to support the understanding of the burden of RSV disease which is important for the implication of future preventive and therapeutic interventions. None of the study procedures is associated with any risk for serious complications. If possible, sample collection will be performed in addition to standard care (e.g. in case of hospitalization with planned blood draws) to prevent an extra moment of discomfort.
There is a risk of minor complications due to study procedures such as a nose bleed after a nose swab or bruise after a blood draw. These complications are generally infrequent and of minor severity.

COVID-19 related part
Information regarding the burden of disease of SARS-CoV-2 and the role of children in transmission is currently lacking. Given the extent and severity of the current pandemic, the burden and risks of participating outweights the knowledge this research could add.

Families who participate in the active birth cohort who gave consent to be informed about new studies will be invited to participate.

The COVID-19 related part consists of 2 parts:
1. Standard household follow-up
Parents are instructed to take a combined oro-and nasopharyngeal swab (viral detection) and a saliva sample (antibodies) every 4-6 weeks from each member of the household during 23 weeks (in total 4 times) and to fill out a short questionnaire. This sample will be tested for SARS-CoV-2 within 72 hours. Taking a combined oro-and nasopharyngeal swab can give a brief moment of discomfort at the moment of sampling. In addition parents are contacted weekly by means of a study app and will be instructed to contact the study team if any member of the household developed respiratory symptoms (cough, sore throat, runny or congested nose, dyspnea) and/or fever and/or loss of taste and smell.

2. Household outbreak study
When any member of the household has symptoms or a household member has a positive SARS-CoV-2 test with the 4-6 weekly screening, all members will take a combined oro-and nasopharyngeal swab, a saliva sample and a blood sample by means of a finger prick. A finger prick can give a brief moment of discomfort at the moment of sampling. Parents will get precise instructions how to do this by themselves and their children. If parents/caretakers are reluctant to take blood samples from a child, a study or home visit will be planned for this procedure. Parents are asked to fill out a short diary (app) about symptom severity for all family members during 21 days. If any other member of the household will develop symptoms, another combined oro-and nasopharyngeal swab and saliva sample will be taken from that household member and the symptom diary will be prolonged for all household members until 21 days after the last member started to develop symptoms. If any of the household members has a positive SARS-CoV-2 test, all household members are asked to collect a stool (SARS-CoV-2 PCR) and saliva sample (SARS-CoV-2 PCR and antibodies) weekly during the period they fill out the diary. The finger prick will be repeated 10 days after the diaries have been finished.
Household members will participate maximum 2 times in the outbreak study.

There is no clear clinical benefit for the subjects participating in the COVID-related part of the study. However, with the results of this study we aim to obtain more information about the burden of SARS-CoV-19 infection in children and their role in transmission which is important for the implication of future preventive interventions (e.g. school closure).

3. CoKids Follow-up Study:
During the extended period from end of the original CoKids study up to the 1st of July 2021, when a household member with ARI symptoms is identified (an index case), the whole household will undergo testing through a combined oro- and nasopharyngeal swab and oral sponges. Only the oro- and nasopharyngeal swab of the index case will be tested initially. When a SARS-CoV-2 infection is established, the rest of the household oro- and nasopharyngeal swabs will be tested for SARS-CoV-2 as well. In addition, the type of SARS-CoV-2 strain will be analyzed for all positive swabs. Serological testing using a finger prick

will only be done in case a SARS-CoV-2 infection of the index case is established. All other routine procedures in the case of a SARS-CoV-2 infection will remain the same as mentioned above in the household outbreak study. When no SARS-CoV-2 infection is detected, no further PCR testing of other household oro- and nasopharyngeal swabs will take place and the Corona outbreak study will not be started.
In the event of new ARI complaints (suspected case) in another household member, the whole household will be asked to collect an oro- and nasopharyngeal swab and salivary sponges. Again only the oro- and nasopharyngeal of the household member with new ARI complaints will be tested for SARS-CoV-2 in the first instance, and when a SARS-CoV-2 infection is established, additional testing of the remaining household swabs will be performed. A household will be tested a maximum of two times during one episode, which is defined as: the onset of complaints within another household member within 5 days after the initial index case.

Additionally, a household that tested positive for SARS-CoV-2 will be matched with a corresponding household who participated in the household outbreak study. These households will be asked to fill out questionnaires to study long-term sequelae of a SARS-CoV-2 infection, such as effects on general well-being/functioning, cognition, fatigue, anxiety & depression and long term symptoms (to study the possible presence of the so called *long-COVID* syndrome). Matching a SARS-CoV-2 positive household with a household from the outbreak study (SARS-CoV-2 negative) gives us the opportunity to evaluate the different clinical symptoms and get a better understanding of the core symptoms of a SARS-CoV-2 infection. These questionnaires will be asked to all family members to fill out 6 and 12 months after infection.
Children aged 0-18 years will receive an additional questionnaire 4 weeks and 12 weeks after their SARS-CoV-2 test.

4. Extension until 6 year of age
Parent of participating children will complete a questionnaire after 4, 5 and 6 years. If there has been a hospital admission due to respiratory complaints in the last year, data from this specific admission will be collected after permission from the parents. There are no direct benefits to participating. The results of the study may contribute to better knowledge about the disease burden of RSV, which is important for future treatment or implementation of prevention strategies.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

- Healthy children, gestation age at least 37+0, born at participating centers.
- Written informed consent obtained from parents.
- Parents ability and willingness to adhere to protocol-specified procedures (active cohort).

Inclusion criteria for COVID-19 related part
- Household member of participating children in the active birth cohort study (including participating children themselves)
- Written informed consent obtained from parents.
- Parents ability and willingness to adhere to protocol-specified procedures

Inclusion criteria for the extension until 6 years of age
- Participated in the RESCEU birth cohort study in the active cohort or, participated in the RESCEU birth cohort study in the passive cohort and were hospitalized because of an ARTI.

- Informed consent obtained from parents.

Exclusion criteria

- History of clinically significant medical illness including but not limited to, cardiovascular, respiratory, renal, gastrointestinal, haematologic, neurological, endocrine, immunological, musculoskeletal, oncological or congenital disorders, as judged by the investigator. Specifically excluded examples include, but are not limited to:
o Immunosuppressed states
o Bronchopulmonary dysplasia/chronic lung disease of infancy
o (Clinically significant) Congenital heart disease
o Down*s syndrome
- Gestational age of less than 37+0 weeks.
- Acute severe medical condition at moment of heel prick (e.g. sepsis, severe asphyxia, for which the child is admitted to the hospital). (Exclusioncriterium only applicable in the active cohort)
- Child in care (with foster parents or at home under supervision of social services).
- Parents not able to understand and communicate in the local language.
- Living outside catchment area of study sites.
- Mother vaccinated against RSV during pregnancy

For the COVID-19 related part:
- None

For the extension until 6 years of age:
- None

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-07-2017
Enrollment:	2500
Type:	Actual

Ethics review

Approved WMO Date:	26-07-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL60218.041.17