STUDY PROTOCOL

RSV ComNet II

Disease burden of RSV in young children in primary care: Italy, United Kingdom and the Netherlands, winter of 2020/21

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NIVEL
Research for better care

Bambino Gesù
OSPEDALE PEDIATRICO

Contents

Prepared by:

The Netherlands
Jojanneke van Summeren, MSc, Nivel, Utrecht, the Netherlands
John Paget, PhD, Nivel, Utrecht, the Netherlands
Saverio Caini, PhD, Nivel, Utrecht, the Netherlands
Michel Dückers, PhD, Nivel, Utrecht, the Netherlands
Mariëtte Hooiveld, PhD, Nivel, Utrecht, the Netherlands
Joke Korevaar, PhD, Nivel, Utrecht, the Netherlands
Janneke Hendriksen, MD, PhD, Nivel, Utrecht, the Netherlands
Adam Meijer, PhD, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands

Italy
Caterina Rizzo, MD, PhD, Bambino Gesù Children's Hospital, Rome, Italy
Elisabetta Pandolfi, MD, Bambino Gesù Children's Hospital, Rome, Italy

Sanofi Pasteur:
Clarisse Demont, PhD, Global Vaccine Epidemiology and Modeling Department, Sanofi Pasteur, Lyon, France
Mathieu Bangert, MD, PhD, Global Vaccine Epidemiology and Modeling Department, Sanofi Pasteur, Lyon, France

1 Aim and motives

ComNet I

In the ComNet I study we developed and evaluated the feasibility of a study protocol to measure the clinical and socio-economic disease burden of laboratory-confirmed RSV infections in young children (<5 years) in primary care.[1] The study protocol was evaluated in the winter of 2019/20 in Italy and the Netherlands and a study report has been prepared.[2] The study report has provided recommendations to finalize the disease burden study protocol to be used in the RSV ComNet II study during the winter of 2020/21.

ComNet II

In the ComNet II study we will use the final study protocol to measure the burden of RSV infections in young children (<5 years) in primary care in three European countries, namely Italy, the United Kingdom (England), and the Netherlands. The finalized disease burden study protocol is based on the experiences of the ComNet I study and described in detail from page 5 onwards.

Research questions

1) What is the clinical burden of RSV infections in children less than 5 years old in primary care in three European countries and what are predictors for high disease burden?
2) What is the socio-economic burden of RSV infections in children less than 5 years old in primary care in three European countries?
3) What is the population-based burden of RSV infections in young children (<5 years) in primary care?

2 RSV ComNet II disease burden study protocol

Study design

The design of the study is a multi-country and multi-centre prospective cohort study in primary care. Countries involved in ComNet II are Italy which has a paediatrician-led primary care system and the United Kingdom (UK) and the Netherlands which have a general practitioner (GP)-led system.[3] In the following text we will use the term primary care physician (PCP) when we refer to a primary care paediatrician or GP.

Infrastructure for data collection

In the ComNet I study we tested two different "data infrastructure systems" to implement the disease burden protocol:

(1) Via a brand new network of PCPs created for the study (in Italy)
(2) Using routine primary care influenza surveillance system (in the Netherlands)

Data collection (including the "system") needs to be adapted to the logistical condition feasible in each country. In Figure 1 an example of the patient selection and recruitment of the Italian and Dutch model are shown.

Italy and the Netherlands will use the same data collection infrastructure ComNet I. The UK will use a combination of both "systems", patients will be recruited via the routine influenza surveillance system (Dutch system), however, informed consent for RSV ComNet is asked at the same time as sampling of the patient (the same as in the Italian system). In addition, the UK will increase swabbing in the <5 year olds with 400 extra swabs on top of the 100 swabs that were normally collected in a season. More detailed information regarding the patient recruitment and selection per country can be found in Annex 1.

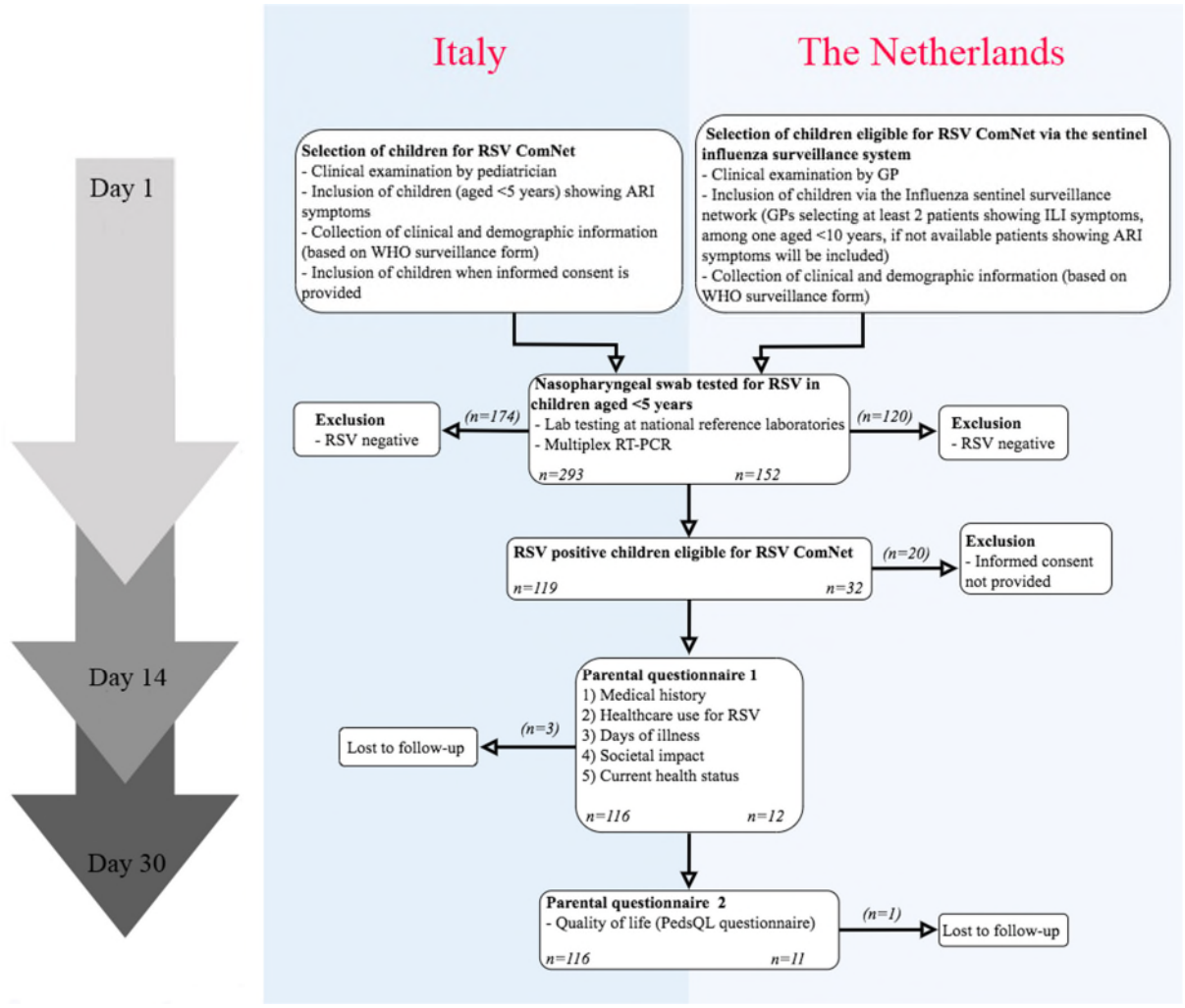

Figure 1. Flowchart of the patient selection & recruitment processes in Italy and the Netherlands in the ComNet 1 study.

Eligibility criteria of participants

Children eligible for sampling (taking a nasopharyngeal swab (note: an oropharyngeal swab is optional)

1) Aged <5 years,
2) Consulting a PCP with symptoms of an acute respiratory infection (ARI)

The ARI case definition is based on the definition published by the World Health Organization (WHO) and include the following criteria: [4,5]

- Acute – defined as a sudden onset of symptoms;
- Respiratory infection – defined as having at least one of the following: shortness of breath, cough, sore throat, coryza;
- Clinician's judgement that the illness is due to an infection*

* This point was added to the definition by the RSV ComNet research team.

In Italy, the ARI case definition will be fully implemented. In the United Kingdom, 400 swabs will be collected using the ARI case definition and 100 will be collected using the the ILI surveillance case definition. In the Netherlands, the study protocol will be implemented in the routine influenza surveillance system and the influenza-like illness (ILI) and ARI case definition will be used.

Eligible for inclusion in RSV ComNet II

1) Sampled children (see criteria above) with a lab-confirmed diagnoses of RSV.

Exclusion criteria

1) Insufficient knowledge about the national language by the parents,
2) Special personal circumstances in the family (based on the judgement of the primary care physician e.g. a recent death in the family)
3) No informed consent

Data collection & measurements

For each child included in the study, data collection will be performed at three time points (Figure 1):

(1) At the day of sampling the patient (swab collection) (Day 1),
(2) Approximately 14 days (preferably 14-18 days) after sampling the patient (Day 14),
(3) Approximately 30 days after sampling the patient (Day 30).

Below is a summary of the topics that will be covered by the three questionnaires. The complete questionnaires are provided from page **9** onwards.

At Day 1, PCPs complete a short questionnaire for each patient. This questionnaire is based on the WHO RSV specimen submission form.[5] In this routine questionnaire, information is collected regarding:

(1) Patient demographics (birth date, gender, and date of swabbing),
(2) Date of onset of clinical symptoms,
(3) Presentation of clinical symptoms,
(4) Medical history of the child (e.g. prematurity, chronic respiratory diseases, other relevant comorbidities, previous RSV infections in the current season, use of Palivizumab).*

At this moment, the PCP should collect a nasopharyngeal swab (possibly also an oropharyngeal swab) and send this to the reference laboratory within 10 days after the swab is collected. **(**See **Day 1 questionnaire, page 9)**

* Note: If the questions regarding the medical history of the child cannot be included in the Day_1 questionnaire due to logistical reasons, they should be included in the Day_14 questionnaire. *This choice is country dependent.*

Virological testing procedures

The nasopharyngeal/oropharyngeal swabs are tested by the reference laboratory using multiplex PCR. In addition, the reference laboratories should gather data regarding the weekly number of swabs analysed, the weekly number of RSV positive cases, and more specific laboratory results for the RSV positive cases e.g. the RSV subtype and co-infections (see **Laboratory information, page 10**).

At Day 14, parents complete the first parental questionnaire, (see **Day 14 questionnaire, page 11**) with questions regarding:

(1) Medical history of the child (e.g. prematurity, chronic respiratory diseases, other relevant comorbidities, previous RSV infections in the current season, use of Palivizumab)*
(2) Health care use of their child since swabbing (number of consultations to PCP, paediatrician, other (paramedical) health care providers, A&E/ Casualty, hospitalizations, ICU admission, duration of hospitalization (days) and/or ICU admission, and medication use)
(3) Number of days of illness
(4) Socio-economic impact on parents or primary caregivers (work absenteeism and productivity losses, absenteeism of school or day care of child)**
(5) Current health status (remaining symptoms and state of recovery, defined as date the child returned to normal activities)
(6) Quality of life (today's health status of the child, measured on a Visual Analogue Scale (VAS))

* Note: Only include questions that are not included in the Day 1 questionnaire *(this choice is country dependent)*
** Note: In a situation where there is only one parent that has the custody over the child, the questions for the second parent should be removed

At Day 30, parents complete the relevant topics of the Day 14 questionnaire* and questions regarding RSV complications (see **Day 30 questionnaire, page 13**):

(1) Health care use of their child since completing Day_14 questionnaire (number of consultations to PCP, paediatrician, other (paramedical) health care providers, A&E/ Casualty, hospitalizations, ICU admission, duration of hospitalization and/or ICU admission, and medication use)
(2) Number of days of illness
(3) Socio-economic impact of both parents or primary caregiver (work absenteeism and productivity losses of parents, absenteeism of school or children day care)**
(4) Current health status (remaining symptoms, and state of recovery, defined as date of returned to normal activities)
(5) Quality of life (Today's health status of the child, measured on a Visual Analogue Scale (VAS) scale)
(6) Complications related to the RSV infection, for example *otitis media* or pneumonia.

* Note: 1 and 3 are introduced with a general question to examine whether the more detailed questions are required.
For example: (1) Has your child used healthcare services related to the RSV disease since completing the Day_14 questionnaire? For example, visits to a GP/paediatrician, A&E/ Casualty, hospital admission or medication use etc.? (yes/no)

3 Questionnaires

Questionnaire at Day_1

Note: This questionnaire is based on the WHO RSV specimen submission form [5]

Pre-filled information
Doctor's Code:
Patient ID code*:
*Note: Patient identification will be country specific and depends on logistics

1) Patient demographics
Date of birth (month and year only):
Gender:
Date of sample collection and completion of form (Day_1):

2) Date of onset of clinical symptoms and 3) presenting clinical symptoms
Sudden onset of symptoms, date:
Shortness of breath: (yes/no)
Wheezing: (yes/no)
Cough with slime: (yes/no)
Cough without slime: (yes/no)
Sore throat: (yes/no)
Coryza: (yes/no)
Illness is due to an infection (clinician's judgement): (yes/no)
Fever ≥ 38 °: (yes/no)
Feeding difficulties: (yes/no)

4) Medical history of the child
Premature birth: (no/yes, number of weeks)
Birth weight, grams:
Chronic respiratory disease: (no/yes, specify)
Malnutrition: (no/yes) – information to be collected from the medical record only
Immuno-comprised: (no/yes)
Other chronic medical condition: (no/yes, specify)
Previous RSV infection this season: (no/yes)
Influenza vaccination this season (no/yes)
Did your child receive preventive medication (Palivizumab [please adapt name according to your country]) this season? (no / yes)

Note: If the questions regarding the medical history of the child cannot be included in the Day_1 questionnaire due to logistical reasons, they should be included in the Day_14 questionnaire. *This choice is country dependent.*

Laboratory information

Specimen details

Type of specimen: (nasal/throat swab / nasopharyngeal aspirate / tracheal aspirate / sputum / BAL)
Date sample received tested:

Results

RSV results: (RSV positive / RSV negative / inadequate sample / sample not tested / sample rejected)
RSV CT value (if RSV positive):
RSV subtype (if known): (RSV A / RSV B)
RNP: (Positive / Negative)
RNP CT value:
Virus co-infections: (yes/no), If yes specify other virus(es):

Questionnaire at Day_14

Pre-filled information

Patient ID code*:
Date of swab / first consultation (Day_1): __/__/____
*Note: Patient identification and date will be country specific and depend on logistics

1) Medical history of the child

Premature birth: (no/yes, number of weeks)
Birth weight, grams:
Chronic respiratory disease: (no/yes, specify)
Malnutrition: (no/yes) - information to be collected from the medical record only
Immuno-comprised: (no/yes)
Other chronic medical condition: (no/yes, specify)
Previous RSV infection this season: (no/yes)
Influenza vaccination this season (no/yes)
Did your child receive preventive medication (Palivizumab [please adapt name according to your country]) this season? (no / yes)

* Note: Only include questions that are not included in the Day 1 questionnaire *(this choice is country dependent)*

2) Health care use related to RSV in the past 14 days

How many contacts did you have with the GP/paediatrician since your child was swabbed?
- Number of phone or e-mail contacts:
- Number of visits to the GP/paediatrician:
- Number of home visits by the GP/paediatrician:

Did your child visit another doctor since he/she was swabbed? (no / yes, specify)
- Type of doctor: (medical specialist / other, specify)
- Number of visits:
- Number of home visits:
- Number of phone or e-mail contacts:

Did your child visit an A&E/ Casualty related to the RSV infection, since he/she was swabbed? (no / yes)
- If yes: How many times did your child visit an A&E/ Casualty?

Was your child hospitalized due to the RSV infection, since he/she was swabbed? (no / yes, specify)
- Hospitalized for how many days? (half a day is possible e.g. 2.5 days)
- Was your child admitted to the intensive care unit (ICU)? (no / yes, number of days)

Did your child require any paramedical help related to the RSV infection, since he/she was swabbed? (no / yes, specify)
- Type of paramedical help: (nurse / nutrition / physiotherapy / other, specify)

Did your child receive any medical treatment related to the RSV infection, since he/she was swabbed? (no/ yes, specify)

Type of medical treatment: (paracetamol / other pain medication / antibiotics / nebulizers / nose spray / cough syrup / other)
Specify: for how many days was the medication used

3) Days of illness

How many days do you consider your child was ill? (half a day is possible e.g. 2.5 days)

4) Socio economic impact

How many days was your child out of day-care or school? (no /not applicable child doesn't go to day-care or school/ yes, __ days) (half a day is possible e.g. 2.5 days)

Which of the following situations fits your situation? If there are multiple situations, please indicate the most common situation.

- I have full-time paid job
- I have part-time paid job, please provide …..%
- I take care of the household and children

Did you need to take sick leave due to your child's illness? (no / yes, __ days) (half a day is possible e.g. 2.5 days)
Were you affected at work due to your child's illness? (no / yes, __ days) (half a day is possible e.g. 2.5 days)

If yes, please estimate the size of the impact during these days?
(Scale 0 to 100, in which 0 = no impact, and 100 = maximum impact)

The following questions are related to your partner or the person who next to you takes on a large part of the child's care.

- *I am the only person that has the custody of my child → Go to topic 5 "current health status"*

Which of the following situations fits your partner's situation (or the person to you takes on a large part of the child's care)? If there are multiple situations, please indicate the most common situation.

- I have full-time paid job
- I have part-time paid job, please provide …..%
- I take care of the household and children

Did this person need to take sick leave due to your child's illness? (no / yes, __ days) (half a day is possible e.g. 2.5 days)
Was this person affected at work due to your child's illness? (no / yes, __ days) (half a day is possible e.g. 2.5 days)

If yes, please estimate the size of the impact during these days?
(Scale 0 to 100, in which 0 = no impact, and 100 = maximum impact)

5) Current health status

Has your child returned to normal activities (e.g. day care, (pre)school). (no / yes, since../../…. (date))
Has your child still got any symptoms related to the RSV infection?

Wheezing or whistling in the chest (yes / no)
Persistent cough with slime (yes / no)
Persistent cough without slime (yes / no)
Nose complaints, e.g. runny nose, stuffy nose (yes / no)
Sore throat: (yes/no)
Shortness of breath: (yes/no)
Fever ≥ 38 °: (yes/no)
Feeding difficulties: (yes/no)

6) Quality of life

We would like to know how good or bad your child's health is TODAY.
The scale is numbered from 0 to 100.

- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.

What is the number that indicates how the health of your child is TODAY?

Questionnaire at Day_30

The following questions are related to the period since completing the previous (Day_14) questionnaire.

[Please make sure that the period we are interested is clear for parents. This is easier in telephone interviews compared to digital questionnaires. When using digital questionnaires it is important to explain in the introduction of the questionnaire what is meant with the 'previous questionnaire'. For example, in the Netherlands we will add a statement that the 'previous questionnaire' was sent to the parents by post, and that parents have used the link in the information letter to complete the questionnaire. If possible, adding the date of completion of the 'previous questionnaire' is recommended.

Pre-filled information

Patient ID code*:
Date of completing the previous (Day_14) questionnaire*: __/__/____
*Note: Patient identification and date will be country specific and depend on logistics

1) Health care use related to RSV

Did your child use health care related to the RSV disease, since completing the previous questionnaire?
For example, visits to a GP/paediatrician, A&E/ Casualty, hospital etc. or medication? (yes/no)
If no → Go to topic 2 "Days of illness"
If yes → continue with the next questions

How many contacts did you have with the GP/paediatrician, since completing the previous questionnaire?

Number of phone or e-mail contacts:
Number of visits to the GP/paediatrician:
Number of home visits by the GP/paediatrician:

Did your child visit another doctor, since completing the previous questionnaire? (no / yes, specify)

Type of doctor: (medical specialist / other, specify)
Number of visits:
Number of home visits:
Number of phone or e-mail contacts:

Did your child visit an A&E/ Casualty related to the RSV infection, since completing the previous questionnaire? (no / yes)

How many times did you and your child visit an A&E/ Casualty?

Was your child been hospitalized related to the RSV infection, since completing the previous questionnaire? (no / yes, specify)

For how many days? (half a day is possible e.g. 2.5 days)
Was your child admitted to the intensive care unit (ICU)? (no / yes, number of days)

Did your child require any paramedical help related to the RSV infection, since completing the previous questionnaire? (no / yes, specify)

Type of paramedical help: (nurse / nutrition / physiotherapy / other, specify)

Did your child receive any medical treatment related to the RSV infection, since completing the previous questionnaire? (no/ yes, specify)

Type of medical treatment: (paracetamol / other pain medication / antibiotics / nebulizers / nose spray / cough syrup / other)

Specify: for how many days was the medication used

2) Days of illness

Do you consider your child was ill since completing the previous questionnaire?

How many days do you consider your child was ill, since completing the previous questionnaire? (half a day is possible e.g. 2.5 days)

3) Socio economic impact

How many days was your child out of day-care or school, since completing the previous questionnaire? (no / not applicable child doesn't go to day-care or school/ yes, __ days) (half a day is possible e.g. 2.5 days)

Did you or your partner need to take sick leave or was your work or your partner's work affected due to your child's illness, since completing the previous questionnaire? (yes/no)

If no → Go to topic 4 "Current health status"

If yes → continue with the next questions

Did you need to take sick leave due to your child's illness? (no / yes, __ days) (half a day is possible e.g. 2.5 days)

Were you affected at work due to your child's illness? (no / yes, __ days) (half a day is possible e.g. 2.5 days)

If yes, please estimate the size of the impact during these days?

(Scale 0 to 100, in which 0 = no impact, and 100 = maximum impact)

The following questions are related to your partner or the person who next to you takes on a large part of the child's care.

- *I am the only person that has the custody of my child*
  → Go to topic 5 "current health status"

Which of the following situations fits your partner's situation (or the person to you takes on a large part of the child's care)? If there are multiple situations, please indicate the most common situation.

- I have full-time paid job
- I have part-time paid job, please provide …..%
- I take care of the household and children

Did this person need to take sick leave due to your child's illness? (no / yes, __ days) (half a day is possible e.g. 2.5 days)

Was this person affected at work due to your child's illness? (no / yes, __ days) (half a day is possible e.g. 2.5 days)

If yes, please estimate the size of the impact during these days?
(Scale 0 to 100, in which 0 = no impact, and 100 = maximum impact)

4) Current health status

Has your child returned to normal activities (e.g. day care, (pre)school). (no / yes, since../../…. (date))
Has your child still got any symptoms related to the RSV infection?

Wheezing or whistling in the chest (yes / no)
Persistent cough with slime (yes / no)
Persistent cough without slime (yes / no)
Nose complaints, e.g. runny nose, stuffy nose (yes / no)
Sore throat: (yes/no)
Shortness of breath: (yes/no)
Fever ≥ 38 °: (yes/no)
Feeding difficulties: (yes/no)

5) Quality of life

We would like to know how good or bad your child's health is TODAY.
The scale is numbered from 0 to 100.

- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.

What is the number that indicates how the health of your child is TODAY?

6) Complications related to the RSV infection

Has a physician diagnosed your child with an *acute otitis media infection* since your child was swabbed? (yes/no)
[Note: it is important to translate *acute otitis media* into the language that is used in daily practice by patients, in Dutch we would say '*middenoorontsteking*' [translation: a middle ear infection]]

Did a physician diagnosed your child with a pneumonia since your child was swabbed? (yes/no)

4 Sample size calculation

- Sampling patients (swabbing):
  In Italy, the UK and the Netherlands we have planned to sample 600, 500 and 200 children that meet the RSV ARI case definition*, respectively.
- RSV positivity rate:
  Based on a RSV positivity rate ranging between 21% (worst case scenario) and 40% (best case scenario)**, we expect between 120-240 (Italy), 105-2000 (UK) and, 40-80 (the Netherlands) RSV positive children.
- Response rate:
  In Italy the response rate in ComNet I was almost 100%, which we expect to be similar for ComNet II. For the Netherlands, we had a response rate of 38%, which we will try to increase in ComNet II to 50%. In the UK we expect a response rate around 75%, this is based on the fact that in the UK questionnaires were collect by telephone interviews similar as in Italy.
- Expected number of ComNet II participants:
  Italy: 120-240 RSV positive children aged <5 years
  UK (England): 79-150 positive children aged <5 years
  Netherlands: 20-40 positive children aged <5 years

* In the Netherlands and the UK sampling takes place based on the ARI case definition and ILI case definition.
** These percentages are based on the ComNet I RSV positivity rates.

In Box 1, we have calculated three scenarios that different sample sizes has on the 95% confidence interval for the primary outcome measure “hospitalization rate”. All scenarios are based on an expected hospitalization rate of 6% found in the ComNet I study. The scenarios are calculated for 100, 150 and 200 positive RSV cases.[6]

Box 1. Influence of different sample sizes on the 95% CI intervals in ComNet II

Outcome measure:
Hospitalization rate: in Italy 6% (7/116)

Assuming 6%, a sample size of 100 RSV positive cases will provide a CI of 1.3%-10.7%
Assuming 6%, a sample size of 150 RSV positive cases will provide a CI of 2.2%-9.8%
Assuming 6%, a sample size of 200 RSV positive cases will provide a CI of 2.7%-9.3%

To investigate predictors for high health care burden and duration of illness, 150 RSV positive cases will not be adequate, however, for these analysis we will use meta-regression analyses by using data from all countries involved in the ComNet study.

5 Data analysis

We are planning the following two papers (for publication in a scientific peer-reviewed journal):

I. Clinical burden of RSV in young children in primary care, including a risk factor analysis for high burden of disease (paper 1)

We will use descriptive statistics to present the demographics of the included population and the clinical burden of children with an RSV infection, i.e. (1) the patient demographics, clinical symptoms and relevant medical history at baseline, (2) the healthcare and medication use over a period of 30 days, and (3) the remaining clinical symptoms and duration of illness at 14 and 30 days after swabbing.

To investigate predictors of high burden of disease we will use two definitions of disease burden:

1) Duration of illness (in days, with the possibility to indicate half a day)
2) Health care usage. Health care usage will be a composed variable including, for example, primary health care consultations, consultations to other medical doctors, hospitalization and consultations to A&E/ Casualty. In ComNet I we defined a high burden as meeting at least one of the following criteria: needed >2 extra consultations to the PCP (additional to the original consultation), one or more consultations to a medical specialist other than the PCP, visit to A&E/ Casualty or hospitalization. However, the definition of high burden will depend on the organization of the health care system in each country, and can therefore be slightly different between countries.

Regression analyses will be used to examine potential risk factors for high burden of RSV infections. Predictors that will be considered for the analysis are based on a literature review, and will include: gender, age, being born in RSV season (for children in the first year of life), prematurity, RSV subtype, and region (based on the ComNet I analysis for Italy which found differences by region). In addition, we will examine if baseline clinical symptoms are predictors for high disease burden.

II. Socio-economic burden of RSV in young children in primary care (paper 2)

The aim of this paper will be to estimate the medical and non-medical costs for young children (<5 years of age) with an RSV infection in primary care. As it is expected that the majority of children will recover within 30 days after disease onset, the time horizon of this study will be 30 days. Medical costs and societal costs (e.g. parents staying at home to care for their children) will be calculated. Costs will be calculated from a societal perspective, indicating that all costs are taken into account regardless of who pays for them. In addition, we will calculate the costs from a health insurance perspective.

Regarding research question 3: estimating the population-based burden of RSV in young children

The primary aim of the RSV ComNet II disease burden protocol is to investigate the clinical and socio-economic burden of RSV on an individual patient level. However, these findings need to be, where possible, translated to RSV burden estimates in small children on a regional and/or country level.

For this analysis we need to calculate RSV incidence rates per country and to calculate the clinical and socio-economic population-based burden on a regional or country level. Therefore, information regarding ARI rates, RSV positivity rates and the catchment area of the PCPs is necessary.

We are currently evaluating methods, including modelling methods, to calculate these RSV incidence rates per country and region (Italy and the Netherlands), and we will report these findings when preparing the RSV ComNet I manuscript.

These same methods will be applied to RSV ComNet II project. Due to a number of methodological issues (e.g. availability of ARI rates), it might not be possible to provide robust estimates for every country or region included in the ComNet II study (see country report RSV ComNet I[2]). Importantly, the results of the population-based estimates will be integrated into the RSV ComNet II papers 1 and 2.

A final statistical analysis plan for both papers will be presented before data-analysis is started. Data will be analysed by country, and when possible, pooled for all three countries.

6 Ethics

Medical Ethical Committee
Each country will apply for medical ethical approval to perform the RSV ComNet II study (if necessary), which is especially important considering the target population is young children aged 0-4 years.

Information for participants and informed consent
The national co-ordination centre in each country is responsible for preparing information for participants (parents or caregivers of children with RSV), and obtaining informed consent forms.

The informed consent form should address issues such as:

- The reasons for collecting the data.
- Which organization(s) will receive the information collected.
- Patients can refuse to participate in the study.
- How long the patient information will be stored.
- How patients can contact the study co-ordinator to correct or delete information collected by the study.

Information for general practitioners and/or paediatricians
The national co-ordination centre in each country is responsible for assessing all local modifications or interferences to the routine influenza surveillance system. Any modifications should be communicated to the participating GPs and/or paediatricians. Topics that should be covered in the information to the GPs and/or paediatricians include:

- General information about the RSV ComNet II study
- General country-specific logistics information
- Inclusion and exclusion criteria
- Instruction to conduct preferably 50% of the swabs in children under 12 months
- Clear and sufficient information for the GPs and/or paediatricians to perform their task, i.e. instructions for swabbing, patient identification, etc.
- The Day_1 questionnaire
- Clear information about the Day_14 and Day_30 questionnaires
- Information regarding the informed consent procedure

7 Project deliverables

Table 1 Products (with expected date of delivery)

Products	Months
1: Medical Ethical Approval in each country	August 2020
2: 'Go / No-Go' decisions in each country	September 2020
3: Start of data collection (database ready for analysis)	1 October 2020
4: End of data collection (database ready for analysis)	May 2021
5: Country Reports for each country	July 2021
6: Scientific paper 1	September 2021
7: Scientific paper 2	October 2021

8 References

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Annex 1: Country-specific details for the recruitment of patients

1) The Netherlands (using the same infrastructure as in ComNet I)

Nivel Primary Care Database - Sentinel Practices

The Dutch network consists of approximately 73 GPs (across 40 practices (53.7 FTEs) covering about 0.8% of the total population, which is representative of age, sex, geographic distribution and urbanisation level. Sentinel GPs are asked to collect a nasal swab and a pharyngeal swab from randomly selected patients with ILI or another ARI for virological testing at the RIVM, Centre for Infectious Diseases, Diagnostics and laboratory Surveillance (IDS).

The current swabbing protocol is the following:

- Minimally, the first two patients with ILI are swabbed on Monday through Wednesday;
- If no ILI patients are swabbed Monday through Wednesday, then, minimally, the first two patients with ILI or another ARI are swabbed Thursday through Sunday;
- For the whole week, at least one child is swabbed under 10 years of age with ILI or ARI.

A network-wide average of approximately 20 specimens is collected every week during the influenza season. In the Netherlands, all inhabitants are enlisted with a general practice (no paediatricians in primary care), so there are population denominators to estimate the disease burden in the community.

Case definition

The ILI case definition in the Netherlands uses the Pel criteria. These are defined as:

1. An acute start, so a maximum prodromal stage of three to four days (included pre-existing infection of the respiratory system at not-ill-making level).
2. The infection should also involve rise in temperature to at least 38^0 Celsius, rectal (note: in practice fever as measured by ear thermometer ≥38◦ is also accepted).
3. At least one of the following symptoms should occur: cough, nasal catarrh, sore throat, frontal headache, retrosternal pain, myalgia.

Dutch GPs use the International Classification of Primary Care (ICPC, version 1) to record symptoms and diagnoses of consulting patients. Upon the recording of an acute respiratory infection (ARI), defined by ICPC codes R74 (acute respiratory infection), R77 (acute laryngitis/tracheitis), R78 (acute bronchitis/bronchiolitis), R80 (influenza) or R81 (pneumonia), a pop-up appears with the question if the patient fulfils the ILI criteria. If not, the case is considered an ARI.

Virological testing

Virological testing will be performed by the RIVM-IDS laboratory, which is one of the two locations of the National Influenza Centre. Swabs have been routinely tested for influenza virus, respiratory syncytial virus (RSV), rhinovirus and enterovirus since the start in 1994, and since 2008 using real-time RT-PCR. The number of pathogens for which tests are performed may be adapted when necessary. Only the costs for increased swabbing, processing of results for inclusion of patients during the RSV ComNet study and contacting GPs and RSV patients/carers will be covered by the study budget. Testing of the swabs is done under ISO 15189 accreditation for medical laboratories.

Data collection procedure
The infrastructure as evaluated in the ComNet I study will be used to invite patients, obtain informed consent and collect the questionnaire data.

Expected number of cases in the Netherlands
Based on data from 2008-2018, there was an average of 173 swabs taken each season in children aged 0-4 using the Dutch ILI case definition (ranging from 125 in 2017/18 to 268 in 2009/10). Among these, there was an average of 34 RSV cases per season (week 40 to 20) in children aged 0-4 (ranging from 22 in 2008/09 to 50 in 2015/16). We aim to have 200 swabs from children under 5 during the 2020/2021 winter season. Therefore, a researcher will contact GPs on a regular basis to remind and motivate them to collect samples in children under 5 years of age.

During the 2019/20, the Netherlands had a 152 swabs in children aged 0-5 years, 32 positive cases (21%) and a response rate of 37,5% (12). The plan for 2020/21 is to be much more proactive in providing information to the GPs and parents, so that we can increase the response rate to 50-60%. With an increase in the size of the sentinel network (funded by Ministry of Health as part of the COVID-19 preparations for 2020/21), we are hoping for 20-40 positive cases during the 2020/21 season.

2) Italy (using the same structure as in ComNet I, but now with three regions)

The Italian Influenza Sentinel Surveillance System
The Italian epidemiological surveillance network consists of 1,000 sentinel GPs and paediatricians reporting ILI cases on a weekly basis during the winter season, representing 2% of the population, representative for age, geographic distribution and urbanisation level. Each participating doctor is given instructions on which day to take the swabs; they collect samples from the first ILI cases observed during the pre-specified days. The system does not collect information on RSV positive cases and uses the ECDC-ILI case definition for recruiting ILI cases. The average number of samples collected since 2000 was 2,500 per season. For this reason, the current ComNet II study will be restricted to a limited network of GPs and paediatricians in three regions (Lazio, Puglia, Liguria).

Case definition
The RSV WHO case definition will be used.[4]

Virological testing
Virological testing will be performed by the Influenza regional reference Laboratories which is part of the National Influenza Centre network and has more than 20 years of experience. Swabs, at the regional reference laboratories are routinely tested for influenza virus, respiratory syncytial virus (RSV), rhinovirus, parainfluenza, adenovirus, enterovirus, etc.

Date collection procedure
The Bambino Gesù Children's Hospital (OPBG) will coordinate the study and will manage the study forms (informed consent form and the study questionnaires). The three regional reference Laboratories (OPBG for the Lazio region, University of Bari for Puglia and University of Genoa for

Liguria) that will participate in the study are part of the Regional Reference Laboratories Network in Italy, under the coordination of the National Influenza Centre and will perform testing.

The infrastructure as evaluated in the ComNet I study will be used to invite patients, obtain informed consent and collect the questionnaire data.

Expected number of cases in Italy
Based on number of swabs collected for influenza surveillance purposes in the two regional references Laboratories from 2010 to 2018, using the ILI-EU case definition there were approximately 500 swabs taken on average each season for children 0-4 years old. We do not therefore expect to have any difficulty in meeting the target of 600 swabs for the 2020/21 season.

3) United Kingdom (England)

Oxford RCGP RSC network
For the winter 2020-21 season, the Oxford Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) will join the ComNet II: Disease burden of RSV infections among young children (<5 years) in primary care.

The Oxford RCGP RSC manages a network of more than 1000 general practices in England that form the national infectious disease sentinel surveillance network. The sentinel network has been providing a weekly infections data return to Public Health England (PHE) since 1964 which has been used to monitor trends in infectious disease and investigate real-world vaccine efficacy. More recently the network has expanded to undertake enhanced surveillance for COVID-19 and has and become a platform for rapid clinical studies of candidate treatments for the novel coronavirus, called the Oxford RCGP Clinical Informatics Hub (ORCHID).

Recruitment of practices for the ComNet II study from England
An invitation will be sent to all practices within the network to participate in ComNet II. Practices will be assessed on the quality of their data returns to the network over the previous year and their swabbing rates if they have been part of the PHE virology swabbing scheme or the DRIVE point of care testing study.

Practices who agree to participate in the study will receive training in how to undertake virology swabbing and how to code cases for the ComNet II study.

They will be asked to take an average of 20 swabs per practice (all ages), per week from over the winter 2020-2021 season, although this number will vary on a week-by-week basis dependent on the levels of circulating respiratory virus in the community.

Recruitment of patients for the ComNet II study
Practices participating in the ComNet study will use the ARI case definition to identify patients suitable for the study. Consented eligible patients will be asked to contribute a nasopharyngeal swab which will be sent to PHE reference laboratory for testing.

Follow-up of RSV positive patients

Follow-up of patients with RSV positive tests will be undertaken by general practice staff by telephone interviews.

Sample size calculation

Over the previous two winter seasons, a total of 4542 virology samples had been collected from an average of 208 virology swabbing practices in the network. Over 2% of swabs were undertaken in from children under the age of 5 years, approximately (100 per year). Overall approximately 7% of swabs were positive for RSV.

Given these figures and the expansion of practices recruited for surveillance in 2020/21 we estimate that we will be able to collect 500 swabs from children under the age of 5 years presenting with ARI.