RSV ComNet I: Disease burden of RSV infections in young children (<5 years) in primary care

Results of the pilot study in Italy & the Netherlands winter of 2019/20

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Clarrise Demont and Mathieu Bangert are employees of Sanofi Pasteur. All the other authors declare they have no conflict of interests to disclose.

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Executive summary

Introduction: Respiratory diseases are one of the leading causes of morbidity and mortality among young children, and respiratory syncytial virus (RSV) is the most common pathogen causing these respiratory diseases. RSV burden of disease studies have mostly been focused on the morbidity and mortality rates of RSV infections. With the development of respiratory syncytial virus (RSV) vaccine candidates and monoclonal antibodies, there is a need to better understand the burden of RSV infections among young children, especially in primary care.

Aim: The aim of this RSV ComNet pilot study is to develop and evaluate the feasibility of a disease burden study protocol to measure the clinical burden, health care utilisation and societal impact of RSV infections in children (<5 years) in primary care. The disease burden study protocol is piloted in two European countries, Italy and the Netherlands, in the winter season 2019/20. In addition, we have described the disease burden in Italy and the Netherlands.

Methods: In this prospective cohort study, children aged <5 years who visited their general practitioner (Netherlands) or paediatrician (Italy) (in the following primary care physician, PCP), met the WHO acute respiratory infection (ARI) case definition for RSV infection and had a positive lab-confirmed test result for RSV were eligible for the study.
At consultation (day 1), the PCP collected a nasopharyngeal swab (in the Netherlands also an oropharyngeal swab) and completed a short swabbing questionnaire (patient demographics and clinical symptoms). Parents completed two subsequent questionnaires, after 14 days (health care utilisation, days of illness, socio-economic impact and current health status) and after 30 days (quality of life, QoL, PedsQL questionnaire).
In Italy, the disease burden study protocol was implemented in a network of paediatricians more often involved in scientific studies and in the Netherlands in an existing routine influenza surveillance system. Another important difference between countries was the method of data collection: in Italy telephone interviews were used compared to digital questionnaires in the Netherlands.

Main findings: In Italy 293 children were swabbed, among which 119 (41%) were RSV positive and 116 were included in the RSV ComNet study. In the Netherlands, 152 were swabbed, among which 32 (21%) were RSV positive and 12 were included in the study. Parents completed the questionnaires in a short amount of time, in Italy the average time was 7 minutes on the Day_14 questionnaire and 10 minutes on the Day_30 questionnaire, in the Netherlands the average time was 4 minutes for both questionnaires. Although most children did return to their normal daily activities fourteen days after swabbing (92% in Italy and 83% in the Netherlands), a significant number of children did have persistent symptoms (34% and 67%, respectively).
The most important lessons learnt from this pilot study were that: 1) the size of the network of PCPs needs to be adequate to capture sufficient RSV positive cases, 2) regular communication between researchers, reference laboratories and PCPs is important for successful patient recruitment, 3) a personal approach to invite children (and parents) to participate in the study leads to a higher response rate, 4) the PedsQL QoL questionnaire is not appropriate in children under the age of five.
The results showed that 6% of the children in Italy (7/116) and 17% of the children (2/12) in the Netherlands were hospitalised. More specific details regarding the clinical burden, health care utilisation and societal impact are reported in the report.
Some small adjustments to the disease burden study protocol for future ComNet studies are suggested in the report. Most importantly we recommend to measure fever in the Day_1

questionnaire, measure the socio-economic impact of the RSV disease on both parents, measure the health care utilisation and socio-economic impact also over the period between the Day_14 and Day_30 questionnaire, and measure the complications related to the RSV disease in the Day_30 questionnaire. In addition, we advise against the use of the PedsQL questionnaire. Currently, we are exploring other opportunities to get insight into the QoL of the children, for example by measuring the impact of the child's illness on the family.

Conclusions: This study showed that it is feasible to implement the RSV ComNet disease burden study protocol in a routine influenza surveillance system, as well as in a network of PCPs more often involved in scientific research. In addition, an RSV infection seems to cause a significant burden in young children (<5 years) in primary care, however, more research with larger sample sizes is needed in the future. For future studies it will be important to estimate the burden of RSV not only on an individual patient level but also on a population level.

COVID-19 statement
Due to the COVID-19 pandemic we had to end the recruitment of patients earlier than originally planned (up until week 20/2020). In the Netherlands, patient recruitment ended in week 14 and in Italy it ended in week 13, but was significantly decreased in weeks 12 & 13 (see results).
The main aim of the pilot study was to evaluate the feasibility of the disease burden study protocol. The premature stop to patient recruitment did not have a large impact on the evaluation of the feasibility of the disease burden study protocol.
However, a consequence of the premature stop is that we could not recruit children during the whole RSV season which has implications for the population-based estimates of RSV incidence and the total number of children included in the study. However, the consequences mainly apply to Italy (and more specifically the Puglia region) as the RSV season in the Netherlands was almost over when patient recruitment ended (see results).

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1 Introduction

Respiratory diseases are one of the leading causes of morbidity and mortality among young children, and respiratory syncytial virus (RSV) is the most common pathogen causing these respiratory diseases in this age group.[1-4] RSV can present in the form of a variety of clinical syndromes, including upper respiratory tract infections, bronchiolitis, pneumonia, exacerbations of asthma and viral-induced wheeze. RSV is highly seasonal and occurs mostly during winter season in temperate climates.[5] Sixty to seventy percent of all children experience an RSV infection before the age of one, and nearly all do so before the age of two.[6]

According to a global burden of disease study, it is estimated that in 2015 approximately 33.1 million young children were infected with RSV, resulting in 3.2 million hospitalisations and 59,600 in-hospital deaths.[1] In Western countries, mortality due to an RSV infection is rare, however, annual hospitalisation rates in the first year of life are estimated to be 3.2-42.7 cases per 1000 children, with a hospital stay length ranging between 2 to 11 days, and 2-12% of cases requiring an intensive care unit admission.[2,7]

The burden of RSV in young children emphasizes the importance of efforts to develop new RSV interventions, for example vaccines, antiviral monoclonal antibodies (mAbs) or treatments.[8-10] The only preventive strategy currently available against RSV is the prophylaxis 'Palivizumab', but this antiviral antibody is only considered cost-effective for certain high risk group infants and requires monthly vaccinations during the winter months.[11] Treatment options are limited to supportive care.[9,12] Several promising candidate RSV vaccines and monoclonal antibodies (with longer half-life times) are in late-stage clinical trials.[8,13,14] Accurate estimates of the burden of RSV, including in primary care, are therefore necessary for the development of future prevention and control policies.

'Burden of disease' is a general term without a universally accepted definition, and refers to the human and economic costs that result from poor health. RSV 'burden of disease' studies in young children (aged 0-4 years), have mostly been focused on the morbidity and mortality rates of RSV infections.[1,6,15,16] Other studies have investigated the clinical and socio-economic burden of RSV infections in young children, however, a meta-analysis showed that of the 365,828 RSV disease episodes included in cost-analysis studies, only 27,286 (7.4%) focused on outpatient and emergency cases.[17] To our knowledge, only two outpatient studies have prospectively investigated the clinical and socio-economic burden of lab-confirmed RSV infections in young children; and both studies collected data in the early 2000s.[18,19] The average annual RSV infection incidence rate in the study in Finland was 275 cases per 1000 children (<3 years), with a mean duration of illness of 13 days, and a parental work absenteeism rate of 136 days per 100 children.[18] In the Australian study (2003), the mean outpatient cost for RSV was 304 Australian dollars (176 Euros) per child.[19] There is a lack of knowledge on the clinical and socio-economic disease burden of RSV infections in young children in primary care.

Data on the clinical and socioeconomic disease burden in primary care is crucial to set appropriate prevention strategies, allocate resources and inform decision-making models to estimate the cost-effectiveness of the implementation of new vaccines and mAbs. The aim of this study to develop and evaluate the feasibility of a study protocol to measure the clinical and socio-economic disease

burden and quality of life, of lab-confirmed RSV infections in young children (<5 years) in primary care.

Considering that routine influenza surveillance systems are implemented worldwide, one hypothesis is that it might be efficient to use these existing structures to identify lab-confirmed RSV positive cases. Therefore, the second aim of the study was to evaluate whether it is possible to implement the disease burden study protocol for RSV in an existing influenza surveillance system. The feasibility of this disease burden study protocol has been evaluated in two European countries: Italy and the Netherlands in the winter of 2019/20.

1.1 Outline of the report

In chapter 2 we have described the disease burden study protocol, the implementation of the disease burden protocol in both countries, the methods to evaluate the feasibility of the disease burden protocol, and methods to examine the disease burden. In chapter 3, the results of the study are divided in a section for Italy and the Netherlands. Chapter 4 gives an overview of the main findings of the RSV ComNet study. In chapter 5, the implications for the RSV ComNet II study protocol are discussed. In chapter 6 we conclude with a general discussion and final conclusions including recommendations for future studies.

2 Methods

2.1 Disease burden study protocol

2.1.1 Study design

The study protocol includes a multicentre and multi-country prospective cohort study in primary care. Paediatric primary care in Europe can be categorised into three distinct groups: (1) paediatrician-led, (2) general practitioner (GP) led and (3) a combination of the two.[20] We chose to implement the pilot study in Italy and the Netherlands as these countries have two different primary care systems, namely paediatrician led (Italy) and GP led (the Netherlands). In the following, we will use the term primary care physician (PCP) when we refer to the paediatrician (Italy) or GP (the Netherlands).

In the Netherlands, the study protocol was implemented within the existing routine influenza surveillance system, while in Italy the disease burden study protocol was implemented in a network of PCPs more often involved in scientific studies.

First, we have described the disease burden study protocol in general and then we provided more details about the implementation of the study protocol in the two countries.

2.1.2 Eligibility criteria participants

Children, aged <5 years, consulting a PCP with symptoms of an acute respiratory infection (ARI), and a lab-confirmed diagnoses of RSV, were eligible for inclusion into the RSV ComNet study.

The ARI case definition was based on the definition published by the World Health Organization (WHO) and included the following criteria: [21,22]

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

Point (3) was added to the definition by the RSV ComNet research team.

In Italy, the ARI case definition was fully implemented. In the Netherlands, the study protocol was implemented in the routine influenza surveillance system and therefore the influenza-like illness (ILI) and ARI case definition was used. The ILI case definition is a specific subset (requiring fever) of the ARI case definition. More detailed information on the case definitions is described in the section "2.2 Implementation of the ComNet study in Italy and the Netherlands".

Exclusion criteria were insufficient knowledge about the national language by the parents, intellectual disabilities of the parents, and/or special personal circumstances in the family (based on the judgement of the primary care physician, for example a recent death in the family).

2.1.3 Data collection & measurements

For each child included in the study, data collection was performed at three moments in time:

(1) At the day of swabbing (Day 1),
(2) Approximately 14 days after swabbing (Day 14),
(3) Approximately 30 days after swabbing (Day 30).

At Day 1, PCPs completed a short swabbing questionnaire for each patient. In this routine investigation request form, information was collected regarding:

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

Parallel, PCPs collected a swab (nasopharyngeal in Italy and nasopharyngeal and oropharyngeal in the Netherlands), and sent them to the reference laboratory. The swabs were analysed preferably within 10 days after collection. **(**See **Annex 1, Day 1 form)**

* In Italy questions regarding medical history were added to the Day_1 questionnaire and in the Netherlands to the Day_14 questionnaire.

At Day 14, parents completed the first parental questionnaire on, (see **Annex 1 Day 14 form**):

(1) Medical history of the child (e.g. prematurity, chronic respiratory diseases, other relevant comorbidities, previous RSV infection in the current season, use of Palivizumab)*,
(2) Health care use of their child in the past 14 days (number of consultations to PCP, paediatrician, other (paramedical) health care providers, emergency department, hospitalisations, ICU admission, duration of hospitalisation and/or ICU admission, and medication use),
(3) Days of illness,
(4) Socio-economic impact (work absenteeism and productivity losses of parents, absenteeism of school or day care of children), and
(5) Current health status (remaining symptoms, and state of recovery, defined as date of returned to normal activities).

* In Italy questions regarding medical history were added to the Day_1 questionnaire and in the Netherlands to the Day_14 questionnaire.

At Day 30, parents completed the second parental questionnaire on:

(1) The child's quality of life, Paediatric Quality of Life (PedsQL) 4.0 questionnaire.[23]
(2) If the child was still hospitalised at Day 14, some extra questions regarding health care use (i.e. duration of hospitalisation, and number of consultations to health care providers) were added to the Day 30 questionnaire. However, in this pilot study none of the children were hospitalised at Day 14 in both countries.

PedsQL 4.0 QoL questionnaire

For the ComNet study we used, as recommended by the developers of the PedsQL 4.0 questionnaire, three different parent proxy-report versions of the PedsQL questionnaire for children aged 1-12 months, 13-24 months, and 2-4 years.[23] The parent proxy report version of the questionnaire was only validated for children aged 2-4 years.[24] The other versions were derived from the PedsQL questionnaire for children aged 2—4 years, but were not tested for validity and reliability yet.

The questionnaires contain five scales: physical functioning, physical symptoms, emotional functioning, social functioning and cognitive functioning. The amount of items per scale is dependent on the studied age group. For each question, a 5-point Likert-scale, is used (0= never a problem; 1= almost never a problem; 2= sometimes a problem; 3= often a problem; 4= almost always a problem).

Virological testing procedures

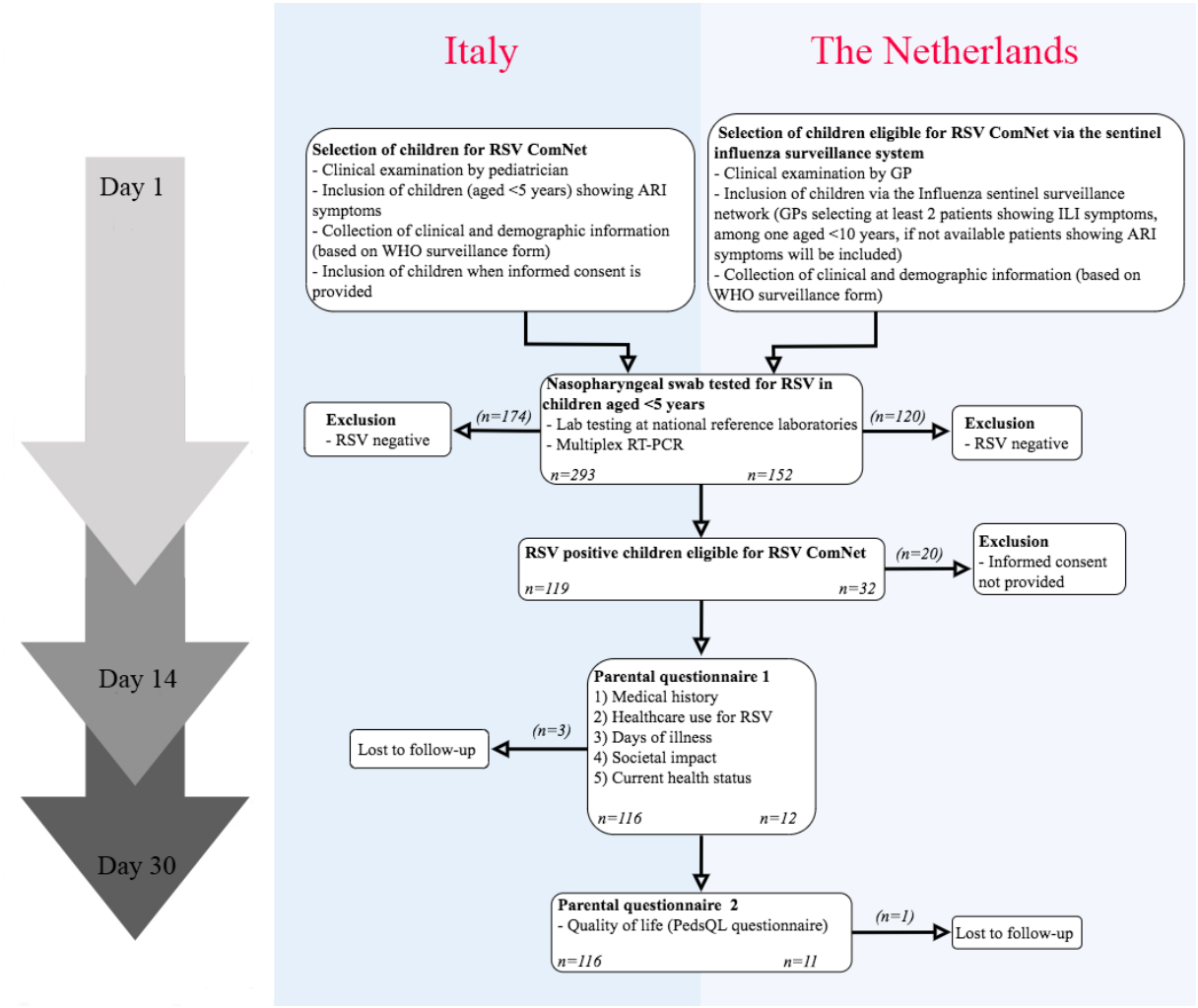
The nasopharyngeal and oropharyngeal swabs were tested using multiplex RT-PCR testing by the reference laboratories in each country. In addition, the reference laboratories gathered data regarding the weekly number of swabs analysed, the weekly number of RSV positive cases, and more specific laboratory results for the RSV positive cases like information concerning RSV subtype and co-infections.

Country	Laboratory
The Netherlands	National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
Italy	Rome: Bambino Gesù Children's Hospital, Rome, Italy Puglia: University of Bari, Bari, Italy

2.2 Implementation of the study protocol

Recruitment of children was performed in the winter season of 2019/20, in Italy (week 47-2019 to week 14-2020) and the Netherlands (week 40-2019 to week 14-2020). The patient selection and recruitment flow was slightly different in Italy and the Netherlands, as shown in Figure 1. Detailed information about the implementation of the study protocol, including the patient selection and recruitment flow, in both countries is described below.

Figure 1. Flowchart of the RSV patient selection and recruitment process in Italy and the Netherlands, 2019-2020.



2.2.1 Italy

Ethical approval
The Medical Ethical Committee of OPBG Medical Centre (Italy) provided a waiver for ethical approval on the 30th of September 2019 (Prot. N 1301). One of the parents (or child-carers) of the recruited children signed an informant consent to participate in the study.

Network of paediatricians & selection of RSV positive children
In Italy, two networks of primary care paediatricians (PCP) involved in other clinical studies - one in the Lazio Region (Central Italy) and one in the Puglia Region (Southern Italy) - were recruited for the study. This involved 12 paediatricians from the region of Lazio, which covers 9.7% of the Italian population, and 12 in the Puglia region, which covers 6.6% of the Italian population. In both regions, we organised a teleconference with paediatricians in order to define the standard operational procedures (SOP) of the study. SOP and guidelines on how to perform the nasopharyngeal swab and with all logistical information for the study were sent through email to all participant paediatricians.

In both regions, the PCP invited children aged <5 years consulting with ARI symptoms (see ARI case definition above) to participate in the RSV ComNet study, and informed consent of parents was obtained.

The PCP collected preliminary information for each patient recruited, including data on the patient demographics (birth date, gender, and date of swabbing), date of onset of clinical symptoms, and the presenting clinical symptoms. In parallel, a nasopharyngeal swab was taken and sent to the collaborating Laboratory in Lazio or Puglia, together with the collected form and signed informed consent. In the two regions, the logistical aspects were approached differently due to the different environment and habits. In Lazio region, we used a system of shipping of the swabs and documents (questionnaire at Day_1 and signed informed consent) through courier. The shipping was organised by the local coordinator (research nurse) in order to collect a sufficient number of swabs per each shipment. Regular telephone contacts (twice a week) with participating paediatricians were performed. In Puglia region, the parents of the recruited children personally delivered the swab with the T0 completed questionnaire and the signed informed consent to the reference Laboratory.

In both regions, respiratory specimens were collected from all eligible ARI patients and analysed using RT-PCR and a commercial kit multiplex RT-PCR for 16 viruses (including RSVA and B) and 3 influenza viruses (Allplex™ Respiratory Full Panel Assay). The laboratories were located inside the two participating regions and are both regional reference laboratories within the network of the National Influenza Center of the National Institute of Health (Istituto Superiore di Sanità, Rome, Italy).

The trigger for study recruitment was the positive notification of a RSV (A or B). In the two regions, the notification was sent from the laboratory to the research nurses/doctors who performed telephone interviews and collected information regarding D_14 and D_30 from the parents of recruited children. The collected data were anonymised by the team using a unique identifier for each positive sample identified.

Sample size
In Italy, the expected number of cases included in the study was based on the WHO Strategy document that suggests countries aim to collect a minimum of 500 respiratory specimens per annum from children aged 0-4 years.[22] Considering the RSV ComNet study piloted the study protocol, we included a smaller number of children aged under 5 at each site (an estimated 400 in Italy).

2.2.2 The Netherlands

Ethical approval
The Medical Ethical Committee of VU Medical Center (Netherlands) provided a waiver for ethical approval on the 9th of August 2019. Informed consent for participating in the study was given by one of the parents of the children.

Network of general practitioners & selection of RSV positive children
In the Netherlands, the existing routine sentinel influenza surveillance network was used to select RSV positive children under 5 years of age for the RSV ComNet study. The sentinel influenza surveillance network included 37 nationally distributed general practices, adding up to 77 GPs, and covering 0.8% of the Dutch population.

Every Dutch GP included in this network was requested to take a nasopharyngeal and an oropharyngeal swab from at least the first two patients encountered from Monday through Wednesday who had symptoms that meet the case definition for ILI; if from Monday through Wednesday no patients with ILI were encountered, GPs were asked to sample at least two patients that meet criteria for ILI or another ARI on Thursday through Sunday. For the whole week, at least one of the sampled patients is preferably under the age of ten years.[25] The ILI case definition is based on the following criteria: (1) an acute start, so a maximum prodromal stage of three to four days, (2) the infection involves a rise in temperature of at least 38° Celsius, (3) at least one of the following symptoms occurs: cough, nasal catarrh, sore throat, frontal headache, retrosternal pain, myalgia.[25] The ARI case definition for influenza described by the ECDC was used.

The combined nasopharyngeal and oropharyngeal swab specimens were sent in one tube virus transport medium to the national reference laboratory in the Netherlands (RIVM) and analysed using in-house real time RT-PCR assays. The specimens were tested for influenza virus type A (positives subtyped), influenza virus B/Victoria and B/Yamagata, respiratory syncytial virus types A and B, rhinovirus and enterovirus (positives typed). Testing of the swabs was done under ISO 15189 accreditation for medical laboratories. The trigger for inviting parents to join the RSV ComNet study was a positive RSV specimen in a child aged <5 years.

Before and during the study, GPs received instructions about the swab collection, the invitation of participants for RSV ComNet and the logistical procedures of the RSV ComNet study. In addition, GPs were regularly contacted when they did not collect the aimed weekly number of swabs.

Invitation of patients for RSV ComNet
Researchers at the RIVM sent an envelope with the RSV positive test result and RSV ComNet study information to the GP of the child. The GP added an address sticker to the envelope and forwarded the study information to the parents. The envelope included the study information and a link to the digital informed consent form and digital questionnaire. The questionnaire data were collected anonymously using a unique identifier for each positive sample identified (defined by RIVM and not

known to Nivel). The key code was kept by the reference laboratory (RIVM). At the end of the Day 14 questionnaire, parents were asked to fill in their e-mail address, and the Day 30 questionnaire was sent to them by e-mail. E-mail addresses were deleted immediately after completing the Day 30 questionnaire or after withdrawing from the study/non-response, whichever came first.

Sample size
In the Netherlands, the expected number of cases included in the study was based on data from 2008-2018. In that period, an average of 173 swabs were taken each season from children aged <5 years (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), ranging from 22 in 2008/09 to 50 in 2015/16. The RSV positivity rate was 19.6% on average (ranging from 10.3% to 30.0%). To increase the total number of swabs collected, 5 (FTE) new sentinel sites were added to the network. Therefore, we expected to collect 200 swabs from children under 5 years of age during the 2019/20 winter season.

2.3 Data analysis pilot study

2.3.1 Feasibility analysis

For the feasibility analysis, we first analysed patient recruitment using the weekly number of patients that were swabbed, the weekly number of RSV positive cases (eligible participants) and the number of parents that responded to the questionnaires. Secondly, we analysed the feasibility of the data collection procedures in the disease burden study protocol, i.e. are the questionnaires collected on time, duration of completion of the questionnaires by parents, recovery of patients after 14 days, and for the Netherlands whether children met the ILI or ARI case definition, and for Italy whether children met the ARI case definition. In addition, for the Netherlands we compared the patient characteristics of the children included in the study (respondents) and non-respondents, because the non-response rate was quite high. In Italy the non-response rate was negligible.

2.3.2 Process evaluation

Study procedures
Next to the quantitative analyses, we also performed a qualitative process evaluation.
In Italy, the paediatricians in both regions were interviewed through a specific questionnaire about their experiences with the RSV ComNet study, and in the Netherlands, the GPs who attended the Annual Sentinel Network meeting on the 19th of January 2020 ('Peilstations' day) were asked about their experiences with the RSV ComNet study. During a short group discussion we discussed topics as patient recruitment, taking the naso- and orpharyngeal swabs, and recommendations to increase patient recruitment.

For both Italy and the Netherlands, we also reported the lessons learnt from setting up the logistical study procedures, what were pros and cons and how was this related to the implementation of the study in a routine surveillance network or via a new network created for this RSV ComNet study.

Health related quality of life (HRQoL)
The PedsQL questionnaire is a widely used questionnaire to measure HRQoL of children in the age categories between 2 and 17 years, using child self-reports (8-17 years) and parent proxy-reports (2-17 years).[24,26] The PedsQL also includes official parent proxy-report versions for children aged 1-12

months and 13-24 months, however, these versions have not been validated yet.[23] To our knowledge, no other validated HRQoL questionnaires were available for children below 2 years of age, and therefore the PedsQL questionnaire was used in this study. To evaluate whether the PedsQL questionnaire is feasible for the use in future RSV disease burden studies, especially in the youngest age groups, research nurses in Italy have tracked a list of questions that were difficult to answer for parents. In the Netherlands, we have evaluated whether parents have reported specific comments on the PedsQL questionnaire in the open question at the end of the Day 30 questionnaire.

2.3.3 Disease burden analysis

Clinical and socio-economic burden

Descriptive statistics were used to describe (1) the patient demographics, clinical symptoms and relevant medical history at baseline, (2) the health care use, medication use, productivity losses of parents, and work and school/day care absenteeism of parents and children in the 14 days after swabbing, and (3) the remaining clinical symptoms and duration of illness at 14 days after swabbing.

Total HRQoL scores and the subscale scores on physical health and psycho-social health were calculated for age groups 1-12 months, 13-24 months and 1-2 years.[27] Scores on the PedsQL questionnaire were reversed and linearly transformed to a 0-100 scale (0=100, 1=75, 2=50, 3=25 and 4=0), where a score of 100 indicated the best quality of life and 0 the worst. The instructions in the PedsQL manual were used to calculate the total and subscale (physical health and psychosocial health) mean scores. To account for missing data, the scores were calculated by summing the items in the scale and dividing this by the number of completed items in that scale. If over 50 percent of the items in a scale were missing, the (sub)scale's mean score of the other children was imputed.[27]

Risk factors for high disease burden

To explore potential risk factors for disease burden, defined as duration of illness and burden on health care utilisation, we performed a linear and logistic regression analyses, respectively. This analysis was only performed for Italy (+100 RSV positive cases). The burden on health care use was a composite variable defined as high or low health care utilisation. A child was categorised as having a high health care burden when he/she met at least one of the following criteria:

(1) ≥2 extra consultations to the PCP (additional to the original consultation),

(2) Consultation to a medical specialist other than the PCP,

(3) Visit to the emergency department, or

(4) Hospitalisation.

Predictors considered for analysis were based on a literature review and data availability, and included: gender, age, being born in the RSV season 2019/20, prematurity, RSV subtype, and clinical symptoms at baseline. Region was also added to the model as health care is organised differently across regions in Italy. Predictors significant in the univariate analyses ($p<0.1$) were included in an initial multivariate regression model, and then we proceeded using a backward selection approach. Predictors with a significance of $p<0.05$ in the multivariate model were retained in the final model. Age and gender were included in the multivariate regression model as standard control variables.

2.3.4 Population based estimates of RSV incidence

To calculate population-based estimates of RSV incidence, two denominators are needed. First, the population denominator and second the number of sampled patients. The population denominator can be calculated by using the catchment area of the included PCPs or by using the population served by the PCPs in the sentinel surveillance system. A reliable estimate of the RSV positivity rate can be calculated when all children that met the ARI case definition were sampled or when a systematic random selection of the children that met the ARI case definition is sampled. The WHO calculated that at least 250 swabs a year are needed per age category to allow a prevalence of 5-10%, with an absolute precision of 2.5% with a 95% confidence.[22] As the RSV incidence might be different for children under <6 months and 6 months to 5 years they recommend to calculate the population based estimates for those subgroups.

In Italy, paediatricians have provided data regarding their catchment area of children under the age of 5 years. In addition, all children who met the WHO ARI case definition for RSV were swabbed. Therefore, it was possible to calculate the weekly ARI rates and weekly proportion of RSV positive cases per 100,000 children. In addition, we could calculate the weekly population based incidence rate of RSV infections for children <5 years of age, however, subgroup analyses per age category were not possible due to small sample sizes. Population-based seasonal estimates of RSV incidence per 100,000 children could be calculated by dividing the total number of RSV positive cases by the size of the population in the catchment area of all PCPs times 100,000. Unfortunately, due to the premature stop of participant inclusion due to COVID-19 (especially in Puglia) it will be a challenge to calculate the seasonal RSV incidence in Italy, but this is something we are planning, especially for the scientific manuscript.

For the Netherlands, data regarding the population denominator was available. However, the sampling of cases was not provided on a systematic basis in the subgroup of children under 5 years. For the routine influenza surveillance, GPs were recommended to swab at least one child under 10 years of age on a weekly basis. Although GPs were recommended to also collect data in very young children, we cannot be sure of a random sampling in children under 5 years of age. In addition, because the study was implemented in the ILI surveillance system, there was an over representation of children that met the more restricted ILI case definition (for example requirement of fever), while RSV often presents without fever (ARI case definition). Therefore, we could not reliably calculate the RSV incidence rates in the Netherlands. The use of modelling techniques to calculate population based incidence rates will not solve the issues regarding the sampling bias for this season.[28] However, Nivel and RIVM are exploring the possibilities to calculate seasonal RSV incidence rates in the future.

3 Results

3.1 Results Italy

3.1.1 Feasibility analysis

We recruited ARI cases from two municipalities located in two Italian regions: Rome in Lazio and Bari in Puglia. The total population of children less than 5 years of age in the two participating regions accounted for 16.5% of the national population aged 0-5 years old. When restricting to the two municipalities were the paediatricians recruited patients, the proportion of the national population included in the study decreased to 5.2% (Table I1).

Tabel 1 Table I1 Population 0-5 years of age

Region	Number	% (n Region/n Italy)
Lazio	285,167	9.9
- Rome	136,380	4.7
Puglia	187,522	6.5
- Bari	13,773	0.5
Italy	2,880,683	

Feasibility patient recruitment

A total of 293 patients with ARI were identified in the two participating centres. The highest number of cases were recruited in week 51/2019 and 3/2020 (Figure I1). The majority of patients (168; 57%) came from the Lazio region, and 125 (43%) were from the Puglia region. In Table I2 and Figure I2 the description of ARI cases characteristics is reported.

Most patients 130 (44%) were younger than 1 year of age, 70 (24%) belonged to the 13-24 months age group and 93 (32.7%) were 25-36 months old.

Figure I1 *Distribution of total swabs and positive RSV cases in Italy, week 47-2019 to 13-2020*

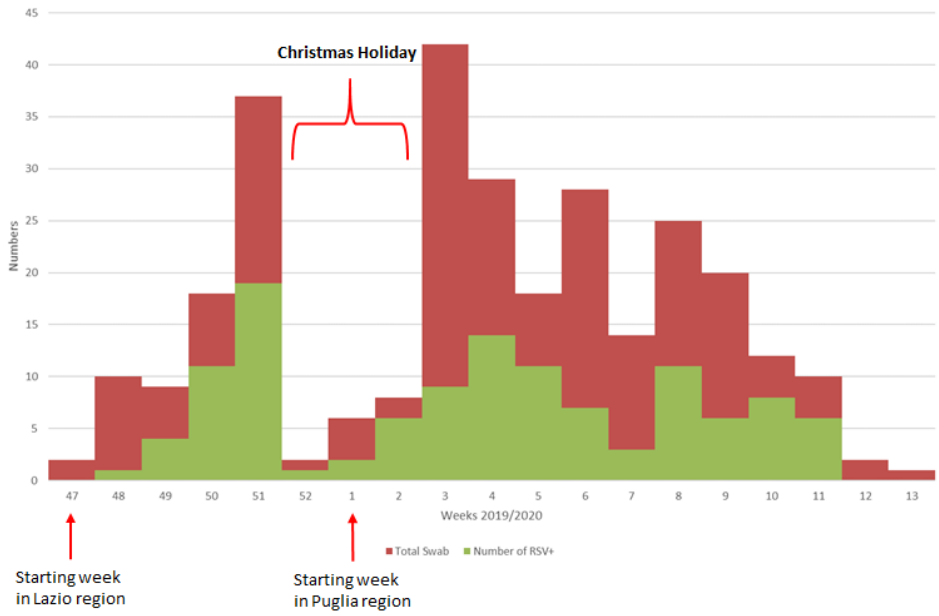
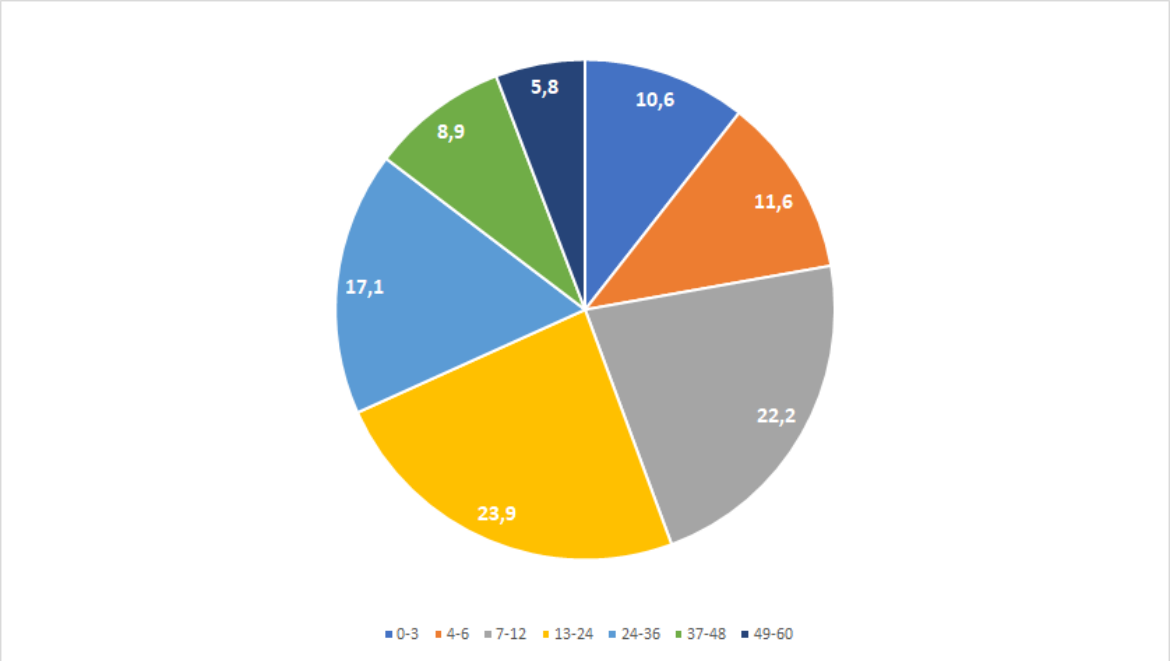


Table I2: *Description of ARI cases characteristics.*

Characteristic	Negative (174)	RSV+ (119)	Total (293)
Region: n (%)			
Lazio	113 (67%)	55 (33%)	168 (57%)
Puglia	61 (49%)	64 (51%)	125 (43%)
Boys, n (%)	100 (57%)	59 (50%)	159
Median age in months (range)	14 (1-60)	18 (2-53)	
Age group ; n (%)	174 (59%)	119 (41%)	293
1-12 months	77 (44%)	53 (44%)	130 (44%)
13-24 months	44 (25%)	26 (22%)	70 (24%)
25-36 months	53 (31%)	40 (33%)	93 (32%)
Prematurity; n (%)	4 (2.3%)	6 (5%)	10 (3%)
Presence of chronic condition; n			
Respiratory disease	3	1	4
Malnutrition	1	0	1
Immunocompromised	0	0	0
Others	2	2	4

Figure I2*. Proportion (%) of recruited ARI cases by age group (in months)*



Feasibility data collection procedures

The average number of days between the date of swabbing and date of disease onset was 2 days (IQR 1.0-3.5) (Table I3). The number of days between disease onset and the swab ranged between 1-3.5 days. The average time needed to complete the Day 14 questionnaire by telephone was 7 minutes (IQR 5-10) and 10 minutes (IQR 7-15) for Day 30. Forty children (33.6%) reported having symptoms after 14th days from symptom onset.

Table I3: Indicators of protocol feasibility in Italy, winter 2019/20

	Italy (n=119)
Feasibility patient inclusion	
Response rate Day_14 (n/N, %)	116/119 (97.5%)
Response rate Day_30 (n/N, %)	116/119 (97.5%)
Feasibility data collection procedures	
Days between disease onset and swab (median, IQR)	2 (1-3.5)
Days between swab and Day-14 (median, IQR)	17 (14.5-20.5)
Days between swab and Day-30 (median, IQR)	32.5 (30.5-35)
Having symptoms 14 days after Day-1 (n,%)	40 (33.6%)
Questionnaire duration time, T_14 (minutes)	7 (5-10)
Questionnaire duration time, T_30 (minutes)	10 (7-15)

3.1.2 Process evaluation

Experiences of the research team

It is feasible and efficient to implement data collection for the RSV disease burden study protocol in a parallel network of paediatricians.

At the beginning of the study, the shipping procedures were first organised by the paediatricians themselves. Then, considering that centralizing the sample shipping was more convenient due to the cost of individual shipment, we identified specific days of samples shipping twice a week. Therefore, the procedures slightly changed and they were organised by a member of the research team. In addition, we performed control actions to increase the number of swabs in the periods in which the paediatricians were not so active, in order to enhance samples collection (see Christmas holiday period).

The increase in the workload/time investment for PIs, or the reference laboratories was minimal as they both recognised the added value of having diagnostic tests results at the primary care level. The collaboration between PIs, the two references laboratories in the two participating regions and the coordination group at OPBG was fruitful. We organised a Protocol and a set of standard operational procedure with a specific workflow with clear written responsibilities for each step included in data collection and information flow.

We organised a specific shipment protocol of samples with biweekly appointments with PIs.

HRQoL questionnaire

In Italy, the questionnaire was administered by telephone. The main concern was the fact that the questions were not adequate to age. Childrens' skills change from month to month, therefore answers to the questions are affected by the age of the child. It is impossible to ask a parent of a child less than 1 year of age if the child had problems with physical functioning (e.g. walking, running),emotional functioning (e.g. feeling afraid or scared, feeling sad or blue, feeling angry, worrying) or social functioning (e.g. playing with other children or others kids don't want to play with him/her). Another example is related to children from 13-24 months of age; if a child in that age is still not walking or talking, it is quite likely that these children do not yet have social abilities and structured cognitive functions. Moreover, in the section dedicated to 2-4 years old children, there are no questions on the clinical pattern and it was very difficult to obtain answers on the emotional status and social life, in particular in the social life section, questions number 4 "not able to do things

that other children his or her age can do" and 5 "keeping up when playing with other children" were similar, the first negative and the second affirmative, respectively.

Evaluation of the study procedures with participating paediatricians

The paediatricians reported no particular workload associated with the study activity and found the study very important as it gives them the possibility of having the information on aetiology of the recruited ARI.

3.1.3 Disease burden analyses

Baseline characteristics of the included children (n=119) are shown in Table I4. 50% of the recruited ARI cases were boys and median age was 15 months (IQR range: 7-30). Cough, coryza and shortness of breath were the most represented symptoms. The proportion of RSVA isolated in the sample was 76% in both region, with highest proportion of RSVA isolated in the Lazio region (87% vs 67%). Other isolated viruses were Rhinovirus (68, 23.2%), Metapneumovirus (10, 3.4%) and Influenza A/H3N2 virus (10, 3.4%).

Health care use and socio-economic burden

The clinical and socio-economic impact of a RSV infection in young children is shown in table I5.

Table I4. Baseline characteristics of children included in RSV ComNet

		Age categories			Region	
	Total (n=119)	**1-12 months** (n = 53)	**13-24 months** (n = 26)	**2-4 years** (n = 40)	**Lazio** (n=55)	**Puglia** (n=64)
Boy (%)	59 (50%)	30 (57%)	13 (50%)	16 (40%)	25 (45%)	34 (53%)
Age in months (*median IQR)*	15 (7-30)	6 (4-9)	19.5 (15-21)	34.5 (29.5-46)	15 (7-33)	15 (6.5-28)
Symptoms						
Shortness of breath	89 (76%)	45 (87%)	15 (60%)	29 (73%)	36 (72%)	51 (80%)
Cough	117 (98%)	52 (98%)	26 (100%)	39 (98%)	53 (96%)	64 (100%)
Sore throat	36 (30%)	16 (30%)	10 (38%)	10 (25%)	20 (36%)	16 (25%)
Coryza	106 (89%)	46 (87%)	26 (100%)	34 (85%)	50 (91%)	56 (88%)
Illness due to infection[a]	99 (85%)	42 (81%)	22 (88%)	35 (88%)	40 (75%)	59 (92%)
Medical history						
Prematurity	6 (5%)	0	4 (15%)	2 (5%)	2 (4%)	4 (6%)
Chronic respiratory disease	1 (1%)	0	0	1 (3%)	0	1 (2%)
Malnutrition	0	0	0	0	0	0
Immunocomprised	0	0	0	0	0	0
Other chronic medical condition	2 (2%)	0	0	2 (5%)	0	2 (3%)
Previous RSV infection in this season	0	0	0	0	0	0
Virological test results						
Other viruses	61 (51%)	26 (49%)	14 (54%)	21 (53%)	31 (56%)	30 (47%)
RSV A (n, %)	91 (76%)	40 (75%)	21 (81%)	30 (75%)	48 (87%)	43 (67%)

Table I5. Clinical and socio-economic impact of RSV infections in young children in the period between swab uptake and 14 days after

		Age categories			Region	
	Total (n=116)	**1-12 months** (n=52)	**13-24 months** (n=25)	**2-4 years** (n=39)	**Lazio** (n=55)	**Puglia** (n=64)
Health care usage						
Extra consultations to PCP *(median, IQR)*						
Consultation	1 (0-2)	2 (1-3)	1(0-2)	1 (0-2)	1 (0-2)	1 (1-3)
Home visit	0	0	0	0	0	0
Phone / e-mail	1 (0-2)	1 (1-3)	1 (0-2)	1 (0-2)	1 (0-2)	2 (1-3)
Emergency department *n (%)*	18 (16%)	11 (21%)	3 (12%)	4 (10%)	3 (6%)	15 (23%)
Number of contacts to other medical specialists *(median, IQR)*	11 (9%)	5 (10%)	1 (4%)	5 (13%)	5 (10%)	6 (9%)
Phone calls/mails and home visits	1 (1-1)	0 (0-1)	1 (1-1)	0	0	1 (0-1)
Consultations	1 (1-1)	1 (1-1)	1(1-1)	1 (1-1)	1 (1-1)	1 (1-1)
Hospitalisation n (%)	7 (6%)	6 (12%)	0	1 (3%)	2 (4%)	5 (8%)
Days *(median, IQR)*	7 (3-9)	7 (3-9)	n/a	4 (4-4)	2.5 (2-3)	7 (7-9)
ICU n (%)	0	0	n/a	0	0	0
Paramedical care *n (%)*	0	0	0	0	0	0
Use of medications and prophylaxes						
Paracetamol	47 (40%)	14 (26%)	16 (61%)	17 (43%)	15 (27%)	32 (50%)
Other pain medication	4 (3%)	0	0	4 (10%)	2 (4%)	2 (3%)
Antibiotics	34 (28%)	8 (15%)	10 (38%)	16 (40%)	15 (27%)	19 (30%)
Other medication	93 (78%)	44 (83%)	20 (77%)	29 (73%)	47 (85%)	46 (72%)
Medication[1]	110 (95%)	46 (88%)	25 (100%)	39 (100%)	49 (94%)	61 (95%)
Medication[2]	68 (57%	20 (38%)	19 (73%)	29 (73%)	30 (55%)	38 (59%)
Palivizumab *(n, %)*	0	0	0	0	0	0
Socio-economic burden						
Days of illness (*median, IQR)*	7 (5-10)	8 (7-10)	7 (5-10)	7 (5-10)	7 (5-12.5)	7 (5-10)
Days out of daycare/school (*median, IQR)*	10 (7-15)	12.5 (7-22.5)	7 (7-15))	8.5 (7-15)	7 (7-15)	10 (6.5-15)
Sick leave caregiver (*n, %)*	62 (53%)	28 (54%)	13 (52%)	21 (54%)	16 (31%)	46 (72%)
Days of sickleave (*median, IQR)*	7 (5-14)	7 (5-14)	7 (3-14)	7 (5-7)	3 (2-12)	7 (5-14)
Impact on work[3] (*median, IQR)*	0.3 (0-0.6)	0.2 (0-0.5)	0.2 (0-0.5)	0.4 (0-0.7)	0.35 (0-0.5)	0.2 (0-0.7)
Returned to daily activity (*n, %)*	106 (92%)	49 (96%)	22 (88%)	35 (90%)	47 (90%)	59 (94%)

Persistent symptoms at day 14 (*n, %)*						
Wheezing/whistling in the chest	12 (10%)	7 (13%)	2 (8%)	3 (8%)	10 (18%)	2 (3%)
Persistent cough with slime	6 (5%)	4 (8%)	2 (8%)	0	4 (7%)	2 (3%)
Persistent cough without slime	20 (17%)	10 (19%)	2 (8%)	8 (21%)	11 (20%)	9 (24%)
Nose complaints	20 (17%)	10 (19%)	7 (28%)	3 (8%)	13 (24%)	7 (1%)
At least 1 persistent symptoms n (%)	40 (34%)	21 (41%)	8 (32%)	11 (28%)	20 (36%)	20 (28%)
Number of symptoms (*median, IQR)*	1 (1-2)	1 (1-2)	1.5 (1-2)	1 (1-2)	2 (1-2.5)	1 (1-1)

Note. [1] Medication included antibiotics, paracetamol, other pain medication and other medication, [2] Medication included antibiotics and pain medication. [3] Impact on work was measured in proportions on a scale of 0-1.

Quality of life

The HRQoL scores are shown in table I6 for each age category sepeartelty, ass different versions of the questionnaire consisted for children in the age categories 1-12 months, 13-24 months and 2-4 years. There were no missing items on the PedsQL questionnaire, and therefore no imputation techniques were used. The mean total score was 85.6 ± 13.9, 84.7 ± 11.4 and 90.3 ± 13.8 for children aged 1-12 months, 13-24 months and 2-4 years, respectively.

Table I6. Health related quality of life scores of children included in the RSV ComNet study 30 days after sampling (n=116)

Quality of life	1-12 months (n=52)	13-24 months (n=25)	2-4 years (n=39)
	Mean ± SD	Mean ± SD	Mean ± SD
Total Scale Score	85.6 ± 13.9	84.7 ± 11.4	90.3 ± 13.8
Physical Health subscale score	*85.0 ± 12.8*	*81.6± 11.9*	*87.1 ± 18.1*
Physical functioning	84.3 ± 18.3	76.0 ± 16.8	N/A
Physical symptoms	85.6 ± 14.0	86.6 ± 10.8	N/A
Psychosocial Health subscale score	86.0 ± 16.1	87.0± 13.6	92.3 ± 12.5
Emotional functioning	82.9 ± 19.1	82.2 ± 17.3	88.3 ± 15.4
Social functioning	91.2 ± 16.5	93.5 ± 11.2	95.5 ± 11.4
Cognitive functioning	90. ± 17.2	89.9 ± 14.4	N/A
School functioning	N/A	N/A	93.5 ± 13.3

Predictors for high disease burden

No multicollinearity between variables was found and all variables met the assumption for linear regression analysis. Results of the linear and logistic regression analysis to investigate predictors for high burden of disease are shown in table I7.

For high health care use, the predictors age, region, shortness of breath and RSV subtype were significant (p<0.1) in the univariate model. However, in the multivariate model only age and region remained significant (p<0.05) for predicting health care usage. A protective effect for age was found, showing a 0.53 decrease in odds on high health care use for each year in age increased (p-value: 0.01), and children from the region of Puglia had 4.38 higher odds on high health care usage compared to children from Lazio (p-value: <0.01). The area under the curve for the final model was 0.75 (95% CI = 0.66-0.84), and the model explained 13.3% of the variance. The Hosmer-Lemeshow goodness-of-fit test showed a good fit (p-value = 0.30). We did not found any significant predictors for duration of illness.

Table I7. Predictors for high burden of disease defined as duration of illness (linear regression analysis) and health care use (logistic regression analysis), n=116

	Duration of illness		**Health care usage**			
	Univariate analysis	Multivariate analysis	Univariate analysis		Multivariate analysis	
Predictor	**β (95%CI)**	**β (95%CI)**	**OR**	**p-value**	**OR**	**p-value**
Age in years	0.55 (-0.90 – 2.00)	0.39 (-1.07 – 1.85)	**0.60**	**0.01***	**0.53**	**0.01***
Gender (girl)	2.25 (-0.53-5.03)	2.22 (-0.61-5.04)	1.00	0.99	1.33	0.49
Region (Puglia)	-0.72 (-3.55-2.10)		**3.93**	**<0.01***	**4.38**	**<0.01***
Shortness of breath	2.34 (-1.00-5.67)		**2.09**	**0.10 ***		
Cough[a]	n/a		n/a			
Sore throat	-0.53 (-3.62-2.56)		0.58	0.18		
Coryza	-3.71 (-8.12 -0.69)		0.61	0.42		
Prematurity	-1.96 (-10.07-6.18)		0.96	0.97		
Born in this year's RSV season	-1.57 (-6.37-3.22)		1.78	0.38		
RSV subtype B	1.74 (-1.57-5.01)		**2.34**	**0.07 ***		

Note: The multivariable model is adjusted for age and gender. All other variables were significant (*) if p < 0.1. Cough was not added to the univariate and multivariate model as there were only 2 negative cases. Age, region, wheezing and RSV subtype were significant in the univariate model for health care usage. The explained variance of the multivariable model was 2.2% for duration of illness and 13.3% for health care usage.

3.1.4 Population based estimates of RSV incidence

In Italy, paediatricians hired within the National Health System are paid to cover a population of a defined size and composition. Therefore, the denominator used is the population of individuals registered to the reporting paediatricians.

In Figure I3 and I4 the weekly ARI rate per 100,000 population by region and the positivity rate by week and region are reported, respectively.

Figure I3 *Weekly ARI rate by region*

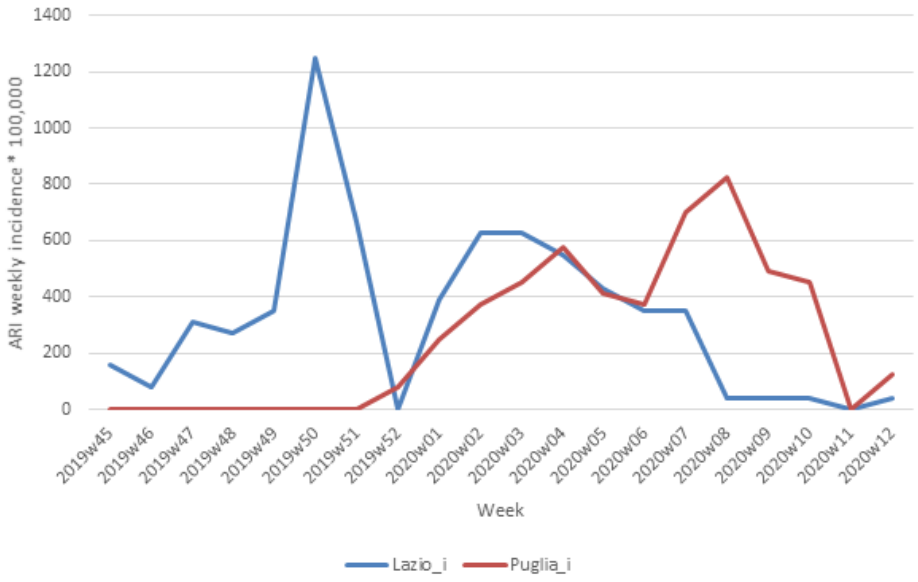


Figure I4*. Positivity rate by region*

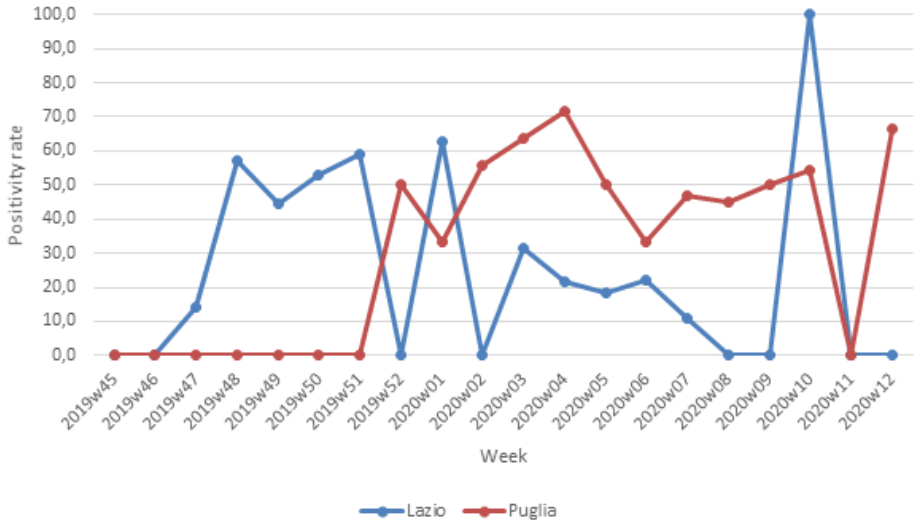


Table I8. Weekly ARI rate per 100,000 by age and region

Week	Lazio				Puglia			
	1-12 months	**13-24 months**	**25-36 months**	**Total**	**1-12 months**	**13-24 months**	**25-36 months**	**Total**
2019w45	215,5	441,8	0,0	156,4	0,0	0,0	0,0	0,0
2019w46	215,5	0,0	70,7	78,2	0,0	0,0	0,0	0,0
2019w47	1077,6	0,0	212,0	312,7	0,0	0,0	0,0	0,0
2019w48	862,1	294,6	70,7	273,7	0,0	0,0	0,0	0,0
2019w49	862,1	441,8	141,3	351,8	0,0	0,0	0,0	0,0
2019w50	2370,7	736,4	1130,7	1251,0	0,0	0,0	0,0	0,0
2019w51	431,0	1472,8	353,4	664,6	363,0	0,0	0,0	0,0
2019w52	0,0	0,0	0,0	0,0	726,0	0,0	0,0	82,4
2020w01	1508,6	441,8	494,7	390,9	363,0	0,0	154,8	247,3
2020w02	862,1	736,4	494,7	625,5	544,5	171,5	464,4	371,0
2020w03	862,1	736,4	141,3	625,5	1088,9	514,6	387,0	453,4
2020w04	1293,1	883,7	212,0	547,3	544,5	514,6	387,0	577,1
2020w05	1293,1	294,6	141,3	430,0	907,4	514,6	309,6	412,2
2020w06	862,1	441,8	141,3	351,8	1633,4	514,6	77,4	371,0
2020w07	1508,6	0,0	0,0	351,8	1996,4	514,6	387,0	700,7
2020w08	215,5	0,0	0,0	39,1	1270,4	343,1	541,8	824,4
2020w09	0,0	147,3	0,0	39,1	907,4	171,5	309,6	494,6
2020w10	215,5	0,0	0,0	39,1	544,5	514,6	232,2	453,4
2020w11	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
2020w12	215,5	0,0	0,0	39,1	181,5	0,0	0,0	123,7

We have shown the weekly ARI rates, for both regions and per age group, and the weekly percentage RSV positives. We are having internal discussions whether we can present reliable weekly and/or seasonal RSV incidence rates for the Italian population, taking into account the limited sample size, and not collecting data for the full season, (in Puglia the start of data collection was delayed and prematurely stopped due to COVID-19). These factors will influence the seasonal burden estimates but this is something we are going to access, especially as it might be important for the scientific manuscript.

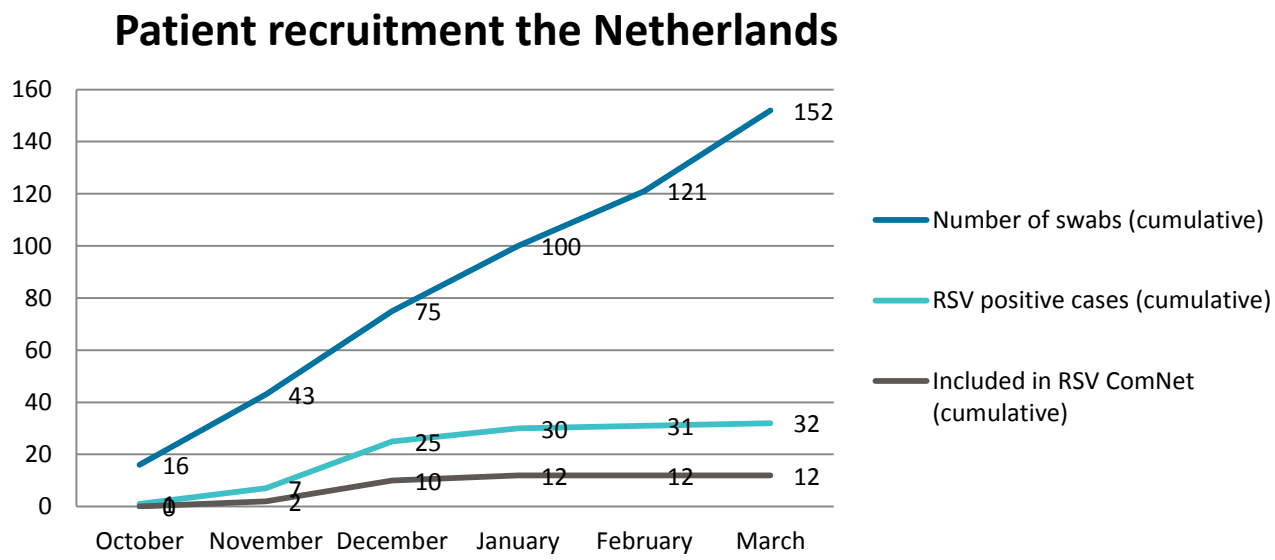
3.2 Results the Netherlands

3.2.1 Feasibility analysis

Feasibility patient recruitment

In the winter season 2019/20 (weeks 40-2019 to 14-2020), a total of 152 swabs of children with ILI or ARI symptoms were collected, among which 32 (21%) were tested positive for RSV. December was the month with the most RSV positive cases, namely 18/32 (Figure 2). The response rate on the first parental questionnaire was 12/32 (38%), only one parent that completed the first parental questionnaire was lost to follow-up on the second parental questionnaire (Table N1, Figure N1).

Figure N1. Cumulative number of swabs collected in the winter season 2019/20 (weeks 40-/2019-14/2020), the cumulative number of RSV positive cases, and cumulative number of included patients in RSV ComNet.



Feasibility data collection procedures

The average number of days between the date of swabbing and date of disease onset was 3 days (IQR 2-4.5) (Table N1). In 4 out of 12 children GPs reported the symptoms as “not acute” on the virological form, while the number of days between onset of disease and taking the swab ranged between 2-5 days suggesting an acute onset of symptoms in all children. The average time needed to complete the parental questionnaires was 4 minutes (IQR 3-5) for Day 14 and 4 minutes (IQR 3-8) for Day 30. Eleven children (92%) did have fever as one of the baseline symptoms, which means that children with fever might be overrepresented in our sample.

Table N1: Indicators of protocol feasibility in the Netherlands, winter 2019/20

	Netherlands (n=12)
Feasibility patient inclusion	
Response rate Day_14 (n/N, %)	12/32 (38%)
Response rate Day_30 (n/N, %)	11/32 (34%)
Feasibility data collection procedures	
Days between disease onset and swab (median, IQR)	3 (2-4.5)
Days between swab and Day_14 (median, IQR)	20 (16.5-30.5)
Days between swab and Day_30 (median, IQR)	36.5 (29.5-39)
Having symptoms 14 days after Day_1 (n,%)	8 (67%)
Questionnaire duration time, T_14 (minutes)	4 (3-5)
Questionnaire duration time, T_30 (minutes)	4 (3-8)
Case definition	
ILI case definition (n, %)	2 (17%)
ARI with fever (n, %)	9 (75%)
ARI without fever (n, %)	1 (8%)

Comparison of respondents and non-respondents

To evaluate whether the respondents to the RSV ComNet study were comparable with the non-respondents we have compared the baseline characteristics (Table N2). The percentage of boys was higher among the respondents (75%) compared to the non-respondents (45%). However, the small number of cases has to be taken into account. In addition, the percentage of children with shortness of breath was slightly smaller among the respondents (50%) compared to the non-respondents (80%), suggesting we might have a small overrepresentation of children with less severe symptoms in the study population. The median age, number of baseline symptoms and distribution between RSV A and B seemed to be comparable between both respondents and non-respondents.

Table N2 Patient demographics between respondents and non-respondents to the RSV ComNet study

	Respondents (n=12)	Non-respondents (n=20)
Boys	9 (75%)	9 (45%)
Age in months median (IQR)	10.8 (8-14.5)	11.5 (5-17)
Symptoms		
Shortness of breath	6 (50%)	16 (80%)
Cough	10 (83%)	20 (100%)
Sore throat	0	3 (15%)
Coryza	8 (67%)	12 (60%)
Illness due to infection	12 (100%)	20 (100%)
Fever	11 (92%)	18 (90%)
Virological test results		
RSV A	9 (75.0%)	12 (60%)

3.2.2 Process evaluation

Experiences of the research team

It is feasible and efficient to implement data collection for the RSV disease burden study protocol in a routine influenza surveillance system. Two advantages for the use of an existing routine influenza surveillance system to collect data were that GPs in the surveillance system were used to collect swabs, and the logistical procedures of the transportation of swabs to the reference laboratories did already exist. Therefore, costs of the study were relatively low.

The collaboration between the GPs, the reference laboratory (RIVM) and the researchers at Nivel worked well. Before the start of the data collection a protocol was written, with a step-by-step description of the procedures and agreements who (GP, RIVM, Nivel) was responsible for each step in the data collection. Our experience was that for the researchers at the reference laboratory it quickly became a routine to forward an extra envelope (with study information for parents) to the GP, when they had a lab-confirmed positive RSV result in a child <5 years. However, we have learnt that it is important that this envelope stands out for a GP (for example by adding a colourful sticker with the name of the study on the envelope), otherwise the envelope could end up in the pile of administrative work of a GP practice. In addition, it was important to send an additional reminder by email to notify the GP that a child was tested positive for RSV and that an envelope with study information for parents needed to be forwarded to the parents. In addition, we performed control actions to increase the number of swabs of GPs that were not so active.

The use of a digital questionnaire system

To ensure the privacy of the children and follow the guidelines of the medical ethical committee in the Netherlands, researchers at Nivel and the RIVM had no access to names and addresses of the children. For this reason, we were not able to directly send an e-mail with study information and access to the digital questionnaire to the parents. Therefore, the GP needed to forward an envelope to parents with study information and an explanation on how to access the digital questionnaire. This extra step might be an additional barrier and could be an explanation for the low response rate in the

Netherlands. After giving informed consent and completion of the first questionnaire, parents provided their e-mail address. The Day 30 questionnaire was sent by e-mail; parents could access the questionnaire only by clicking on the link in the e-mail. Seven out of 12 parents did complete the Day 30 questionnaire within seven days, and four parents completed this questionnaire after having received a reminder. The Day 30 questionnaire was completed by 8 out of 11 parents on the same day as the reminder e-mail was received.

HRQoL questionnaire

As there was no validated HRQoL in very young children available, we have gathered additional information regarding the feasibility of this questionnaire, to evaluate whether we can use this questionnaire in future ComNet studies. In total, 11 parents have completed the Day_30 (HRQoL) questionnaire. Among those 11 parents, 2 reported a comment on the HRQoL questionnaire, while no comments were given on the Day_14 questionnaire. One of the parents reported it was not possible to complete all questions because the child could not walk yet, and a second parent got irritated by the questionnaire because the questions were in their eyes not related to the RSV infection.

Evaluation of the study procedures with participating GPs

Eight GPs provided their feedback regarding the logistical procedures of the ComNet study. We have used this feedback to improve the logistical procedures during the study. The feedback was collected during the Annual Network meeting for GPs in the influenza surveillance system on 19 January 2020.

We started this meeting with a statement about whether the GPs thought the number of RSV cases this season was comparable to previous seasons. Three GPs thought the number of RSV cases in their practice was lower, 3 thought the number of RSV cases were comparable and 1 GP thought the number of RSV cases was higher compared to previous seasons. Seven of the GPs had swabbed one or more children <5 years this season. One GP mentioned she had not swabbed children under the age of 5 years because she also participated in another study. For the other study, the swab collection in children fulfilling the ARI case definition was arranged by a researcher of the University Medical Center of Utrecht. There was no consensus among the GPs whether it was more difficult to collect swabs in young children compared to adults. One GP said: “Parents do think it is sad for their child to perform the nasopharyngeal and oropharyngeal swab collection procedure because the child was already very ill”, while another GP said he used the swab collection and corresponding diagnostic tests as a tool to reassure parents. A third GP said she did the motivational work to recruit children in the routine influenza surveillance (by asking parents), but the practice nurse was actually taking the swabs. Some of the GPs said they only collected the nose swab in very young children because that was less burdensome for children.

GPs mentioned that the logistical procedures regarding the data collection for RSV ComNet worked well for them; the procedures did not take up much extra time. GPs mentioned that there was no time during consultation to introduce the RSV ComNet study. Some of the GPs (or practice nurses) therefore contacted the parents by phone before forwarding the envelope with the study information or included an additional note in the envelope with the study information. The experience of the project team is that parents did appreciate this extra notification by the GP. Finally, we asked GPs how we could best motivate them to increase the swabbing of patients, including children. They mentioned that regular awareness e-mails about the importance of swabbing children was a good way to motivate them. In addition, they could be motivated with some elements of competition, for example, by comparing the number of swabs they have collected versus the average of other GPs.

3.3.3 Disease burden analyses

Patient characteristics of children included in RSV ComNet are shown in table N3.

Table N3. patient characteristics of children in RSV ComNet (n=12)

	Included children n (%)
Boys	*9 (75%)*
Age in months median (IQR)	*11 (8-15)*
Symptoms	
Shortness of breath	*6 (50%)*
Cough	*10 (83%)*
Sore throat	*0*
Coryza	*8 (67%)*
Illness due to infection	*12 (100%)*
Fever	*11 (92%)*
Medical history	
Prematurity	*1 (8%)*
Chronic respiratory disease	*0*
Malnutrition	*1 (8%)*
Immunocompromised	*0*
Other chronic medical condition	*0*
Previous RSV infection this season	*0*
Virological test results	
Co-infections[1]	*3 (25.0%)*[2]
RSV A	*9 (75.0%)*

Note: [1]Co-viruses tested for were influenza virus type A (positives subtyped) A, influenza A(H1N1)pdm09, influenza virus B/Victoria and B/Yamagata, respiratory syncytial virus types (A and B), adenovirus, rhinovirus and enterovirus (positives typed). [2]Two children were co-infected with the rhinovirus and one with the enterovirus.

Health care use and socio-economic burden

The clinical and socio-economic impact of a RSV infection in young children is shown in table 5. Children had a median of 1 (IQR 1-2) extra regular consultation to the PCP after the initial visit, and 1 phone or email contact (IQR 0-1). Two children <1 year old were hospitalized for 1 day and 9 days respectively. None of the children were hospitalised after 14 days (date of completion of the first parental questionnaire) or needed a visit to the intensive care unit.

The median duration of the RSV infection was 9.5 days (IQR 7-14), children did miss a median of 3 (IQR 1.5-4.5) school/daycare days, and 7 out of 12 parents did miss workdays due to the child's illness (median of missed workdays was 2 (IQR 0-3.5). After 14 days, 10 out of 12 children did return to normal activities according to the parents, however, in 8 out of 12 children parents reported a median of 2 (IQR 1-2) remaining symptoms (Table N4).

Table N4. Clinical and socio-economic impact of RSV infections in young children in the period between swab uptake and 14 days after

	Included children (n=12)
Health care usage	
Extra consultations to PCP	
Regular consultation (median, IQR)	*1 (1-2)*
Home visit (median, IQR)	*0 (0-0)*
Phone / e-mail contact (median, IQR)	*1 (0-1)*
Emergency department (n, %)	*3 (25%)*
Consultations to other medical specialists (n, %)	*2 (17%)*
Hospitalisation (n, %)	*2 (17%)*
Days hospitalised (median, IQR)	*5 (1-9)*
ICU n(%)	*0 (0%)*
Paramedical care (n, %)	*0 (0%)*
Use of medication and prophylaxes	
Paracetamol (n, %)	*3 (25%)*
Other pain medication (n, %)	*1 (8%)*
Antibiotics (n, %)	*4 (33%)*
Other drugs (n, %)	*2 (17%)*
Medications[1] (n, %)	*5 (42%)*
Medication[2] (n, %)	*4 (33%)*
Palivizumab (n, %)	*0 (0%)*
Socio-economic burden	
Days of illness (*median, IQR)*	9.5 (7-14)
Days out of daycare/school (*median, IQR)*	3 (1.5-4.5)
Sick leave caregiver (*n, %)*	7 (58%)
Days of sick leave (*median, IQR)*	3 (2-4)
Impact on work (*median, IQR)*	2 (1.5-2.5)
Returned to daily activity (*n, %)*	10 (83%)
Persistent symptoms at day 14	
Wheezing/whistling in the chest (*n, %)*	0
Persistent cough with slime (*n, %)*	1 (13%)
Persistent cough without slime (*n,%)*	5 (63%)
Nose complaints *(n,%)*	7 (88%)
Number of symptoms (*median, IQR)*	2 (1-2)

Note. [1] Medication included antibiotics, paracetamol, other pain medication and other medication, [2] Medication included only antibiotics and pain medication.

Quality of life

The HRQoL scores at Day_30 are shown in table N5. As different versions of the questionnaire are used for children in the age categories 1-12 months, 13-24 months and 2-4 years, the scores are shown for each age category separately. The number of missing items on the PedsQL questionnaire was zero, and therefore no imputations were necessary. The mean total score for children aged 1-12 months was 64.2 *± 15.3 and for children aged 13-24 months 76.1 ± 16.7.*

Table N5. *Health related quality of life scores of children included in the RSV ComNet study 30 days after sampling* (n = 12)

Quality of life	*1-12 months (n=8) Mean ± SD*	*13-24 months (n=3) Mean ± SD*
Total Scale Score	*64.2 ± 15.3*	*76.1 ± 16.7*
Physical Health subscale score	*60.5 ± 14.4*	*73.2 ± 14.7*
Physical functioning	*52.6 ± 24.2*	*75.9 ± 11.2*
Physical symptoms	*65.3 ± 11.1*	*70.8 ± 18.1*
Psychosocial Health subscale score	*67.2 ± 17.0*	*78.2 ± 19.5*
Emotional functioning	*57.0 ± 23.1*	*70.1 ± 26.4*
Social functioning	*79.7 ± 17.6*	*88.3 ± 12.6*
Cognitive functioning	*85.2 ± 18.9*	*83.3 ± 14.7*
School functioning	*N/A*	*N/A*

Note. No children between 2-4 years were included in the RSV ComNet study in the Netherlands.

Predictors for disease burden

Unfortunately, the number of included children in the Netherlands was below 50 and therefore we could not examine predictors for disease burden in the Netherlands.

3.3.4 Population based estimates of RSV incidence

For the Netherlands, it was not applicable to calculate population based RSV incidence rates. For a more detailed explanation see the methods section. In the discussion we have outlined what is needed to calculate population-based estimates of RSV based on the experience of the influenza surveillance network

4 Summary of the main findings

4.1 Feasibility of disease burden study protocol

The first aim of the study was to evaluate whether it was feasible to investigate the disease burden in young children with RSV (<5 years) in primary care. Therefore, a disease burden study protocol was developed to prospectively measure the clinical burden, health care utilisation and societal impact of an RSV infection in primary care.

This disease burden protocol was implemented in two European countries: Italy and the Netherlands. However, the implementation methods differed slightly between the two countries. In Italy, the disease burden protocol was implemented in a network of paediatricians more often involved in research activities, and in the Netherlands in an existing routine influenza surveillance system. Another important difference between countries was the methods of data collection. In Italy the paediatrician invited the child (and parents) to participate in the study during the first consultations, and a research nurse used telephone interviews to collect the questionnaire data (day_14 & day_30), while in the Netherlands parents of RSV positive children were invited with a letter from the GP, and digital questionnaires (day_14 & day_30) were collected. This study showed that the disease burden study protocol can be implemented relatively easy in a scientific network of paediatricians or added to the logistical procedures of a routine influenza surveillance system. The workload for primary care physicians, reference laboratories and parents was low. This makes it easy to extend the RSV ComNet network and include new countries.

As no validated QoL questionnaires were available for children below 2 years of age, we have paid extra attention to the feasibility and appropriateness of the QoL questionnaire. In both countries, parents were having difficulties completing the QoL questionnaire. This was mainly related to the fact that children under 2 years of age did not acquire all skills that are asked for in the questionnaire, relating to the developmental age of the child and not to the RSV infection. Although the QoL questionnaire was validated in children aged 2-4 years, research nurses in Italy noticed that even in those children questions related to the emotional status and social life were difficult to answer for parents.

The most important lessons learnt from this pilot study were:

1) The size of the network needs to be sufficient to capture an adequate number of RSV positive cases yearly (or one can decide to implement the study for multiple seasons).
2) Regular communication between researchers, reference laboratories and primary care physicians is important for successful patient recruitment.
3) The PedsQoL questionnaire is not appropriate for the youngest children aged 0-2 years.
4) A more personal approach to invite children (and parents) to the study is most successful. In our opinion, it is feasible and time-saving to use digital questionnaires, however, a personal invitation from a primary care physician or a member of the research team will be helpful to increase the response rate on the digital questionnaires significantly.
5) Implementation of the disease burden study protocol in a country requires customisation regarding the logistical procedures to collect the data.

4.2 Clinical burden, health care utilisation and societal impact

The second aim was to measure the disease burden of RSV in young children in primary care. In Italy, 119 RSV positive children were included and in the Netherlands 12. Therefore, comparisons between countries should be made cautiously.

Our study showed a high percentage of cough and nose complaints at the onset of the RSV infection in both countries, and in 50% (NL) and 75% (IT) of the children the PCP reported shortness of breath, which suggests that a considerable proportion of the children had lower respiratory tract symptoms. In addition, we found a high number of co-infections in both countries (51% Italy and 25% the Netherlands), however, it has to be noted that the number of co-viruses tested for differed between countries (14 co-viruses in Italy and 4 in the Netherlands).

The median duration of illness was 7 (IQR 5-10) and 9.5 (IQR7-14) days for Italy and the Netherlands, respectively. After 14 days, 31% of the children (36/116) in Italy and 67% of the children (8/12) in the Netherlands reported at least one persistent clinical symptom. However, parents reported that 92% of the children (106/116) in Italy, and 83% of the children (10/12) in the Netherlands were returned to their normal daily activity level. Therefore, we recommend for the ComNet II study protocol to also measure the health care utilisation and societal impact over the period between the Day_14 and Day_30 questionnaire.

In both countries, the median number of additional consultations to a PCP was one (additional to the first consultation). Moreover, 16% (Italy, 18/116) and 25% (Netherlands, 3/12) of children visited an emergency department, and 6% (Italy, 7/116) and 17% (Netherlands, 2/12) of children were hospitalised. The RSV infection also has significant impact on the society, as the percentage of caregivers that reported sick leave was 53% and 58% in Italy and the Netherlands, respectively, for a median number of 7 (IQR 5-14) and 2 (0-3.5) days.

For Italy, a significant association between high health care use and younger age in years (OR: 0.53, p-value: 0.01) and region (OR: 4.38, p-value: <0.01) was found. We could not identify any predictor for the duration of illness. No prediction model was built based on the Dutch data because of the small sample size. More studies and larger sample sizes are needed to identify predictors for RSV disease burden in primary care.

Finally, figures with the weekly ARI incidence rates and RSV positivity rates for Italy are shown in the results section.

5 Implications for ComNet II

The final RSV ComNet disease burden study protocol for ComNet II will be ready by the end of July 2020. In the following, we provide an overview of the proposed changes to the current ComNet I study protocol.

5.1 Disease burden study protocol ComNet II

The design of the study, the eligibility criteria of participants, and the timing of measurements will not be changed.

At Day 1, we will add some additional questions regarding the baseline symptoms in order to get more insight in the severity of the disease, i.e. is this more related to upper respiratory tract symptoms or lower respiratory tract symptoms. Additional symptoms that will be measured include fever, feeding difficulties, birth weight, cough with and without slime, and wheezing.

At Day 14, the basis of the questionnaire remains unchanged. However, we will specify the level of detail regarding medication use (in Italy more detailed information was collected compared to the Netherlands, for example regarding over the counter medication). In addition, specific information regarding nebulizers will be added as this is common practice in some countries. Finally, we will ask about the productivity losses and work absenteeism of both parents/caregivers instead of only one parent.

At Day 30, the most comprehensive changes will be made to the original ComNet I questionnaire.

I. We will repeat most questions from the Day 14 questionnaire*, i.e. the questions related to:

   (1) Health care utilisation,
   (2) Days of illness,
   (3) Socio-economic impact,
   (4) Current health status.

   *(For more details regarding the questions see section 2.1.3 “data collection & measurements” in the country report).

To avoid unnecessary burdening of parents, we will start the Day_30 questionnaire with two short questions whether the child used health care or there was some kind of socio-economic impact in the period between 14 days and 30 days. If the answer to these questions were negative the more detailed questions will be skipped.

II. We will add questions regarding complications due to the RSV infection, like otitis media (which needs to be carefully defined), and pneumonia.

III. We are exploring the possibilities for another approach to measure the QoL of the children. We are currently thinking about measuring the QoL of the primary caregiver as an estimate of the impact of the child’s illness on the family. In that case, it is important that the QoL questionnaire is focused on the social and emotional impact that a sick child has on the family. Another possibility is to use a newly developed disease specific QoL questionnaire for very young children with RSV based on other questionnaires. This is currently under development by a team of Sanofi Pasteur members.

5.1.1. Sample size calculation

Our recommendation is to choose hospitalisation rate as the primary endpoint in sample size calculations for future burden of disease studies in young children in primary care. Hospital admission causes high clinical burden for the child and their family and it is a significant cost driver of health care costs, resulting in high health care burden, especially in the youngest children. However, there is limited knowledge about the socio-economic burden of RSV infections in young children from a broader societal perspective. To our knowledge, only two studies in the community or primary care setting have investigated the socio-economic burden of RSV from a broader societal perspective.[18,19] Both studies showed that indirect costs, like productivity losses and work absenteeism of parents, have a significant impact on the socio-economic burden, and are even the key cost drivers for RSV infections in children.[18,19] Although the hospitalisation rate is highest in the youngest children, the Italian results showed that the direct costs seem to be consistent between age categories. In addition, indirect costs, like absenteeism of school or daycare, will be more visible in toddlers compared to the infants. A unique selling point of the RSV ComNet disease burden study protocol is that the protocol is designed to measure not only the clinical burden and health care utilisation, but it is also measuring the socio-economic burden from a societal perspective. Therefore, for future studies we recommend measuring socio-economic disease burden to include children aged 0-5 years. Results of these studies can be used to predict the benefits of future prevention methods. Box 1 showed the sample size calculation for the ComNet II study based on the results of the RSV ComNet I pilot.

Box 1. Sample size calculation ComNet II (Johnston, 2019)
Children aged 0-4 years

Outcome measure:
Hospitalisation 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%

RSV positivity rate in children <5:
Italy: 119/293 (40,6%) – WHO ARI Case Definition
The Netherlands: 32/152 (21,1%) – ILI and ARI Case Definition
We have used the Lazio RSV positivity rate (32.7%) as data collection was started and stopped in the middle of the season in Puglia

Assuming the WHO ARI Case Definition and the Italian results, approximately 450 swabs will be sufficient to reach 150 RSV positive specimens. Depending on the expected response rate of parents in a given country, the number of swabs that are needed can be estimated.

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

6 General discussion & conclusions

This is one of the first studies that prospectively measured the clinical burden, health care utilisation and societal impact of RSV infections in young children in primary care. Previous studies investigating burden of RSV infections in young children wre mainly focused on morbidity and mortality, and data were mostly collected retrospectively using hospital registration data.[1,6,17]

The study suggests that RSV causes a significant burden in young children consulting a primary care physician. The clinical burden seems comparable between countries and within regions in Italy, however, some differences in health care utilisation and societal impact between Italy (also between regions) and the Netherlands were found. The reason for this might be differences in the organisation of the health care system and cultural differences for example in health care seeking behaviour and in the caring of children (parental roles, availability of parents to look after a sick child, family support mechanisms (e.g. grandparents), availability of kindergartens, care of children in general, etc.). In Italy, for example, a decentralised health care system exists, allowing autonomy to regions in their health care organisation, while in the Netherlands a centralised health care system is used.[30,31] This means that differences in health care usage between the Lazio and Puglia region may be caused by regional differences in the health care system, rather than actual difference in severity of disease, as region appears to have no effect on the duration of illness. Future studies need to take into account differences in health care organisation and cultural differences when extrapolating disease burden estimates to other regions or countries.

A new finding presented in this study is that the burden of RSV is not only related to clinical burden and health care utilisation, but RSV infections in young children also have a significant impact on the society (resulting in work absenteeism and productivity losses of parents), even in a primary care population. Only two studies, conducted in the early 2000s, have measured indirect (societal) costs of RSV infections in primary care, and those studies also showed a significant impact on the society.[18,19] However, the number of participants in primary care studies is limited so far, and therefore more studies are needed to measure the clinical burden, health care utilisation and societal impact of RSV infections in young children in primary care with more precision.

A large number of co-infections in RSV positive cases were shown in this study, especially in Italy. This might be due because the number of co-viruses tested in Italy was larger in comparison to the Netherlands, but also larger compared to other published studies.[32] However, a meta-analysis showed no differences in severity or health care utilisation between RSV mono-infected and RSV co-infected children under the age of 5 years, except for the RSV-human metapneumovirus (hMPV) co-infection.[32]

In the Netherlands, the circulation of RSV this winter was low compared to previous years, resulting in a low percentage of RSV positive cases on the tested specimens. One of the reasons might be the warm winter season, as a previous study showed an association between RSV health care utilisation and cold temperature.33,34

COVID-19 pandemic

A limitation of our study is that both countries experienced the COVID-19 pandemic (officially announced on 11/March/2020) and data collection was stopped earlier than planned. Presumably, this would not have affected the Dutch data collection procedure, as there were no new cases in the weeks prior to the

COVID-19 outbreak. In Italy, data collection was still ongoing and it is therefore likely that the pandemic has limited the number of participants included in the study, and the calculation of a seasonal RSV incidence rate in Italy was hindered.

6.1 Conclusions

This study showed that it is feasible to implement the disease burden study protocol in a routine influenza surveillance system, as well as in a network of primary care physicians more often involved in scientific research. In addition, an RSV infection seems to cause a significant burden in young children (<5 years of age) in primary care, however, larger sample sizes are needed to provide reliable estimates.

Recommendations for the ComNet II study

- Extension of the RSV ComNet network to other European countries.
- Calculation of the socio-economic impact (expressed in costs) of an RSV infection in young children in primary care.

Recommendations for future research (beyond ComNet II):

- Creation of a long-term follow-up cohort of the participants in the RSV ComNet studies to investigate the long-term impact of RSV infections, including complications.
- More research on comparative primary care studies is needed, so that the RSV ComNet study results can be better interpreted and extrapolated to a national or regional (European) level.
- Implementation of the (adapted) RSV ComNet disease burden study protocol in middle and low income countries.
- Implementation of the RSV ComNet disease burden study protocol in a prospective cohort study in a hospital population to measure individual patient burden.
- Implementation of the disease burden study protocol to a population of children with other respiratory infectious diseases, for example influenza. This ensures comparison of the disease burden between infectious diseases.
- Investigation of the impact of co-infections, especially hMPV, on disease severity, including insight in the clinical impact of RSV with other viruses.
- Research into the differences in medication use for RSV, especially antibiotic use, between countries or between regions within countries in the case of a decentralised health care system.
- Research on the impact of COVID-19 and social distancing measures on the epidemiology of RSV and other respiratory infections should be encouraged.

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Annex 1 Questionnaires used in ComNet I

Day 1 form

Note: This questionnaire is based on the WHO RSV specimen submission form [22]

Pre-filled information

Doctor's Name/code:
Patient ID code:
Date of birth :
Gender:
Date of sample collection and completion of form (T_1):

Patient identification

[country specific, depends on logistics]

Clinical information

Modified ARI-definition (see Box above for information)

Sudden onset of symptoms, date:
Shortness of breath: (yes/no)
Cough: (yes/no)
Sore throat: (yes/no)
Coryza: (yes/no)
Illness is due to an infection (clinician's judgement): (yes/no)
Bacterial throat infection (e.g. streptococcal angina or scarlet fever): (yes/no)

Further clinical information; pre-existing medical conditions

Prematurity: (no/yes, number of weeks)
Chronic respiratory disease: (no/yes, specify)
Malnutrition: (no/yes)
Immunocomprised: (no/yes)
Other chronic medical condition: (no/yes, specify)
Previous RSV infection this season: (no/yes)

Note: If these questions (the pre-existing medical conditions above) cannot be included the T_1 questionnaire, they should be included in the T_14 questionnaire.

Laboratory information

Specimen details

Type of specimen: (nasal/throat swab / nasopharyngeal aspirate / tracheal aspirate / sputum / BAL)

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: (Postive / Negative)

RNP CT value:
Co-infections

Day 14 form

Pre-filled information
Patient ID code:
Date of birth :
Gender:

Date: __/__/____

1) Pre-existing medical conditions

Note: These questions should only be included if they are not included in the T_1 questionnaire.

Prematurity: (no/yes at least 3 weeks early, number of weeks (range 3-17 weeks)
Chronic respiratory disease: (no/yes, specify)
Malnutrition: (no/yes)
Immunocomprised: (no/yes)
Other chronic medical condition: (no/yes, specify)
Previous RSV infection this season: (no/yes)

2) Health care use related to the RSV infection
Did your child receive preventive medication (Palivizumab [please adapt name according to your country]) this season? (no / yes)

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 emergency room related to the RSV infection, since he/she was swabbed? (no / yes)

Was your child been hospitalised related to the RSV infection, since he/she was swabbed? (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 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 / other)

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/ yes, __ days)
Did you or your partner need to take sick leave due to your child's illness? (no / yes, __ days)
Were you or your partner affected at work due to your child's illness? (no / yes, __ days)

If yes, please estimate the size of the impact during these days?
(0 = no impact, 4 = maximum impact)

We will add some extra questions regarding the non-direct health care costs.

5) How is your child doing now?

My child is currently hospitalised. (yes/no) → stop the questionnaire
He/she has 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? (no / yes, specify below)

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)
Other symptoms _____

Other comments?

If you have any other comments regarding (the effects of) your child's RSV infection, you can write them down below.

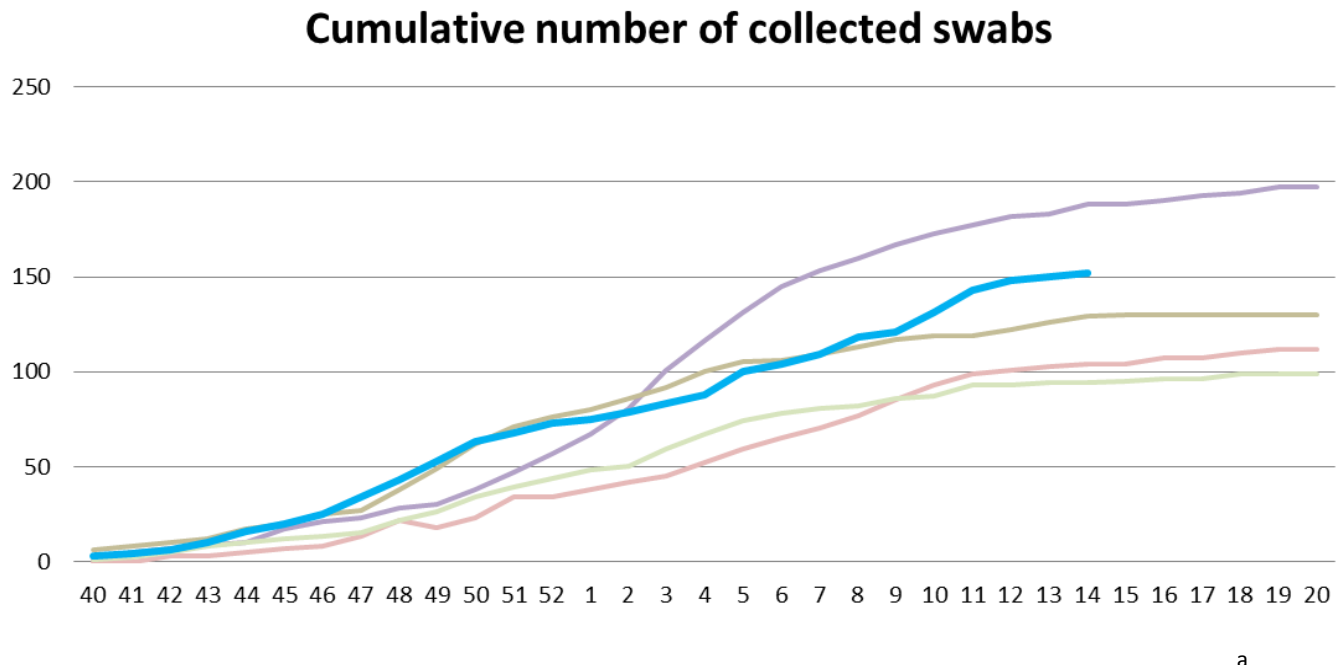
Annex 2 Extra information on the feasibility of data collection using the Dutch sentinel influenza surveillance system

For the Netherlands, we have examined whether the number of swabs in children <5 years of age increased compared to the previous 4 seasons, as we received a budget to increase the number of swabs in children <5 years of age in the Dutch sentinel network.

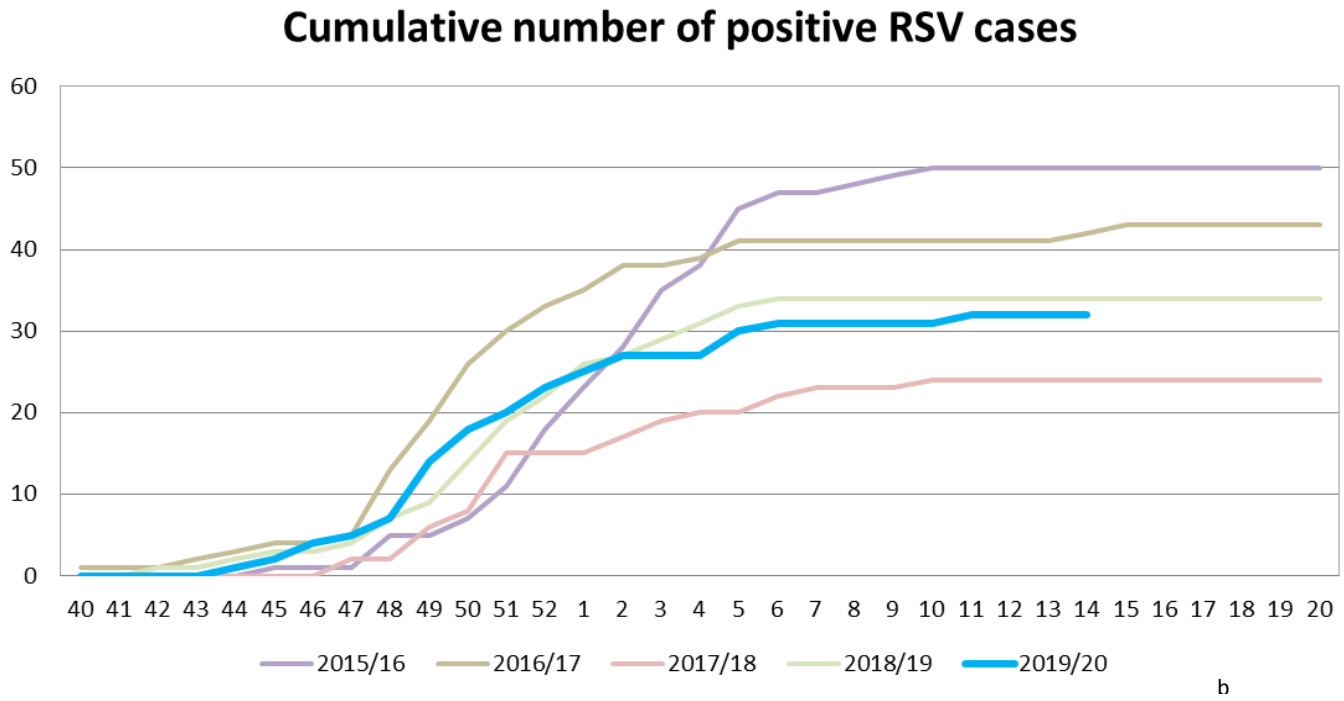
In the RSV season of 2019/20 (week 40/2019-14/2020) we collected a total number of 152 swabs from children <5 years, of which 32 cases were RSV positive (21%) (Figure N2). This was a higher number in comparison with the four previous seasons, with the exception of the 2015/16 season when 188 swabs were collected. The 2019-20 RSV season in the Netherlands was very mild compared to other seasons based on the relatively low percentage positive of 21% compared to 27%-36% in the four previous seasons. Since the collection of swabs was discontinued in week 14, this percentage of 21% is probably overestimated. The premature end of the patient recruitment due to the COVID-19 pandemic did not have a significant impact on patient recruitment numbers as the RSV season was largely over, which was in line with the end of previous RSV seasons in the Netherlands (Figure N2).

One of the aims of the study was to test the feasibility of the implementation of the study protocol in an existing influenza surveillance network. Therefore, we have further investigated the influence of case definition (ILI or ARI) on the percentage positive of RSV. For this analysis, we have used the case definition (ILI or ARI) the GP has reported on the virological form, which might be less objective compared to a case definition based on actual symptoms. In the RSV seasons 2015/16 to 2019/20, the percentage positives of RSV in children who met the ARI case definition was higher on average 33% (range 27-43%) compared to the percentage positive in children who met the ILI case definition on average 22% (range 14-29%). In a regular season more “ILI swabs” compared to “ARI swabs” were collected in children <5 years of age, on average 80 “ILI swabs” (range 71-85) and 61 “ARI swabs” (range 40-97).

Figure N2 shows the cumulative number of sampled patients (a) and cumulative number of RSV positive cases (b) in children <5 years of age in the seasons 2015/16 to 2019/20. In 2015/16 the cases in week 53 are added to week 1.



a



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