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The burden of respiratory syncytial virus in children under 5 years of age in Norway

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SUMMARY

Objectives: To estimate age-specific incidence of medically attended respiratory syncytial virus (RSV) infections in hospitalised Norwegian children and describe disease epidemiology.
Methods: Active prospective hospital surveillance for RSV in children <59 months of age was conducted during 2015–2018. All febrile children 12–59 months of age were enrolled, whereas children <12 months were enrolled based on respiratory symptoms regardless of fever. Surveillance data were linked to national registry data to estimate the clinical burden of RSV.
Results: Of the children enrolled, 1096 (40%) were infected with RSV. The highest incidence rates were found in children 1 month of age, with a peak incidence of 43 per 1000 during the 2016–2017 season. In comparison, children 24–59 months of age had an infection rate of 1.4 per 1000 during the same winter season. The peak season was during the 2016–2017 winter, with an incidence rate of 6.0 per 1000 children 0–59 months of age. In the study population a total of 168 (15%) of the infected children had pre-existing medical conditions predisposing for more severe disease. High infection rates were found in this population.
Conclusions: Children with comorbidities showed high hospital contact rates, but the majority of children in need of medical attention associated with RSV infection were previously healthy.

Introduction

Respiratory syncytial virus (RSV) is the most important pathogen causing viral lower respiratory tract infection (LRTI) in young children worldwide and is estimated to cause 33.1 million acute LRTIs in children under 5 years of age annually[1, 2]. Within the first year of life two-thirds of all infants are infected with RSV, and almost all children have been exposed by the age of two[3, 4]. Despite the high prevalence of the disease[5,9], few data are available on the RSV burden in Norway, and previous studies were either single center[6, 7] or register-based only[8].

Most children infected with RSV develop mild upper respiratory tract symptoms, but some will experience acute LRTI such as bronchiolitis or pneumonia. Risk factors for more severe infections include young age, prematurity, bronchopulmonary dysplasia, con-

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genital heart disease, neuromuscular impairment and immunodeficiency[10]. Treatment is mainly supportive[11] and preventive measures are currently limited to hand hygiene, the use of personal protective equipment in hospital settings, and passive immunization by monoclonal antibodies, which are provided free of charge for defined risk groups in Norway[12]. Of the leading pathogens causing LRTI morbidity and mortality worldwide, RSV is the only one still lacking a vaccine[13], making it one of the world's greatest unmet vaccine needs[14]. Substantial effort has been put into RSV disease prevention since the first failed vaccine attempt in the 1960s[15–17]. In recent years there have been promising advances in the development of vaccines and monoclonal antibodies against RSV, the rapid progression in the field is encouraging[18]. In 2015, the WHO highlighted the need for global estimates of RSV disease burden[5]. Especially age specific data in infants is of high priority, to identify subgroups who would benefit from prophylaxis.

In 2014, Norway established a unique, active, hospital-based sentinel surveillance network to monitor trends in vaccine preventable diseases. The Norwegian Enhanced Paediatric Immunization Surveillance (NorEPIS) consists of five large hospitals with a combined catchment population approaching 44% of the pediatric population in Norway. During 2015–2018, NorEPIS implemented RSV surveillance among children < 5 years of age during three consecutive winter seasons.

The primary aim of this study was to provide age-specific incidence rates of medically-attended RSV infections in Norway. The secondary aim was to estimate hospitalization incidence rates for subgroups of children with known risk factors for development of severe RSV.

Methods

Subjects and study design

RSV surveillance was implemented during the winter season for three consecutive years from 2015 to 2018. Surveillance was conducted from week 40 through week 20, except for the first season when surveillance was implemented from week 49 through week 20. All children <5 years of age referred to hospital with fever were prospectively enrolled, whereas children <1 year of age were enrolled based on respiratory symptoms regardless of fever (Fig 1). Both inpatient and outpatient cases were eligible for enrolment. One hospital mainly enrolled inpatients. Study personnel obtained informed consent from at least one of the legal guardians prior to inclusion. Consent from any legal guardian not present during the hospital stay was retrospectively obtained within two months following study inclusion. Clinical and demographic data, and information about healthcare use was collected using a standardized questionnaire, by medical record review, and through a patient and/or caregiver interview.

Sample processing

Nasopharyngeal samples were collected from enrolled patients within 72 h of admission to the hospital, using a flocked swab or nasopharyngeal aspirate. The samples were analysed for RSV in the hospital microbiology laboratories using routine real-time polymerase chain reaction (PCR).

Registry data sources

Collected data were linked to national health registries using unique personal identification numbers. The Norwegian Patient Registry[20] (NPR) records International Classification of Diseases (ICD-10) diagnoses for all hospital visits in Norway. The Norwegian public health-care system is free of charge for children <16 years of age, and no private hospitals provide inpatient pediatric emergency care. Thus, all pediatric admissions for LRTI, including RSV infection, are registered in NPR. Further, comorbidities associated with severe outcome are likely to be registered in the hospital records and appear in the NPR. For each patient included in the prospective study, registry data were retrieved on all diagnoses the participant had received between 2014 and 2019. The Norwegian Primary Care Registry[21] (KUHR) contains data from all publicly funded general practitioners and primary care emergency clinics in Norway. KUHR uses the International Classification of Primary Care (ICPC-2) and the ICD-10 diagnostic system. For each study patient, data were retrieved on congenital heart disease, pulmonary disease, immunosuppression and cancer.

The Medical Birth Registry of Norway[22] (MBRN) contains information about all pregnancies and births in Norway. For each study patient, data were retrieved on gestational age, trisomy 21 and congenital heart disease.

The three registers together cover all governmental-funded health care in Norway, accounting for 100% of all acute admissions.

Data on the use of the monoclonal antibody, palivizumab, was extracted from the Norwegian Prescription Database[23].

Population data on individual age-groups was retrieved from Statistics Norway[24] (SSB).

National hospital data

The total number of hospital contacts registered during the winter seasons from 2015 to 2018 and diagnosed with RSV-specific ICD-10 codes (J20.5; J21.0; J12.1; B97.4) was retrieved from NPR, for all Norwegian children younger than 5 years of age.

Risk groups

Children were considered to be in high-risk groups if they were born prematurely (gestational age <37 weeks), or had been diagnosed with underlying conditions such as trisomy 21, congenital heart disease, bronchopulmonary dysplasia (BPD), chronic respiratory disease other than BPD, neuromuscular disease, immunosuppression and cancer. Children with these conditions were identified through MBRN, and through ICD-10 codes in NPR (Supplementary data 1). Linkage to KUHR did not add additional information on the comorbidities of interest within the cohort.

Data analysis

The data was analysed using Stata Statistical Software: Release 15. College Station, Texas StataCorp LLC.

RSV incidence rates were calculated for both inpatients and outpatients. Outpatient contacts were defined as any patient referred to hospital from a primary care unit, assessed at the hospital and sent home within 6 h from arrival. Inpatients were likewise referred from a primary care unit but hospitalized for further care. The final definition of a hospital contact as inpatient or outpatient was based on how the stay had been reported to the NPR when discharged from the hospital.

Any additional hospital contact within a time period of 21 days was defined as part of the same disease episode. A period of 21 days was chosen based on review of the medical records of enrolled children. If the same patient had both in- and outpatient contacts during the 21 day period, only the inpatient contact was used.

Age in months was based on the difference between the day of admission, and the date of birth.

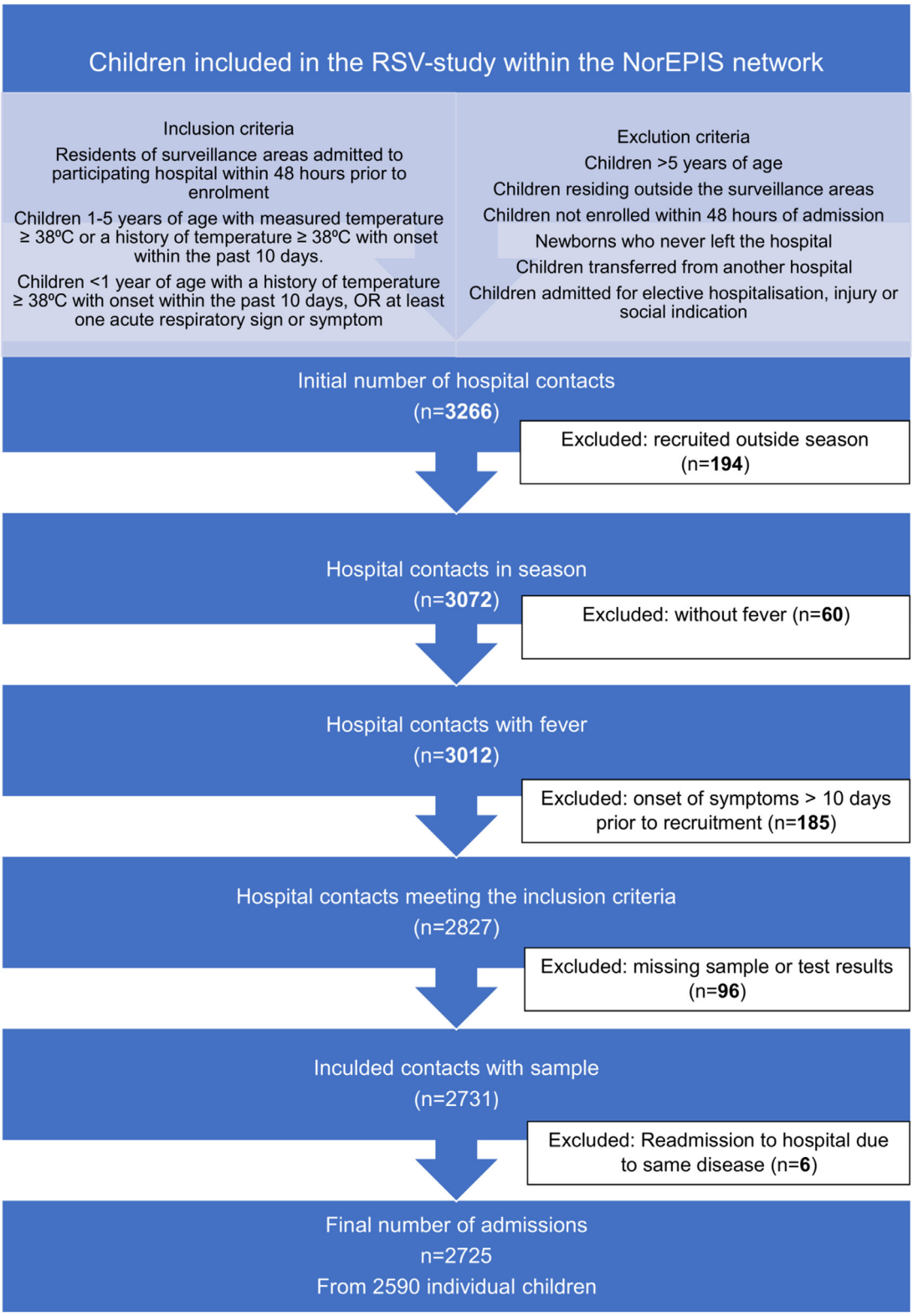

Fig. 1. Inclusion criteria and flowchart of the recruitment process.

Estimate of RSV-related disease episodes

Not all children coded for RSV have a positive RSV PCR. Conversely, not all children testing positive for RSV receive an RSV-specific disease code. The total number of RSV infections in the population was estimated based on the proportions of RSV-confirmed cases and RSV-coded cases in the prospectively collected data.

All study participants who received ICD-10 codes specific for RSV were identified. The proportion of true RSV cases among these children was calculated based on laboratory PCR results, available for all children. For RSV-positive cases in the study cohort, all cases

also receiving an RSV-specific ICD-10 code were identified, to calculate the proportion of RSV-confirmed cases who also received an RSV-specific code. To estimate the total number of RSV infections during the study period, the proportions were applied to the number of RSV-specific ICD-10 codes received from the NPR, for both the NorEPIS study catchment area and for all of Norway. Details of the calculations are provided in Table 1.

Estimate of age-specific RSV infections

To estimate age-specific incidence rates for inpatients, we applied the proportion of RSV cases in each age group in the prospective cohort, to the total number of RSV-coded disease episodes from 0 to 59 months of age received from NPR. For each age group we then calculated and applied the proportions to the background population as described above.

For outpatients we were unable to apply this method to age strata because the proportion of confirmed RSV cases receiving RSV-specific ICD-10 codes was too low. The age-specific incidence rates in the outpatient population were estimated from the total incidence rates per season for all children 0–59 months of age, and then stratified by age, based on the age distribution among RSV-positive patients in the NorEPIS study population.

For children $\geq$12 months, the denominator for incidence rates were based on 1st January population. For children $<$12 months, the population size for each month was requested from SSB, and the denominator for incidence rates was based on mean population size through the year.

Estimates of disease episodes by comorbidity

For children with comorbidities, the number of disease episodes was extrapolated from the percentage of confirmed RSV cases with each comorbidity in the study population and the estimated total number of disease episodes during the three study seasons.

The denominator was requested from NPR and based on the same ICD-10 codes as used to identify comorbidities in the study population (Supplementary data 1).

Ethics

The study was reviewed and approved by the Regional committees for medical and health research ethics - South-East A (2015/956).

Results

Study population

During the three RSV seasons studied, 3266 hospital contacts were enrolled in the study. Patients who fulfilled all study criteria and had virological testing performed, are presented in Fig. 1. A total of 2590 children 0–59 months of age, with 2725 independent hospital contacts were included in the analysis. In the study cohort 21.5% of all children had two or more hospital contacts within the 21-day period used to define one disease episode.

A total of 1096 had confirmed RSV infection equivalent to 40% of all hospital contacts included in the study. Of these, 949 (86.6%) were $<$24 months old, 482 (44.0%) were $<$ 6 months, and 301 (27.5%) were $<$ 3 months. Age and sex distributions are presented in Table 2.

Seasonality

Of the three RSV seasons studied, the second season started earlier, lasted longer and had more cases compared to thse two other seasons. The highest number of RSV-positive cases registered was during week 3 to week 6 in all study seasons. The observed pattern of two low seasons and one high season could correspond to a biannual pattern, but since surveillance was limited to three consecutive seasons we are unable to confirm this pattern.

Fig. 2 shows the weekly number of hospital contacts, as well as the percentage of RSV-positive cases tested.

Rates of RSV infections

Rates of RSV-associated disease episodes were estimated for inpatients and outpatients for each study season and are summarized in Table 3. Different estimates were calculated for the NorEPIS catchment area, and for all of Norway.

Inpatients

The estimated incidence rate of RSV infections for the NorEPIS catchment area was highest during the 2016–2017 winter season with 6.0 RSV cases per 1000 children 0–5 years of age, and 14.1 cases/1000 age 0–1 years. The lowest rate occurred during the 2015–2016 season 2.9 per 1000 children 0–5 years of age, and 7.0/1000 age 0–1 years. The estimated mean incidence rate for all 3 seasons was 4.1 per 1000 children 0–5 years of age in the NorEPIS catchment area, and 4.3 in all of Norway.

Outpatients

The seasonality pattern observed among outpatients was similar to the pattern among inpatients. The incidence rate of RSV infections in outpatients in the NorEPIS catchment area was 2.8 per 1000 in 2015–2016, 5.5 in 2016–2017 and 2.6 in 2017–2018. The highest rate of infections was among children 0–1 year of age, with 7.0 per 1000 children during the 2016–2017 season.

Age-specific incidence rates

Age-specific incidence rates are presented in Fig. 3, with upper and lower estimates. The highest incidence of RSV infections in the study population was in the age group 1–2 months, with a peak during the winter season 2016–2017, during which 43 per 1000 children were hospitalized for RSV. The lowest rate of RSV infections was in the oldest age group of 24–59 months.

Incidence of RSV infections in children at risk for severe disease

In the NorEPIS study population 496 (18%) children had one or more comorbidities. Of the 1096 RSV confirmed cases 168 (15%) children had comorbidities. Palivizumab was administered to 27 children throughout the season of enrolment[12]. Four children were hospitalized for RSV infections concurrently to palivizumab treatment.

Estimates of the mean annual incidence of RSV cases in children under 59 months of age, with comorbid disease predisposing for severe outcome, are shown in Table 4. For premature children born at gestational age 22–27 weeks, the mean incidence rate was 14 per 1000, and 12 for children born at gestational age 28–36 weeks. The highest rate of RSV confirmed cases was found in children suffering from immunosuppression with a rate of 56 per 1000 per year, and in children with a diagnosis of BPD with a rate of 44 per 1000.

Discussion

We estimated incidence rates of medically attended RSV infection in children under 59 months of age in a large prospec-

Table 1
Details of methods used to estimate the true numbers of RSV cases in the study catchment area and for all of Norway.

Inpatients[a]	Study cohort[b]				RSV coded patients in background population[c]		Proportion of RSV codes in study catchment area compared to Norway[d]	Proportion RSV-positive with RSV code (95%ci)[e]	Proportion with RSV-code who also are RSV-positive (95%ci)[e]	Estimated number of true RSV cases (upper and lower estimate)[f]	
	Disease episodes		RSV ICD10 code		Study catchment area	Norway				Study catchment area	Norway
	RSV+ a	RSV- b	RSV+ p	RSV- q	X	y	$r = x/y$	$t = p/a$	$u = p/(p+q)$	x*u/t	y*u/t
Season 1	234	285	198	4	340	855	0.40	0.85 (0.79–0.89)	0.98 (0.95–0.99)	394 (363–426)	990 (913–1072)
Season 2	337	347	292	9	718	1665	0.43	0.87 (0.83–0.90)	0.97 (0.94–0.99)	804 (752–858)	1864 (1745–1989)
Season 3	143	279	129	5	405	912	0.44	0.90 (0.84–0.95)	0.96 (0.92–0.99)	432 (392–476)	973 (883–1071)
Outpatients[g]	Study cohort[b]				RSV coded patients in background population[c]		Proportion of RSV codes in study catchment area compared to Norway[d]	Proportion RSV-positive with RSV code (95%ci)[h]	Proportion with RSV-code who also are RSV-positive (95%ci)[h]	Estimated number of true RSV cases (upper and lower estimate)[f,h]	
	Disease episodes		RSV ICD10 code		Study catchment area	Norway				Study catchment area	Norway
	RSV+ a	RSV- b	RSV+ p	RSV- q	X	y	$r = x/y$	$t = p/a$	$u = p/(p+q)$	x*u/t	y*u/t
Season 1	135	250	30	5	99	139	0.71	0.22 (0.16- 0.30)	0.86 (0.70–0.95)	382 (229–607)	536 (321–852)
Season 2	167	228	39	2	182	296	0.61	0.23 (0.17–0.31)	0.95 (0.83–0.99)	741 (498–1054)	1206 (810–1714)
Season 3	62	194	19	1	111	175	0.63	0.31 (0.20–0.44)	0.95 (0.75–1.0)	344 (191–567)	543 (301–893)

[a] Inpatients were defined as any patient referred from a primary care unit, assessed at the hospital emergency room and hospitalized for observation and/or care for more than 6 h.
[b] Patients recruited in the NorEPIS study.
[c] Number of RSV coded cases registered at the National Patient Registry of Norway.
[d] The study catchment area includes 44% of the Norwegian pediatric population < 59 months of age. Given an equal burden of RSV across the country, a proportion closer to 0.44 indicates more similar use of ICD10 codes between the 2 areas.
[e] Proportions of RSV-positive who also received RSV-code, and proportion of children with RSV-code who were also RSV-positive are exemplified by the calculations for all children from 0 to 59 months of age. For children with an inpatient hospital contact, separate proportions were calculated for each age group in Fig. 3.
[f] Upper and lower estimate based on the 95% confidence intervals of the proportions, t and u.
[g] Outpatient contacts were defined as any patient referred to hospital from a primary care unit, assessed at the hospital and sent home within 6 h from arrival.
[h] Proportions of RSV-positive who also received RSV-code, and proportion of children with RSV-code who were also RSV-positive, were calculated for all outpatients from 0 to 59 months of age. To estimate the number of RSV cases within each age group in Fig. 3, the age distribution of outpatient RSV cases in the study population were applied to the estimated true number of RSV cases in the 0–59 months population.

Table 2
Characteristics of children under 59 months of age with or without RSV infection.

	Inpatient[a]			Outpatient[b]						
	N positive/ total tested (% positive)[c]	OR[d] (95% ci)	P[e]	N positive/ total tested (% positive)[c]	OR[d] 95% Ci	P[e]				
Age group										
0 m	61/134	(45.5)	ref	–	10/33	(30.3)	ref	–		
1 m	101/187	(54.0)	1.41	(0.90–2.19)	0.13	24/64	(37.5)	1.38	(0.56–3.39)	0.48
2 m	69/124	(55.6)	1.50	(0.92–2.45)	0.11	28/62	(45.2)	1.89	(0.77–4.64)	0.16
3–5 m	115/200	(57.5)	1.62	(1.04–2.52)	0.03	63/137	(46.0)	1.96	(0.87–4.42)	0.11
6–11 m	88/260	(33.9)	0.61	(0.40–0.94)	0.02	79/199	(39.7)	1.51	(0.68–3.35)	0.31
12–23 m	174/413	(42.1)	0.87	(0.59–1.29)	0.49	121/349	(34.7)	1.22	(0.56–2.65)	0.61
24–59 m	84/282	(29.8)	0.51	(0.33–0.78)	0.002	61/217	(28.1)	0.90	(0.40–2.00)	0.80
Sex										
Male	375/909	(41.3)	ref	–	228/630	(36.2)	ref	–		
Female	317/691	(45.9)	1.21	(0.99–1.47)	0.07	158/431	(36.7)	1.02	(0.79–1.32)	0.88
Hospital[f]										
Oslo University Hospital, Ullevål	230/543	(42.4)	ref	–	159/440	(36.1)	ref	–		
Akershus University Hospital	110/252	(43.6)	1.05	(0.78–1.43)	0.73	89/220	(40.5)	1.20	(0.86–1.67)	0.28
Østfold Hospital, Kalnes	112/268	(41.8)	0.98	(0.73–1.31)	0.88	105/296	(35.5)	0.97	(0.71–1.32)	0.85
St. Olavs University Hospital	129/280	(46.1)	1.16	(0.87–1.55)	0.31	4/5	(80.0)	7.07	(0.78–3.79)	0.08
Stavanger University Hospital	111/257	(43.2)	1.03	(0.77–1.40)	0.82	29/100	(29.0)	0.72	(0.45–1.16)	0.18
Study season[g]										
2015/2016	224/508	(44.1)	ref	–	145/396	(36.6)	ref	–		
2016/2017	327/672	(48.7)	1.20	(0.90–1.51)	0.12	177/407	(43.5)	1.33	(1.00–1.77)	0.05
2017/2018	141/420	(33.6)	0.64	(0.49–0.84)	0.001	64/258	(24.8)	0.57	(0.40–0.81)	0.002

[a] Inpatients were defined as any patient referred from a primary care unit, assessed at the hospital emergency room and hospitalized for observation and/or care for more than 6 h.
[b] Outpatient contacts were defined as any patient referred to hospital from a primary care unit, assessed at the hospital and sent home within 6 h from arrival.
[c] Number of RSV positive cases compared to the total number of children tested and included in the study, followed by the percentage of positive test results in subgroups of children.
[d] Odds ratio for RSV positivity for each group as compared to the group of reference.
[e] Univariate logistic regression.
[f] Inpatient and outpatient surveillance were conducted for three consecutive RSV seasons in 5 Norwegian hospitals.
[g] RSV surveillance were conducted from week 40 through 20 during the 2016/2017 and 2017/2018 seasons, and from week 49 through 20 during the 2015/2016 season.

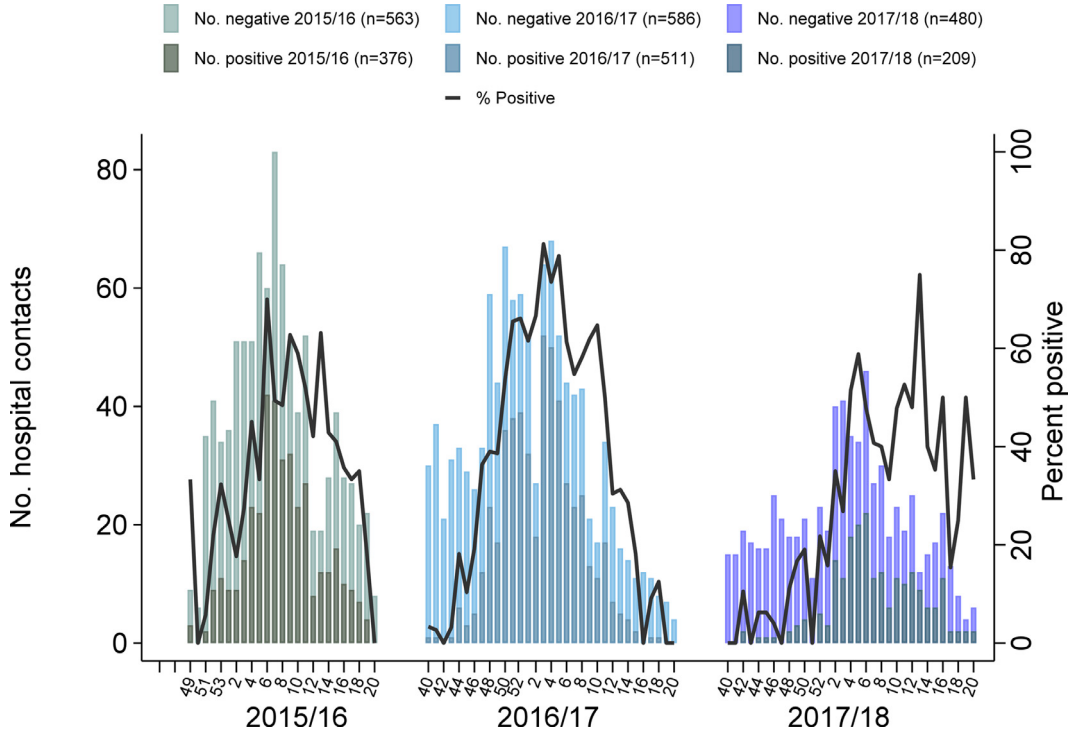

Fig. 2. Number of RSV tested participants, and proportion positive through three seasons.

Table 3
Mean incidence of RSV hospital cases in children under 59 months of age with RSV infection in Norway, by study season and age.

Rate per 1000 children; with upper and lower estimates						
Inpatients[a]						
	0–59 months		**<12 months**		**12–59 months**	
Catchment area	Incidence	(lower-upper estimate)[b]	Incidence	(lower-upper estimate)[b]	Incidence	(lower-upper estimate)[b]
2015–2016[c]	2.9	(2.7–3.2)	7.0	(6.4–7.7)	1.6	(1.4–1.9)
2016–2017[d]	6.0	(5.6–6.4)	14.1	(13.1–15.2)	3.3	(2.9–3.8)
2017–2018[d]	3.3	(3.0–3.6)	8.6	(7.7–9.6)	1.6	(1.3–1.9)
Mean 2015–2018	4.1	(3.9–4.3)	9.9	(9.4–10.4)	1.8	(1.8–1.9)
Norway						
2015–2016[c]	3.2	(3.0–3.5)	10.1	(9.2–11.1)	1.7	(1.4–1.9)
2016–2017[d]	6.1	(5.8–6.6)	18.6	(17.3–20.1)	3.2	(2.8–3.6)
2017–2018[d]	3.2	(2.9–3.6)	11.0	(9.8–12.3)	1.4	(1.2–1.7)
Mean 2015–2018	4.3	(4.1–4.4)	13.3	(12.6–14.0)	1.8	(1.7–1.9)
Outpatients[e]						
	0–59 months		**<12 months**		**12–59 months**	
Catchment area	Incidence	(lower-upper estimate)[b]	Incidence	(lower-upper estimate)[b]	Incidence	(lower-upper estimate)[b]
2015–2016[c]	2.8	(1.7–4.5)	5.3	(2.2–11.7)	2.0	(1.0–3.5)
2016–2017[d]	5.5	(3.7–7.9)	10.0	(6.1–15.4)	4.8	(2.2–9.0)
2017–2018[d]	2.6	(1.4–4.3)	8.0	(2.9–17.5)	1.2	(0.5–2.3)
Mean 2015–2018	3.6	(2.8–4.6)	7.4	(5.1–10.5)	2.5	(1.7–3.5)
Norway						
2015–2016[c]	1.8	(1.1–2.8)	4.3	(1.8–9.4)	1.2	(0.6–2.0)
2016–2017[d]	4.0	(2.7–5.7)	9.3	(5.7–14.3)	3.2	(1.4–6.0)
2017–2018[d]	1.8	(1.0–3.0)	7.2	(2.6–15.7)	0.8	(0.3–1.5)
Mean 2015–2018	2.5	(1.9–3.1)	6.6	(4.5–9.4)	1.6	(1.1–2.3)

[a] Inpatients were defined as any patient referred from a primary care unit, assessed at the hospital emergency room and hospitalized for observation and/or care for more than 6 h.

[b] Upper and lower estimates are based on the 95% confidence intervals of the proportions of RSV-positive who also received RSV-code, and proportion of children with RSV-code who were also RSV-positive, as exemplified in table 1. Separate proportions were calculated for each season, for outpatients and inpatients, and for each age group.

[c] Rates of infection are listed from week 49 through week 20 for the 2015–2016 season.

[d] Rates of infection are listed from week 40 through week 20 of the 2016–2017 and 2017–2018 seasons.

[e] Outpatient contacts were defined as any patient referred to hospital from a primary care unit, assessed at the hospital and sent home within 6 h from arrival.

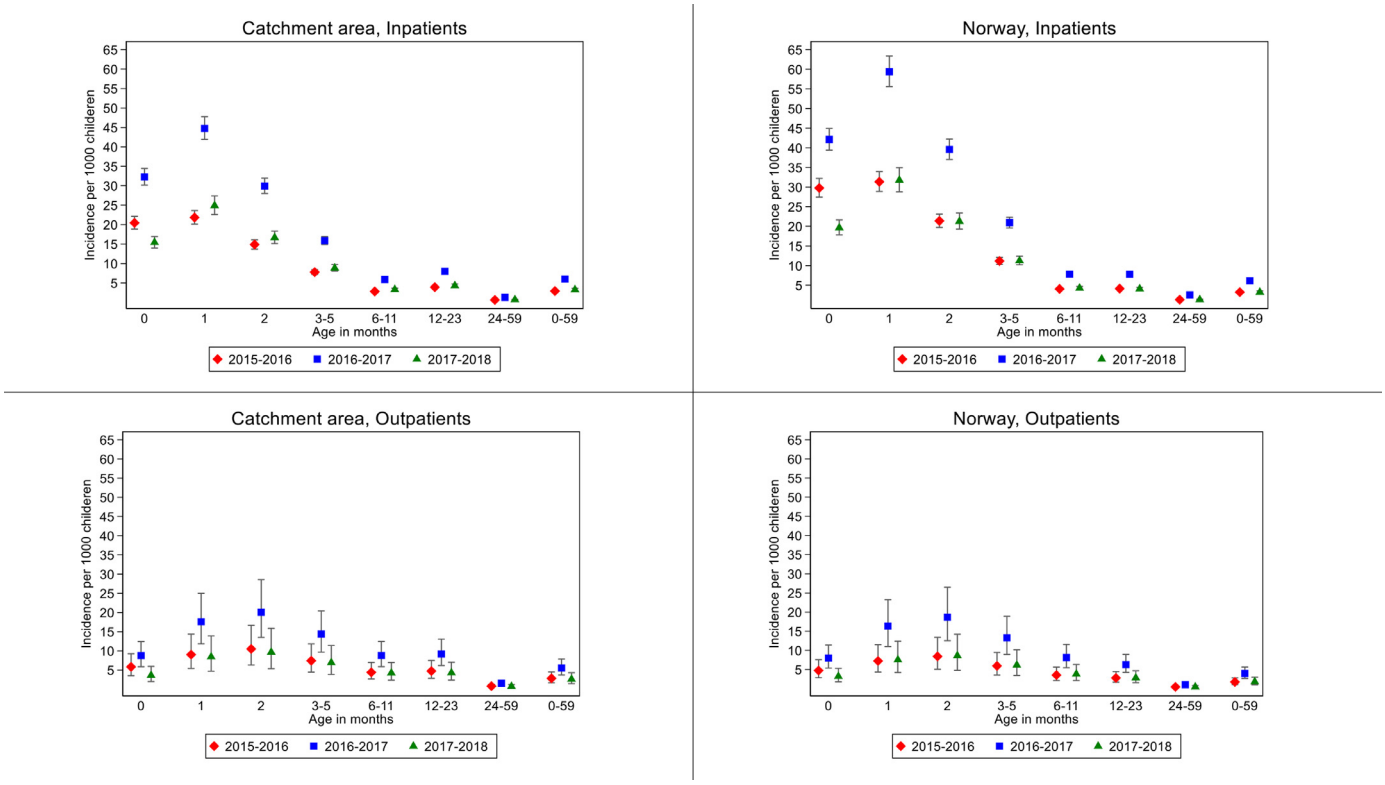

Fig. 3. Estimated Incidence of RSV infections per 1000 children according to age and season. Whiskers indicate the upper and lower estimate.

Table 4
Mean annual incidence of RSV infections per 1000 children by risk-groups in children under 59 months of age in Norway, 2015–2018.

Risk-group[a]	NorEPIS contacts	Norway, 2015–2018			
	Hospital contacts[b]	RSV-pos[c] (%)	Population[d]	Estimated cases (lower-upper estimate)[e]	Incidence of RSV-cases (lower-upper estimate)
No comorbidity	2229	928(85%)	274,191[f]	1684 (1588–1785)	6.1 (5.8–6.5)
Prematurity by gestational age					
28–36 weeks	285	108(9.9)	15,308	195 (184–207)	12.7 (12.0–13.5)
22–27 weeks	42	9(0.8)	1134	15 (15–17)	14.1 (13.5–15.2)
Trisomy 21	22	8(0.7)	508	15 (14–15)	27.6 (26.8–30.2)
Congenital heart disease	178	52(4.7)	7672	94 (89–100)	12.3 (11.6–13.0)
Pulmonary disease[g]	69	21(1.9)	1044	38 (36–40)	36.4 (34.4–38.6)
Bronchopulmonary dysplasia	65	17(1.6)	713	31 (29–33)	43.5 (40.6–45.7)
Immunosuppression	45	11(1.0)	360	20 (19–21)	55.6 (51.9–58.3)
Cancer[h]	15	5(0.5)	306	9 (9–10)	29.4 (28.1–31.6)
Neuromuscular disease	55	14(1.3)	1771	(24–27)	14.1 (13.5–15.2)

[a] ICD-10 codes used to identify risk-groups are provided in supplementary data.
[b] Total number of hospital contacts in the NorEPIS cohort.
[c] Number of RSV positive contacts in the NorEPIS cohort.
[d] Mean size of background population during the three study years.
[e] Estimated mean annual number of RSV positive hospital contacts in Norway.
[f] Estimate of population size with no comorbidity equals the total population 0–59 months of age, followed by subtraction of the population in each subgroup of comorbidities.
[g] Pulmonary disease not including asthma or bronchopulmonary dysplasia.
[h] Cancer patients receiving active chemotherapeutic treatment.

tive hospital cohort study in Norway conducted prior to the onset of the SARS-CoV-2 pandemic. We found a substantial disease burden of RSV among infants during the first year of life with the highest incidence occurring at one month of age. This is in line with the findings of Reeves et al.[8] who studied RSV hospitalizations in Norway for the same time period based on registry data alone. We consider our estimates to be more credible as these are based on active hospital-based surveillance data with virologic testing, as opposed to registry data alone Estimates of RSV infections based on health registry data alone have been reported from several other countries[25–28]. Some studies have shown that health administrative data can be used to identify RSV-related hospitalizations[29], while others found that the use of RSV-specific coding alone had low sensitivity[30]. Methods using RSV-specific coding from health registries rely on the child having microbiological testing during the hospital visit. All children included in this prospective cohort study were systematically tested for RSV by RT-PCR. RSV specific ICD-10 codes from health registries were then weighted according to the RSV proportions obtained from the prospectively collected data. The access to laboratory-confirmed data strengths our study compared to estimates based on registry data alone. In our study we estimated a national RSV incidence

of 13.3 per 1000 children <12 months of age, and 1.8 in the age group 1–4 years. In contrast, Reeves et al.[8] estimated an average incidence of RSV related hospitalization of 21.1 per 1000 children <1 year of age, and 2.1 per 1000 children aged 1–4 years. However, these estimates were based on counting all hospital contacts as independent cases, including readmissions in the same patients. As many children have more than one contact for the same episode of disease, considering all contacts and readmissions within 21 days as one disease episode better reflects the true incidence. This difference in methodology may explain lower incidence rates reported in our study compared to the findings of Reeves et al.

Our study may, however, underestimate the true incidence of RSV infections, as data was collected during only 3 consecutive RSV seasons. RSV burden is known to have a biannual pattern[31–33], and in our data we observed two seasons with low transmission and one season with high transmission (Table 3). Had the study been conducted during different seasons, our mean estimated incidence of disease episodes could have been higher. Restricting data analysis to only the last two study seasons increases the mean RSV incidence for children <1 year of age by approximately 15%, demonstrating the impact of seasonality on the estimates (supplementary data 2).

Further, RSV testing practice in the prospective study cohort is likely to have increased the number of tests performed compared to the usual clinical setting. As test results were not blinded to the attending physician, coding practice may have changed towards increased use of RSV-specific coding in the study hospitals. In addition, increased RSV-testing in the prospective study could potentially have increased RSV-testing for children not included in the study. Such changes in testing and coding at study hospitals might lead us to underestimate the incidence of RSV-related hospitalisations outside the catchment area. This may particularly affect results for outpatient cases, who in a non-study setting rarely receive an RSV-specific code due to either delay in test results or lack of testing. Indeed, only 22–31% of RSV-positive outpatients in the study received an RSV-specific ICD-10 code, compared to 86–95% of inpatients, in whom a test result is usually available on discharge (Table 1). Our estimates for RSV-related outpatient cases are higher for the catchment area compared to the national estimates. The proportion of Norwegian children residing in the study area was 44%. Of the total number of RSV-specific codes registered nationally, the study area contribution was 64% for outpatients and 43% for inpatients (Table 1). This strengthens the validity of the inpatient estimates.

Previous studies suggest that the burden of RSV in the outpatient setting has not been fully recognised, and there is a need for more epidemiological data describing the disease burden among outpatients[31,32,34]. When comparing our estimates for RSV-related outpatient cases to other studies[33,34], they are considerably lower. Some of this difference could be explained by the setup of the Norwegian healthcare system. In Norway, any child visiting the emergency ward of a hospital must be referred by a general practitioner or general emergency department, meaning that our outpatient numbers do not reflect RSV-related visits to primary healthcare providers, but only children referred to secondary care, whom the paediatrician did not consider sick enough for admission.

Our estimates of age-specific rates of RSV related hospitalizations are in line with other studies reporting on small age strata, who also found the highest incidence during the second month of life[25,26,35,36]. In community based studies[31,37] the peak incidence seems to be somewhat later.

Because RSV surveillance was conducted simultaneously with influenza surveillance the study inclusion criteria were designed to allow broad enrolment in both the RSV and influenza arms of the study. The presence of fever as a criterion for inclusion of children older than 12 months of age is a limitation to our study. Children younger than 12 months are included in the study based on either respiratory symptoms or fever. The presence of low-grade fever is common in RSV disease, but not pathognomonic[5,27,28,38]. A meta-analysis found no significant association between fever and RSV compared to other respiratory viruses[39]. One study found that lack of fever in RSV cases in a hospital setting was primarily in children younger than 12 months. For the age group 12–24 months all RSV cases developed fever as part of their disease course. For children 24–36 months of age, low grade fever was present in 94% of children hospitalized for RSV disease[40]. This finding is supported by another study in which fever duration is positively correlated with age[41]. The use of fever as an inclusion criterion for children older than 12 months of age could lead us to underestimate the actual number of RSV infections in our study.

The majority of children in need of hospital care due to RSV infection in our study were previously healthy. For children at risk of severe disease, the highest hospitalization rates were found in children with immunosuppression and bronchopulmonary dysplasia. For premature children, the denominator of the incidence rate was based on data from MBRN, which includes all live-born children but does not take into account mortality among premature infants before discharge from the neonatal intensive care unit. The true number of premature children at risk is likely lower and we may therefore underestimate RSV incidence in this population. Even though the incidence rates among children with pre-existing medical conditions are high, we still find that the majority of the RSV burden occurs among children with no pre-existing medical conditions.

The incidence of RSV-related inpatient cases are high in young children, and decline quickly with age. Our study supports previous findings, that the major burden of RSV occurs among previously healthy children, with no co-existing medical conditions, or other characteristics that identify them as being at risk of severe disease. This study was conducted prior to the SARS-CoV-2 pandemic, and RSV resurgence is expected as non-pharmaceutical measures for infection control ease[19]. This is likely to lead to substantial RSV outbreaks, with the youngest and most susceptible for severe disease having limited protection from maternal antibodies.

Our findings suggest that intervention against RSV is not only beneficial for children with underlying medical conditions, but also for otherwise healthy young children.

The norwegian enhanced pediatric immunisation surveillance (NorEPIS) network

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Disclaimer

Data from the Norwegian Patient Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

Declaration of Competing Interest

Elmira Flem is currently employed by Merck Sharp & Dohme Corp., Drammen, Norway, a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey. The work for the current study was conducted by Dr. Flem under the previous affiliation. The author(s) hereby declare that no other conflicts of interest exist.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.12.008.

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