Burden of Respiratory Syncytial Virus Infection During the First Year of Life

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Summary: In a prospective study of infants during their first RSV season, one third had a symptomatic laboratory-confirmed RSV infection. Acute otitis media developed as a complication in 77% of infants with RSV, while 7% of them were hospitalized with bronchiolitis.

Running head: Burden of RSV in Infants

Word counts: Abstract: 200; Text: 2606

FOOTNOTE PAGE

Financial support

This work was supported by Janssen Pharmaceutica NV Belgium by a grant paid to the Hospital District of Southwest Finland (a secondary employer of T.H.). ArcDia International Ltd, Turku, Finland, provided the rapid antigen detection tests for the study. T.H. is a member of the Respiratory Syncytial Virus Consortium in Europe (RESCEU). RESCEU has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 116019. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

Potential conflicts of interest

T. H. has been a consultant to AstraZeneca, Janssen, and Sanofi Pasteur. All other authors report no potential conflicts.

Abstract presentation

The results were presented in part as an abstract at the 37th Annual Meeting of the European Society for Paediatric Infectious Diseases, Ljubljana, Slovenia, 6–11 May 2019.

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ABSTRACT

Background. Although many infants with respiratory syncytial virus (RSV) infection are hospitalized, most infants are treated as outpatients. Limited data are available on the burden of RSV in outpatient infants.

Methods. In a prospective study, we enrolled 431 newborn infants and followed them for a 10-month period (September-June). During each respiratory illness, we examined the infants and obtained nasopharyngeal specimens for the detection of RSV. The parents completed daily symptom diaries throughout the study.

Results. Among 408 active participants, the seasonal incidence rate of RSV illness was 328.4 per 1000 (95% confidence interval [CI] 275.2-389.0). Infants with ≥1 sibling had a 1.9-fold higher incidence of RSV illness than those without (95% CI 1.3-2.8; *P* = .0007). Acute otitis media developed in 103 (76.9%) of 134 infants with RSV infection, and 95 (70.9%) were treated with antibiotics. Nine (6.7%) infants with RSV were hospitalized, for a seasonal incidence rate of RSV hospitalization of 22.1 per 1000 (95% CI 10.1-41.9).

Conclusions. The outpatient burden of RSV is heavy on infants during the first year of life. Acute otitis media is a frequent complication of RSV, and it should be included in cost-effectiveness analyses of prevention or treatment of RSV infections in infants.

Key words: burden of illness; infant; respiratory syncytial virus; vaccines; monoclonal antibodies; antiviral agents.

BACKGROUND

Respiratory syncytial virus (RSV) is a major worldwide cause of morbidity and mortality in young children and the leading cause of hospitalization for acute lower respiratory tract infection in infants [1-6]. The burden of RSV is most pronounced among the youngest infants. According to a recent global estimate, 1.4 million infants younger than 6 months of age are annually hospitalized with RSV-associated lower respiratory tract infection [1].

In the absence of safe and effective RSV vaccines or antivirals, the management of RSV illness has remained largely supportive. In recent years, however, recommenced and widespread efforts to combat the disease have led to the development of several candidate vaccines, monoclonal antibodies, and antiviral agents against RSV [7-11].

Although the burden of RSV-associated hospitalization of young infants is heavy and well-established, most infants with RSV infection, even those in the youngest age groups, are managed as outpatients. There are limited data available on the burden of RSV among infants treated in the outpatient setting [2, 12-16]. A better understanding of the burden of illness would be necessary to inform the development and optimal use of various interventions targeted against RSV as well as for evaluation of their cost-effectiveness. This study was designed to assess the full burden of RSV illness in infants during their first year of life.

METHODS

Study Design and Subjects

This prospective cohort study was performed at a single primary care study clinic in Turku, Finland, during the respiratory season of 2017-2018. Infants who were born at Turku University Hospital between June-August 2017 were eligible for participation if they lived within the catchment area of the hospital, the parents were able to understand and communicate in Finnish language, and the infant did not have any major congenital defects or serious chronic illnesses (e.g. severe congenital heart or lung disease or genetic, immunologic, or metabolic disorder). Approximately half of all children born during the enrollment period were enrolled in this study. Enrolled infants were considered active participants if they visited the study clinic at least once or if the parents returned at least one of the two symptom diaries, and if the parents did not inform the study personnel that their child had been treated for respiratory symptoms somewhere else than at the study clinic. Of 431 infants initially enrolled, 408 (95%) were considered active participants. The baseline characteristics of these infants are presented in Table 1.

Ethics

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland, and the study was conducted in accordance with the Declaration of Helsinki. The parents of all participating children provided their written informed consent prior to commencement of the study. The families were not compensated for their participation.

Study Conduct

The infants were followed for a 10-month period from 1 September 2017 to 30 June 2018. During this time, the parents were instructed to bring their child for clinical examination at the study clinic every time the child had fever or any signs or symptoms of respiratory tract infection. The study clinic was open every day, including weekends and holidays. All visits were free of charge to the families, and there was no limit for the number of visits. At each visit, the infants were thoroughly examined by a study physician who completed a structured medical record that contained the history, signs and symptoms, clinical findings, diagnosis, and treatment. To enable diagnosing complications that might develop after the initial visit, the infants were routinely re-examined on days 5-7 after the onset of illness and additionally whenever the parents deemed it necessary.

Background information about the infant and the other family members were obtained from the parents by using a questionnaire. During the follow-up period, the parents were asked to complete 2 daily symptom diaries (one for September-January and another for February-June) that consisted of daily charts inquiring about the signs and symptoms of the child and medications given.

Viral Diagnosis

At the first visit during each episode of respiratory illness, regardless of the severity of symptoms or the presence or absence of fever, 2 nasopharyngeal flocked swab specimens (Ultra minitip, Copan Italia s.p.a, Italy) were obtained for determination of the viral etiology of the illness. One of the specimens was inserted into a dry vial and analyzed by multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) for 16 viruses at the Department of Clinical Microbiology, Turku University Hospital (Allplex^{TM} Respiratory Panels 1-3, Seegene

Inc., South Korea). The other specimen was analyzed onsite at the study clinic by an automated rapid antigen test identifying 11 respiratory tract pathogens (mariPOC® respi test, ArcDia International Ltd, Finland). The order of sampling for the tests was not standardized.

Definitions

The diagnosis of acute otitis media (AOM) required the presence of middle-ear effusion as detected by pneumatic otoscopy, signs of inflammation of the tympanic membrane, and at least 1 sign of acute infection. AOM was considered to be associated with RSV if it was diagnosed within 14 days after the visit at which RSV was first detected, if the infant had remained symptomatic, and if no other virus was detected in the meantime. Bronchiolitis was diagnosed in infants with distinct respiratory distress or tachypnea, or expiratory wheezing or inspiratory crackles heard on auscultation at the study clinic by a physician. When calculating the duration of RSV illness, all consecutive days on which the infant had fever, rhinitis, or cough as recorded in the daily diary were included; the minimum interval between consecutive episodes of respiratory illness was 2 days.

Statistical Analysis

The incidence rates of RSV infections were calculated by dividing the numbers of RSV-positive episodes by the numbers of infants at risk and expressed per 1000 infants. Confidence intervals (CIs) for incidence rates and their ratios and testing of the differences in incidence rates between different subgroups were based on the Poisson distribution. Comparison of proportions between the groups was performed by the χ^2 test or Fisher´s exact test. Two-sided *P* values of <.05 were considered to indicate statistical significance. All

statistical analyses were performed with StatsDirect, version 3.2.7 (StatsDirect Ltd, Cambridge, UK).

RESULTS

Incidence of RSV Illnesses

Among the 408 active participants, 134 episodes of laboratory-confirmed RSV infection were diagnosed, resulting in a seasonal incidence rate of 328.4 per 1000 infants (95% CI 275.2-389.0). RSV group A strains were detected in 46 (34.3%) and group B strains in 87 (64.9%) of the 134 cases; the virus group could not be determined in 1 (0.7%) case. In 133 (99.3%) cases, the diagnosis of RSV was based on RT-PCR; the assay was not performed in 1 hospitalized infant. Besides RSV, 1 other virus was detected by multiplex RT-PCR in 45 (33.8%) cases and 2 other viruses in 7 (5.3%) cases. Antigen detection was positive for RSV during 118 (92.9%) of 127 infections in which it was performed (111 detections at the initial visit and 7 during the follow-up). The monthly numbers of infants with RSV infection are presented in Figure 1.

The incidence rates of RSV illnesses were 341.3 per 1000 (95% CI 266.6-430.6) among boys and 315.0 per 1000 (95% CI 242.1-403.0) among girls, corresponding to an incidence rate ratio (IRR) of 1.1 (95% CI 0.8-1.5; *P* = .64; Table 2). Infants who had at least one sibling had a significantly higher incidence of RSV illness than those without any siblings (IRR 1.9 [95% CI 1.3-2.8]; *P* = .0007). None of the other demographic factors had a significant impact on RSV incidence rates in the infants.

Clinical Features and Management of RSV Illnesses

The mean age of the 134 infants at the time of RSV diagnosis was 6.8 months (range, 3.2-9.9), and 71 (53.0%) of them were boys. AOM was the most frequent complication of RSV infection, occurring in 103 (76.9%) infants (Table 3); the diagnosis of AOM was made at the initial visit in 39 cases and at a follow-up visit in 64 cases. Bronchiolitis was diagnosed in 55 (41.0%) infants, and respiratory distress or tachypnea were confirmed in 32 (23.9%) cases. Expiratory wheezing was documented in 49 (36.6%) infants at the study clinic by a physician, and wheezing was present in altogether 87 (64.9%) cases when also parental reports in the symptom diaries were included. A total of 95 (70.9%) infants received antibiotic treatment. None of the infants was diagnosed with pneumonia, and there were no deaths. No significant differences were observed in any clinical features between infants with RSV A and B infections or between infants with RSV single and co-infections.

RSV Hospitalizations

Altogether 12 (9.0%) of 134 infants with RSV infection were referred to the emergency department, and 9 (6.7%) of them were hospitalized (Table 3). The seasonal incidence rate of RSV hospitalization in the entire cohort of 408 infants was 22.1 per 1000 (95% CI 10.1-41.9). Of the 134 infants with RSV infection, 5 (12.8%) of 39 infants aged <6 months at the time of RSV illness were hospitalized, compared with 4 (4.2%) of 95 infants ≥6 months of age (risk ratio, 3.0 [95% CI 0.9-10.0]; *P* = .12). All hospitalized children were diagnosed with bronchiolitis, and 1 of them required treatment at the intensive care unit.

Duration of RSV Illness

Data on the duration of symptoms were available for 121 (90.3%) of 134 RSV illnesses. The mean duration of illness was 12.0 days (SD 5.7), and the mean durations of rhinitis and cough were 10.4 (SD 5.4) and 10.0 days (SD 4.7), respectively. Fever >37.5^{o}C was reported by the parents in 68 (56.2%) of 121 infants, with the mean duration of 2.8 days (SD 1.7); the mean maximum fever in these infants was 38.8^{o}C (SD 0.6). Altogether 99 (81.8%) infants received medication for fever or pain, with a mean number of doses of 14.1 (SD 10.5) during the RSV illness.

DISCUSSION

Our prospective study provides direct evidence for the great burden of RSV infections in a large, representative, and carefully followed cohort of infants during their first RSV season. Overall, one third of the infants experienced a symptomatic laboratory-confirmed RSV infection during the first year of life. This finding is in agreement with previous studies from different parts of the world that have consistently demonstrated that 30-40% of infants are infected with RSV by the age of 1 year [12-17].

Because RSV-associated hospitalizations represent the most severe forms of the illness, it is reasonable that development of preventive measures for these severe manifestations is a high priority [18-20]. However, it is important to notice that 93% of young infants with symptomatic RSV in our study were managed as outpatients. The outpatient burden of RSV is easily unrecognized, particularly because specific viral diagnosis of RSV is rarely made in the outpatient setting [2].

Acute otitis media developed as a complication of RSV illness in 77% of the infants, which confirms previous findings about a leading role of RSV in predisposing young children to AOM [14, 21-23]. The strikingly high rate of AOM in our cohort was probably due to two major factors. First, our study subjects had a high risk of AOM because of their age. The risk of development of AOM increases rapidly after 6 months of age, and the incidence of AOM is highest in children around 1 year of age [24]. Second, our study design included routine follow-up examinations at the study clinic after the initial visit at which RSV was diagnosed. As the incidence of AOM peaks on days 3-4 after the onset of respiratory symptoms [23, 25, 26], studies relying on clinical examinations performed only in the early course of the illness may substantially underestimate the true incidence of AOM as a complication. This was demonstrated also in our present study in which more than 60% of all AOM diagnoses were made after the initial visit to the study clinic.

Although AOM is a condition that infrequently requires hospitalization, it generally leads to treatment with antibiotics especially in young children [27]. Assuming that one-third of infants acquire an RSV illness during their first year of life and that three-quarters of those receive antibiotic treatment for AOM, approximately 25% of all infants will get at least one course of antibiotics due to RSV alone by their first birthday. It is well-established that a respiratory viral infection initiates the cascade of events that ultimately leads to development of AOM as a complication [28]. Analogously to the proven efficacy of influenza vaccines to prevent influenza-associated AOM [29, 30], it is possible that prevention of RSV infection in infants would also substantially reduce the incidence of RSV-associated AOM and the related use of antibiotics. Furthermore, because AOM is probably a major driver of

RSV-related costs in outpatient infants, it should be included in any cost-effectiveness calculations related to RSV prevention or treatment.

The incidence of RSV was almost 2-fold higher in infants with at least 1 sibling than in those without. This finding corroborates earlier studies that have assessed the transmission of RSV within families. Studies carried out in different countries have consistently identified other family members and especially older siblings as the primary source of RSV infection in infants [31-33]. These findings suggest that a “cocooning” strategy of prevention of RSV infections by vaccination of the family members and other close contacts of high-risk infants could prove effective in reducing the burden of RSV in young infants [19].

Young infants are considered one of the primary target populations for the development of an RSV vaccine, but effective immunization of newborns in time to provide protection during the first months of life is faced with great challenges [18-20]. Therefore, the main strategy for protecting the youngest infants against RSV by vaccination is currently focused on maternal vaccination during pregnancy [11, 20, 34]. However, the duration of protection afforded by placental transfer of antibodies is probably limited and may not extend beyond the first months of infancy. As our study and other recent data indicate, there is a great medical need to prevent RSV infections also in older infants and young children, who form another target group for RSV vaccine development [14, 18]. Furthermore, the availability of effective monoclonal antibodies and antiviral agents against RSV might provide substantial benefits also for outpatient children [35-37].

The main strengths of our study include the careful follow-up of a representative cohort of infants enrolled soon after birth; unlimited daily access to the study clinic for clinical examinations and treatment; and nasopharyngeal sampling for identification of the viral etiology of the infection during each respiratory illness regardless of the severity of symptoms. There are also some limitations that require consideration. First, because the infants in our cohort were born during the summer months prior to the subsequent RSV outbreak emerging in the autumn, the rates of RSV hospitalization are not directly applicable to infants who are born right before or during the RSV epidemic. Second, although the follow-up period contained the entire RSV season, inclusion of additional seasons and research sites would have increased the accuracy of the estimates. Third, we could obtain specimens for RSV detection only from infants who visited the study clinic, and some infants with very mild symptoms of RSV may have been left undiagnosed. However, the clinical significance of such mild illnesses might be considered as limited, and in any case inclusion of such cases would have only increased the RSV incidence rates observed in our study.

In conclusion, our prospective cohort study demonstrates a great burden of RSV illness in outpatient infants during their first year of life. In particular, the high frequency of AOM as a complication of RSV in this age group requires attention when assessing the cost-effectiveness of various preventive measures or therapies being developed for RSV infection.

ACKNOWLEDGMENTS

We are grateful to all participating infants and their families and to the entire personnel involved in the performance of the study.

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Table 1. Baseline characteristics of the 408 active participants in the follow-up cohort.

Variable	**No. of children**	**%**
Age at start of follow-up, mo		
<1	133	32.6
1 to <2	163	40.0
2 to <3	112	27.5
Sex		
Boys	208	51.0
Girls	200	49.0
Birth weight, g		
<1500	3	0.7
1500-<2500	20	4.9
≥2500	385	94.4
Gestational age, wk		
<32	4	1.0
32-36	23	5.6
≥37	381	93.4
Method of delivery		
Vaginal	349	85.5
Cesarean section	59	14.5
Number of siblings		
0	178	43.6
1	142	34.8
2	59	14.5
≥3	29	7.1
Maternal smoking during pregnancy		
Yes	20	4.9
No	388	95.1
Smoking in the household		
Yes	77	18.9
No	331	81.1

Table 2. Incidence rates and rate ratios of RSV illnesses among different subgroups of children.

Variable	No. of RSV illnesses	No. of infants in follow-up	Incidence rate per 1000 infants (95% CI)	Incidence rate ratio (95% CI)	P value
Sex					
Boys	71	208	341.3 (266.6-430.6)	1.1 (0.8-1.5)	.64
Girls	63	200	315.0 (242.1-403.0)		
Gestational age, wk					
<37	14	27	518.5 (283.5-870.0)	1.6 (0.9-2.9)	.075
≥37	120	381	315.0 (261.1-376.6)		
No. of siblings					
≥1	95	230	413.0 (334.2-504.9)	1.9 (1.3-2.8)	.0007
0	39	178	219.1 (155.8-299.5)		
Method of delivery					
Vaginal	118	349	338.1 (279.9-404.9)	1.2 (0.7-2.3)	.41
Cesarean section	16	59	271.2 (155.0-440.4)		
Asthma or atopy in mother					
Yes	50	155	322.6 (239.4-425.3)	1.0 (0.7-1.4)	.87
No	84	253	332.0 (264.8-411.1)		
Asthma or atopy in father					
Yes	45	127	354.3 (258.5-474.1)	1.1 (0.8-1.6)	.54
No	89	281	316.7 (254.4-389.8)		
Asthma or atopy in sibling[a]					
Yes	35	79	443.0 (308.6-616.2)	1.1 (0.7-1.7)	.61
No	60	151	397.4 (303.2-511.5)		
Smoking in the household					
Yes	21	77	272.7 (168.8-416.9)	0.8 (0.5-1.3)	.34
No	113	331	341.4 (281.4-410.4)		

[a] Calculated for infants with at least one sibling (n = 230). Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus.

Table 3. Clinical features and management of RSV illnesses in 134 infants.

Variable	**RSV group A (n = 46)**	**RSV group B (n = 87)**	**Any RSV[a] (n = 134)**
Acute otitis media	34 (73.9)	68 (78.2)	103 (76.9)
Bronchiolitis	24 (52.2)	30 (34.5)	55 (41.0)
Respiratory distress or tachypnea	10 (21.7)	21 (24.1)	32 (23.9)
Expiratory wheezing			
During clinical examination at study clinic	21 (45.7)	28 (32.2)	49 (36.6)
Additionally at home by parental report	11 (23.9)	27 (31.0)	38 (28.4)
Antibiotic treatment	31 (67.4)	63 (72.4)	95 (70.9)
Referral to emergency department	3 (6.5)	8 (9.2)	12 (9.0)
Hospitalization	2 (4.3)	6 (6.9)	9 (6.7)

[a] Including 1 infant with RSV in whom the viral group could not be determined.

Data are presented as n (%). Abbreviation: RSV, respiratory syncytial virus.

FIGURE LEGEND

Figure 1.

Monthly detections of RSV infections in the study cohort during the respiratory season of 2017-2018. The line showing the total numbers of RSV infections includes 1 infant in whom the RSV group (A or B) was not determined.