Four year incidence of Respiratory Syncytial Virus infection in infants and young children referred to emergency departments for lower respiratory tract diseases in Italy: the "Osservatorio VRS" Study (2000-2004)

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SUMMARY

Respiratory Syncytial Virus (RSV) is a frequent cause of hospital admission in young children and high risk babies such as premature newborns, or babies with underlying cardiac or pulmonary disease, or immunodeficiency. Outbreaks occur most frequently in the cold season in areas with temperate and Mediterranean climates. Aim of the "Osservatorio VRS" Study was to describe the time-related pattern of RSV epidemics in Italy, across four consecutive epidemics, from 2000 to 2004. Nasal specimens for RSV detection were obtained and tested by an immunoenzymatic test. A total of 2110 children were tested for RSV determination, the rate of children with RSV infection was 21%, and that of children hospitalized for RSV disease was 49%.

Considering the whole study period, the RSV epidemics started in October-November and ended in May, showing a peak incidence in February, with a median of 28.1% and a maximum of 48.9%. Analysis of monthly distribution of each year of the study showed a biennial trend for an earlier appearance. A different epidemiological pattern of the infection was observed among the three national areas. In conclusion, even though the mechanism governing RSV infection periodicity remains unknown, its awareness in the absence of an RSV surveillance system as in Italy, may be useful for scheduling RSV prophylaxis and for hospital resource management.

KEY WORDS: RSV, epidemiology, lower respiratory tract diseases

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INTRODUCTION

Respiratory Syncytial Virus (RSV) is an important pathogen and a frequent cause of hospital admission in young children (Simoes, 1999; Hall, 2001). The most common clinical presentation of RSV infection in infants is bronchiolitis, an acute lower respiratory tract infection (LRTI), requiring hospitalization in 1-2% of cases (Simoes, 1999; Hall, 2001; Howard *et al.*, 2000; Leader *et al.*, 2003). A greater prevalence of severe forms of LRTI is found in high risk children, i.e. premature newborns and babies, with underlying cardiac or pulmonary disease, or immunodeficiency (Meissner, 2003; Cabalka, 2004). In these children RSV associated morbidity and mortality is higher than that of healthy children (Meissnerr, 2003; Cabalka,

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2004; Wang *et al.*, 1995; Lanari *et al.*, 2002; Navas *et al.*, 1992).
RSV infection is typically characterized by yearly epidemics, whose appearance varies with latitude, altitude and climate. Outbreaks occur most frequently in the cold season in areas with temperate and Mediterranean climates and in the wet season in tropical countries with seasonal rainfall (CDC, 2004; Robertson *et al.*, 2004; Medici *et al.*, 2004; Rossi *et al.*, 2005; Stensballe *et al.*, 2003). Epidemiological studies in children living in temperate and tropical climates have identified a typical pattern in the peaks of RSV outbreaks and hospitalizations, with periods of late small epidemics alternating with periods of early large ones (Stensballe *et al.*, 2003; Van der Sande *et al.*, 2004; Mullins *et al.*, 2003; Duppenthaler *et al.*, 2003; Weigl *et al.*, 2002; Eriksson *et al.*, 2002; Chang *et al*, 2002; Lyon *et al.*, 1996; Waris, 1991). Changes in RSV antigenic characteristics (Waris, 1991; Papadopoulos *et al.*, 2004; Johansen *et al.*, 1997; Reese *et al.*, 1991; Hall *et al.*, 1990; Mufson *et al.*, 1987), variations in population immunity (Stensballe *et al.*, 2003; Haus *et al.*, 1999) and environmental factors (Stensballe *et al.*, 2003; Duppenthaler *et al.*, 2003; Weigl *et al.*, 2002; Florman *et al.*, 1988) are thought to be responsible for the alternation of major and minor epidemics.
Epidemiological data on RSV infection in multiple seasons are lacking in Italy. Analysis of the "Osservatorio VRS" Study (Medici *et al.*, 2004; Rossi *et al.*, 2005) conducted among infants and young children referring to Emergency Departments (EDs) for acute respiratory infection, allowed us to compare the incidence and seasonal distribution of RSV infection in Italian children across four consecutive epidemics, from 2000 to 2004. Aim of the study was to describe the time-related pattern of RSV epidemics in Italy to deduce the most effective time period for administration of prophylactic measures to high-risk patients.

PATIENTS AND METHODS

Study design and patient population
The study population consisted of children, aged ≤ 4 years, referred to EDs between 9 a.m. and 8 p.m. during the RSV season outbreaks (from October to April) for acute respiratory infection (rhinitis, pharyngitis, otitis, sinusitis, laryngitis, bronchitis, wheezy bronchitis, bronchiolitis, or pneumonia), possibly related to RSV infection, over four consecutive RSV seasons (from 2000 to 2004). Types of acute respiratory diseases were classified by a board of experts representative of the study centers and based on criteria employed in a previous epidemiological Italian study (Lanari *et al.*, 2002).
Pediatric centers, with regular activity of EDs throughout Italy, participated in this multicenter, epidemiological, surveillance program (8 centers during the first, 14 during the second, and 13 during the third and fourth seasons).
Each hospital sought written informed consent from parents consistent with local requirements for enrolment of pediatric patients prior to performing any RSV related study procedure. Children aged > 4 years without acute respiratory infections and/or lacking in informed consent were excluded from the study. After collection of basic demographic information on medical history, the physician treated the patients according to his/her symptoms and disease severity. No follow-up was performed. No restriction on prior or concomitant therapy was considered and no randomization was applied.
Standardization of clinic diagnostic and managing criteria was defined in concert with participant centers. Clinical assessments, including a chest radiogram and nasal specimens for RSV detection, were obtained at each hospital. In particular, dry mid nasal swabs were obtained and put in a tube containing 1 ml of phosphate buffered saline solution. The tube had to be tilted gently but firmly before screwing the cap tightly. Then the samples were sent to the Microbiology Laboratory of each hospital, to check for the presence of the RSV by an immunoenzymatic test (TestPack® RSV, Abbott) within the next 24 hours.
Other respiratory viruses were not tested. All children were treated according to standardized protocols and were either hospitalized or sent home according to the severity of the disease and/or response to therapy.

Data analysis
The primary variable for the analysis was the percentage of RSV positive children out of the total number of children tested for each month of the

epidemics and separately for each year of the study. This calculation was also done for the four years of the study as a whole, by considering the median (plus 25th and 75th percentile of the distribution) and the maximum of each month. Each analysis was computed for the whole sample of subjects and separately for each national area to which the centers belonged (North, Center and South). Analysis of monthly RSV trends was kept descriptive and no formal statistics was applied to these data.

Demographic and main clinical data, including the rate of RSV related hospitalization and LRTI, were also computed and compared among the four years by analysis of variance (continuous variables) or Chi-square test (categorical variables). Analysis by national areas was kept descriptive.

Analysis of demographic and clinical data was limited to the epidemic season (from October to April), while that of the RSV trends was expanded to June, in order to allow a more detailed description of RSV epidemiology.

RESULTS

Demographic and clinical characteristics of the study population

Out of a total of 37119 children referred to pediatric EDs, 2110 (5.7%) were enrolled in the study and tested for RSV determination. Of these 433 were RSV positive (20.5%). The demographic and clinical characteristics of the children enrolled during the four RSV seasons are illustrated in Table 1.

Across the four epidemic seasons, the populations were similar for gender, rate of preters, birth weight, rate of children with very low birth weight and with previous infection, and expo-

TABLE 1 - *Demographic and clinical characteristics of the children tested for a possible RSV infection in the four seasons of the "Osservatorio VRS" Study between October and April (data are shown as percentages or means ± SD).*

	1st Season (2000-2001) n=272	*2nd Season (2001-2002) n=756*	*3rd Season (2002-2003) n=558*	*4th Season (2003-2004) n=524*	*p*	*Whole period (2000-2004) n=2110*
RSV positive (%)	31	19	22	15	<0.001	21
RSV related hospitalizations (%)	57	37	57	49	<0.001	49
RSV related lower tract respiratory infections (%)	88	76	91	91	<0.001	85
Males (%)	52	56	56	55	NS	55
Age (months, mean±SD)	16±15	18±17	16±15	17±15	<0.05	17±16
Gestational age (weeks, mean±SD)	38±2	39±2	39±2	38±2	<0.001	39±2
Low gestational age (≤35 weeks, %)	9	6	7	9	NS	7
Weight at birth (gr, mean±SD)	3167±611	3189±568	3140±574	3107±585	NS	3153±580
Very low birth weight (<1500 gr, %)	2	1	2	2	NS	2
Chronic Lung Disease (%)	17	8	6	6	<0.001	8
Previous RSV infection (%)	24	22	18	19	NS	21
Use of corticosteroids or bronchodilators (%)	49	41	35	46	<0.001	42
Smokers in the household (%)	52	55	53	58	NS	55

sure to environmental cigarette smoking. During the first and third seasons the rate of RSV positive children, RSV related hospitalizations and LRTI was greater than during the second and last seasons of the study ($p<0.001$). Age, gestational age, rate of children with chronic lung disease (CLD) and of those using corticosteroids or bronchodilators in the previous 3 months, were not homogeneous ($p<0.001$), though a periodical trend was not observed.
When data were analyzed separately for each national area (North, Center and South) and for each season, no systematic differences in prevalence of RSV infection and other characteristics of RSV disease and risk factors were observed between the areas (Table 2).

Monthly distribution of RSV infection
Considering the whole study period (2000 to 2004), the RSV epidemics started in October-November and ended in May, showing a peak of incidence in February, with a median of 28.1% and a maximum of 48.9% (Fig. 1). Analysis of monthly distribution of each year of the study

TABLE 2 - *Demographic and clinical characteristics by national area (North, Center and South) of the children tested for a possible RSV infection in the four seasons of the "Osservatorio VRS" Study between October and April (data are shown as percentages or means ± SD).*

	1st Season (2000-2001)			*2nd Season (2001-2002)*			*3rd Season (2002-2003)*			*4th Season (2003-2004)*		
	North	*Center*	*South*	*North*	*Center*	*South*	*North*	*Center*	*South*	*North*	*Center*	*South*
	n=70	*n=91*	*n=111*	*n=220*	*n=156*	*n=380*	*n=131*	*n=125*	*n=302*	*n=197*	*n=142*	*n=185*
RSV positive (%)	26	24	41	16	21	21	29	29	17	13	25	9
RSV related hospitalizations (%)	37	26	54	19	22	32	33	38	53	25	38	69
RSV related lower tract respiratory infections (%)	62	87	81	39	87	63	61	91	65	51	97	81
Males (%)	54	55	48	57	62	53	50	58	58	61	56	48
Age (months, mean±SD)	15±14	21±17	12±13	20±16	19±17	17±18	15±14	14±14	18±16	20±15	15±14	16±14
Gestational age (weeks, mean±SD)	38±2	39±2	38±3	39±2	39±2	39±2	39±2	39±2	39±2	39±2	38±3	38±2
Low gestational age (35 weeks, %)	9	9	9	4	4	8	4	6	8	6	13	9
Weight at birth (gr, mean±SD)	3180±640	3340±550	3020±610	3280±600	3190±560	3140±550	3200±560	3210±520	3090±600	3200±590	3070±620	3040±540
Very low birth weight (<1500 gr, %)	1	0	5	1	1	1	1	0	2	3	2	2
Chronic Lung Disease (%)	6	14	26	6	11	9	0	6	8	10	6	2
Previous RSV infection (%)	17	25	26	17	18	27	10	16	22	14	16	27
Use of corticosteroids or bronchodilators (%)	34	51	56	34	40	46	28	45	34	42	53	45
Smokers in the household (%)	37	43	68	48	56	60	49	48	57	49	54	69

showed a trend for an earlier appearance and an overall greater prevalence of the epidemics during the first (2000-2001) and third (2002-2003) seasons, as compared to the second (2001-2002) and fourth (2003-2004) seasons (Fig. 2).
A different epidemiological pattern of infection was observed among the three national areas. As a matter of fact, season outbreaks tended to occur earlier in the northern and central, and later in the southern areas. In the south the peak incidence tended to be less consistent than in the other national areas (Fig. 3). The periodicity of the season epidemics observed throughout the country also extended to analysis of each separate national area (Fig. 4).

DISCUSSION

The "Osservatorio VRS" Study, performed during four consecutive RSV epidemics, from 2000 to 2004 is the first Italian observational study aimed at defining the epidemiological pattern of RSV infection in young children (aged ≤4 years) referring to hospitals for acute respiratory infections (Medici *et al.*, 2004; Rossi *et al.*, 2005). In the course of the four years of the study, the rate of children with RSV infection was 21%, that of children hospitalized for RSV disease 49% and that of children with RSV related LRTI was 85%. These results are in line with those of other epidemiological studies performed in western countries (Lanari *et al.*, 2002; Stensballe *et al.*, 2003).
In Italy, as observed for other temperate countries, the RSV season varied substantially by year and by area (CDC, 2004; Robertson *et al.*, 2004; Stensballe *et al.*, 2003). The RSV infection reached a peak incidence in February and was characterized by some year-to-year variation, with an earlier onset and greater prevalence during the first (2000-2001) and third (2002-2003) seasons and a later onset and lower prevalence during the second (2001-2002) and last (2003-2004) seasons. This pattern was also associated with an overall higher proportion of infected children, a higher rate of RSV related hospitalizations and of clinical evidence of LRTI in the course of the

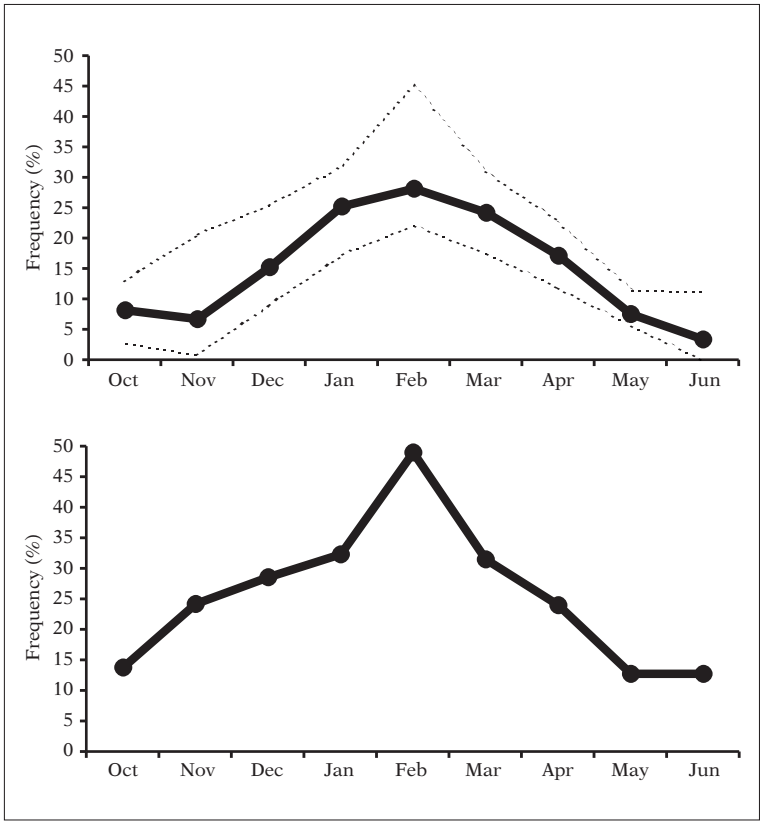

FIGURE 1 - *Monthly trends of RSV infection in Italy for the whole study period. Upper panel refers to the median plus 25th and 75th percentiles of distribution (dotted lines) in the four years of the study. Lower panel reports the maximum value (per month) across the four years.*

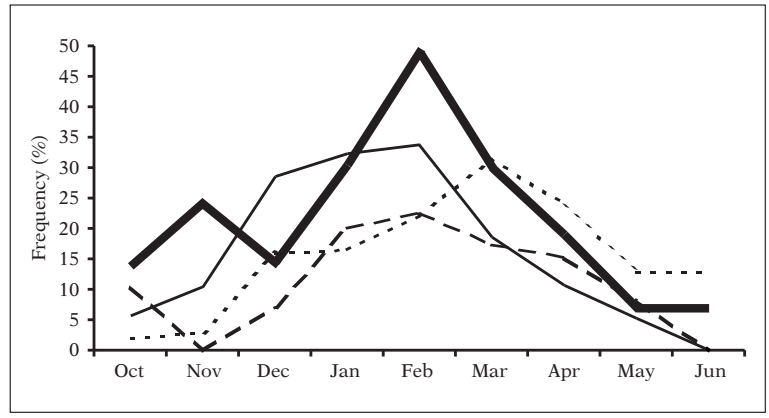

FIGURE 2 - *Monthly trend of RSV infection in Italy during each of the four consecutive epidemic seasons (1st season: thick continuous line; 2nd season: dotted line; 3rd season: thin continuous line; 4th season: dashed line).*

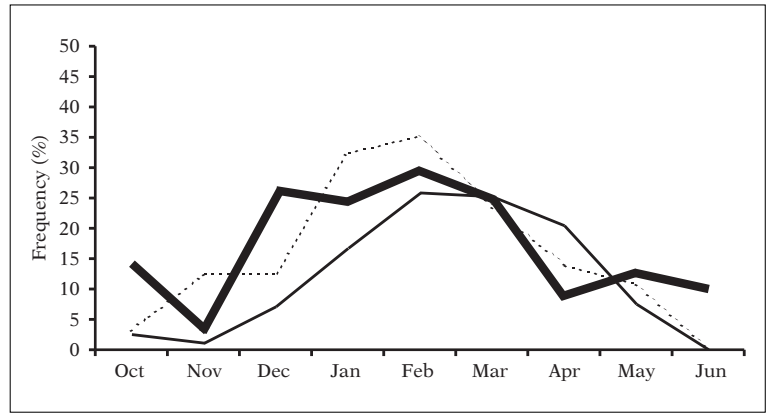

FIGURE 3 - *Monthly trends of RSV infection in the three national areas (North: thick line; Center: dotted line; South: thin line). Data are shown as the medians of distribution in the four years of the study.*

first and third (27% for RSV infection, 57% for RSV hospitalizations and 90% for LRTI) as compared to the second and fourth seasons (17%, 43% and 84%, respectively).

Several studies conducted in temperate, but also in tropical climates, have identified a periodical pattern in the peaks of RSV epidemics and RSV hospitalization rates, with late small outbreaks alternating with early large ones (CDC, 2004; Robertson *et al.,* 2004; Stensballe *et al.,* 2003; Van der Sande *et al.*, 2004; Mullins *et al.*, 2003; Duppenthaler *et al.*, 2003; Weigl *et al.*, 2002; Eriksson *et al.*, 2002; Chang *et al.*, 2002; Lyon *et al.*, 1996; Waris, 1991). Such a pattern was also evident from our data, but we have no explanation for it. Attempts have been made in the past to explain seasonality and variability of RSV epidemics. Geographic and climatic factors are clearly associated with the epidemics. Cold climates favor changes in the respiratory mucosa microenvironment which influences host susceptibility to infection and RSV survival outside the body, but also induce indoor crowding, which is responsible for intensive exposure to the virus (Stensballe *et al.,* 2003; Duppenthaler *et al.*, 2003; Weigl *et al.*, 2002; Florman *et al.*, 1988). Susceptibility to RSV infection may also be related to cyclic changes in protective immunity in the population. For instance, a decreased herd of immunity in the population, particularly among mothers, may increase the risk of infection in newborns (Stensballe *et al.,* 2003; Haus *et al.*, 1999).

Differences in the epidemics may also be due to a different spread of the RSV or to genomic variants. There is a predominance of different RSV genomic types each year, some types being present in consecutive epidemics, while others seem to disappear or become undetectable, being replaced by emerging types. Thus a temporal fluctuation of genomic types, presumably caused by selective pressure exerted by host immunity,

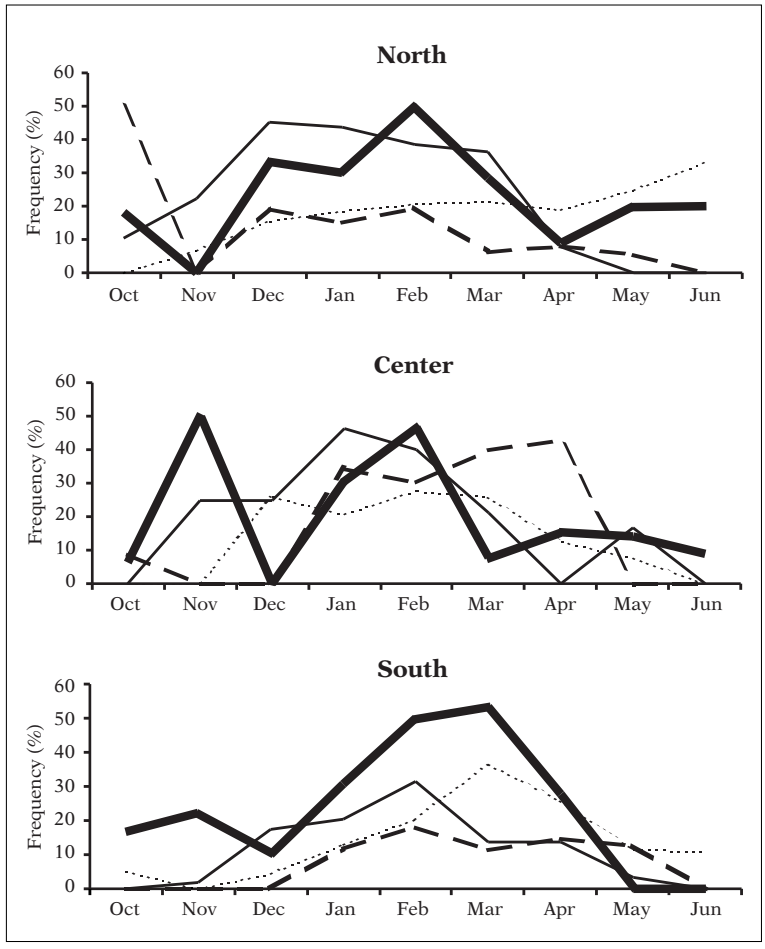

FIGURE 4 - *Monthly trends of RSV infection in the three national areas. Data are shown for each of the four consecutive epidemic seasons (1st season: thick line; 2nd season: dotted line; 3rd season: thin line; 4th season: dashed line).*

rather than by a molecular evolution in strains induced or directed by immunoselective pressure, may be responsible for the periodicity of RSV epidemics (Waris, 1991; Papadopoulos *et al.*, 2004; Johansen *et al.*, 1997; Reese *et al.*, 1991; Hall *et al.*, 1990; Mufson *et al.*, 1987).

Results of the "Osservatorio VRS" Study also demonstrated RSV seasonal variation by area. Winter time in Italy is particularly cold and long in the Northern regions, situated at higher latitude, while it is warmer and shorter in the South. This may explain why epidemics tended to have an early onset and late offset in the North and a late onset in the South, a phenomenon which is common to other countries with extremely varying latitudes (CDC, 2004; Stensballe *et al.*, 2003). We cannot exclude that these differences may be due to differences in the clinical characteristics of RSV disease and risk factors across the different regional areas. However, when such differences were found they were not systematic or were not replicated during successive epidemics, and might be ascribed to a random effect due to the relatively small sample of subjects included in this sub-group analysis.

Interpretation of results of this study also deserves some caution. First, the fact that more centers were included in the study after the first season, may have introduced differences in the season epidemics, possibly due to differences in the number of children studied and in the management of children with RSV in the various centers. However, this was not the case for two reasons:

a) evaluation of the epidemiological and clinical data of RSV infection epidemics in the 8 centers involved in the first season gave results similar to that observed when considering all the 13-14 study centers (data not shown);
b) a periodicity was observed also between the

second and fourth seasons which basically included the same centers.

Second, the difference in prevalence and incidence of RSV infection could also be ascribed to differences in the population of children enrolled. Classically, the greatest morbidity for RSV infection occurs among "high risk" children. However, though a statistically significant difference was observed for gestational and chronological ages, CLD and use of corticosteroids or bronchodilators, distribution of these and other risk factors was not quantitatively different among the four years of the study.

In conclusion, even though the mechanism governing RSV infection periodicity remains unknown, its awareness in the absence of an RSV surveillance system, as in Italy, may be useful for scheduling RSV prophylaxis and for hospital resource management.

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