**Respiratory syncytial virus**  
Part II: Epidemiology of infantile respiratory infections

Author: Gordana Mlinaric-Galinovic, MD, PhD

Department of Microbiology University Medical School of Zagreb and Department of Virology, Croatian National Institute of Public Health and, Rockefellerova 12, 10000 Zagreb, Croatia

### 2.1. Viral acute respiratory tract infections

Respiratory syncytial virus (RSV) is a major cause of acute lower respiratory tract infections (LRTI) in infants and young children in both developed and developing countries (1-6). RSV accounts for 25% of hospital admissions of infants and young children for pneumonia, and for up to 43% of cases of bronchiolitis in this age group (5). In the USA, RSV was estimated to cause 73,400-126,300 hospitalizations annually for bronchiolitis and pneumonia among children younger than 1 year (7). RSV infection was detected in 23.3% of infants and children hospitalized for any acute respiratory tract infection (ARTI) (8-10). It has been estimated that more than half of infants who are at risk will become infected during an RSV epidemic (1). The attack rates among susceptible infants and children are extraordinarily high, approaching 100% in settings such as day-care centers where large numbers of susceptible infants are present (11).

In our 11 consecutive years (1994-2005) of studying RSV infections in children in Croatia, it was discovered that RSV caused the greatest number of overall ARTIs (32.3%), followed by adenoviral infections in 3.9% cases, parainfluenza viral infections in 3.7% instances and influenza virus infections in 2.9% cases (10). Almost the same percentage (33.6) of RSV infections among ARTIs was found in an earlier season (1986/87) (12). When infections caused by human metapneumovirus (HMPV) were further explored, this virus ranked third, after adenovirus and RSV among children with ARTI (13), which is more or less in agreement with the second-only position of HMPV in the finding of Williams JV at al (14). While the incidence of RSV infections declined with age (from 42% to 16% from birth to 5 years of age), the incidence of infections due to other viruses remained within the range of 6 to 15% in the same age range (10).

### 2.2. Sex, race and age

Infection rates are unrelated to either race or sex, although illness is more severe in male infants (15-17). However, in our study, RSV showed the highest prevalence (75%) among Caucasian children in Texas, USA (18). Also, higher hospitalization rates were associated with RSV infections at a younger age (<1 year) in black and Hispanic ethnicity, and with the presence of chronic underlying illness (17). In the USA, the estimated number of RSV hospitalizations per 1,000 children was 388 for those with bronchopulmonary dysplasia and 92 for those with congenital heart disease (19).

RSV infections manifest themselves as mild upper respiratory tract infections (URTIs) or LRTIs: bronchitis, bronchiolitis, and pneumonia (9,20-22). In our study among RSV-positive inpatients, aged 0-10 years, for the period 2009-2010, the virus proved to cause bronchiolitis in 30.19% and pneumonia in 13.49% cases (22) (Figure 1).

Figure 1. Distribution of clinical syndromes caused by respiratory syncytial virus by age groups and clinical syndromes in Zagreb and Zagreb County during 2009 and 2010

Rates of illness are highest among infants 1 to 6 months of age, peaking between 2 and 3 months of age. The prevalence of RSV infections drops with age. The results of this
study showed that in Croatia 63.8% of all RSV infections occurred in the first 6 months of life, 18.6% in the second 6 months of life, 12.4% in the second year of life, and only 4% in children 2 to 5 years old (20). Said values, however, do oscillate depending on the season (9,23,24). In newborn infants LRTIs are sparing during the first 6 weeks of life, while RSV-positive newborn infants usually produce URTI (25-27). However, Bruckova et al. reported 60% of LRTIs at the premature children’s’ ward (28). Our study showed that LRTIs were less common (bronchitis 20%, bronchiolitis 10%, pneumonia 20%) in neonates than in other infants and small children (12,20,29) (Figure 2).

![Figure 2. Finding of respiratory syncytial virus in 44 neonates with respect to syndrome and sex, Zagreb, Croatia (1986-1987)](image)

Out of 20 RSV-positive neonates, 10 were premature, and no significant statistical difference in susceptibility to the infection was noticed among premature children (Chi-square=0.0, p > 0.05) (29). In the USA, the estimated number of RSV hospitalizations per 1,000 children was 70 for children born at <28 weeks’ gestation, 66 for those born at 29-33 weeks, 57 for those born at 33-36 weeks, and 30 for children born at term with no underlying medical condition (19).

2.3. Reinfection

Primary infection is often associated with significant morbidity, particularly in infants younger than six months of age or with underlying cardiopulmonary disease, as well as in infants from lower socioeconomic groups in both industrial and developing countries (30,31). By age 2, virtually all children will have been infected with RSV (32).

Reinfection with RSV is common, and older children and adults are not immune (33,34). In older children and adults, reinfection with RSV is frequent, but the disease is milder than in infancy. Children previously infected with a virus of one type appear to be somewhat less susceptible to repeated infections with a virus of the same type, perhaps due to residual antibodies specific to the G protein (35). Asymptomatic forms of disease are rare even in reinfections (15, 36,37).

RSV infections in adults and the elderly represent reinfections in which the hosts have had many prior episodes (38,39). A common cold–like syndrome is the illness most commonly associated with RSV infection in adults (8). Severe lower respiratory tract disease with pneumonitis can occur in elderly (often institutionalized) adults and in patients with immunocompromising disorders or treatment, including recipients of bone-marrow and solid-organ transplants (40,41)

2.4. Transmission

The virus is transmitted either directly or indirectly through large droplets via fomites and direct contact with secretion (42). RSV is transmitted primarily by close contact with contaminated fingers or fomites and by self-inoculation of the conjunctiva or anterior nares. Virus may also be spread by coarse aerosols produced by coughing or sneezing, but it is inefficiently spread by fine-particle aerosols. Target cells for the virus are ciliary epithelium cells in the respiratory tract (43). The attack rate in household contacts of infected children is about 40% (44). The spread of virus within a family is efficient; up to 40% of siblings may become infected when RSV is introduced into the family setting (44). RSV is also an important nosocomial pathogen (45,46). During an outbreak, it can infect pediatric patients and up to 25 to 50% of the staff in pediatric wards (47). Ward
personnel probably has a central role in introducing and spreading the virus.

Incubation period for RSV disease is 3-5 days (16). LRTI symptoms usually appear 1-3 days after the onset of rhinorrhea by spreading via respiratory epithelium or through aspirated secretion (8). The virus shedding phase is shorter in adults than in children (1.6 vs. 3.9 days) (44). Virus shedding may last for ≥2 weeks in children and for shorter periods in adults. In immunosuppressed patients, shedding can be prolonged by several weeks.

### 2.4. Outbreaks

2.4.1. Climate zones

Infection with RSV is seen throughout the world in regular, predictable intervals that in temperate climate occur in late fall, winter, or spring and last up to 5 months (9,15,16,20). RSV seasons vary in different parts of the world. In Rochester, New York, USA, RSV outbreaks usually start in October and end in April, generally peaking in January (3). In Galveston, Tx, RSV outbreak usually starts in October or November, peaking in December and January, and ends in March (18,48). The virus is rarely encountered during the summer (Figure 3).

![Figure 3. The prevalence of respiratory syncytial virus infections, mean monthly temperature, and number of clear days during the period 1994-2005 in Croatia](image)

In months with an average temperature over 25°C there are virtually no RSV infections, whereas the latter appear most often in months with an average temperature under 5°C (Analysis of variance, p > 0.001) (49). In tropical or subtropical areas, outbreaks usually occur during the rainy season (50). In northern tropical area in Asia, RSV season is associated with a decrease in temperatures and increase in rainfall (51). In northern tropical areas of South America, RSV is present year round, with some increase in months with dry weather (52). In southern tropical areas in South America, RSV occurs in the dry cool season (53).

2.4.2. Circulation pattern

Monophasic and annual RSV epidemics were found in Great Britain (54), Belgium (55), the USA (56,57), South America (58,59), Japan (60) and China (61).

The biennial pattern of RSV outbreaks was noted in Germany, Switzerland, Austria, Finland and Sweden (62-67), and Croatia. It was established that RSV outbreaks in Croatia have been occurring in two-year cycles for at least the past 15 years (49,68,69). Thus, RSV epidemics in Croatia peaked in December/January of years 1994/95, 1996/97, 1998/99, 2000/01, 2002/03, and 2004/05 (“large seasons”), and March/April of years 1996, 1998, 2000, 2002, and 2004 (“small seasons”) (49). The role of climate (the effects of air temperature and humidity) in causing this epidemic pattern was studied in northwest Croatia. Climate conditions correlated only with those RSV seasons when outbreaks peaked in December/January, and not with those outbreaks which occurred in the spring (March/April) (49). In large seasons, the number of RSV cases was inversely related to the average maximum daily temperature (Pearson correlation coefficient; r = -0.7; p<0.001) (Figure 4) and directly linked to average maximum air humidity (Pearson correlation coefficient; r = 0.6; p<0.001) (Figure 5).

![Figure 4. Seasonal occurrence of respiratory syncytial virus infections and average maximum temperature (1994-2005) in Croatia](image)
In small seasons, however, the number of RSV cases was not significantly correlated with temperature (r = 0.06; p=0.64) and was inversely associated to relative humidity (r = -0.3; p<0.01).

Since the two-year periodicity of RSV infections in Croatia could not be related to climatic factors, we examined whether this epidemiological characteristic of RSV infections in Croatia could be associated with a regular exchange of the two viral subtypes (70,71). However, biennial virus cycles were found to be persistent, although the predominant RSV subtype in the first two epidemic waves was subtype B, while in the second two subtype A. Consequently, according to current findings, it may be concluded that neither of the predominant RSV types and genotypes has an effect on the periodicity of RSV infections in Croatia (70,71, 72) (Figure 6).

Many earlier studies have attempted to explain the epidemic pattern of RSV activity, but an explanation for this epidemic variation has not been identified. The possibility of one extensive epidemic partially immunizing infants, thereby postponing the next epidemic and reducing it in size, has been considered. The result of RSV type circulation for the 0-5 age group matches the result for the 0-1 age group, which does not argue in favor of the above hypothesis (71).

Recent studies have investigated the genotypic pattern of RSV strains during epidemics. In a 2-year virus cycle there was a 64% reduction in the incidence of infection by a homologous strain compared to a 16% reduction against a heterologous strain (73). A possible correlation between newly emerging genotypes and higher chances for reinfection eventually lead to large outbreaks (55,60).

References:
1. Parrott RH, Kim HW, Arrobio JO, Hodes DS, Murphy BR, Brandt CD, Camargo E, Chanock RM.


