

Respiratory Syncytial Virus infection: a decade of contributions

Infezione da Virus Respiratorio Sinciziale: analisi retrospettiva di 10 anni

Alfredo Blanco del Val¹, José María Eiros Bouza², Agustín Mayo Íscar³, M. Rosario Bachiller Luque⁴, Beatriz Blanco del Val⁵, Antonio Sánchez Porto⁶, Raúl Ortiz de Lejarzu²

¹San Agustín Primary Health Center, Burgos, Spain;

²Department of Microbiology, Hospital Clínico Universitario, Valladolid, Spain;

³Department of Biostatistics, Faculty of Medicine, University of Valladolid, Spain;

⁴Department of Pediatrics, Faculty of Medicine, University of Valladolid, Spain;

⁵Anesthesiology Service, Hospital General Yagüe, Burgos, Spain;

⁶Department of Microbiology, Hospital La Línea, Cádiz, Spain

■ INTRODUCTION

Viral lower respiratory tract infections are a major cause of morbidity and mortality, especially in childhood [1]. RSV is the most frequent cause of lower respiratory tract disease in children under 2 years, and the cause of 70% or more of episodes of childhood bronchiolitis, especially in its severe forms [2-7]. Its spread is so effective, that almost the entire population is infected with RSV during the first years of life. However, since immunity is not complete after the initial infection, reinfections can often be seen throughout life affecting older children and adults, although in these populations only the upper respiratory tract is more often affected [8].

In all geographic regions studied worldwide evidence of RSV infection has been found. Even in very different climatic conditions, RSV infection appears to have similar features [4, 6, 9-12]. RSV is the only viral respiratory agent, along with the influenza virus, which is clearly responsible for a considerable number of infections every year [4, 6, 13].

Outbreaks of RSV infection are annual and the regional RSV season is determined by the geographical equator, the disease being associated with the rainy season in the North and the dry season in the South, which seems to correspond to the variations in temperature and humidity with the spread of RSV [14]. Outbreaks are grouped into different regions of our environ-

ment from October to May, while they are rare during the months of June to September.

We review the RSV cases diagnosed in the Valladolid HCU's Department of Microbiology, over a decade, and describe the annual epidemic curve they present.

■ MATERIALS AND METHODS

Valladolid is a Spanish city located in the centre of the northern plateau in a valley between the confluence of the Esgueva and Pisuerga rivers, at an altitude of 691 metres above sea level. It has a continental climate, with extreme temperatures in both winter and summer, with short autumn and spring times. The reference population of the area of influence of the HCU during the study period varied between 221,482 and 286,817 inhabitants, the average population per year being 274,046 inhabitants.

We performed a retrospective study of the period between 1990 and 2000, during which part of the data on the temperature and humidity occurring during those 11 years was collected, these being provided by the Ministry of the Environment, the National Institute of Meteorology through the *Castilla y León* Region's Meteorology Centre, measured at the observatory of Valladolid. At the same time, all the cases which were diagnosed as positive for RSV in Valladolid HCU's Microbiology Department during that period were also collected, resulting from week-

ly bulletins of aetiology statement of diseases submitted by the above-mentioned Department to the National Epidemiology Centre, under the *Instituto de Salud Carlos III* in Madrid, corresponding to the cases diagnosed and treated in the Hospital and its area of influence.

Diagnostic techniques employed throughout these eleven years in the detection of RSV were of both direct detection methods (direct immunofluorescence and cell culture) and indirect detection methods (enzyme-linked immunoassay and complement fixation reaction).

RESULTS

The months with lower temperatures correspond to those between the months of November and February, with average temperatures ranging between 4.5 and 7.7°C, while the warmest were the months of June to September with averages falling between 18.1 and 22.5°C (Table 1). With regard to the variations in humidity, the months with highest values were the months of November through February, with values of 62-92%, and months with lower values corresponding to the period between June and September, with values between 42 and 64% humidity (Table 2).

There were a total of 427 cases diagnosed at Valladolid HCU's Microbiology Department, as positive RSV by the different diagnostic

methods used, throughout the period of the study. The annual incidence of RSV positive cases registered in the HCU of Valladolid and its area of influence throughout the period 1990-2000 ranged from 5.64 to 22.3 cases per 100,000 inhabitants per year, with an average of 14.1 cases per 100,000 inhabitants per year. Interestingly, three peaks of incidence may be observed during the study period, in 1996, 1998 and 2000 (Figure 1).

The data collected weekly were grouped per year. A distribution in two outbreaks every year can be observed: one at the beginning of the year (end of the season) corresponding to the months of January to April (weeks 1-17) and another outbreak at the end of the year (early season) in the months of October to December (weeks 32-43), coinciding with the months with lower temperatures and higher humidity (Figure 2). It could be corroborated that the duration of each RSV season ranged from 5-6 months during the two years of the study. Every year saw a seasonal break or slip-free detection of RSV-positive cases coinciding with the months with higher temperatures and lower humidity, these being the months of July to mid October (weeks 27-42) (Table 2).

The first week of isolation varied from week 43 (end of October) and week 5 (beginning of February) throughout the period studied, reaching 81.8% of the first isolation between weeks 43 and 51 (November-December).

Table 1 - Monthly and annual average temperatures (Celsius degrees) recorded in Valladolid in the period 1990-2000.

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Mean
1990	3.8	9.3	9.8	9.2	15.7	19.8	23.7	23.2	20.6	13.2	6.4	3	13.1
1991	3.9	4.4	8.9	9.3	13.1	19.3	22.6	24.1	19.8	10.7	7.6	4.7	12.4
1992	2	5.3	8.8	11.3	16.8	15.5	23.1	22.6	17.7	10.9	8.9	5.6	12.4
1993	2.3	5.3	8.3	10	13.6	18.7	21.1	22.2	15.5	10.1	6.4	6.3	11.6
1994	4.1	5.7	10.9	9.6	14.6	18.9	24.2	23	15.9	13.6	9.4	6.1	13
1995	5.6	7.4	9.1	12.2	16.5	19.6	23.3	22.2	15.7	15.9	9.9	6.4	13.6
1996	7	4.8	8.6	11.5	13.4	20.1	22.3	20.6	16.7	13	8.3	5.6	12.7
1997	4.8	8.6	12	13.6	14.9	16.9	20.5	22.6	20.2	15.6	8.8	5.6	13.7
1998	6.2	8.1	11.1	9.5	14.3	19.4	22.4	23.2	18.6	12.3	7.6	3	13
1999	3.8	5.3	8.6	11.3	16.2	19.4	23.4	22.1	18.3	13.3	5.6	4.6	12.7
2000	1.9	8.3	9.3	9.3	15.6	20	20.9	21.3	18.6	12.5	7.2	7.4	12.7
Mean	4.5	6.4	9.6	10.7	14.8	19.6	22.4	22.5	18.1	13	7.7	5.1	20.7

Table 2 - Monthly and annual average humidity (%) recorded in Valladolid during the period 1990-2000.

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Mean
1990	89	77	58	67	60	52	42	43	55	69	86	80	65
1991	81	77	71	61	52	50	48	42	55	69	73	79	63
1992	78	62	55	53	53	59	43	46	55	77	85	88	63
1993	92	68	63	63	65	56	44	45	64	79	81	87	67
1994	83	72	65	59	63	50	44	47	62	74	83	86	66
1995	79	77	59	51	54	49	50	50	63	66	78	85	63
1996	82	74	68	67	67	53	45	53	58	68	76	86	66
1997	87	73	52	57	62	58	56	54	59	69	83	86	66
1998	81	73	58	67	62	54	47	46	58	68	74	84	6
1999	81	69	61	62	64	53	49	55	63	76	81	87	67
2000	82	72	59	75	69	47	47	46	52	70	83	81	65
Mean	83	72	61	62	61	53	47	48	59	71	80	84	65



Figura 1 - Annual incidence rate of RSV-positive cases per 100,000 inhabitants in Valladolid HCU and its surrounding area.

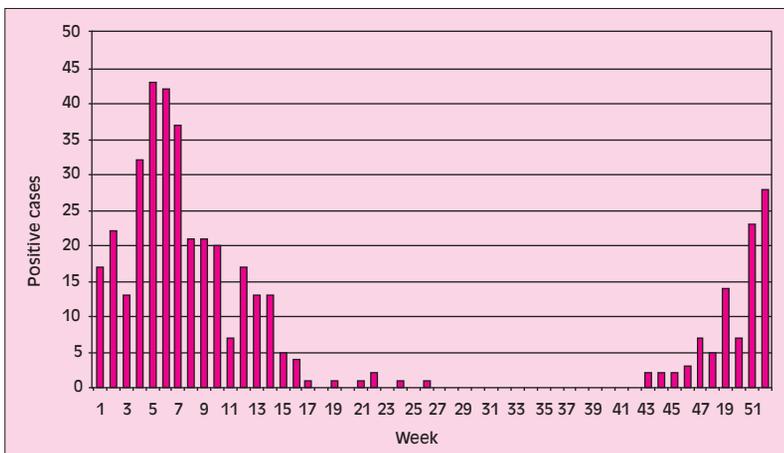


Figura 2 - Distribution of cumulative weekly RSV-positive cases in Valladolid HCU in 1990-2000.

The week when the most RSV-positive cases were detected varied from week 51 (December), with 7 cases, and week 7 (February) with 9 cases, coinciding with the lowest temperatures 5.1-6.3°C, and highest humidity 72-84%. The peak incidence weeks throughout the study period corresponded to weeks 6 and 9 (February) in 80% of the years studied (Table 3, Figure 3).

As regards seasons, that with the highest number of RSV-positive cases was the 99-00 season with 58 cases, while that with the fewest cases filed was the 92-93 season with 10 cases, the arithmetical mean being 39.4 cases per season. The number of cases remained relatively stable during the last six seasons remaining, with an average of 46.2 cases per season, compared

with 29.3 cases per season for the first four seasons analysed.

Table 3 and Figure 3 summarize other relevant details of the seasons:

- In only one of the ten seasons, 98-99, a maximum peak incidence occurred before the end of the year ahead of what happened during the other seasons.
- In two of the ten seasons [92-93, 94-95] the first RSV isolation did not occur until after the beginning of the year, still lagging behind what happened the other seasons.
- In three (92-93, 94-95, 96-97) of the last ten seasons the last RSV isolation occurred after April.

If we refer to the years studied, the year with

Table 3 - First and last weeks of cases in annual epidemics of RSV infection in Valladolid HCU in 1990-2000.

Season	Week first diag	Week max diag	Week last diag	No. cases
1990-91	51	5	10	13
1991-92	49	7	16	33
1992-93	5	6	26	10
1993-94	43	51 and 2	13	61
1994-95	2	6	15	37
1995-96	47	4	19	57
1996-97	47	3 and 5	22	52
1997-98	50	6	17	30
1998-99	45	51 and 52	13	43
1999-2000	49	5	12	58
				Total: 394
*Cases from January to April 1990 are not included because they correspond to the 1989-1990 season.				

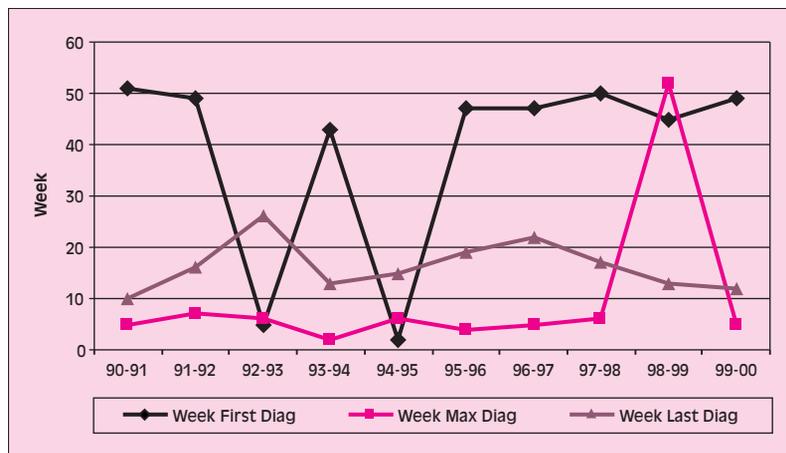


Figure 3 - First and last week of the RSV epidemics as well as the weeks with the highest number of positive diagnoses in Valladolid HCU in 1990-2000.

the highest number of RSV-positive cases was 1996 with 66 cases and 1991 the year when fewer cases occurred with 16 cases, while the annual average during this period was 38.8 cases. In the period studied two peaks in the detection of RSV-positive cases were distinguished, the main one going from weeks 5 to 7, coinciding in February, with between 39-43 cases per week and another at weeks 51 and 52, with 23 to 28 cases per week, corresponding to the last weeks of December. However, it may be stated that there are significant values from weeks 49 to 14.

■ DISCUSSION

We observed that each year the clustering of cases was associated with two outbreaks, one at the beginning of the year and another one at the end, coinciding with the coldest and wettest months. These findings are consistent with those reported by others close to our area, who observed that outbreaks of RSV infection are annual, the RSV season extending from November to March, presenting infection peaks around the month of January. Such outbreaks can even be delayed to the months of March or April [15-21]. Our results are consistent with those described by Alonso et al. who analysed the trends at the beginning and end of epidemics of acute RSV bronchiolitis in part of the study area, noting that epidemics begin in September and October, the highest peak observed in January and lowest in August, ending in February, March and April [22]. Likewise they documented when the epidemic season began earlier, it also ended sooner. They observed a cyclic period every 12 months over the years studied, showing a circannual rate.

In our study, a distribution of two outbreaks per year was also observed, at the beginning and end of the year coinciding with the coldest and wettest months. These outbreaks have an average duration of six months (October to April). Coinciding with other authors we observed a seasonal break or slip free of RSV-positive cases every year, coinciding with the months of higher temperatures and lower humidity, from July to October [23-26].

We conclude that in our area, RSV infections follow a cyclical pattern which is repeated every 12 months, in which RSV outbreaks are related inversely to changes in temperature and in direct proportion to changes in humidity which occur throughout the different seasons. The epidemiological characteristics described above should alert doctors in the months of highest incidence to RSV as a possible causal agent of the different disease patterns and may well encourage a suitable approach for managing both clinical and possible complications in which this infection may result.

In the same way, these findings have to be considered when planning RSV immunisation programmes, either with humanized monoclonal antibodies, or with different vaccines whose studies and clinical trials are at an advanced stage of research. Such vaccines should be able to prevent lower respiratory tract infections, hospitalizations and deaths associated with RSV infection. An indirect benefit will be a reduction in secondary complications such as otitis media, sinusitis and infrequent bacterial superinfection.

Keywords: Respiratory Syncytial Virus, bronchiolitis, epidemiology, outbreaks, climatic conditions.

RIASSUNTO

Respiratory Syncytial Virus (RSV) is the main cause of acute lower respiratory tract infections in children under 2 years. Its distribution is worldwide and even in very different climatic conditions, it appears to have similar features. It is known to produce a significant amount of infections each year. We present the results of a retrospective review of positive cases of RSV detected in the Microbiology Laboratory of the Hospital Clínico Universitario of Valladolid in the period between 1990 and 2000, dealing with its presentation at the given time with the weather variables of

temperature and humidity. The clustering of cases was associated with two outbreaks each year, one at the beginning and the other at the end of the year, coinciding with the coldest and wettest months. This pattern was repeated each of the years in question, with the onset of the first isolation between the months of October and February, and ending between March and June, showing the highest peaks of isolation during the month of February. Therefore, every year we observe a break or seasonal slip matching the months with higher temperatures and lower humidity.

SUMMARY

Il virus respiratorio sinciziale (VRS) è la principale causa di infezione acuta delle basse vie respiratorie nei bambini di età inferiore a 2 anni. La sua diffusione a livello mondiale, anche in condizioni climatiche molto diverse, presenta caratteristiche simili.

Nel presente articolo vengono presentati i risultati di un'analisi retrospettiva dei casi di infezione da RSV rilevati nel Laboratorio di Microbiologia dell'Hospital Clínico Universitario di Valladolid nel periodo 1990-2000, analizzandone la distribuzione temporale in relazione ai valori di temperatura e umidità ambientali.

In ciascun anno del periodo studiato, è stata osservata una concentrazione dei casi in due periodi e specificamente all'inizio e alla fine dell'anno, ovvero in coincidenza con i mesi più freddi e più umidi.

Questo andamento si è ripetuto in maniera costante ogni anno, con i primi casi rilevati nel periodo tra ottobre e febbraio e gli ultimi nel periodo tra marzo e giugno; il maggior numero di casi è stato rilevato nel mese di febbraio.

Ogni anno è stata osservata una pausa stagionale in concomitanza dei mesi più caldi e meno umidi.

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