Rev. Inst. Med. trop. São Paulo
36 (3): 255-264, maio-junho, 1994

ETIOLOGY AND SEVERITY OF COMMUNITY ACQUIRED PNEUMONIA IN CHILDREN FROM URUGUAY: A 4-YEAR STUDY

Maria HORTAL (1), Adela SUAREZ (2), Cristina DELEON (2), Miguel ESTEVAN (2), Maria Cristina MOGDASY (3), José Carlos RUSSI (1), Myriam CONTERA (3) & Miguel MENY (3).

SUMMARY

The 4-year study (1987-1990) covered the major clinical-epidemiological characteristics of pneumonia in children as diagnosed at the emergency service of the Children's Hospital, as well as etiologies, and factors involved in the most severe cases.

Etiology was determined in 47.7% of the 541 pneumonia cases, involving 283 pathogens of which 38.6% were viruses and 12.6% bacteria. Viral and mixed etiologies were more frequent in children under 12 months of age. Bacteria predominated in ages between 6 and 23 months. Among the viruses, respiratory syncytial virus predominated (66%). The bacterial pneumonias accounted for 12.2% of the recognized etiologies. The most important bacterial agents were *S. pneumoniae* (64%) and *H. influenzae* (19%). *H. influenzae* and mixed infections had a relevant participation during the 1988 season, pointing to annual variations in the relative participation of pathogens and its possible implication in severity of diseases. Correlation of severity and increased percentage of etiological diagnosis was assessed: patients with respiratory rates over 70 rpm, or pleural effusion and/or extensive pulmonary parenchyma compromise yielded higher positive laboratory results. Various individual and family risk factors were recognized when comparing pneumonia children with healthy controls.

KEYWORDS: Pneumonia; *Hemophilus influenzae*; *Streptococcus pneumoniae*; Viral pneumonia.

INTRODUCTION

Since 1984, acute respiratory infection (ARI) etiologies have been investigated in Uruguay either in cohort children or in outpatients and inpatients. The distribution of the agents was determined as well as the main clinical entities [10, 12]. Prospective studies covered the most deprived groups of children, receiving medical care from the Ministry of Public Health.

Between 1987 and 1990 a hospital-based study on pneumonia in children less than 5 years of age was carried out. The pneumonia cases were enrolled on a systematic form enabling a comparative overview of the variations that occurred either in the clinical-radiological presentation of the pneumonias or in the etiologic agent participation*. It is generally accepted that to obtain representative epidemiologic data, it is necessary to cover prolonged periods of time. By the end of the first year the most relevant agents associated to pneumonia were detected, confirming that viruses predominated

* Informed consent was obtained from the patients' parents or gardians, and Ministry guidelines for human experimentation were followed.

(1) Central Public Health Laboratory
(2) Children's Hospital
(3) ARI Program, Div. Epidemiology, Ministry of P. Health.
Address for correspondence: M. Hortal, M.D., M.P.H. - Av. 8 de Octubre 2720, Montevideo 11.600, URUGUAY. FAX: (598) 2 807014.

also in Uruguay, with respiratory syncytial virus (RSV) as the most frequently identified agent, and that most of the severe cases were associated to a bacterium, *Streptococcus pneumoniae* (S. pn) or *Hemophilus influenzae* (Hi) [13]. This was only a partial insight of the problem. Later, annual variations in disease severity were documented, perhaps related to the agents behaviour and to cocirculation of microorganisms.

This paper describes the major clinical-epidemiological characteristics of the child population with pneumonia as diagnosed at the emergency service of the Children's Hospital, detected etiologies, outcome of disease and risk factors involved in the most severe pneumonias.

MATERIALS AND METHODS

Definitions

- *Pneumonia*, was defined on clinical-radiologic basis, as was routinely done at the Emergency Service. Briefly, pneumonia was considered when an elevated respiratory rate for age was present with or without chest indrawing, abnormal auscultation signs and pathologic images. The definition also comprised bronchiolitis with fever over 38.5°C or an X-ray documented infiltrate. Only patients with community-acquired pneumonia were enrolled, disregarding previous antibiotherapy or days elapsed since the onset of disease.
- According to WHO definition for different ages, *respiratory rates* [19] were considered to be increased when they were $\geq$60 breaths per minute for infants less than 2 months old, $\geq$ 50 for those children between 2 and 11 months of age, and $\geq$ 40 in children aged 12 months or more.
- *Severity* criteria was based in the following: respiratory rate $\geq$70 breaths per minute, pneumonia with pleural compromise and/or extensive pulmonary parenchyma involvement or cavitation. Thus subpopulation groups were recognized among the total number of enrolled cases.
- *Radiologic diagnosis of pneumonia* included any of the following: diffuse intersticial infiltrate, one or more subsegmental parenchyma infiltrates, segmental parenchyma infiltrates, lobar opacification, parenchymal densities, cavitation and/or pleural effusion.
- *Mixed infections* were defined as those having more than one recognized agent either viruses, bacteria, chlamydia or a combination of 2 or 3.
- *Nutritional status* was based on weight for age according to the NCHS/CDC tables.

Patients and controls

Five hundred and forty one children between 28 days and 5 years old, were enrolled at the Emergency Service of the Children's Hospital, four days a week, from May 1987 to November 1990. Medical history, results of physical examination verified by one of the 4 program pediatricians, and X-ray data of each patient at the time of enrollment were recorded on a precoded form. Data on evolution, and outcome were also collected.

Children with severe pneumonia, living in Montevideo, were visited in their home by pediatrician, between 30 and 45 days after discharge from the hospital, to check their long term recovery.

- Matched controls (n=308) were enrolled during 1988 and 1989, at an outpatient clinic, where many children attended for health control and/or for vaccination. Control children were healthy, with no medical history of IRA hospitalization, free of antibiotic treatment, without obvious IRA within the family when enrolled. They were entered in the study within 15-20 days after the index pneumonia case was diagnosed and matched by age and sex.

ETIOLOGIC STUDIES

Bacteriology [2]

For bacteriologic investigation several samples were collected: blood, for one blood culture, and for serum at the acute phase of the illness, and pharyngeal swab; pleural effusion was also collected when present and a drainage was indicated. Bacterial etiology of pneumonia was assessed in blood or pleural culture results, and/or antigen detection by CIE and/or latex in the pleural effusion.

Virology [3]

Detailed viral procedures have been published elsewhere [12]. Briefly, in every enrolled case a nasopharyngeal aspirate (NPA) was obtained. It was inoculated in Hep-2, LLC-MK2, MDCK and MRC5. When a virus was isolated, the identification was performed by indirect immunofluorescence (IIF) with polyclonal antisera to Influenza A (IA), (IB), RSV, Parainfluenza (P 1) and (P 3), adenovirus (AD). Smears were prepared with NPA cells, to detect specific antigens for the already men-

tioned viruses by IIF. Positive results were recorded either according to virus isolation and/or antigen findings by IIF in NPA cells.

Chlamydia trachomatis [2]

Since 1989, an additional NPA was taken from children aged less than 6 months to investigate *C. trachomatis* (C. tr); the supernatant of the NPA was inoculated in cycloheximide treated Mc Coy cells, an aliquot was saved for ELISA test and a smear with the cells was also prepared for the detection of specific antigens by IIF.

Statistical analysis

A statistical package (SYSTAT, version 3.0; Systat, Evanston, III) was used for data analysis. Univariate analysis was used to look for risk factors and for those associated to etiologies in pneumonias. The association was evaluated by the odd ratio and their respective confidence intervals.

RESULTS

Patients characteristics

Population demographics of the pneumonia cases are shown in Fig. 1. As noted in this Fig., the age of the pneumonia patients had an even distribution over the 4 years of the study. The mean age was 16.7 months (SD=13.8), but more than 80% of the enrolled children were under 24 months of age. Sex distribution also did not change over time. In all, 290 children were males, and 251 females.

Of the 541 cases entered in the study, 71.4% lived in Montevideo. The remaining ones were referred from other parts of the country (23.4% from areas surrounding the capital city and 5.3% from distant places).

At admission 34.3% of the patients had already received antibiotic treatment.

Of the 541 children, 15.3% of patients had a low birth weight (< 2.500 g) and 21.2% weighed less than 3.000g at birth. Almost half of the children (47%) were below normal weight for their age, and 22.4% were in the 5th percentile. No significant differences were detected in the nutritional status of children enrolled along the different years of the study.

Significant differences were found when comparing the patients with the control group: only 9.7% of the control children had low birthweight (p=<0.002) and in

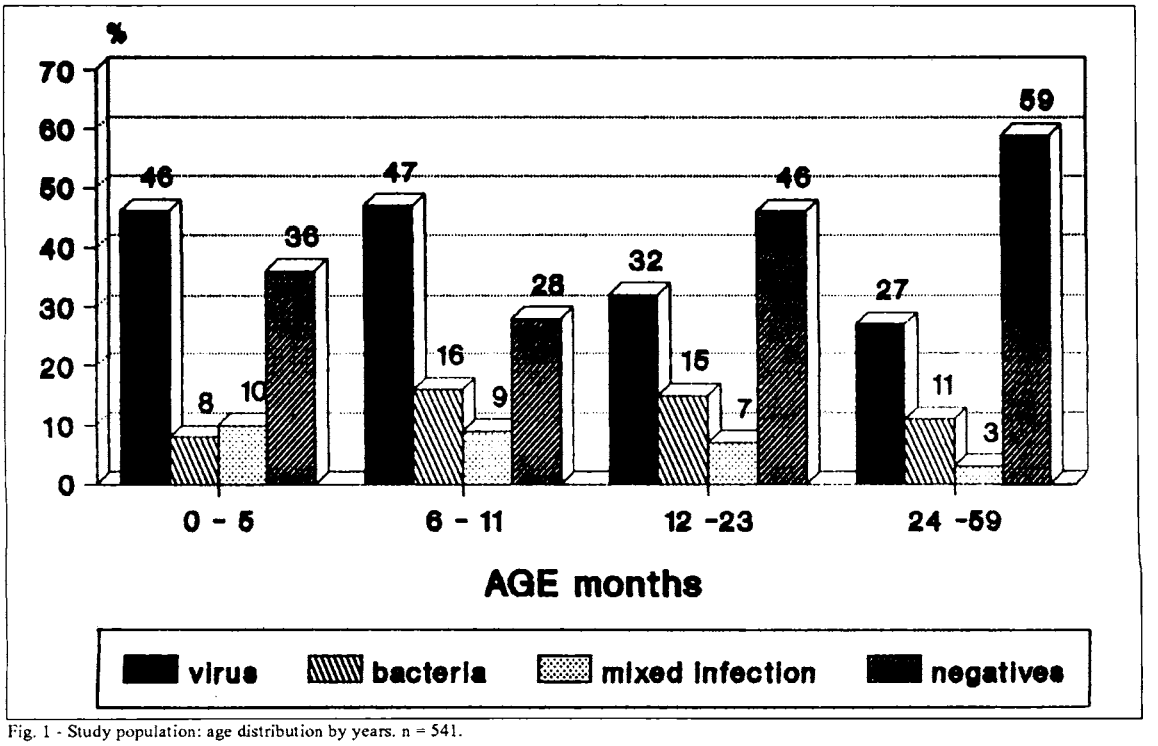

Fig. 1 - Study population: age distribution by years. n = 541.

TABLE 1

Individual and family risk factors in pneumonia patients and healthy controls.

Risk factor	Reference	Odd Ratio	95% confidence interval	
			lower	higher
No breast-feeding	Breast-feeding	4.97	2.93	8.44
Nutritional status				
Percentile < 5	percentile > 20	2.76	1.77	4.31
Percentile > 5-<10		2.06	1.12	3.78
Percentile >10-<20		1.83	1.16	2.89
Birthweight < 2.500g	birthweight > 2.550g	1.64	1.05	2.56
Immunization				
No or incomplete	complete	2.73	1.95	3.82
Sibling's number				
2-5	no siblings	1.50	1.09	2.06
> 5		1.75	1.10	2.79
Mother's age				
< 20 years	between 20-44 y	1.68	1.10	2.57
> 44 years		5.38	1.61	17.95
No control during pregnancy	controlled	4.63	2.81	7.62
Prenatal hospitalization	none	2.00	1.35	2.97
Mother alone	stable couple	2.34	1.49	3.68

28.3%, their nutritional status was below normal weight for age; 10.9% were above the 5th percentile (p=<0.001).

The analysis of other risk factors is summarized in Table 1. When pneumonia children were compared with controls, no differences were seen between groups in terms of controlled variables (age, sex, and date of enrollment). Individual and family risk factors indicated

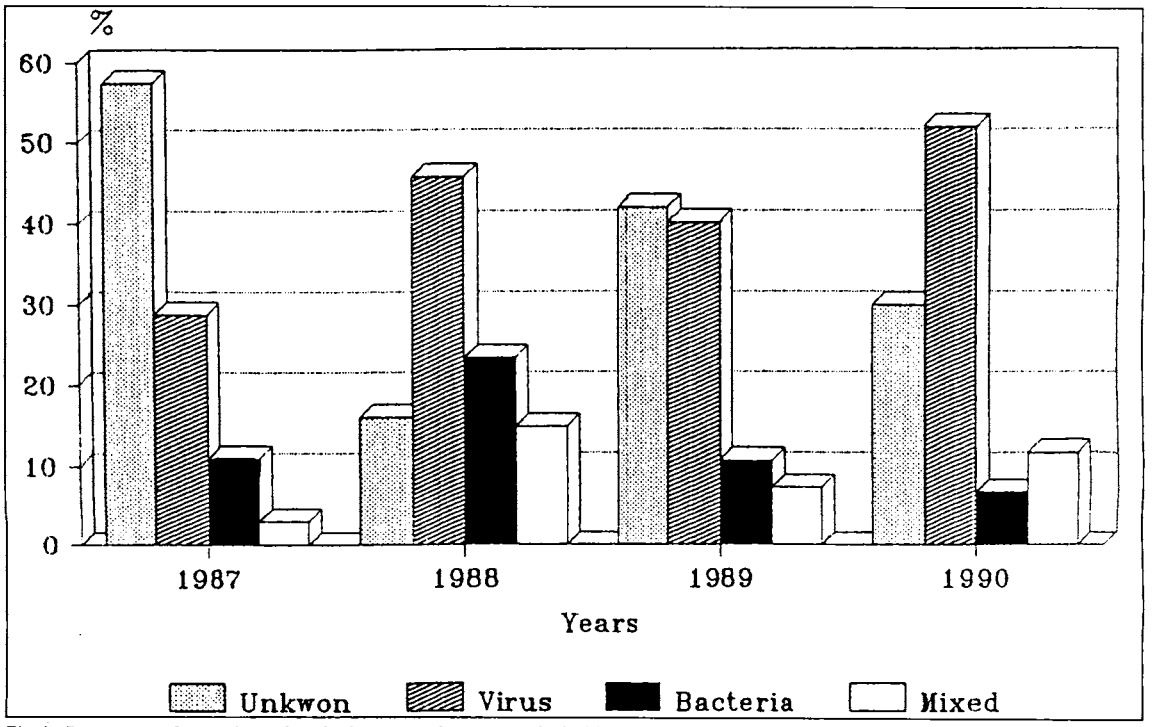

Fig. 2 - Percentages of recognized etiologies in pneumonias. Annual distribuition (1987-1990).

TABLE 2

Mixed infections by group of agents

Agents	YEARS 1987 n	% t=101	1988 n	% t=155	1989 n	% t=141	1990 n	% t=119	Total n	% t=516
Virus/Vir.	0	-	6	3.9	5	3.5	7	5.4	18	3.5
Vir./Bact.	2	1.9	13	8.4	4	2.8	2	1.7	21	1.4
Vir/Vir/Bact.	0	-	1	0.6	0	-	0	-	1	0.2
Vir.Bact/Bac.	0	-	1	0.6	1	0.7	0	-	2	0.4
Vir/Chlam.*	-	-	-	-	-	-	2	1.7	2	0.4
Bact/Bact.	1	0.99	1	0.6	0	-	0	-	2	0.4
Total	3	3.0	22	14.2	12	7.1	11	9.2	46	8.9

* Diagnosed since 1989

disparate experiences between the children with pneumonia and the control group.

Underlying pathology

Review of the past medical history showed that 127 study children (30%) had experienced one or more previous ARI episodes that required hospitalization. Of these, 84 (15.5%) had been previously hospitalized with pneumonia, 43 (8%) with bronchiolitis and 20 (3.8%) with severe otitis media; 11.5% of the children had been hospitalized due to severe diarrheal disease.

Additional underlying illnesses not requiring hospitalization were recorded in 9.7% of patients (Down syndrome, gastric reflux, congenital conditions, anemia, etc.).

Etiology

During the study period 47.7% of the cases had a recognized etiology. Annual distribution of the different etiologies is shown in Figure 2. The highest percentages of positive cases occurred in 1988, and the lowest in 1987. The increase of etiologies recorded in 1988 was mainly mediated by bacteria and mixed infections.

TABLE 3

Total number of identified agents by year

Viruses	1987 t=101 n	%	1988 t=155 n	%	1989 t=141 n	%	1990 t=119 n	%	Total t=516* n	%
RSV	26	25.7	50	32.3	33	23.4	29	24.4	138	26.7
Paraflu	2	2.0	3	1.9	5	3.5	7	5.9	17	3.3
Influenza A	1	0.9	9	5.8	-	-	11	9.2	21	4.1
Influenza B	-	-	2	1.3	3	2.1	-	-	5	0.97
Adenovirus	-	-	1	0.6	5	3.5	7	5.9	13	2.5
Others **	-	-	6	3.9	8	5.7	1	0.8	15	2.9
	29	**28.7**	**71**	**45.8**	**54**	**38.3**	**55**	**46.2**	**209**	**40.5**
Bacterias										
S. pneumoniae	10	9.9	21	13.5	10	7.0	7	5.8	48	9.3
H. influ.b	1	0.9	10	6.5	2	1.4	1	0.8	14	2.7
H.inf.non typ.	-	-	1	0.6	-	-	-	-	1	0.2
Staph.aur.	-	-	3	1.9	3	2.1	-	-	6	1.2
Salmonella	-	-	1	0.6	-	-	-	-	1	0.2
Chlam.trach.	-	-	-	-	2	1.4	2	1.7	4	0.7
Total	**11**	**10.9**	**36**	**23.4**	**17**	**12.0**	**10**	**8.4**	**74**	**14.3**

* No data = 25; ** include enteroviruses, HSV and non-identified

Changes in the relative participation of the pathogens were also documented: bacterial etiologies were higher in 1988 and lower in 1990, while viral etiologies, although remaining more stable over the whole period, showed a considerable fluctuation between 1987 and 1990. The frequency of the mixed infections (N=48) also varied (Table 2); although present every year their increase in 1988 was remarkable.

The absolute numbers of viral, bacterial and chlamydia identified agents are shown in Table 3. Two hundred and eighty three pathogens were identified: 209 viruses (38.6%), 70 bacteria (12.9%) and 4 C. tr (0.7%).

Age distribution by etiologies is shown in Fig. 3 . Viral infections were more frequent under 12 months of age (60.4%) and bacteria predominated in ages of 6 to 23 months (67.7%). In 46 children aged between 28 days and 90 days, recognized etiologies were higher than in other age groups (65.2%). Viruses predominated (54.4%), mixed infections ranged second involving either 2 viruses or a virus and C. tr. In 2 cases C. tr was the only identified agent. Bacterial participation was nill, despite 2 *Staphylococcus aureus* isolated in a single blood culture that were considered as non interpretable result.

RSV was the most frequent recognized viral agent. It was primarily associated with pneumonia in children under one year of age (61.4%). As expected for a temperate climate country, the annual outbreaks lasted an average of six months (May-October). Its participation in bacterial mixed infections was relatively low: 7.2% compared with 17.6% of adenoviruses. In bacteria-virus infections, RSV was mainly associated to S. pn. IA and IB were second in frequency, being both detected during the study period. IA (H1N1) circulated in 1987. IA (H3N2) was isolated in 1988 and in 1990. IB cocirculated with IA in 1988, and alone in 1989.

P1 and P3 viruses ranged third in frequency among the identified viruses. These pneumonia cases were mainly sporadic and mediated by type 3.

Identified AB were few (n=13), partially because of technical problems related to the quality of the available reagents. Nevertheless six of the strains were derived from very severe pneumonias in children younger than ≤18 months. Five of the strains were part of mixed infections (3 plus RSV, 1 Hi type b; and 1 S. pn and Hi type b) and 2 required intensive care for mechanical ventilation support.

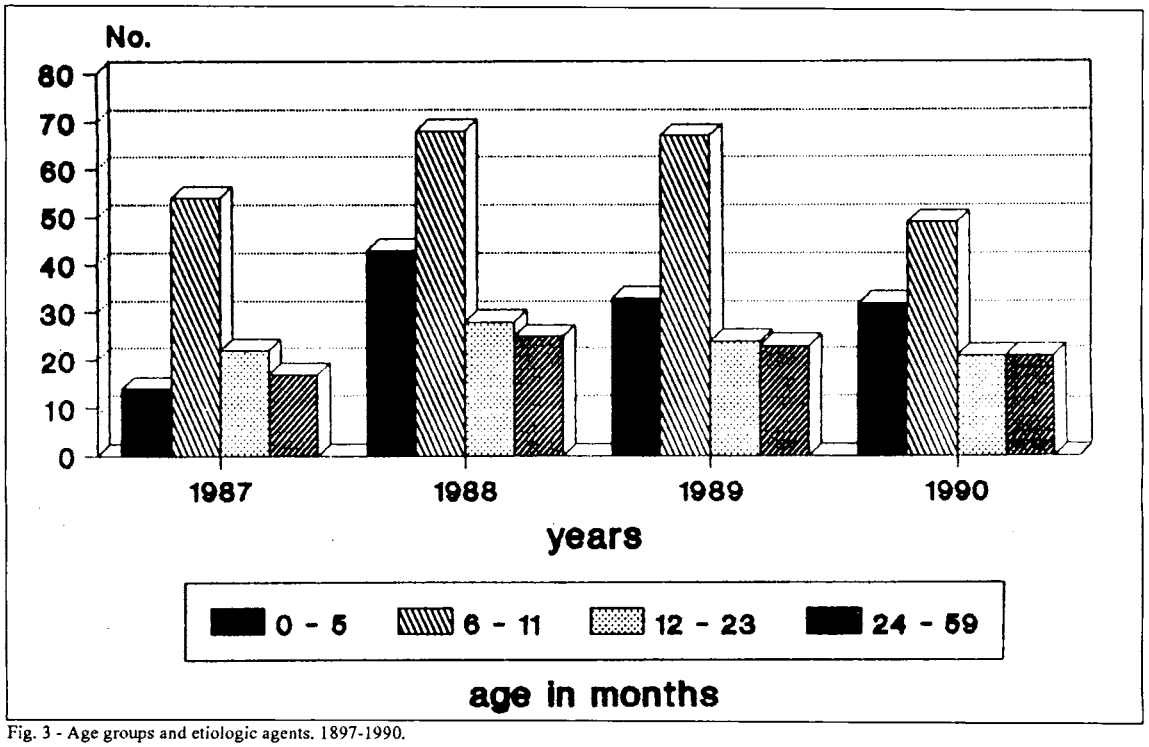

Fig. 3 - Age groups and etiologic agents. 1897-1990.

S.pn, present every year, was the most important bacterial agent, involved in 9.3% of all the pneumonias. The average age of the patients with pneumococcal pneumonia was 7.8 months (range 2 to 37 months). When attending the emergency service, the time elapsed since the onset of the disease, averaged 7 days. Of 48 cases, 29.2% had pleural compromise and 10.4% cavitation. S. pn was involved in 3 fatal cases.

Pneumococcal etiology was probably underestimated because of the cases with pleural involvement, in only 49.2% of the cases the fluid was available. When this pathogen was found in a mixed infection, it was mainly associated to a virus (8 RSV, 2 P 3, 2 AD, 1 enterovirus and 1 IB) or to another bacteria in 3 cases (2 Hi, 1 salmonella).

Antibiotic susceptibility to penicillin of invasive strains was almost 100%; this was not the case for cotrimoxazole as 13.5% intermediate, and 15.4% resistant strains were found.

Hi was second in bacterial etiology frequency (2.9%).

All invasive strains (n=17), were type b, except one non-typable isolate from pleural fluid. The mean age of the patients was 14.5 months (range 5-49 months). In two cases meningitis was also present. Four cases had associated otitis media and one patient also had osteoarthritis. Four patients had respiratory distress and 2 children died. Pleural involvement was frequent (8 pleural effusions; 2 pleuritis), as well as cavitation (n=6).

None were beta lactamase producers.

Group of patients selected according to

Radiologically severe lesions: Of 541 pneumonias, 75 had pleural effusion (13.5%) and 87 (16.1%) an extensive X-ray documented pulmonar parenchyma involvement or cavitation. In Table 4, the annual variation in frequencies is shown. Increased, frequencies of pleural effusions were documented in 1987 and 1988. In 1988 the total increase of radiologically severe cases was remarkable (40.9%). Pneumonias with pleural effusion were scattered from autumn to spring, but small clusters of cases occurred at the beginning and at the end of the cold season.

Of the patients with microbial study of the pleural effusion, 17 lived in Montevideo (5.7%), and 15 were referred from distant places (12.5%). Time elapsed since the onset of the disease averaged 5.5 days for patients from Montevideo and 9.3 for those from other places. The mean age of the patients was 19 months (SD=11.53).

Etiologic diagnosis was achieved in 66.6% of the studied fluids, although 54.8% of the patients had received antibiotic treatment before attending the Emergency Service.

Etiologies detected in patients with severe pulmonary damage were 51.8%; this percentage added to that found in patients with pleural effusion yield a high percentage of etiological recognition not detected in the whole pneumonia population.

Respiratory rate ≥70 breaths per minute: Of 534 patients, 81 had a respiratory rate ≥ 70 breaths per minute. Four cases had this respiratory rate without retractions. Three patients died. Twenty six of these patients (32.1%) were already included in the radiologically severe group.

The etiologic diagnosis was achieved in 60% of the cases. Viruses were involved in 43.5% of them (7 mixed infections and 30 viral).

Outcome

TABLE 4

Severe pneumonias according to radiology by years

Year	n	Pleural effusions #/%	Pareenchyma Compr. #/%	Total severe #/%
1987	107	19/17.8	8/7.6	27/25.2
1988	164	31/18.9	36/22.0	67/40.9
1989	146	16/11.0	26/17.8	42/28.8
1990	122	7/6.7	17/13.9	26/20.6
Total	539*	73/13.6	87/16.1	160/29.7

missing data, 2.

TABLE 5

Days of hospitalization: cases with certified etiology versus cases with negative results.

Agents	Positive		Negative		p values **
	X	SD	X	SD	
Bacterial	15.266	12.184	8.224	7.146	.000
Viral	8.446	8.480	9.644	8.327	.131
Selected agents					
RSV	8.829	8.786	9.299	8.258	.589
adenovirus	12.583	14.513	9.081	8.186	.154
H. influenzae	17.143	15.397	8.923	7.938	.300
S. pneumoniae	16.022	12.342	8.435	7.452	.000

** t-test of the means

Duration of hospitalization related to the etiologies is shown in Table 5. Bacterial etiologies were significantly associated to a longer stay in hospital when compared with cases without a recognized etiology.

Fatal cases[6]: A letality of 3% was recorded throughout the study-period. The 16 deaths were evenly distributed along time. The age of the dead children averaged 7.5 months, but several of them were aged one month. Most of the fatal cases remained without an etiologic diagnosis, as pathogens were identified only in five. In spite of the high frequency of RSV cases, this virus was only involved in one death along with a P 3. S. pn alone or in mixed infections was present in 3 cases, and Hi in 2 (1 type b and 1 non-typable).

Increased respiratory rate $\geq$70 rpm at admission was observed in 7 patients. Ten were radiologically considered as severe pneumonias. Twelve of the fatal cases presented one or two severity markers.

A closer analysis of the data allowed to assess that pneumonia was directly responsible for this death of 9 children while in the other 7 cases extrarespiratory causes were present.

Home visits: Difficulties were faced when home visits were attempted to check the most severe pneumonias. Forty-three percent of the cases were missed because the addresses could not be located, the families had moved or were absent when visited. Of the 65 examined children, 24 were in good health, 23 had persistent respiratory symptoms (rales, cough), 3 were hospitalized again due to respiratory disease, and 15 had underlying diseases or malnourishment.

DISCUSSION

As is worldwide observed, in Uruguay [8, 11], S. pn and Hi type b were the two most important bacterial agents causing pneumonia in children under 5 years of age. Also as reported by other investigators, RSV predominated among the viral etiologies, with a relative frequency of 66% [22, 24]. Besides, severity of AD pneumonias cannot be overlooked, because a new subtype of the virus involved in fatal cases, has recently been recognized in South America [4, 15].

Due to the difficulty to detect bacteriemia in only one blood culture, and the high proportion of patients already treated with antibodies when attending the emergency service, we assumed that other bacterial pneumonias had undergone undiagnosed [16, 17]. Antibiotic treatment before blood collection probably filtered out the milder cases of bacterial disease which would have respond to therapy. Besides increases the proportion of children with viral pneumonia. Therefore the data presented apply to our study population, that probably represent a common place in our countries where free use of antibiotics is allowed.

Assuming that standard diagnostic techniques were used during the 4-year study period, a correlation between severity of disease and increased percentage of positive results can be proposed. Probably, in more severe pneumonias, larger involvement of the respiratory tract occurs, hence a higher shedding of viral agents furnishes richer samples that improve diagnostic possibilities.

The results obtained by the community-based studies in which most of ARI cases were mild supports this hypothesis. The viral diagnosis was 15.3% for the family follow-up, and 17% for a local outpatient clinic [12].

Several factors as increased number of bacterial etiologies, higher number of recognized mixed infec-

tions, as well as changes in the biological characteristics of the viruses, may have contributed to the severity found in the 1988 season. IA subtype H3N2 was reintroduced in the children population after 3 years of absence [14]. A similar fact occurred with RSV subgroup A, that became prevalent after a year of reduced activity [20]. Further characterization of RSV strains showed that genetic variations had also occurred in the 1988 outbreak [5].

Although S. pn remained as the predominant bacterial agent in 1988, a change was noticed in the frequency of HIb participation. Differences in invasiveness of different serotypes of S.pn have been described [15]. Also variations in outer membrane proteins and LPS of HIb and of non capsulated strains have been proposed as responsible for the changes in strain virulence [1, 9, 23].

According the collected data, different patterns of disease were observed during the 4-year study. Years 1987 and 1989 were average, with the traditional winter outbreaks, and almost a classical balance between viral and bacterial etiologies. In 1988 increased bacterial and mixed infections altered this balance, with an unusual increase in severe cases. The opposite occurred in 1990, as most of the cases were mild, viral etiologies predominanted and bacterial or complicated pneumonias were scarce.

To conclude it is possible to say that the studied population belong to a vulnerable group, that severe pneumonia cases persist, perhaps due to increse in virulence of the agents, and/or due to problems related to case management and parent's health education.

RESUMO

Etiologia e severidade de pneumonia adquirida comunitariamente em crianças uruguaias: um estudo de 4 anos.

O estudo de quatro anos de duração (1987-1990) abarcou as principais características clínico-epidemiológicas de pneumonia em crianças, tal como foi diagnosticado no serviço de emergência do Hospital Infantil, e também as etiologias e fatores implicados nos casos mais severos.

Determinou-se a etiologia em 47.7% dos 541 casos de pneumonia, que incluiam 283 patógenos, dos quais 38.6% eram virus e 12.6% bactérias. Observou-se etiologia viral e mista mais freqüentemente nas crianças de menos de 12 meses. A etiologia bacteriana prevaleceu nas idades entre 6 e 23 meses. Com relação aos virus, a predominância foi de RSV com prevalência de 66% do total de virus.

Os mais importantes agentes bacterianos foram S. *pneumoniae* (64%) e *H. influenzae* (19%).

O *H. influenzae* e as infecções mistas incidiram significativamente durante 1988 assinalando variações anuais na severidade das doenças.

Observou-se correlação entre a gravidade dos casos e a alta porcentagem de diagnóstico etiológico: pacientes com ritmos respiratórios mais altos que 70rpm, derrame pleural ou com comprometimento extenso de parênquima pulmonar, apresentaram maior índice de positividade laboratorial.

Reconheceu-se vários fatores de risco individuais e familiares ao comparar crianças com pneumonia com controles sadios.

ACKNOWLEDGEMENTS

We thank the U. S. National Academy of Sciences/ National Research Council for financial support by means of a grant from the U. S. Agency for International Development, and to Swedish Agency for Reseach Cooperation with Developing Countries for their financial support during the 4th year of the study. We also thank to Dr. J. Bale for her very comprehensive support and to Dr. P. Charache for her thoughtful suggestions about this manuscript.

REFERENCES

1. BAKEMKAMP, S. J.; MUNSON, R. S. & GRANOFF, D. M. - Subtyping isolates of *H. influenzae* type b by outer membrane protein profiles. **J. infect. Dis., 143**: 668-676, 1981.

2. BOSTID RESEARCH GRANTS PROGRAM - Manual on procedures for diagnosis of respiratory viral pathogens. Washington DC. Borad on Science and Technology for International Development, National Research Council, 1986.

3. BOSTID RESEARCH GRANTS PROGRAM - Manual on procedures for diagnosis of respiratory bacterial pathogens, Washington DC, Board on Science and Technology for International Development, National Research Council, 1986.

4. CARBALLAL, G.; SIMINOVICH, M.; MURTAGH, B. et al. - Etiologic clinical and pathologic analysis of 31 fatal cases of acute respiratory tract infection in Argentinian children under 5 years of age. **Rev. infect. Dis., 12** (suppl. 8): S1074-S1080, 1990.

5. CRISTINA, J.; MOYA, A.; ARBIZA, J. R. et al. - Evolution of the G

and P genes of human respiratory syncytial virus (subgroup A) studied by the RNase A mismatch cleavage method. **Virology, 184**: 210-218, 1991.

6. MINISTERIO DE SALUD PUBLICA, DIVISIÓN DE ESTADISTCA. Uruguay, 1990.

7. DONOWITZ, G. R. & MANDELL, G. L. - Acute pneumonia. **In:** MANDELL, R. G.; GORDON, J. E. & BENNET, J. E. ed. *Principles and practices of infectious diseases*. 2. ed., New York, John Wiley & Sons, 1985. p. 394-404.

8. GRAY, G. M.;CONSERVE, G. M. & DILLON, H. C. - Serotypes of *S. pneumoniae* causing disease. **J. infect. Dis., 140**: 979-983, 1979.

9. HANSEN, E. J. - Non capsular surface antigens and their association with virulence of *H. influenzae* type b. **In:** AYOUB, E. M.; BRANCHE, W. C.; CASSEL, G. H. & HENRY, T. J., ed. *Microbial determinants of virulence and host response*. Washington D. C, ASM, 1990. p. 45-54.

10. HORTAL, M.; FERRARI, A. M.; RUSSI, J. C. & ESTEVAN, M. - Infecciones respiratorias agudas intratoracicas en niños hospitalizados, Uruguay 1984-86. **Bol. méd. Hosp. infant.** (Méx.), **47**: 624-629, 1990.

11. HORTAL, M.; BENITEZ, A.; CONTERA, M. et al. - A community-based study of acute respiratory tract infections in children in Uruguay. **Rev. infect. Dis. 12** (suppl. 8): S966-S973, 1990.

12. HORTAL, M.; RUSSI, J. C.; ARBIZA, J. R. et al. - Identification of viruses in a study of acute respiratory tract infections in children from Uruguay. **Rev. infect. Dis., 12**(suppl. 8): S995-S997, 1990.

13. HORTAL, M.; MOGDASY, M. C.; RUSSI, J. C.; DELEON, C. & SUAREZ, A. - Microbial agents associated with pneumonia in children from Uruguay. **Rev. infect. Dis., 12** (suppl. 8): S915-S922, 1990.

14. KILBOURNE, E. D. - The epidemiology of influenza. **In:** KILBOURNE, E. D., ed. *Influenza*. New York, Plenum Medical Book, 1987. p. 255-289.

15. KAJON, A.; MURTAGH, P.; GARCIA, S. F. et al. - A new genome type of adenovirus 3 associated with severe lower respiratory infection in children. **J. med. Virol., 30**: 73-76, 1990.

16. MARRIE, T. J.; DURANT, H. & YATES, L. - Community-acquired pneumonia requiring hospitalization: 5-year prospective study. **Rev. infect. Dis., 11**: 586-599, 1989.

17. MUNSON, R. S.; KABEER, M. F.; LENOIR, A. A. & GRANOFF, D. M. - Epidemiology and prospects for prevention of disease due to *H. influenzae* in developing countries. **Rev. infect. Dis., 11**(suppl. 3): S588-S597, 1989.

18. MUSSER, J. M.; KROLL, J. S.; GRANOFF, D. M. et al. - Global genetic structure and molecular epidemiology of encapsulated *H. influenzae*. **Rev. infect. Dis., 12**:75-111, 1990.

19. ORGANIZACIÓN PANAMERICANA DE LA SALUD - Tratamiento del niño con infección respiratoria aguda. 1987. (Serie Paltex, No. 15).

20. RUSSI, J. C.; DELFRARO, A.; ARBIZA, J. R. et al. - Antigenic characterization of respiratory syncytial virus associated with acute respiratory infections in Uruguayan children from 1985 to 1987. **J. clin. Microbiol., 27**: 1464-1466, 1989

21. SELWYN, B. J. - The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. **Rev. infect. Dis., 12** (suppl. 8): S870-S888, 1990.

22. TURNER, R. B.; LANDE, A. E.; CHASE, P.; HILTON, N. & WEINBERG, D. - Pneumonia in pediatric outpatients: cause and clinical manifestations. **J. Pediatr., 111**:194-200, 1987.

23. WEISER, J. N.; LINDBERG, A. A.; MANNING, E. J.; HANSEN, E. J. & MOXON, E. B. - Identification of a chromosomal locus for expression of lipopolysaccharide epitopes in *H. influenzae*. **Infect. Immun., 57**: 3045-3052, 1989.

24. WEISSENBACHER, M.;CARBALLAL, G.; AVILA, M. et al. - Etiological and clinical evaluation of acute lower respiratory tract infections in young Argentinian children: an overview. **Rev. infect. Dis., 12**(suppl. 8):S889-S898, 1990.

Recebido para publicação em 06/07/1993.
Aceito para publicação em 10/03/1994.