An epidemiological study of RSV infection in the Gambia

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Objective To describe the epidemiology of respiratory syncytial virus (RSV) infection in a developing country.
Methods The work was carried out in three hospitals for primary cases and in the community for secondary cases in the western region of the Gambia, West Africa. RSV infection was diagnosed by immunofluorescence of nasopharyngeal aspirate samples in children younger than two years admitted to hospital with acute lower respiratory infection (ALRI). Routine records of all children with ALRI were analysed, and the incidence rates of ALRI, severe RSV-associated respiratory illness and hypoxaemic RSV infections were compared. A community-based study was undertaken to identify secondary cases and to obtain information about spread of the virus.
Findings 4799 children with ALRI who were younger than two years and lived in the study area were admitted to the study hospitals: 421 had severe RSV-associated respiratory illness; 55 of these were hypoxaemic. Between 1994 and 1996, the observed incidence rate for ALRI in 100 children younger than one year living close to hospital was 9.6 cases per year; for severe RSV-associated respiratory illness 0.83; and for hypoxaemic RSV-associated respiratory illness 0.089. The proportion of all ALRI admissions due to RSV was 19%. Overall, 41% of children younger than five years in compounds in which cases lived and 42% in control compounds had evidence of RSV infection during the surveillance period.
Conclusion RSV is an important cause of ALRI leading to hospital admission in the Gambia. Morbidity is considerable and efforts at prevention are worthwhile.

Keywords Respiratory syncytial virus, Human/pathogenicity; Respiratory syncytial virus infections/epidemiology; Respiratory tract infections/etiology; Anoxemia; Patient admission; Hospitals; Measles; Epidemiologic factors; Health services accessibility; Households; Epidemiologic studies; Gambia (*source: MeSH, NLM*).

Mots clés Virus syncytial respiratoire humain/pathogénicité; Virus syncytial respiratoire, Infection/épidémiologie; Voies aériennes supérieures, Infection/étiologie; Anoxémie; Admission malade; Hôpital; Rougeole; Facteurs épidémiologiques; Accessibilité service santé; Ménages; Etude analytique (Epidémiologie); Gambie (*source: MeSH, INSERM*).

Palabras clave Virus sincitial respiratorio humano/patogenicidad; Infecciones por virus sincitial respiratorio/epidemiología; Infecciones del tracto respiratorio/etiología; Anoxemia; Admisión del paciente; Hospitales; Sarampión; Factores epidemiológicos; Accesibilidad a los servicios de salud; Hogares; Estudios epidemiológicos; Gambia (*fuente: DeCS, BIREME*).

Bulletin of the World Health Organization 2002;80:562-568.

Voir page 566 le résumé en français. En la página 567 figura un resumen en español.

Introduction

Respiratory syncytial virus (RSV) is the most important cause of acute lower respiratory tract infections (ALRI) in early childhood in industrialized countries (*1–3*). Outbreaks occur annually during the winter months in temperate climates (*1, 4, 5*). A high proportion of children become infected when they encounter the virus for the first time, and almost all children become infected the second time (*4, 6, 7*).

In a study from Washington (DC), 40% of all RSV infections in children in their first year of life involved the lower respiratory tract, and 1% of infected infants had to be admitted to hospital (*4, 6*). In a study from Houston, 33% of children with an RSV infection had a lower respiratory tract infection, and 1.6% had to be hospitalized (*8*). The sex distribution among children with RSV infections severe enough to be admitted to hospital in industrialized countries is 1.5–2:1 (boys:girls) (*9–11*), but the distribution between sexes in milder cases is more equal (*5, 10, 12, 13*).

Reinfection with RSV is common. A study in Tecumseh, Michigan, found that 20% of children aged 5–9 years became infected or reinfected within one year of the original episode (*14*). The reinfection rate was 10% in children aged 15–19 years and 3–6% in adults aged 20–50 years.

In developing countries, few studies have attempted to quantify the importance of ALRI caused by RSV (*15–20*). Reported incidence rates vary between 18 per 1000 children younger than one year for hospitalization with RSV-associated ALRI in Bedouins in southern Israel (*18*) to 198 per 1000 child-years for children aged up to 18 months in a community-based study from Colombia (*15*).

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Ref. No. **01-1587**

To obtain more information about the importance of RSV infection in developing countries, we started surveillance for RSV in the western region of the Gambia in 1993. This paper reports the epidemiology of RSV infection leading to hospital admission and the spread of infection in the community on the basis of data collected between 1993 and 1997.

Methods

Hospital surveillance

Surveillance for RSV disease was undertaken in the only three hospitals in the western region of the Gambia that regularly admit children with ALRI and at which oxygen is available:

- The Royal Victoria Hospital in Banjul on the coast, which is the paediatric referral hospital for the western half of the Gambia.
- The Medical Research Council Hospital in Fajara, approximately 15 km from Banjul, which serves a mainly periurban population.
- Sibanor Mission Hospital, 80 km inland, which serves a mainly rural population.

Surveillance started at the Royal Victoria and Medical Research Council hospitals in October 1993 and in Sibanor in January 1994. For the purpose of this report, surveillance ended in December 1997. Children admitted to the hospitals were screened for RSV disease by study personnel if they presented to hospital during working days (Monday to Friday), they had an admission diagnosis of any form of ALRI (as documented in the case chart by the hospital physicians), they were younger than two years and their guardians consented. Children who were admitted overnight, at weekends or on public holidays were screened the next working day, if they were available on the ward for nasopharyngeal aspirates to be taken. Children with clinical measles were not sampled. The clinical spectrum of disease of these cases has been described (*21*).

At the same time, details of all ALRI admissions were retrieved from the routine discharge records kept in the study hospitals during the study.

Community study

A community study to obtain information about the spread of RSV in the compounds in which infected children lived took place in 1993–94. Compounds — in which members of an extended family share a common central space and some social tasks, such as cooking — are the usual unit of residence in the Gambia.

As soon as a hospital identified a confirmed case of RSV (the index case), a field worker visited the child's compound and obtained consent for a visit by a field team from the head of the compound. The visit usually happened within one week of the index case being admitted to hospital, and children younger than five years were examined for evidence of respiratory infections. If a respiratory infection — upper or lower — was diagnosed, a nasopharyngeal aspirate was taken and transported on ice to the laboratory. Serum samples were taken on the initial visit and on a final visit six weeks later. Between these two visits, a field worker visited the compound twice a week and took nasopharyngeal aspirate samples from any child who had developed a respiratory tract infection since the previous visit.

During 1993, only the compound in which the index case lived was investigated in this way. During 1994, a neighbouring compound was investigated in addition to the index case's compound, to obtain information about spread of RSV between compounds.

Laboratory methods

RSV was detected by immunofluorescence (*21*). Serum samples were assayed for neutralizing antibodies against RSV with a microneutralization assay against RSV group A (Tracy strain) and B (strain 18537) (*22*). Briefly, heat-inactivated sera were diluted serially with Eagle's minimum essential medium (EMEM) with 2% fetal calf serum in 96-well, tissue-culture plates, starting at a $3\log_2$ dilution. RSV (50 µl $\pm$ 100 tissue culture infective dose $(TCID)_{50}$) was added to each well. Positive control wells contained medium rather than serum, and negative control wells contained only medium. The mixtures were incubated at 35 °C for 1 hour. After incubation, 100 µl of trypsinized HEp-2 cells ($2–4 \times 10^4$ cells) in EMEM with 10% fetal calf serum was added to each well. The sealed plates were maintained at 35 °C in an atmosphere of 5% carbon dioxide. Twenty-four hours after the positive control wells showed 100% cytopathic effect, the cells in all wells were fixed with 10% formalin and stained with 1% crystal violet. The neutralizing antibody titre was defined as the final serum dilution at which a greater than 50% reduction in cytopathic effect occurred. Reference sera were run with each batch for standardization, and paired samples were run in the same batch.

Statistical methods

Hospital admissions were included as cases of ALRI if the hospital discharge book contained a discharge diagnosis of ALRI. Children admitted with signs of ALRI and for whom nasopharyngeal samples tested positive were classified as cases of RSV infection. Hypoxaemic cases are a subgroup of RSV cases in whom pulse oximetry shows that transcutaneous haemoglobin oxygen saturation is less than 90%. The study covered only part of 1993, so cases found in 1993 were excluded from the hospital-based part of the study and when the average annual incidence rate was calculated.

Incidence rates were calculated as the number of hospital admissions per year divided by an estimate of the population at risk. The numbers of children aged 0–1 years and 1–2 years in each village for each year of the study were estimated from 1993 census data (Central Statistics Department, Department of State for Finance and Economic Affairs, Banjul, The Gambia) using Sprague coefficients (*23*) after smoothing in age bands of five years by Arriaga's method (*24*).

We allowed for population growth between 1993 and the end of the study with projected figures to the final year of the study, by applying the population growth rates for 1983–93 for each local government area. The estimated population in the catchment area for 1994 — the first year of the study — was 20 338 children younger than 1 year and 19 908 children aged 1–2 years. Poisson regression (or negative binomial regression where there was overdispersion) was used to estimate incidence rate ratios and 95% confidence intervals for the effects of age, sex and transport cost to hospital. Transport cost — the one-way transport fare for the usual means of public transport (bus, boat or taxi) to the nearest hospital — was estimated for each settlement in the western region of the

Gambia (See Fig. 1). Estimates of incidence rate ratios were adjusted for effects of population density and residence in an urban or rural area by including appropriate variables in the regression models.

Cumulative incidence rates of RSV infection for case and control compounds during six weeks of follow-up were compared by using conditional logistic regression. Detection of RSV in a nasopharyngeal aspirate or a twofold increase in titre between paired serum samples was considered to be evidence of infection. Analyses were performed using Stata version 6 (Statacorp, Texas).

The study was approved by the Gambian Government and Medical Research Council Laboratories Ethical Committee. All treatments given corresponded to the best medical care available in the Gambia.

Results

Hospital admissions

During the years 1994–97, 5557 children under two years of age admitted to one of the three study hospitals had a documented discharge diagnosis of ALRI. Of these, 301 had no village of origin documented, 423 came from outside the western region and 34 had no sex documented. Overall, 4799 children with ALRI were included in the study. Of these, 392 had an additional diagnosis of measles (314 of these cases occurred in 1997).

Nasopharyngeal aspirates were taken from 2252 (47%) of the children included in the study. Reasons for a sample not being taken included the child being admitted during weekends or holidays, absence of the patient from the ward for investigations and lack of documentation of an admission diagnosis on the patient's chart.

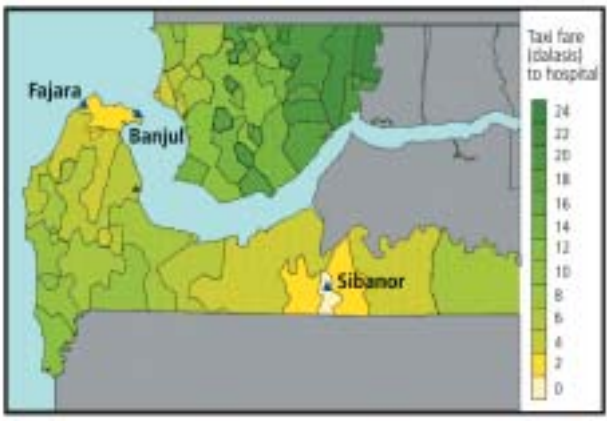
During the study period, 421 children younger than two years who lived in the study area were admitted to hospital with a documented RSV infection. Fig. 2 shows the seasonality of ALRI admissions with a peak in the rainy season. The monthly number of children with clinical measles is also included (Fig. 2).

The observed incidence rates for hospital admissions of children with ALRI, severe RSV-associated respiratory illness and RSV-associated respiratory illness with hypoxaemia were highest in areas closest to the study hospitals (Fig. 3). Between 1994 and 1996, the average observed incidence of hospital admissions for children younger than one year living in Banjul with ALRI was 5.27 per 100 child-years; with RSV-associated severe respiratory illness 0.87 per 100 child-years; and with RSV-associated hypoxaemia was 0.11 per 100 child-years. For the rural district of Foni Bintang Karanai, which is closest to Sibanor Mission Hospital, the respective values were 16.0, 1.77 and 0.2 per 100 child-years. Observed incidence rates decreased as the costs of transport to hospital increased (Fig. 3; Table 1). The observed incidence rates in 1997 were lower than the average for the individual years 1994–96; the incidence rate ratio (1997:1994–96) for ALRI was 0.82, for severe RSV infection 0.32 and for RSV-associated hypoxaemia 0.27.

Incidence rates for ALRI were significantly ($p<0.05$) higher in males, younger children, children from rural settlements and especially children from smaller rural settlements (Table 1). Severe RSV-associated respiratory illness followed a similar pattern, but the increase in incidence rates for children from smaller and rural settlements was less pronounced. The incidence of hypoxaemic RSV-associated respiratory illness varied with age but was not associated significantly with sex or distance from hospital, and the incidence was only slightly higher in children from small rural settlements than in those in other groups. Incidence rate ratios for a variety of factors are shown in Table 1.

Overall, 18.7% of children with ALRI from whom nasopharyngeal aspirates were taken (47% of cases) tested positive for RSV.

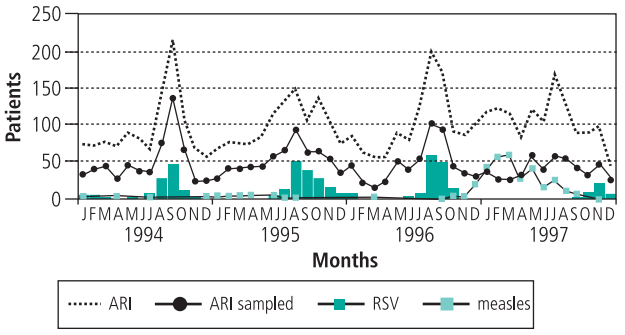
Fig. 1. **Contour map of the western region of the Gambia showing the minimum transport fare (one way) to one of the study hospitals.** Fares are in Gambia dalasis (10 dalasis = US$ 1)



Fajara: Medical Research Council Hospital
Banjul: Royal Victoria Hospital
Sibanor: Mission Hospital

WHO 02.133

Fig. 2. **Monthly numbers of ALRI admissions, children sampled by nasopharyngeal aspirate, children admitted with ALRI positive for RSV by month and measles cases among children younger than two years living in the western region of the Gambia**



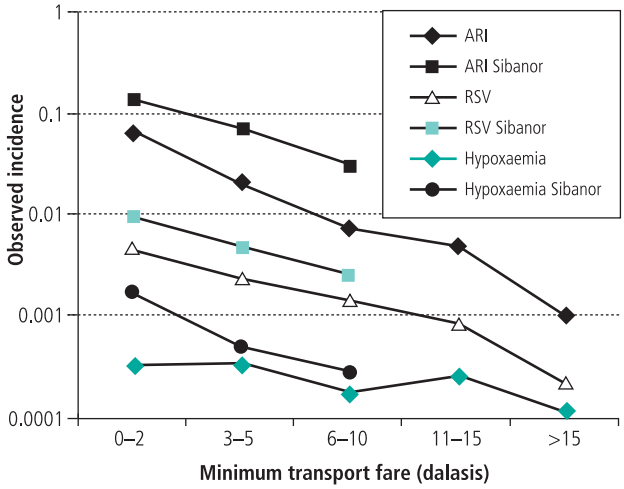
ALRI = acute lower respiratory tract infection; RSV = respiratory syncytial virus; ARI = acute respiratory infection.

WHO 02.110

Measles cases

In the first half of 1997, a measles outbreak affected the study area (Fig. 2). We excluded from the calculations presented above ALRI cases associated with measles in which the child was admitted to hospital. For measles, the observed incidence rate of hospital admissions in children younger than one year for whom the transport fare to the hospital was 2 dalasis or less was 1.1 cases per 100 child-years. The incidence rate ratio for an increase in taxi fare of 1 dalasi was 0.74 (95% CI 0.69–0.78) and for the second year of life compared with the first was 0.44 (0.34–0.56). Boys had severe measles more often than

Fig. 3. **Unadjusted incidence of hospital admissions in children younger than one year according to the one-way transport fare from their home to the hospital**



Data are shown separately for Sibanor Mission Hospital and the other two hospitals (MRC and RVH).

10 dalasis = US$ 1.

WHO 02.111

girls (incidence rate ratio 1.23, 95% CI 0.98–1.56), but the finding was of borderline significance.

Household study

During 1993, visits were made to compounds in which 81 index cases lived and in 1994, visits were made to 22 case compounds and 22 neighbouring control compounds. The mean numbers of children younger than 5 years were 5.2 (SD 3.5) and 5.1 (SD 3.0) for case and control compounds, respectively. Nasopharyngeal aspirate samples and paired serum samples were taken from 237 children in case compounds and 83 children in control compounds. The mean age of children in each of these groups was 29 (SD 17) months. In 85 (27%) of the 320 children studied there was an elevated antibody titre or virus was detected by immunofluorescence.

During 1993, when only case compounds were studied, 14% of the children had evidence of infection with RSV. In 1994, 41% of the children in the case compounds and 42% of those from control compounds had evidence of RSV infection (matched odds ratio 1.66, 95% CI 0.39–6.97). The rate of infection in individual compounds ranged from 0% to 100%. Infection rates were lowest in children aged 2–3 years (16%) and highest in children aged 0–1 and 4–5 years (33%). Incidence rates of infection did not differ significantly between case and control compounds or between age groups.

Discussion

The results of a household study showed that RSV circulated widely in the community during outbreaks of RSV in the Gambia. A considerable number of children in the compounds we investigated had evidence of recent infection. This figure is likely to be an underestimate, because compounds were visited only after an index case — usually a young infant — was admitted to hospital. It is possible that compounds were visited when the number of new cases was already declining, so the total number of infected children in the compounds visited may have been as much as double the number that we observed.

The study started during an RSV outbreak in 1993, and so more compounds were visited towards the end than the start of the outbreak. This might explain the lower number of infected children compared with that for the next year. In community-based studies in industrialized countries, infection rates of between 69% and 98% have been observed during the first year of life, with little or no decline in rates in the second year of life (*8, 25*). Monto found a yearly infection rate of 19.7% in children aged 5–9 years (*14*). In a family study, Hall reported an overall infection rate of 29% for infants and 63% for children within infected families (*26*).

Distance from hospital

In the hospital-based part of the study, we showed that the further a child with ALRI or RSV-associated severe respiratory illness lived from the hospital, the less likely they were to be admitted to hospital. Encouragingly, and to our surprise, this effect was less noticeable for children with hypoxaemic RSV-associated respiratory illness. As the three study hospitals are the only ones in the western region that provide oxygen, this finding indicates that the referral system worked best for the most severe cases of infection.

The influence of distance — or the expense associated with it — on the observed incidence of disease in health facilities was marked, and would appear obvious. It is surprising, therefore, how rarely investigators have adjusted for distance in previous studies (*27, 28*). We used transport fares rather than distance, as we believed that they best reflect the actual obstacle to seeking health care in situations where most patients have to use public transport. Our finding indicates that the need to spend more than a minimum amount on transport (2 dalasis = US$ 0.20) directly translates into reduced access to health services, which will mainly affect the poor.

The incidence rate for admission to hospital of children with ALRI who were younger than one year and who lived in compounds near to health facilities was around 10% per year — lower than that reported in other studies (*15, 19, 29–32*). The children in our study represented only the more severe end of the spectrum of ALRI, however — cases severe enough to be admitted to hospital despite pressures on hospital beds.

Severe RSV-associated illness

The incidence of severe RSV-associated respiratory illness that we observed is likely to be a substantial underestimate. Samples were taken from only half the children with ALRI, and in those we are likely to have missed an additional number of cases, as diagnosis with immunofluorescence alone has limited sensitivity (*33, 34*). The transport of samples from distant health facilities may have further decreased the yield.

On the basis of the proportion of children from whom nasopharyngeal samples were taken, we estimate that the real incidence of admissions with severe RSV-associated ALRI is over 3% per year in children younger than one year. This is similar to the incidence reported for Alaskan Natives (*35*), but higher than that reported in Bedouins from southern Israel (*18*).

Factors affecting incidence rates

We found a higher incidence of ALRI in boys than in girls — an almost universal finding in ALRI. Observed incidence rates for ALRI and RSV-associated respiratory illness were higher in rural settings than in urban settings and in small

Table 1. **Incidence rate ratios for different variables that influence the incidence of hospital admission in children with all ALRI (excluding measles), severe RSV infection and hypoxaemic RSV infection during 1994–96**

Variables	Incidence rate ratio (95% CI)		
	All ALRI	RSV infection	Hypoxaemic RSV infection
Transport cost (dalasis)			
0–2	1	1	1
3–5	0.31 (0.29–0.34)	0.51 (0.39–0.65)	0.88 (0.40–1.94)
6–10	0.089 (0.078–0.10)	0.26 (0.18–0.38)	0.39 (0.13–1.19)
11–15	0.036 (0.027–0.049)	0.14 (0.07–0.28)	0.39 (0.09–1.70)
>15	0.008 (0.004–0.015)	0.03 (0.008–0.14)	0.15 (0.02–1.35)
Sex			
Female	1	1	1
Male	1.23 (1.16–1.32)	1.26 (1.03–1.55)	1.58 (0.89–2.80)
Age (months)			
0–11	1	1	1
12–23	0.55 (0.51–0.59)	0.33 (0.26–0.41)	0.22 (0.11–0.46)
Settlement type and size			
Urban	1	1	1
Rural ⩾1000 inhabitants	1.89 (1.73–2.07)	1.23 (0.93–1.62)	1.1 (0.51–2.37)
Rural <1000 inhabitants	2.92 (2.65–3.21)	1.65 (1.19–2.28)	2.37 (1.04–5.41)

ALRI = acute lower respiratory tract infection.
RSV = respiratory syncytial virus.
CI = confidence interval.

villages than in large villages. Most small villages are poorer than large ones, and this might indicate the influence of overall living standard on the incidence of ALRI. The effect of this influence was less pronounced in groups of children with severe RSV infection.

An interesting finding is the low number of RSV cases observed in 1997, after three years of regular large outbreaks. It is intriguing that this coincided with an increasing number of measles cases in the community, after several years without any measles cases. It is possible that some degree of cross-protection exists between RSV and the measles virus, which are both paramyxoviruses (*36*). A recent report showing that hospitalization rates in children with RSV in the United States increased over twofold between 1980 and the time of writing could point in the same direction, as this increase happened when measles vaccination was controlling measles effectively (*37*).

Conclusion

We have shown that RSV is an important cause of cases of ALRI severe enough to lead to hospital admission in the Gambia. It is not possible to estimate the burden of mortality due to RSV in our study, but morbidity is considerable and efforts at prevention are likely to be worthwhile. ■

Acknowledgements

We thank Saikou Badgie, Foday Drammeh, Saikou Mendy, Fatou Bah and Mariama Madi for identifying patients. We thank Toni Piedra of Baylor College, Houston (TX), for help in setting up the neutralization assays and the nursing staff and physicians on the wards of the study hospitals for the care of the admitted patients. We thank the records department of Royal Victoria Hospital (Mrs Amie Njai) and Medical Research Council Hospital for retrieving and providing patients' records, the statistics department of the Government of the Gambia for providing census data and George Lahai for help in managing the data. We thank Sam Walters for commenting on the manuscript.

Funding: The study was funded by the British Medical Research Council and, for part of the time, by Praxis Lederle Biologicals, West Henrietta, New York, USA, and the Society of Friends of the Hannover Medical School. MWW was supported by Deutsche Forschungsgemeinschaft grant We 1379/3-1.

Conflicts of interest: none declared.

Résumé

Etude épidémiologique de l'infection à VRS en Gambie

Objectif Décrire l'épidémiologie de l'infection par le virus respiratoire syncytial (VRS) dans un pays en développement.

Méthodes L'étude a été réalisée dans trois hôpitaux pour les cas primaires et dans la communauté pour les cas secondaires dans la partie occidentale de la Gambie, en Afrique de l'Ouest. L'infection à VRS a été diagnostiquée par immunofluorescence sur des échantillons rhinopharyngés prélevés par aspiration chez des enfants de moins de 2 ans hospitalisés pour une infection aiguë des voies respiratoires inférieures. Les dossiers de tous les enfants atteints d'infections aiguës des voies respiratoires inférieures ont été analysés et les taux d'incidence de ces infections, des maladies respiratoires graves associées au VRS et des infections à VRS avec hypoxémie ont été comparés. Une étude dans la communauté a été réalisée pour identifier les cas secondaires et obtenir des informations sur la propagation du virus.

Résultats Parmi les enfants de moins de 2 ans résidant dans la zone d'étude, 4799 ont été admis dans les hôpitaux de l'étude pour une infection aiguë des voies respiratoires

inférieures : 421 présentaient une maladie respiratoire grave associée au VRS, avec hypoxémie pour 55 d'entre eux. Entre 1994 et 1996, le taux d'incidence observé des infections aiguës des voies respiratoires inférieures chez 100 enfants de moins d'un an résidant à proximité de l'hôpital était de 9,6 cas par an ; il était de 0,83 pour les maladies respiratoires graves associées au VRS et de 0,089 pour les maladies respiratoires associées au VRS avec hypoxémie. Par rapport à l'ensemble des cas d'infections aiguës des voies respiratoires inférieures, ceux dus au VRS représentaient 19 %. Au total, 41 % des enfants de moins de 5 ans résidant dans le même quartier que les cas et 42 % de ceux des quartiers témoins ont présenté des signes d'infection à VRS pendant la période faisant l'objet de la surveillance.

Conclusion Le VRS est une cause importante d'infections aiguës des voies respiratoires inférieures conduisant à une hospitalisation en Gambie. Il entraîne une morbidité considérable et les efforts de prévention sont justifiés.

Resumen

Estudio epidemiológico de la infección por el VRS en Gambia

Objetivo Describir la epidemiología de la infección por el virus respiratorio sincitial en un país en desarrollo.

Métodos El trabajo se llevó a cabo en tres hospitales para los casos primarios y en la comunidad para los casos secundarios, en la región occidental de Gambia, África occidental. Los casos de infección por el VRS fueron diagnosticados mediante inmunofluorescencia de muestras del aspirado nasofaríngeo en los niños menores de dos años ingresados en el hospital con infección aguda de las vías respiratorias inferiores (IAVRI). Se analizaron los registros ordinarios de todos los niños con IAVRI, comparándose las tasas de incidencia de IAVRI, enfermedad respiratoria grave asociada al VRS e infecciones hipoxémicas por el VRS. Se emprendió un estudio comunitario para identificar los casos secundarios y obtener información sobre la propagación del virus.

Resultados En los hospitales en cuestión ingresaron 4799 menores de dos años con IAVRI que vivían en la zona estudiada: 421 sufrían trastornos respiratorios graves asociados al VRS, y de ellos 55 presentaban hipoxemia. Entre 1994 y 1996, la tasa de incidencia observada para las IAVRI en 100 niños menores de un año que vivían cerca del hospital fue de 9,6 casos anuales, para la enfermedad respiratoria grave asociada al VRS fue de 0,83, y para la enfermedad respiratoria hipoxémica asociada al VRS, de 0,089. La proporción de ingresos por IAVRI debidos al VRS fue del 19%. Globalmente, el 41% de los menores de cinco años de los complejos de viviendas en que habitaban los casos y el 42% de los complejos de control mostraron signos de infección por el VRS durante el periodo de vigilancia.

Conclusión El VRS es una causa importante de los casos de IAVRI que acaban siendo hospitalizados en Gambia. Dada esa considerable morbilidad, las actividades de prevención están justificadas.

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