

Respiratory syncytial virus infection: denominator-based studies in Indonesia, Mozambique, Nigeria and South Africa

Susan E. Robertson,¹ Anna Roca,² Pedro Alonso,³ Eric A.F. Simoes,⁴ Cissy B. Kartasasmita,⁵ David O. Olaleye,⁶ Georgina N. Odaibo,⁷ Mark Collinson,⁸ Marietjie Venter,⁹ Yuwei Zhu,¹⁰ & Peter F. Wright¹¹

Objective To assess the burden of respiratory syncytial virus (RSV)-associated lower respiratory infections (LRI) in children in four developing countries.

Methods A WHO protocol for prospective population-based surveillance of acute respiratory infections in children aged less than 5 years was used at sites in Indonesia, Mozambique, Nigeria and South Africa. RSV antigen was identified by enzyme-linked immunosorbent assay performed on nasopharyngeal specimens from children meeting clinical case definitions.

Findings Among children aged < 5 years, the incidence of RSV-associated LRI per 1000 child-years was 34 in Indonesia and 94 in Nigeria. The incidence of RSV-associated severe LRI per 1000 child-years was 5 in Mozambique, 10 in Indonesia, and 9 in South Africa. At all study sites, the majority of RSV cases occurred in infants.

Conclusion These studies demonstrate that RSV contributes to a substantial but quite variable burden of LRI in children aged < 5 years in four developing countries. The possible explanations for this variation include social factors, such as family size and patterns of seeking health care; the proportion of children infected by human immunodeficiency syndrome (HIV); and differences in clinical definitions used for obtaining samples. The age distribution of cases indicates the need for an RSV vaccine that can protect children early in life.

Keywords Respiratory syncytial virus infections/epidemiology/immunology; Respiratory tract infections/virology/diagnosis; Child, Preschool; Infant; Severity of illness index; Indonesia; Mozambique; Nigeria; South Africa (*source: MeSH, NLM*).

Mots clés Virus respiratoire syncytial, Infection/épidémiologie/immunologie; Voies aériennes supérieures, Infection/virologie/diagnostic; Enfant âge pré-scolaire; Nourrisson; Indice de gravité; Indonésie; Mozambique; Nigéria; Afrique du Sud. (*source: MeSH, INSERM*).

Palabras clave Infecciones por virus sincitial del tracto respiratorio/virología/diagnóstico; Preescolar; Lactante; Índice de severidad de la enfermedad; Indonesia; Mozambique; Nigeria; Sudáfrica (*fuentes: DeCS, BIREME*).

Arabic

Bulletin of the World Health Organization 2004;82:914-922.

Voir page 920 le résumé en français. En la página 921 figura un resumen en español.

Introduction

The role of viruses in the causation of acute lower respiratory infections (LRI) in developing countries was systematically examined almost 20 years ago in a series of studies sponsored by the Board on Science and Technology for International Development (BOSTID) of the United States National Academy of Sciences (1). In these studies, which encompassed both community-based and hospital-based surveillance, respiratory

syncytial virus (RSV) was identified as the predominant cause of LRI in children who were aged < 5 years (1). However, only two of the BOSTID studies (2, 3) — both from the Americas — were denominator-based and thus addressed the impact of RSV.

Recent reviews of the epidemiology of RSV in developing countries (4, 5) have identified few additional denominator-based studies that examine the role of RSV in causing severe

¹ Medical Officer, World Health Organization, Department of Immunization, Vaccines and Biologicals, 1211 Geneva 27, Switzerland (email: robertsons@who.int). Correspondence should be sent to this author.

² Senior Investigator, Manhiça Health Research Centre, Manhiça, Mozambique and Centre de Salut Internacional, Hospital Clinic, IDIBAPS, Barcelona, Spain.

³ Scientific Director, Manhiça Health Research Centre, Manhiça, Mozambique and Head, Centre de Salut Internacional, Hospital Clinic, IDIBAPS, Barcelona, Spain.

⁴ Professor of Pediatrics, Section of Infectious Diseases, University of Colorado School of Medicine, Denver, CO, USA.

⁵ Professor of Pediatrics, Department of Child Health, School of Medicine, Padjadjaran University, Bandung, Indonesia.

⁶ Professor of Virology and Consultant Virologist, University of Ibadan Medical School, Ibadan, Nigeria.

⁷ Lecturer Grade 1 (Virology), University of Ibadan Medical School, Ibadan, Nigeria.

⁸ Research Manager, Agincourt Health and Population Unit, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa.

⁹ Senior Medical Natural Scientist, Special Pathogens Unit, National Institute for Communicable Diseases, Sandringham, South Africa.

¹⁰ Assistant in Biostatistics, Vanderbilt University School of Medicine, Nashville, TN, USA.

¹¹ Professor of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, USA.

Ref. No. 04-013011

(Submitted: 6 March 2004 – Final revised version received: 27 July 2004 – Accepted: 29 July 2004)

LRI, despite the fact that RSV is the most common viral cause of LRI. Globally, only six studies provide information on the incidence of LRI caused by RSV among children in developing countries; however, these studies did not assess RSV impact in the same age groups, did not use the same diagnostic methods, and one carried out only a few months of surveillance (2, 3, 6–9) (Table 1). Recognizing that there was scant recent evidence for the role of RSV in causing LRI among children in developing countries, WHO recommended that new studies be undertaken in developing countries and developed a standardized protocol (10). The objectives of the protocol are to determine the age-specific incidence of RSV-associated respiratory infections in children < 5 years of age, assess the severity of acute respiratory infections due to RSV, and determine the seasonal variation of infections. In this paper we report the results of studies based on the WHO protocol undertaken in Indonesia, Mozambique, Nigeria and South Africa.

Study sites

Indonesia

In Indonesia the study site consisted of two communities near Bandung on the Island of West Java: a suburban site, Cikutra (population 53 000) and a rural site, Ujung Berung (population 42 000). Each community has a physician-staffed primary health-care centre and a hospital. The field team consisted of 102 female community health workers (kaders) and 17 supervisors. Kaders visited each household weekly. Private sector physicians were included in the study. The study was conducted by the Health Research Unit, School of Medicine, Padjadjaran

University and Hasan Sadikin General Hospital, Bandung, in conjunction with the Department of Pediatrics, University of Colorado School of Medicine, Denver, Colorado, United States.

Mozambique

In Mozambique the Manhiça District has a total population of 130 000 but the health research study site included only 35 000 people (11). Manhiça District Hospital is the referral health facility for the district. Surveillance for RSV was conducted passively among hospital outpatients aged < than 1 year and among inpatients aged < 5 years. There is no private sector health care. The study was conducted by the Manhiça Health Research Centre with the Ministry of Health of Mozambique, the School of Medicine, Maputo, and the School of Medicine, Barcelona, Spain.

Nigeria

In Nigeria the two study communities were Eleta, a sector of Ibadan (population 10 000), and Ijaye (population 11 302), a rural village 20 km from Ibadan. The total population of Ibadan is 4 million. Nurses with previous clinical research experience were present in the study communities daily, and they visited each study household weekly. Private sector medical services were not included in the study. The study was conducted by the Department of Virology and the Institute of Child Health of the University of Ibadan Medical School.

South Africa

In South Africa the study was conducted at the Agincourt Health and Population field site located in a remote rural area

Table 1. Incidence of respiratory syncytial virus-associated lower respiratory infections in studies from developing countries

Country (study site)	Dates	Method of case ascertainment	Denominator (age group)	Diagnostic tests	Incidence of all LRIs ^a (age group)	Incidence of RSV-associated ^b LRIs (age group)	Reference no.
Brazil (Rio de Janeiro)	January 1987–December 1989	Weekly home visits	<i>n</i> = 262 (< 5 years)	IFA, ^c culture	64/1000 child-years (< 5 years)	14/1000 child-years (< 5 years)	2
Colombia (Cali)	February 1977–February 1979	Passive surveillance at 5 primary health-care clinics	<i>n</i> = 8 748 (< 15 years)	Culture, serology	70/1000 child-years (< 15 years)	6/1000 child-years (< 15 years)	6
Colombia (Cali)	October 1986–April 1988	Weekly home visits	<i>n</i> = 340 (birth cohort)	IFA, culture	1710/1000 child-years (< 1.5 years)	198/1000 child-years (< 1.5 years)	3
Gambia (Western Region)	January 1994–December 1996	Passive surveillance of admissions to 3 hospitals	<i>n</i> = 20 338 (< 1 year)	IFA, serology	96/1000 child-years (0–11 months)	8/1000 child-years (< 1 year)	7
Indonesia (Lombok Island, 83 villages)	January 2000–December 2001	Passive surveillance of admissions to 5 hospitals	<i>n</i> = 30 000 (< 2 years)	ELISA ^d	60/1000 child-years (< 2 years)	10/1000 child-years (< 2 years)	8
Israel (Negev Region)	1 January 1987–15 April 1987	Passive surveillance of admissions to 1 hospital	<i>n</i> = 8 323 (< 1 year)	ELISA, culture, serology	Not reported	10/1000 child-years (< 1 year)	9

^a LRI = lower respiratory infection.

^b RSV = respiratory syncytial virus.

^c IFA = immunofluorescent antibody test.

^d ELISA = enzyme-linked immunosorbent assay.

Table 2. Study dates, case ascertainment, child-years of observation, clinical case definitions, number of specimens tested and number of specimens positive for respiratory syncytial virus (by ELISA) in four developing countries^a

Country (study site)	Dates	Method of case ascertainment	Child-years of observation (age group)	Clinical criteria for collecting nasopharyngeal specimen	No. of specimens	No. RSV positive ^b
Indonesia (Bandung)	February 1999–January 2001	Weekly household visits	1420 (< 5 years)	LRI ^c : cough or difficulty in breathing with increased respiratory rate or indrawing or stridor or wheezing or apnoea	640	97
Mozambique (Manhiça)	February 1999–January 2000	Passive surveillance of hospital outpatients < 1 year old	1342 (< 1 year)	LRI: cough or nasal discharge or difficulty breathing with increased respiratory rate or indrawing or stridor or wheezing or apnoea	2036	135
		Passive surveillance of hospital inpatients < 5 years old	6020 (< 5 years)	idem	344	30
Nigeria (Ibadan)	June 1999–May 2001	Weekly household visits	1579 (< 5 years)	LRI: increased respiratory rate, and/or indrawing, and/or cough	426	148
South Africa (Agincourt)	April 2000–March 2001	Passive surveillance at 6 primary health-care clinics	8258 (< 5 years)	Severe LRI: at least three of the following symptoms – increased respiratory rate, indrawing, stridor, wheezing, apnoea	663	71

^a Specimens tested by enzyme-linked immunosorbent assay (ELISA).

^b RSV = respiratory syncytial virus.

^c LRI = lower respiratory infection.

600 km east of Johannesburg (12). The site includes 21 villages (total population 68 000) served by six primary health-care clinics staffed by nurses; RSV surveillance was conducted passively at these clinics. There are no private sector health services in this area. The study was conducted jointly by the National Institute for Communicable Diseases and the University of the Witwatersrand, Johannesburg.

Methods

Active surveillance

In Indonesia and Nigeria surveillance was active; there were weekly visits to households with children aged < 5 years. In both countries cultural traditions call for infants to remain at home for the first 40 days of life. In Nigeria household visits were conducted by research nurses who were able to collect nasopharyngeal specimens from infants with LRIs even during this time. In Indonesia household visits were conducted by community health workers. Children with LRIs were escorted to a clinic by the community health worker, and the nasopharyngeal specimen was collected by a physician. Despite the fact that it is traditional to keep infants at home for the first 40 days of their life in Indonesia, mothers did not refuse to bring their children to a clinic when this was recommended.

Passive surveillance

In Mozambique and South Africa surveillance was passive. In Mozambique two groups of patients who lived in the designated study area and who presented to the study hospital with LRI were enrolled: outpatients aged < 1 year and inpatients aged < 5 years. In South Africa, patients living in the designated study area who presented with a severe LRI to one of six outpatient clinics were enrolled in the study. For Mozambique and South Africa, the denominators for the incidence calculations

included all children in the age group living in the study area. In Mozambique outpatients and inpatients were seen by research staff (nurses or physicians), while in South Africa outpatients were seen by primary health-care nurses who were responsible for all health-care delivery. During the study the essential drugs supply to the South African study clinics was disrupted, and this led to declines in patient attendance.

Case definitions

A child was defined as having an LRI if she or he had a cough or difficulty breathing and one or more of the following: fast breathing, lower chest wall indrawing, stridor, wheezing or apnoea. Fast breathing was defined as ≥ 60 breaths per minute in children aged < 2 months, ≥ 50 per minute in children aged 2–11 months, and as ≥ 40 per minute in children aged 12–59 months (10). A severe LRI was defined as an LRI with lower chest wall indrawing or stridor or as any LRI where hospital admission was advised by a physician (13).

The studies in Indonesia and Mozambique used the definitions recommended in the WHO protocol. Other sites adapted the clinical definitions to their local settings, as described in Table 2. This made it difficult to determine precise gradations of the severity of LRIs between sites. At the South African site the main diagnosis was severe LRI, while in Nigeria all LRIs were recorded without differentiating between those that were severe and those that were not.

Specimen collection and laboratory methods

Nasopharyngeal specimens were collected by instilling 1–2 ml of normal saline solution into the child's nasopharynx and collecting the wash material in a test tube or by aspiration. Specimens were stored at 4–8 °C and transported to the laboratory the same day.

Susan E. Robertson et al.

Commercial enzyme-linked immunosorbent assay (ELISA) kits (Abbott Diagnostics GmbH, Wiesbaden, Germany, and Sanofi Diagnostics Pasteur, Marnes la Coquette, France) were used to detect RSV antigen. ELISA tests were conducted within 24 hours of specimen collection; however, during April 2000–March 2001 in South Africa and May–July 2000 in Indonesia, specimens were frozen at -70°C and tested later (within 3 months).

Study population and observation periods

For each site a census of children aged 0–59 months was conducted prior to the start of the study and adjusted thereafter for births, deaths and migration.

To allow site-to-site comparisons of annual incidence rates and in order not to inadvertently include a disproportionate number of RSV seasons, only 12-month periods have been considered in this paper. For Mozambique and South Africa the study period was 12 months; for Indonesia and Nigeria it was 24 months (Table 2). Observation time includes only weeks when individuals in the appropriate age group were available; individuals were excluded for 2 weeks after each proven RSV episode and when they reached 60 months of age.

Data analysis

For each study survival analysis and 95% confidence intervals were calculated using STATA or SPSS software.

The incidence of respiratory illness and RSV-specific illness was calculated for children aged < 1 year and aged < 5 years per 1000 child-years of observation by severity of symptoms.

The crude RSV incidence per 1000 child-years was calculated for the following age groups: 0–2 months, 3–5 months, 6–8 months, 9–11 months, 12–23 months and 24–59 months. This was done for all RSV-associated LRIs in Indonesia and Nigeria and for RSV-associated severe LRIs in Mozambique and South Africa.

For each study site, the monthly number of RSV cases, amount of rainfall (mm) and mean temperature were graphed.

Ethical approval

Written informed consent was obtained from parents or guardians of children who participated in these studies. Each study was reviewed and approved by the ethical committee of the responsible institution and by the Secretariat Committee on Research Involving Human Subjects at WHO in Geneva, Switzerland.

Results

LRIs and severe LRIs

The incidence of LRIs per 1000 child-years for children aged < 5 years was 191 in Indonesia and 270 in Nigeria (Table 3). In children aged < 1 year, the LRI incidence was 178 in Indonesia, 323 in Nigeria and 509 in Mozambique. The incidence of severe LRIs among children aged < 5 years was 22/1000 child-years in Indonesia, 68 in Mozambique and 80 in South Africa. For children aged < 1 year, the incidence of severe LRIs was 25/1000 child-years in Indonesia, 126 in Mozambique and 332 in South Africa.

RSV-associated LRIs and severe LRIs

RSV causes a spectrum of respiratory illness and thus the incidence of RSV decreased as the severity of illness increased. In children aged < 5 years, the incidence of RSV-associated LRIs was 34/1000 child-years in Indonesia compared with 94/1000 child-years in Nigeria (Table 3). Among children aged < 1 year, the incidence of LRIs attributable to RSV was 30/1000 child-years in Mozambique, 41/1000 child-years in Indonesia and 116/1000 child-years in Nigeria. Where severe LRI attributable to RSV could be clearly distinguished (in Mozambique, South Africa and Indonesia) the incidence attributable to RSV in children aged < 1 year was nearly identical (15–16/1000 child-years). The uniformity of the impact of RSV on infants remained

Table 3. Incidence of lower respiratory infection, severe lower respiratory infection, and respiratory syncytial virus-associated lower respiratory infection and severe lower respiratory infection per 1000 child-years among children aged < 1 year and < 5 years in four developing countries

Country (study site)	Incidence per 1000 child-years ^a							
	LRI ^b		RSV-associated ^c LRI		Severe LRI		RSV-associated severe LRI	
	<1 year	<5 years	<1 year	<5 years	<1 year	<5 years	<1 year	<5 years
Indonesia (Bandung)	178 (151–206)	191 (175–207)	41 (28–54)	34 (27–41)	25 (15–35)	22 (16–27)	16 (8–25)	10 (6–14)
Mozambique (Manhiça, outpatients)	509 (472–549)	Not done	30 (22–41)	Not done	Not done	Not done	Not done	Not done
Mozambique (Manhiça, inpatients)	Not done	Not done	Not done	Not done	126 (108–147)	68 (62–75)	15 (10–20)	5 (3–7)
Nigeria (Ibadan)	323 (297–349)	270 (257–283)	116 (107–125)	94 (89–99)	Not done	Not done	Not done	Not done
South Africa (Agincourt)	Not done	Not done	Not done	Not done	332 (308–365)	80 (75–86)	15 (9–22)	9 (7–10)

^a Figures in parentheses are 95% confidence intervals.

^b LRI = lower respiratory infection.

^c RSV = respiratory syncytial virus.

despite an overall incidence of severe LRIs in Mozambique that was 13 times higher than in Indonesia. Similarly, among children aged < 5 years the incidence of severe LRIs attributable to RSV was 5–10/1000 child-years, with overlap of 95% confidence intervals for all sites.

Proportion of LRIs and severe LRIs associated with RSV

The proportion of LRIs caused by RSV was high in Nigeria (35% among children aged < 5 years and 36% among children aged < 1 year) and Indonesia (18% among those aged < 5 years and 23% among those aged < 1 year) but only 6% among children aged < 1 year in Mozambique.

For severe LRIs, the proportion attributable to RSV was high in Indonesia (45% among children aged < 5 years and 64% among children aged < 1 year) but strikingly lower in Mozambique (7% among children aged < 5 years and 12% among children aged < 1 year) and South Africa (11% among children aged < 5 years and 5% among children aged < 1 year), presumably as a result of LRIs being caused by other pathogens.

RSV incidence by age group

RSV-associated LRIs occurred in all age groups in Nigeria and in all age groups in Indonesia except among children aged < 3 months (Fig. 1). In Mozambique and South Africa severe RSV-associated LRIs occurred throughout the first year of life (Fig. 2).

Seasonal distribution

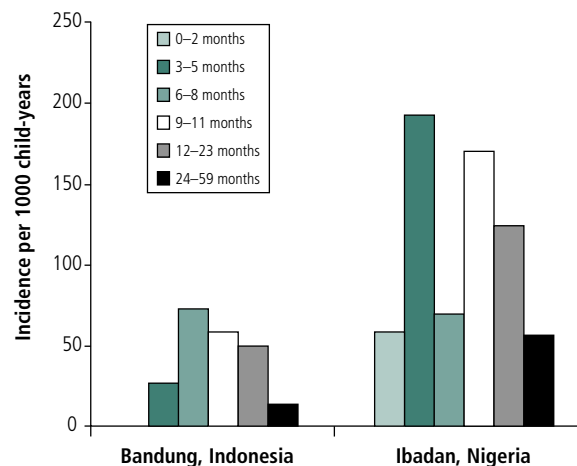
In Indonesia and Mozambique RSV cases occurred primarily during the rainy season, while in Nigeria and South Africa, RSV cases occurred mainly during the dry season (Fig. 3).

Discussion

This series of studies provides further evidence about the burden of RSV in developing countries and the potential role of new vaccines in preventing this burden. The total incidence of LRIs occurring among children aged < 1 year was lowest in Indonesia and highest in Mozambique where 50% of children who presented to a clinic had an LRI and 13% were hospitalized. Comparison data from a cohort study of children aged < 5 years in the United States (14) that were analysed in the same way showed an incidence of LRIs that fell within the range reported for sites in developing countries (Y. Zhu and P. Wright, unpublished data, 2004). Among infants, the proportion of LRIs attributable to RSV was 36% in Nigeria, 23% in Indonesia and 16% in the United States compared with 6% in Mozambique. For severe LRIs, the proportion attributable to RSV was high in Indonesia but low in Mozambique and South Africa. This appears to reflect a greater burden of other causes of LRIs in the countries of southern Africa, including respiratory complications of HIV and malaria.

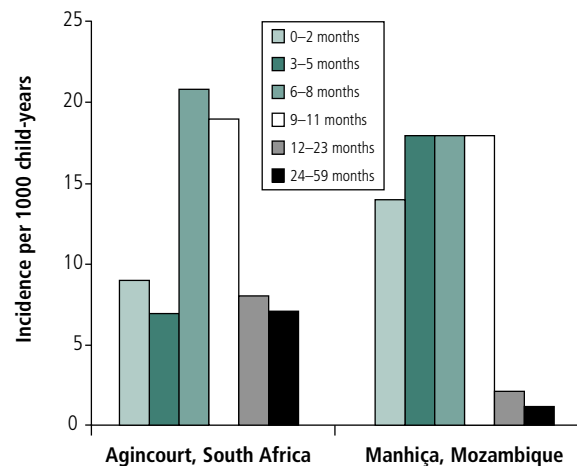
These data demonstrate that RSV causes a substantial burden to children aged < 5 years, with rates of RSV-associated LRIs and severe LRIs similar to those reported in earlier studies from developing countries (Table 1). The rates of RSV-associated severe illness among children aged < 1 year in Indonesia, Mozambique and South Africa (15–16/1000 child-years, Table 3) are remarkably similar to rates of hospitalization for RSV among children aged < 1 year in studies from industrialized countries,

Fig. 1. Incidence of respiratory syncytial virus-associated lower respiratory infection per 1000 child-years of observation among children aged < 5 years in Indonesia and Nigeria, by age group



WHO 04.149

Fig. 2. Incidence of severe lower respiratory infection associated with respiratory syncytial virus per 1000 child-years of observation among children aged < 5 years in South Africa and Mozambique, by age group

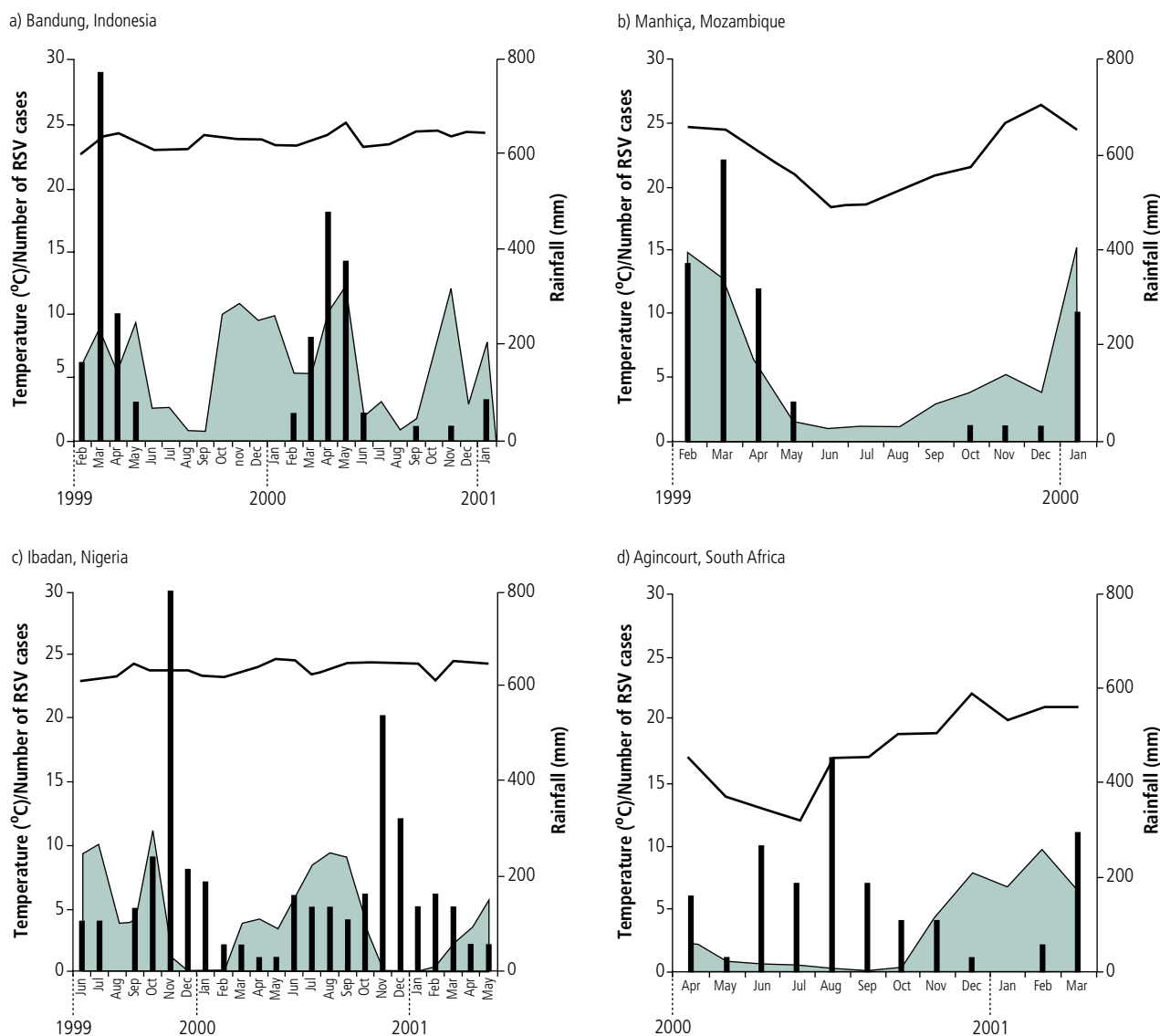


WHO 04.150

including Austria (6/1000 child-years) (15), England (20/1000 child-years) (16), Germany (12/1000 child-years) (17), Norway (10/1000 child-years) (18), the United States (20/1000 child-years) (14) and Switzerland (5/1000 child-years) (19).

Results from Mozambique demonstrate that when the numerator includes children with milder but still clinically important presentations, RSV incidence rates are higher and strikingly similar to data from the United States (Y. Zhu and P. Wright, unpublished data, 2004). For the total number of acute respiratory infections prompting a clinic visit for children aged < 1 year, the rate was 79/1000 child-years in Mozambique and 114/1000 child-years in the United States. The parallels between the two sites also include the progression to LRI (30/1000 child-years in Mozambique and 54/1000 child-years in the United States) and severe LRI (15/1000 child-years in Mozambique and 20/1000 child-years in the United States).

Fig. 3. **Seasonality of respiratory syncytial virus (RSV) infection at sites in four countries.** Each graph depicts the number of RSV cases in children aged < 5 years (bars), mean temperature (line) and mean rainfall (shaded area) by month



WHO 04.151

Passive surveillance at health facilities (hospitals or clinics) depends on the study population using them. A study in the Gambia found that the greater distance children with an RSV-associated LRI lived from the hospital, the less likely they were to be admitted (7). Incidence data from the passive surveillance studies (Mozambique and South Africa) were not analysed by distance from home to health facility. In Mozambique the study was conducted at a research site where rates of health-care utilization are generally high. At the South African study site health-care utilization rates may not have been high, and there was a documented drop in clinic attendance rates during the study due to a shortage of medications: thus, the findings represent minimum estimates of the burden of severe LRIs.

Other social factors that may have contributed to differences in RSV rates included the sheltering of infants for the first 40 days of life (Indonesia and Nigeria) and having large numbers of other children present in families, compounds and in the community. As with other infectious diseases transmit-

ted by the respiratory route, large families with many children (16, 20) and/or the use of day care (21) facilitate the spread of RSV infection (5).

A study from Johannesburg, South Africa, conducted at an urban referral hospital demonstrated that human immunodeficiency virus (HIV) infection has an effect on the presentation, course and epidemiology of RSV infection (22). However, the results of this study became available only after the four studies presented in this paper were already in progress, and we did not assess the HIV status of the children enrolled or of their mothers. However, antenatal serosurveys conducted by other investigators found that the proportion of HIV-positive pregnant women was 19% in South Africa, 15% in Mozambique, 5% in Nigeria and 0% in Indonesia, and these data give an idea of the relative prevalence of HIV (23). Up to one-third of infants born to HIV-infected mothers will also be infected. Thus, at the RSV study sites the proportion of HIV-infected children can be roughly estimated as 6% in South Africa, 5% in

Mozambique and 2% in Nigeria. This may explain the higher rates of severe LRIs in the southern African sites: however, an increase in RSV-specific LRIs was not seen in our data.

Malaria could be another confounding infection mimicking an LRI. In Mozambique and Nigeria the entire population is at risk for endemic malaria, although the risk is considerably lower in Indonesia and South Africa (24). In countries where malaria is endemic, most children experience their first malaria infection during the first 24 months of life. Malaria in children may present as an acute febrile illness with respiratory distress (24). Several studies have described the difficulties in discerning the real cause of infection in children in malaria-endemic areas with signs and symptoms of an LRI (25, 26). Population-based studies to determine the overlap of symptoms between malaria and LRIs in children are planned.

Measles and pertussis are important causes of respiratory disease that are largely preventable with vaccines. The coverage of infants in 1998 with one dose of measles vaccine and three doses of pertussis vaccine was above 90% in Indonesia, 76–87% in Mozambique and South Africa and 21–26% in Nigeria (27). Low vaccine coverage rates in Nigeria suggest that respiratory diseases in young children at the Ibadan study site may be due in part to measles or pertussis (28) but this was not assessed in our study, and the overall rates of LRIs in Nigeria were not higher than at other sites.

RSV cases in children younger than 3 months of age were documented in all countries except Indonesia. The occurrence of cases in young infants suggests the potential value of maternal immunization against RSV to protect the youngest children (29). For all studies the highest incidence of RSV occurred during the child's first year, indicating the need for a vaccine that can be given early (30).

In this group of studies, every site had an annual peak period of RSV infection. The peak season for RSV was correlated with the presence or absence of rainfall in some countries but there was no overall pattern. Although the Mozambican and South African sites are located only 200 km apart, it is striking that the RSV peak occurred at different times of year, and that it occurred during the rainy season in Mozambique and during the dry season in South Africa. In Nigeria and South Africa RSV was present nearly all year, although this was not the case for the sites in Indonesia or Mozambique. These studies add to the global knowledge of the seasonality of RSV infection but do not provide an overarching explanation for the seasonality of this virus (4, 31).

A limitation of our studies was that they relied on a single laboratory test for detecting RSV antigen, the ELISA test. This is likely to have led to underestimates of the disease burden. Use of multiple methods, including immunofluorescent antibody tests, virus isolation and polymerase chain reaction, in addition to the ELISA test may be the best option for detecting all respiratory illnesses occurring as a result of RSV. However, in the field settings described in this paper the ELISA test was the only practical choice. Compared with virus isolation, using the ELISA test to detect RSV has been shown to have a sensitivity of 94% and a specificity of 97% (32). During the past decade ELISA tests for RSV have been used for the majority of studies on the burden of the disease and in a number of studies of therapeutic agents (33). Also the studies we report focused on a single respiratory pathogen and thus do not shed light on the relative importance of viral and bacterial pulmonary infections.

The evidence from these studies documents a substantial disease burden associated with RSV in selected developing countries but the picture remains incomplete. The incidence of RSV was more consistent between sites in developing countries and the United States than the overall rates of LRIs. This variation may have resulted from the clinical definitions used or from illnesses that confound the clinical definition, but it probably represents true differences in the frequency of LRIs. As the potential for a paediatric RSV vaccine draws closer, additional denominator-based information on RSV epidemiology in developing countries will be needed, particularly from Asia, the eastern Mediterranean, and among children infected with HIV. For all sites, participation in the WHO Collaborative Group on RSV led to further development of field research and laboratory capacity (11, 34–38). The WHO protocol worked as a guide for surveillance of RSV disease, and it continues to be available for future investigators (10). New studies of RSV burden should ideally be community based, with a known population denominator and active surveillance by dedicated research staff who are able to obtain specimens at the household level. ■

Acknowledgements

Thanks to Dr R. Haimanot, Dr J. Nokes, Dr L. Quintó, Dr. B. Schoub, and Dr M. Weber for helpful comments. WHO provided financial support for these studies. Core funding for the Manhica Health Research Centre is provided by the Spanish Agency for International Cooperation; A. Roca is supported by RICET-C03/04–10.

Conflicts of interest: none declared.

Résumé

Infection à virus respiratoire syncytial (VRS) : études de morbidité en population en Indonésie, au Mozambique, au Nigeria et en Afrique du Sud

Objectif Évaluer la charge de morbidité due aux infections des voies respiratoires inférieures (IVRI) associées au virus respiratoire syncytial (VRS) chez les enfants de quatre pays en développement.

Méthodes À l'aide d'un protocole OMS, on a réalisé une surveillance prospective en population des infections respiratoires aiguës chez les enfants de moins de 5 ans sur des sites se trouvant en Indonésie, au Mozambique, au Nigeria et en Afrique du Sud. On a identifié l'antigène RSV par des tests ELISA sur des échantillons nasopharyngiens provenant d'enfants répondant aux définitions de cas cliniques.

Résultats Parmi les enfants de moins de 5 ans, l'incidence des infections des voies respiratoires inférieures associées au VRS pour 1000 enfants-années était de 34 en Indonésie et de 94 au Nigeria. L'incidence des IVRI graves associées au VRS pour 1000 enfants-années était de 5 au Mozambique, de 10 en Indonésie et de 9 en Afrique du Sud. Sur tous les sites étudiés, la majorité des cas de VRS touchaient des nourrissons.

Conclusion Ces études montrent que le VRS contribue de manière substantielle, quoique très variable, à la charge d'IVRI pesant sur les enfants de moins de 5 ans de quatre pays en développement.

Cette variabilité s'explique notamment par : des facteurs sociaux, tels que la taille de la famille et les schémas de recours aux soins médicaux, la proportion d'enfants contaminés par le VIH et des différences entre les définitions cliniques utilisées pour obtenir les

échantillons. La distribution en fonction de l'âge des cas indique qu'on a besoin d'un vaccin anti-VRS qui protège les enfants à un stade précoce de la vie.

Resumen

Infección por el virus sincitial respiratorio: realización de estudios basados en el denominador en Indonesia, Mozambique, Nigeria y Sudáfrica

Objetivo Evaluar la carga de infecciones de las vías respiratorias inferiores (IRI) asociadas al virus sincitial respiratorio (VSR) entre los niños en cuatro países en desarrollo.

Métodos Se utilizó un protocolo de la OMS para la vigilancia prospectiva poblacional de las infecciones respiratorias agudas entre los niños menores de 5 años en varios sitios de Indonesia, Mozambique, Nigeria y Sudáfrica. La detección del antígeno VSR se realizó mediante pruebas de inmunosorción enzimática aplicadas a muestras nasofaríngeas de los niños que cumplían la definición de caso clínico.

Resultados Entre los niños menores de 5 años, la incidencia de IRI asociada a VSR por 1000 niños-año fue de 34 en Indonesia y 94 en Nigeria. La incidencia de IRI grave asociada a VSR por

1000 niños-año fue de 5 en Mozambique, 10 en Indonesia y 9 en Sudáfrica. En todos los sitios de estudio, la mayoría de los casos de VSR se dieron en lactantes.

Conclusión Estos estudios demuestran que el VSR es responsable de una carga sustancial pero muy variable de IRI entre los niños menores de 5 años en cuatro países en desarrollo. Como posibles explicaciones de esas diferencias habría que citar algunos factores sociales, como el tamaño de la familia y las pautas de búsqueda de atención de salud; la proporción de niños infectados por el VIH; y las diferentes definiciones clínicas usadas para obtener las muestras analizadas. La distribución de edades de los casos muestra que es necesario conseguir una vacuna anti-VSR que proteja a los niños en sus primeros años de vida.

Arabic

References

- Selwyn BJ on behalf of the Coordinated Data Group of BOSTID Researchers. The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries. *Reviews of Infectious Diseases* 1990;12 Suppl 8:S870-88.
- Sutmöller F, Andrade Ferro ZP, Asensi MD, Ferreira V, Mazzei IS, Cunha BL. Etiology of acute respiratory tract infections among children in a combined community and hospital study in Rio de Janeiro. *Clinical Infectious Diseases* 1995;20:854-60.
- Borrero I, Fajardo L, Bedoya A, Zea A, Carmona F, de Borrero MF. Acute respiratory tract infections among a birth cohort of children from Cali, Colombia, who were studied through 17 months of age. *Reviews of Infectious Diseases* 1990;12 Suppl 8:S950-6.
- Weber MW, Mulholland EK, Greenwood BM. Respiratory syncytial virus infection in tropical and developing countries. *Tropical Medicine and International Health* 1998;3:268-80.
- Simoës EAF. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *Journal of Pediatrics* 2003;143 Suppl 5:S118-26.
- Berman S, Duenas A, Bedoya A, Constain V, Leon S, Borrero I, et al. Acute lower respiratory tract illnesses in Cali, Columbia: a two-year ambulatory study. *Pediatrics* 1983;71:210-8.
- Weber MW, Milligan P, Sanneh M, Awemoyi A, Dakour R, Schneider G, et al. An epidemiological study of RSV infection in the Gambia. *Bulletin of the World Health Organization* 2002;80:562-8.
- Djelantik IGG, Gessner BD, Soewignjo S, Steinhoff M, Sutanto A, Widjaya A, et al. Incidence and clinical features of hospitalization because of respiratory syncytial virus lower respiratory illness among children less than two years of age in a rural Asian setting. *Pediatric Infectious Disease Journal* 2003;22:150-6.
- Dagan R, Landau D, Haikin H, Tal A. Hospitalization of Jewish and Bedouin infants in Southern Israel for bronchiolitis caused by respiratory syncytial virus. *Pediatric Infectious Disease Journal* 1993;12:381-6.
- Wright PF, Cutts FT. *Generic protocol to examine the incidence of lower respiratory infection due to respiratory syncytial virus in children less than five years of age: field test version*. Geneva: World Health Organization; 2000. WHO document WHO/V&B/00.08.

11. Loscertales MP, Roca A, Ventura PL, Abacassamo F, Dos Santos F, Sitaube M, et al. Epidemiology and clinical presentation of respiratory syncytial virus infection in a rural area of southern Mozambique. *Pediatric Infectious Disease Journal* 2002;21:148-55.
12. Tollman S. The Agincourt field site — evolution and current status. *South African Medical Journal* 1999;89:853-8.
13. World Health Organization. *Acute respiratory infection in children: case management in small hospitals in developing countries – a manual for physicians and other senior health workers*. Geneva: WHO; 1995.
14. Fisher RG, Gruber WC, Edwards KM, Reed GW, Tollefson SJ, Thompson JM, et al. Twenty years of outpatient respiratory syncytial virus infection: a framework for vaccine efficacy trials. *Pediatrics* [Online version] 1997;99:e7, available from: <http://www.pediatrics.org/cgi/content/full/99/2/e7>
15. Resch B, Gusenleitner W, Mandl C, Müller W. Epidemiology of respiratory syncytial virus infection in Southern Austria. *Pediatric Infectious Disease Journal* 2000;19:587-8.
16. Sims DG, Downham MAPS, McQuillin J, Gardner PS. Respiratory syncytial virus infection in north-east England. *BMJ* 1976;2:1095-8.
17. Weigl JAI, Puppe W, Schmitt HJ. Incidence of respiratory syncytial virus-positive hospitalizations in Germany. *European Journal of Clinical Microbiology and Infectious Diseases* 2001;20:452-9.
18. Ørstavik I, Carlsen KH, Halvorsen K. Respiratory syncytial virus infections in Oslo 1972-1978. *Acta Paediatrica Scandinavica* 1980;69:717-22.
19. Brandenburg AH, Jeannot PY, Steensel-Moll HA, Ott A, Rothbarth PH, Wunderli W, et al. Local variability in respiratory syncytial virus disease severity. *Archives of Disease in Childhood* 1997;77:410-4.
20. Monto AS, Lim SK. The Tecumseh study of respiratory illnesses. III. Incidence and periodicity of respiratory syncytial virus and *Mycoplasma pneumoniae* infections. *American Journal of Epidemiology* 1971;94:290-301.
21. Henderson FW, Collier AM, Clyde WA, Denny FW. Respiratory syncytial virus infections, reinfections and immunity: a prospective, longitudinal study in young children. *New England Journal of Medicine* 1979;300:530-4.
22. Madhi SA, Schoub B, Simmank K, Blackburn N, Klugman KP. Increased burden of respiratory viral associated severe lower respiratory tract infections in children infected with human immunodeficiency virus type-1. *Journal of Pediatrics* 2000;137:78-84.
23. World Health Organization, UNAIDS, UNICEF. *Epidemiological fact sheets by country 2000*, available from: http://www.who.int/emc-hiv/fact_sheets
24. World Health Organization, UNICEF. *Africa malaria report 2003*. Geneva: WHO; 2003. WHO document WHO/CDS/MAL/2003.1093.
25. English M, Punt J, Mwangi I, McHugh K, Marsh K. Clinical overlap between malaria and severe pneumonia in African children in hospital. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996;90:658-62.
26. O'Dempsey TJ, McArdle TF, Laurence BE, Lamont AC, Todd JE, Greenwood BM. Overlap in the clinical features of pneumonia and malaria in African children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993;87:662-5.
27. World Health Organization, Department of Vaccines and Biologicals. *WHO vaccine-preventable diseases monitoring system: 2002 global summary*. Geneva: WHO; 2002. WHO document WHO/V&B/02.20.
28. World Health Organization, Department of Child and Adolescent Health and Development. *Management of the child with a serious infection or severe malnutrition: guidelines for care at the first-referral level in developing countries*. Geneva: WHO; 2000. WHO document WHO/FCH/CAH/00.1.
29. Munoz FM, Piedra PA, Glezen WP. Safety and immunogenicity of respiratory syncytial virus purified fusion protein-2 vaccine in pregnant women. *Vaccine* 2003;21:3465-7.
30. Wright PF, Karron RA, Belshe RB, Thompson J, Crowe JE, Boyce TG, et al. Evaluation of a live, cold-passaged, temperature-sensitive, respiratory syncytial virus vaccine candidate in infancy. *Journal of Infectious Diseases* 2000;182:1331-42.
31. Stensballe LG, Devasundaram JK, Simoes EAF. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. *Pediatric Infectious Disease Journal* 2003;22 Suppl 2:S21-32.
32. Olson MA, Shuck KM, Sambol AR. Evaluation of Abbott TestPack RSV for the diagnosis of respiratory syncytial virus infections. *Diagnostic Microbiology and Infectious Disease* 1993;16:105-9.
33. Groothuis JR, Simoes EAF, Levin MJ, Hall CB, Long CE, Rodriguez WJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. *New England Journal of Medicine* 1993;329:1524-30.
34. Roca A, Loscertales M-P, Quintó L, Pérez-Breña P, Vaz N, Alonso PL, et al. Genetic variability among group A and B respiratory syncytial viruses in Mozambique: identification of a new cluster of group B isolates. *Journal of General Virology* 2001;82:103-11.
35. Roca A, Abacassamo F, Loscertales M-P, Quintó L, Gómez-Olivé X, Fenwick F, et al. Prevalence of respiratory syncytial virus IgG antibodies in infants living in a rural area of Mozambique. *Journal of Medical Virology* 2002;67:616-23.
36. Roca A, Quintó L, Abacassamo F, Loscertales MP, Gómez-Olivé FX, Fenwick F, et al. Antibody response after RSV infection in children younger than 1 year of age living in a rural area of Mozambique. *Journal of Medical Virology* 2003;69:579-87.
37. Venter M, Madhi SA, Tiemessen CT, Schoub BD. Genetic diversity and molecular epidemiology of respiratory syncytial virus over four consecutive seasons in South Africa: identification of new subgroup A and B genotypes. *Journal of General Virology* 2001;82:2117-24.
38. Venter M, Collinson M, Schoub BD. Molecular epidemiological analysis of community circulating respiratory syncytial virus in rural South Africa: comparison of viruses and genotypes responsible for different disease manifestations. *Journal of Medical Virology* 2002;68:452-61.