THE EPIDEMIOLOGY OF RESPIRATORY SYNCYTIAL VIRUS (RSV) INFECTIONS IN SOUTH AFRICAN CHILDREN

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Objectives. To review the incidence, outcomes and risk factors associated with respiratory syncytial virus (RSV) infection in South African children.

Design. Review of published literature and laboratory records.

Methods. Review of the published literature. Articles listed on MEDLINE with 'South African' or 'children' and 'respiratory syncytial virus' or 'acute respiratory tract infections' as text words were retrieved. We analysed the data on respiratory virus activity from January 1990 to June 1996. Data were obtained from the National Institute for Virology database, which includes information on viral respiratory infections from the seven academic virology departments in South Africa.

Results. Acute respiratory tract infections cause approximately 8% of all deaths in the under-5 age group in South Africa. The published hospital-based incidence of RSV infection varies from 3% to 18%. Mortality rates in these studies were between 12% and 43%. Risk factors identified for severe RSV infection requiring hospitalisation were malnutrition, prematurity, age < 6 months, vitamin A deficiency, environmental pollution and congenital heart disease. There is a seasonal peak in RSV cases, with the majority occurring in winter.

Conclusions. Acute respiratory tract infections and RSV infections are an important cause of mortality and morbidity in young children in South Africa. However, currently available information from laboratory records and published South African literature is not sufficient to assess the impact of this infection. Age-specific incidence data in the 0 - 5-year age group are essential for the rational planning and implementation of future vaccine strategies, public health interventions and treatment of RSV infections.

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Worldwide approximately 14 million children under 5 years of age die each year, with 30% of these deaths attributed to acute respiratory tract infections (ARIs).[1] According to estimates from the World Health Organisation (WHO), mortality from ARIs in developing countries is 30 - 70 times higher than in developed countries and correlates closely with infant mortality rates.[2] ARI is an important health problem for South African children in terms of morbidity and mortality[3] and is the commonest reason for health service utilisation in this age group.[4,5]

There are few published studies from Africa examining the aetiology, epidemiology, risk factors, clinical features and outcomes of ARI. Furthermore, study designs and laboratory methodologies are not standardised, making it difficult to relate these findings to South African children. However, existing mortality data from other developing countries confirm that ARI is the most important cause of death in children under 5 years of age.[5] Reported ARI case fatality ratios are variable, but appear to be highest in children under 12 months of age. Incidence data from these countries also indicate the high number of ARI cases in young children, with 12.7 - 16.8 new episodes of ARI per 100 child-weeks at risk being reported. Most of these episodes occur in children under 18 months of age.[6]

Various risk factors have been associated with increased ARI incidence in developing countries. These include maternal age and education level,[6] overcrowding,[7] malnutrition,[8] indoor air pollution[9] and parental smoking.[10] Viral agents are recovered more frequently than bacterial agents from ARI cases and the most frequent virus detected is respiratory syncytial virus (RSV).[10, 11-14] The predominant bacterial agents are *Streptococcus pneumoniae* and *Haemophilus influenzae*, particularly in children with lower respiratory tract infections.[15]

RSV morbidity and mortality are preventable. RSV vaccine research has progressed considerably in the last few years, with various live attenuated and subunit vaccines likely to become available in the near future.[16] Trials with these vaccines in developed countries have shown marked decreases in severe disease and have been used successfully in young children (under 12 months of age) in the presence of maternal antibody.[17] A successful preventive strategy currently available includes the use of vitamin A supplementation in high-risk children[18] and in severely ill patients.[19] Immune prophylaxis with RSV-specific immunoglobulin has been used successfully in normal infants and infants at high risk for ARI, as well as in those with underlying bronchopulmonary dysplasia and congenital heart disease.[20] With the success of RSV immunoglobulin therapy there has been increased interest in the development of RSV-specific monoclonal antibodies that would have the advantage of being directed specifically at particular epitopes of the virus, and could be used to deliver much higher antibody concentrations in smaller doses.[21] This latter strategy is being pursued as a therapeutic alternative rather than as a preventive approach.

Treatment for severe RSV also exists in the form of antiviral therapy with ribavarin, a guanosine nucleotide analogue. Inconsistent strategies for treatment of severely ill children using ribavarin, bronchodilator and anti-inflammatory therapies have led to variable results and controversy concerning this approach.[22] Nevertheless, the current recommendation of the American Academy of Pediatrics Committee on Infectious Diseases is to use ribavarin in all potential candidates for treatment.[21] Antiviral and monoclonal antibody immune therapies are expensive. Therefore, before successful implementation of these treatments in developing countries the burden of severe RSV infection must be established, and clear guidelines for therapy and rigorous cost-efficiency analysis must be done.

More appropriately for South Africa and other developing countries, the implementation of relatively simple public health interventions and a comprehensive approach to primary health care will decrease the burden of RSV infection in children. This approach used in conjunction with future vaccine strategies and selective use of antivirals and monoclonal antibodies is needed to address the ARI problem in developing countries.

This study was undertaken to estimate the current burden of disease caused by RSV in South African children using laboratory-based data, and to review the incidence, outcomes and risk factors associated with severe RSV infections in the existing published South African literature.

METHOD

Literature review

A literature search was done through MEDLINE and articles from 1970 to 1997 with 'South African' or 'children' and 'respiratory syncytial virus' or 'acute respiratory tract infections' as medical subject headings and text words were retrieved. These articles were evaluated for references describing South African patients or having authors from South Africa. The references of these articles were then inspected for secondary references from South Africa. Articles were included if they contained details of at least one of the following, namely monthly number of cases, age or sex distribution, outcome, nutritional status, isolation of bacteria or viral diagnosis.

Laboratory data

Respiratory virus activity is monitored at the National Institute for Virology (NIV) using both passive and active surveillance methods, which have been described in detail elsewhere.[23] Briefly, passive surveillance entails collating all positive respiratory virus results per month per academic medical virology department in South Africa. This collation includes departments at the following universities: Cape Town, Orange Free State, KwaZulu-Natal, MEDUNSA, Pretoria, Stellenbosch and Witwatersrand. A *Surveillance Bulletin* is published every

month for all viral infections and is available in the public domain. Active surveillance in the form of a 'viral watch programme' maintained by the NIV also contributes to the data in the *Surveillance Bulletin*. The viral watch programme consists of sentinel sites in Gauteng based at general practitioners, factory and university clinics. Data collected broadly represent a cross-section of socio-economic and different age groups and is specifically aimed at monitoring influenza virus activity. Data used in this analysis was taken from the *Surveillance Bulletin* from the beginning of January 1990 to the end of July 1996.

Data analysis

Data analysis was done using Epi-Info version 5.0. Mean isolation rates per month for total viral respiratory pathogens and for RSV alone were calculated and plotted as 3-month running averages. These averages, in keeping with WHO and National Institute of Allergy and Infectious Diseases (NIAID) recommendations, were used to manipulate monthly RSV data, thus plotting smoother curves for reference.[16]

RESULTS

Literature review

Seven South African studies from 1974 to 1997 were identified on the basis of the criteria outlined. These publications and a summary of the RSV/ARI information they contain are shown in Table I. One study was laboratory-based[23] and all the rest were done on hospital-based populations. No community-based incidence or prevalence studies were found. The design and execution of each identified study was different. The articles included descriptive studies[23-27] and two case-control studies.[18,28]

A variety of laboratory methodologies were used for virus detection in the papers that specifically identified an aetiological agent.[23,24,27,28] The methods used ranged from the gold standard of virus culture (most specific, least sensitive) to enzyme-linked immunosorbent assays (most sensitive, least specific). Only one paper used an immunofluorescent assay, the currently preferred methodology for RSV diagnosis.[29] The incidence of RSV was highest (18%) in the study conducted in high-risk, severely ill infants from an intensive care unit (ICU).[24] In the other three studies[23,27,28] that measured RSV incidence, the proportion of RSV-infected children ranged from 3% to 6%.

Outcome was measured in terms of the proportion of children in the study population who died during the study period (mortality rate). Calculation of the mortality rate was only possible in those studies that included a denominator for the identified group under examination. The highest mortality rate of 43% was found in the severely ill ICU children.[24] The next highest mortality was also associated with high-risk children, in this case children with congenital heart disease,[26] although other non-high-risk infants from the paediatric wards were also included in this study. The lowest mortality rate in this series of studies was 12%.[25]

The following risk factors for severe ARI/RSV infection were identified: prematurity;[25] young age (perinatal,[25] under 6 months[26] or under 12 months[23,24,27]); congenital heart disease;[26] and malnutrition,[24,25] including specifically vitamin A

Table I. Indexed South African studies and relevant indicators identified on literature review

Study (year)	Population	*N*	RSV (%)	Lab. method	MR (%)	Significant risk factors
Naude *et al.*[24] (1974)	Hospital ICU	44	18	Culture	43	Malnutrition Age < 12 mo.
Adams *et al.*[25] (1978)	Hospital	441	ND	ND	12	Perinatal Prematurity Malnutrition
Scragg and Rubidge[26] (1978)	Hospital	19 399	ND	ND	27	Age < 6 mo. CHD
Joosting *et al.*[27] (1979)	Hospital	3 790	4	Culture	ND	Autumn peak Age < 12 mo.
McAnerney *et al.*[23] (1994)	Laboratory	4 133	3	Culture, IFA, ELISA	ND	Age < 12 mo.
Wesley and Loening[28] (1996)	Hospital	48	6	Culture ELISA	ND	None
Dudley *et al.*[18] (1997)	Hospital	67 ELISA	ND	ND	ND	Vitamin A deficiency

RSV = respiratory syncytial virus; MR = mortality rate; ND = not done; CHD = congenital heart disease; IFA = immunofluorescent assay; ELISA = enzyme-linked immunosorbent assay.

deficiency.[18] However, a more recent case-control study found no differences at all in risk factors examined (overcrowding, indoor air pollution and malnutrition) between cases and controls.[28]

Only one group examined the seasonal variation of respiratory tract infections.[27] They identified an increase in RSV infections during late autumn, with a peak incidence during the winter months of June, July and August.

Laboratory data

Fig. 1 shows the monthly 3-month running average of positive specimens identified at the seven academic medical virology departments in South Africa from January 1990 to the end of July 1996. Overall, there were very few positive RSV specimens. The rate of positive specimens was between 1 and 20, with each year having a variable yield. During the winter peaks of 1995 and 1996 the isolation rate was much greater than during any of the other years included in the analysis, reaching 17 isolates in 1995 and 20 in 1996. The 1996 isolation data only included monthly data up to the end of July. Peak RSV activity for each year spanned the winter months of June, July and August. The lowest activity was seen during summer (November - March), with variable activity in spring and autumn.

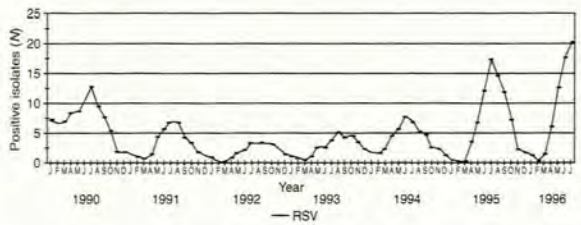

Fig. 1. Three-month running average of RSV isolations from January 1990 to July 1996 — combined data from all seven academic virology laboratories in South Africa.

Fig. 2 shows the monthly proportion (%) of RSV-positive specimens in relation to the total number of respiratory virus isolations during the period, including the beginning of January 1992 to the end of December 1995. RSV isolates were only a minor proportion of the overall respiratory isolates, with the peak isolation of RSV in July 1994 contributing to only 6% of the total. Most respiratory virus activity, as diagnosed by these laboratories, was due to influenza, and RSV-positive specimen yield was relatively minor.

Discussion

There are only seven South African studies describing the incidence, outcomes and risk factors associated with ARI and RSV infections in South African children. All the studies identified by this review were conducted on hospital-based samples. No community-based study describing the age-specific incidence of this infection in children under 5 years of age has been published.

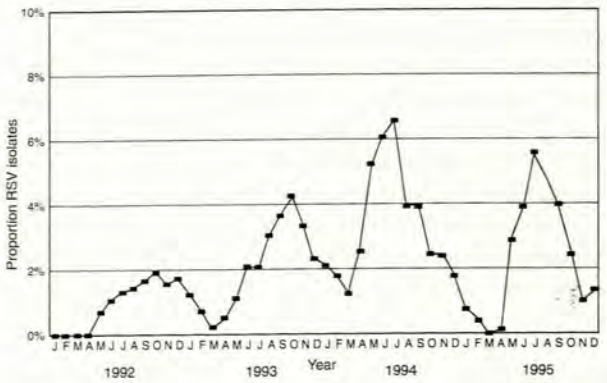

Fig. 2. Three-month running average of the proportion of RSV isolates in relation to total laboratory respiratory isolates from January 1992 to December 1995.

In the absence of any other data, indirect measures of the burden of ARI and RSV in South Africa are generally used. These include infant mortality rates, under-5 disease-specific mortality rates, and published data from other developing countries. The average infant mortality rate in South Africa of 40.2/1 000[30] reflects the considerable burden of infectious diseases in the under-5 age group, but does not indicate specific causes of mortality in this group. ARI accounts for approximately 8% of all deaths in infants and children in South Africa; it is the third most common cause of death in the under-5 age group, with perinatal causes and diarrhoeal diseases accounting for 33% and 19% of all deaths respectively.[30] Some of the deaths in the 'perinatal group' may also be caused by ARI and RSV, but no figures exist for RSV-specific deaths in children under 5 years of age.

Data from a recent hospital-based African study[12] show a relatively low mortality rate due to RSV of 2% and an RSV incidence of 28%. These rates are certainly different to the rates described in the South African literature reviewed here, where the highest isolation rate was 18% and the highest mortality rate 43%.[24] Community-based RSV studies from other African countries[13,31] also demonstrate a much lower mortality rate (3%) than that reported in the South African literature. Nevertheless, it remains difficult to extrapolate these findings to South African children because of the vast socio-economic, climatic and regional differences that exist within Africa and even within South Africa itself.

Published risk factors associated with RSV infections from other developing countries show that it is mainly children between 0 and 6 months of age who are infected with RSV,[32] that male children are more frequently infected (60%) than female children,[33] and that there is a marked seasonality of RSV outbreaks, with these occurring predominantly during the wet

season or cold winter months.[15] This pattern is also seen in developed countries,[34] where peak RSV activity occurs during the winter months. Bacterial co-infections that have been identified are generally caused by two pathogens, namely *S. pneumoniae* and *H. influenzae*. However these two pathogens are usually only isolated in 20% or so of children with lower respiratory tract infections.[35] Malnutrition has also been associated with RSV infections but the association is not consistent, with some studies finding fewer RSV infections in malnourished children,[36] and others concluding that malnutrition is a predisposing factor for this infection.[18,25,26] Socio-economic indicators (maternal age and maternal education levels, indoor air pollution) have consistently been associated with an increased risk of ARI in developing countries.[6] Finally, a study from the USA[37] found that RSV infections were not more common in HIV-infected children than in non-HIV-infected children. However this study clearly demonstrated prolonged shedding of RSV by HIV-positive children. Prolonged shedding of RSV in these children must therefore be anticipated, and special precautions must be taken to prevent nosocomial spread in chronic care facilities. The possibility of this method of nosocomial spread may be an important public health consideration in RSV-infected children in South Africa because of the high rate of HIV perinatal transmission and increasing HIV incidence in this age group.

In an attempt to find another indirect indicator of RSV infection in South African children, laboratory isolation data from all seven academic virology centres in the country from January 1990 to July 1996 were analysed. Laboratory data provide only partial information regarding RSV infections in children, and there are a number of limitations to using these data. Firstly, the 'viral watch' programme at the NIV has been designed for the specific purpose of monitoring influenza activity in adults. Other respiratory virus findings are detected as part of a respiratory virus screen that is done on all specimens regardless of the age of the patient. However the majority of specimens sent to the laboratories are from adults. Therefore, the number of RSV isolates in children is small compared with the total number of isolates recovered from all the specimens received. This distinction is illustrated in Fig. 2, which shows that RSV isolates contribute only a minor proportion of the overall respiratory virus isolates in South African laboratories.

Furthermore, the passive surveillance data gathered from the seven academic medical virology departments are from selected patients who are severely ill, in ICUs, or who have a clinically unclear diagnosis. Routine specimens from all children with acute respiratory tract infections suspected of being viral are not usually taken or sent to the laboratory. The main reasons for this are the high cost of the tests, the delay in reaching a specific diagnosis and the fact that management strategies do not change even if a specific viral diagnosis is obtained. Therefore, the specimens received by the laboratories represent a very selected population. Finally, within the South African virological laboratory circuit different methodologies of various sensitivities and specificities are used to diagnose respiratory virus infections. This heterogeneity adds another confounding factor to the interpretation of respiratory virus isolation data.

If the maternal and child health goal of the South African Department of Health (1995),[30] namely to reduce infant mortality rates by 50% by the year 2000,[30] is to be achieved, accurate community- and hospital-based prevalence and incidence data on ARI and RSV disease in children must be obtained. Once the age-specific incidences of ARI and RSV infections are known, rational planning and implementation of health interventions can be instituted. Simple, effective and cheap public health interventions may be undertaken, for example vitamin A supplementation and careful monitoring of RSV/HIV co-infected children to prevent nosocomial spread of RSV. Baseline incidence information will also be extremely important when effective vaccines to prevent severe RSV infections become available in the not-too-distant future. The impact of vaccines against RSV infection on South African infant deaths can only be assessed if accurate baseline incidence data exist for this infection. Finally, the targeted use of specific RSV treatment modalities, in the form of antivirals and immunoglobulin therapy, may then be possible.

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