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Respiratory syncytial virus in adults with severe acute respiratory illness in a high HIV prevalence setting

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention, USA or the National Institute for Communicable Diseases, South Africa.

Competing interests

All authors declare that they have no commercial or other associations that may pose a conflict of interest.

Ethics

The SARI protocol was approved by the University of the Witwatersrand Human Research Ethics Committee (HREC) and the University of KwaZulu-Natal Human Biomedical Research Ethics Committee (BREC) protocol numbers M081042 and BF157/08, respectively.

Author contributions

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Background—There are limited data on the epidemiology of respiratory syncytial virus (RSV) illness in HIV-infected adults or the elderly in Africa. We studied the epidemiology of RSV-associated severe acute respiratory illness (SARI) hospitalizations in adults in South Africa from 2009 through 2013.

Methods—Individuals admitted to sentinel surveillance hospitals were investigated by respiratory tract swabs for RSV, using a multiplex real-time polymerase chain reaction assay. The incidence of RSV-associated SARI was calculated for the one site with population denominators.

Results—Of 7796 participants investigated, 329 (4%) tested positive for RSV. On multivariable analysis, HIV-infected individuals with RSV-associated SARI had greater odds of being in the age groups 18–44 and 45–64 years (odd ratios (OR) 26.3; 95% confidence interval (CI) 6.2–112.1 and OR 11.4; 95% CI 2.6–50.0) compared with those ≥65 years and being female (OR 2.7; 95% CI 1.4–5.4). The relative risk of hospitalization with RSV-associated SARI was 12–18 times higher in HIV infected individual compared to that of HIV-uninfected.

Conclusion—The incidence of RSV-associated SARI was higher in HIV-infected individuals and those aged 65 years and older. Further studies are warranted to describe the disease association of RSV detected in adults with SARI.

Keywords

Respiratory syncytial; virus; HIV; South Africa

Introduction

There are limited data on the epidemiology of respiratory syncytial virus (RSV) infection in adults and older children in high HIV prevalence settings like South Africa. In high income countries with a lower HIV burden, the burden of hospitalization with RSV in the elderly has been described as similar to that of influenza.[1–4] Also, RSV infection has been reported to be more severe in the elderly, people living in long term care facilities, immune compromised individuals (specifically those with stem cell and lung transplants) and individuals receiving chemotherapy.[4–6] Other risk factors in adults include underlying cardiac disease and chronic respiratory illness.[7] In a prospective hospital-based surveillance programme in the United States amongst elderly (≥65 years), RSV was identified in 11% of pneumonia episodes, 11% of chronic obstructive pulmonary disease episodes, 5% of congestive heart failure events and 7% of asthma cases.[8]

In South Africa the highest HIV prevalence occurs among adults aged 15–49 years and was 17% in 2012.[9] Of the HIV-infected adults eligible for antiretroviral treatment on the guidelines applicable during the study period (CD4+ T cell count <350/mm^3) it was estimated that 29% in 2009 and 52% in 2011 had initiated treatment.[10]

We aimed to describe the effects of HIV on the incidence, epidemiology and clinical characteristics of RSV-associated severe acute respiratory illness in adults in South Africa.

Methods

Description of the surveillance programme and study population

The Severe Acute Respiratory Illness (SARI), prospective hospital-based sentinel surveillance programme, was implemented in February 2009. We include data from February 2009 through December 2013. The programme is active in four of the nine provinces of South Africa including at Chris Hani-Baragwanath Academic Hospital (CHBAH) in an urban area of Gauteng Province, Edendale Hospital in a peri-urban area of KwaZulu-Natal Province, Matikwana and Mapulaneng Hospitals in a rural area of Mpumalanga Province and Klerksdorp and Tshepong Hospitals in a periurban area of the Northwest Province (added in June 2010).

Study procedures

Individuals admitted to sentinel hospitals within seven days of onset of symptoms were screened for SARI per World Health Organization (WHO) case definition.[11] The criteria included: (1) documented sudden onset of fever (>38 °C) or patient-reported fever, (2) cough or sore throat, and (3) shortness of breath, or difficulty breathing. Only patients with symptom duration of 7 days or less were included in this analysis. Admission criteria and inhospital treatment protocols (including intensive care (ICU) admission) were at the discretion of the attending physician. There is limited access to ICU beds in South African public hospitals, protocols for ICU admission vary between hospitals and are based on the number of beds available. Oxygen therapy is however, widely available in the general ward setting. All patients admitted (those who spent a night in hospital) from Monday through Friday were eligible for enrolment and enrolled if the WHO case definition was met. At CHBAH, due to the large numbers of subjects and limited resources, enrolment was limited to two of every five working days per week; the selected days varied systematically. Logs were maintained for the total numbers of hospitalized individuals (including those enrolled over weekends and public holidays) who met the study case definitions and of those enrolled by the study-staff. Structured case investigation forms were completed for demographic and clinical information. Enrolled subjects were followed up until death, out-referral to a step-down facility or discharge. A nasopharyngeal (NP) and an oropharyngeal (OP) swab were collected for respiratory virus testing. Blood samples were collected for pneumococcal *lytA* polymerase chain reaction (PCR) testing and anonymous linked HIV testing by HIV-ELISA was undertaken for those subjects among whom HIV-testing was not undertaken by the attending physician. The collection of blood for bacterial culture and sputum for *Mycobacterium tuberculosis* (TB) testing was done at the discretion of the attending physicians.

Laboratory methods

Upper respiratory secretion samples (combined NP and OP) were transported in a single vial of viral transport medium at 4–8 °C to reach the National Institute for Communicable Diseases (NICD) within 72 h of collection. Any storage of sample at the surveillance site was in a temperature regulated refrigerator (4–8 °C). Respiratory specimens were tested by multiplex real-time reverse-transcription PCR (RT PCR) assay for 10 respiratory viruses (respiratory syncytial virus; influenza A and B viruses, parainfluenza virus 1, 2 and 3;

enterovirus; human metapneumovirus; adenovirus and rhinovirus) as detailed elsewhere.[12] *Streptococcus pneumoniae* was identified by quantitative real-time PCR detecting the *lytA* gene from whole blood specimens.[13]

Evaluation of HIV infection status

HIV testing was requested by admitting physicians when clinically indicated according to standard practice. This included HIV enzyme-linked immunosorbent assay (ELISA) testing with confirmation by ELISA on a second specimen. In addition, for consenting patients, an anonymized linked dried blood spot specimen was taken for determination of HIV status by ELISA.

Definitions

Underlying chronic medical conditions included asthma, chronic lung disease, chronic heart disease, liver disease, renal disease, diabetes mellitus, immune-compromising conditions other than HIV infection based on solicitation from the individual and medical-record review.

Calculation of incidence

The incidence of RSV-associated SARI hospitalizations was estimated for Soweto (CHBAH) – the only site for which population denominator data were available. CHBAH is the only public hospital serving a community of about 1 million (persons aged ≥ 18 years in 2012). We estimated the incidence of RSV-associated SARI hospitalizations per 100 000 population, the numerator was calculated using the number of RSV-positive SARI hospitalizations and adjusting for non-enrolment (refusal to participate, non-enrolment during weekends and limited sampling of two of the five adult wards) and the dominator being the mid-year population for each of the age groups. All individuals hospitalized with SARI during the study period were logged and this was used to estimate the number of SARI cases not enrolled during the study period. The actual number of RSV-associated cases was then multiplied by the adjustment factor. Adjustment factors were calculated for each age group (18–44 years, 45–64 years and ≥65 years). Incidence calculations using the adjusted number of cases, stratified by age group and HIV status and divided by the mid-year age specific population estimates for each year.[14] The HIV prevalence in the study population, by age group, was estimated from the projections of the Actuarial Society of South Africa (ASSA) AIDS and Demographic model[9] and used to impute denominators for numbers of HIV-infected individuals in the population. Confidence intervals for incidence estimates were calculated using the Poisson distribution. Age-specific and overall age-adjusted incidence of RSV-associated SARI in HIV-infected and HIV-uninfected persons was determined using log-binomial regression. Incidence is calculated for the complete years (surveillance started late in 2009) of surveillance 2010, 2011 and 2012. In 2013 enrolment was down-scaled at this site and so incidence calculations were not done for this year.

Seasonality

A description of the seasonality of RSV-associated SARI and total SARI hospitalizations was done by calculating the detection rate of RSV (number of cases of RSV divided by total SARI cases) by month for each year of the study.

Statistical analysis

A descriptive analysis was conducted for demographic and clinical factors associated with SARI in those individuals with RSV-associated SARI. A separate univariate and multivariable analysis by logistic regression was conducted to compare HIV-infected and HIV-uninfected patients with RSV-associated SARI, in which all available information on cases were used. A sensitivity analysis was conducted to explore the effect of missing HIV results on our findings. We repeated the analysis in two scenarios, first considering all those with missing result as HIV-uninfected and secondly considering all those with missing results as HIV-infected. Age group, duration of hospitalization, duration of symptoms and year were defined as categorical variables in multiple levels. All other variables were defined as the presence or absence of the attribute excluding missing data. Multivariate models were explored for univariate association with p value of <0.1. Statistical significance was decided on p value of 0.05 or less. Data were analysed using Stata® version 12 (StataCorp Limited, College Station, Texas, USA).

Ethical considerations

The protocol was approved by the Research Ethics Committees of the Universities of the Witwatersrand and KwaZulu-Natal. This surveillance was deemed non-research by the United States of America's Centers for Disease Control and Prevention (CDC) and did not need human subjects review by that institution. Written informed consent was obtained from all participants.

Results

From February 2009 through December 2013, 7872 individuals aged 18 years and older were enrolled who met the case definition of SARI. The majority of subjects were enrolled at the CHBAH (68%; 5380) and were female (4901; 62%). HIV results were available for 89% (7039/7872) of enrolled subjects, with an overall sero-positivity of 76% (5321/7039). Only 46% (1673/3657) of individuals known to be HIV-infected at enrolment were on antiretroviral treatment (ART) at the time of admission.

Demographic and clinical characteristics of patients with RSV-associated SARI

Of the 7872 enrollees, 7796 (99%) were tested for RSV which was detected in 4% of cases (329). The detection rate in HIV-infected 228/5297 (4%) and HIV-uninfected patients 57/1708 (3%) was similar (p = 0.079). The overall detection rate of RSV was similar across all age groups (18–44 years: 4%, 217/5129; 45–64 years: 4%, 93/2138; ≥65 years: 4%, 19/529, p = 0.738). The detection rate of RSV varied by year and was 2% in 2009 (20/1215); 4% (84/2004) in 2010; 4% (72/1981) in 2011, 6% (119/1861) in 2012 and 5% (34/735) in 2013 (p < 0.001). Other demographic and clinical characteristics of RSV-associated compared to RSV-negative SARI cases were similar (data not shown). The median duration

of symptoms prior to hospitalization was 4 days (range 0–7). *S. pneumoniae* was detected in 8% (25/304) of RSV-associated cases. In 64% (209/329) of cases, RSV was the only virus detected on PCR. The common co-infections with RSV included rhinovirus (16%; 52/329) and adenovirus (15%; 50/328). Influenza virus was detected in (6%; 21/329) of cases (Table 1).

The median duration of hospitalization for RSV-associated SARI cases was 6 days (range 1–41), 48% (155/329) of subjects required supplemental oxygen therapy and 1% (2/325) required mechanical ventilation. The overall case fatality ratio (CFR) for RSV-associated cases was 9% (29/314) (Table 1).

HIV-infection and RSV-associated SARI

The overall prevalence of HIV among RSV-associated cases was 80% (228/285). The HIV prevalence by age group was 87% in 18–44 years (166/228), 73% in 45–64 years (59/81) and 21% in those ≥ 65 years (3/14). HIV-uninfected individuals were at greater odds of having an underlying illness (excluding HIV and tuberculosis) than HIV-infected individuals (OR 4.1, 95% CI 1.9–8.9). The case fatality ratio in HIV-infected individuals (9%; 21/218) was similar to HIV-uninfected individuals with RSV-associated SARI (9%; 5/53), p = 0.965 (Table 2). On multivariable analysis age group (18–44 years: adjusted odds ratio (aOR) 26.3; 95% CI 6.2–112.1 and 45–64 years: aOR 11.4; 95% CI 2.6–50.0), female sex (aOR 2.7; 95% CI 1.4–5.4), underlying illness (excluding HIV and tuberculosis) (aOR 0.3; 95% CI 0.1–0.7) and longer symptom duration prior to hospitalization (2 to <5 days aOR 4.4 (95% CI 1.7–11.0) and 5–7 days aOR 4.2 (95% CI 1.6–10.4) compared to <2 days) remained associated with HIV infection in patients with RSV-associated SARI (Table 2). In the sensitivity analyses all associations remained significant (data not shown).

Incidence of hospitalization in HIV-infected and HIV-uninfected individuals with RSV-associated SARI

The overall incidence (per 100 000 population) of RSV-associated SARI was 30 (95% CI 26–34) in 2010, 22 (95% CI 19–25) in 2011 and 30 (95% CI 27–34) in 2012. The incidence of RSV-associated SARI was higher in HIV-infected individuals compared to HIV-uninfected individuals for all age groups (Table 3). HIV-infected individuals with RSV-associated SARI had a higher incidence of hospitalization across all age groups and in an age adjusted model in each year studied (2010; aRR 18 (95% CI 13–24), 2011; aRR 12 (95% CI 8–16), 2012; aRR 14 (95% CI 11–19)) (Table 3).

Elderly patients with RSV-associated SARI

Among the elderly (≥65 years age), 4% (19/529) tested positive for RSV. Patients aged ≥65 with RSV infection years had a 6 times greater odds of having an underlying illness (other than HIV and TB) as compared to patients aged 45–64 years (OR 6.8, 95% CI 2.4–19.7) and twice the odds of those aged 18–44 years (OR 2.4 95% CI 1.8–5.1). Although most of the deaths occurred in the 18–44 year (18/207, 9%) and 45–64 year age groups (7/89, 8%), the case fatality ratio was highest in the ≥65 years age group (4/18, 22%), p= 0.143. Three quarters of the patients aged ≥65 years who died were HIV-infected (3/4: 75%) and 50% (2/4) had an underlying illness (other than HIV and TB). The elderly (both HIV-infected and

HIV-uninfected individuals) experienced the highest incidence of hospitalization with RSV-associated SARI across all three years (Table 3).

Seasonality

Although RSV was detected all year round in South Africa, a small seasonal peak was seen between February and June, in most years the detection rate was more than 20% during these months. There was considerable variation between the years of study (Fig. 1). There was no marked seasonal variation in the total number of SARI hospitalizations (data not shown).

Discussion

We describe a high incidence of hospitalization in HIV-infected adults with RSV-associated SARI; however, these individuals did not have more severe outcomes with respect to prolonged hospitalization and mortality when compared to HIV-uninfected individuals. Similar to other published data, elderly patients (≥65 years) had a higher incidence of RSV-associated SARI hospitalization, greater odds of having underlying illnesses and trended to having higher CFR than younger patients.[3–5]

Although immunocompromised states are considered a risk factor for RSV-associated SARI, data specific to HIV-associated immunocompromised individuals are confined to a number of case reports of severe RSV-associated SARI in HIV-infected individuals.[15–19] These authors describe a clinical syndrome similar to that of *Pneumocystis jirovecii* pneumonia and one patient developed acute adult respiratory distress syndrome. Available evidence suggests that the immune response to RSV infection requires both humoural and cellular elements, specifically CD4+ and CD8+ T cells which are critical in terminating an acute RSV infection. Antibodies may provide protection against re-infection, although this response may wane with time, meaning individuals over time will revert to being susceptible to re-infection.[18] Studies in children with defective T cell function demonstrate prolonged viral shedding and increased disease severity.[20,21] CD4+ T cells are important for the production of interleukin and cytokines. Evidence is available for the link between lack of these cytokines and disease severity,[22] though other studies have failed to show this association.[23–26] Conversely there is also evidence to suggest cellular responses may contribute to disease. Histological studies indicate that RSV infection is associated with extensive obstruction of the small airways caused by inflammatory cells, cellular debris and oedema caused by peri-bronchiolar lymphoid aggregate; these inflammatory cells include neutrophils, CD4+ and CD8+ T cells.[26] Individuals with compromise to their immune systems, like HIV-infected adults, may be more at risk of severe infection but the role of a decreased immune response may need further description.

HIV infection is often associated with increased susceptibility to diseases due to intracellular pathogens, such as *P. jirovecii*, *M. tuberculosis*, *Mycoplasma avium-intracellulare* (MAI) infection, *Legionella* and intracellular viruses such as cytomegalovirus (CMV). Data are not presented for these pathogens as co-infections for this analysis. One important potential co-infection common in HIV-infected individuals was tested for in our study and the proportion

of cases with *S. pneumoniae* co-infection is similar to the proportion of *S. pneumoniae* co-infection all cause SARI infections admission in our study setting.[27]

Sensitive PCR technology for the detection of respiratory virus from samples taken from the upper airways poses the question of disease association or viral colonization. In a population based study in Kenya; Bigogo et al., found a high detection rate of RSV in individuals older than 5 years of age presenting with SARI but found similar, although not significant, detection rates of RSV in controls (OR 1.22 (95% CI: 0.82–1.83)).[28] Conversely Feiken et al. describe disease association with RSV detection by comparing healthy controls to those admitted to hospital with acute respiratory illness (OR 2.9 (1.3–6.6)), across all age groups.[29] A preliminary analysis in our setting comparing healthy controls (people attending outpatient clinics with no respiratory illness in 14 days prior to visit) to SARI cases admitted to hospital fitting the same clinical case definition as those in this study suggests that HIV-infected individuals with RSV are at increased odds of hospitalization (OR 4.2 (95% CI: 1.2–14.9) in the 25–54 year age group and OR 7.4 (95%CI: 1.2–46.8) in those older than 55 years).[30]

There are varying reports of the incidence of RSV-associated lower respiratory tract infection or RSV-associated SARI. These range from 2.9 to 130 per 100 000 population. Some of the differences in reported incidence may be explained by the different definitions of respiratory illness, whether by clinical case definition, or radiological confirmed pneumonia, geographic local and different reporting of age group. However, in all population-based studies across developing and developed worlds, similar trends to those in our study are described with incidence rates increasing in the older age groups.[1,2,31–35]

The specific case fatality ratio for RSV-associated SARI described in this analysis is similar to the all cause SARI case fatality ratio described in our setting.[36] Modelling done in South Africa describes excess mortality associated with the RSV season in South Africa among adults aged 25–44 years (high HIV prevalence age group).[37] The relative risk of death in HIV-infected compared to HIV-uninfected in this age group was RR 81.7 in all cause death data and RR 73.4 in pneumonia and influenza deaths data however excess mortality in was not seen in the RSV season in elderly patients. In a similar modelling study done in our setting, excess hospitalizations were described during the RSV season in the <5 year age group but not in individuals older than 20 years of age.[38] This study was conducted in a medically insured population which may not have similar characteristics to the study population in this study. Specific studies to address risk factors for hospitalization with RSV-associated SARI and the attributable fraction of disease would be of value to further describe the disease association in RSV-associated SARI in adults.

In this study of hospitalized adults in South Africa, RSV was detected all year round with an increase in detection from February to June in most years. When we compare these data to data from hospitalized children at the same sites, the RSV season appeared more marked in children aged <5 years. In children during the seasonal peaks the detection rate of RSV in children hospitalized with SARI reached 60% in some years.[39] The peak in this analysis was 31% in week 10 of 2013.

There were a number of limitations to this study: (1) Data on underlying illnesses were collected from a structured interview which may have been subject to recall bias; (2) We were not able to describe the degree of immune compromise in the elderly or the general condition of the elderly; (3) Opportunistic infections such a *P. jirovecii* and TB were not reported in this study period which does not allow the description of the association between RSV-positive SARI and these pathogens in HIV-infected individuals; (4) Our study was limited by the unavailability or paucity of data on HIV indices such as ART. Furthermore, we did not clinically stage patients with HIV and it is also possible that admission criteria for known HIV-infected patients may differ by attending physician and hospital; (5) One of the most common reasons for non-enrolment was that the patient was too ill to consent; this may bias our estimation of severity; Previously published data from the same surveillance programme found a 10% non-enrolment rate into the surveillance programme, of whom 50% were too ill to consent and 11% refused to participate with the remainder having a variety of reasons for refusal.[40] (6) Our confidence interval may not account for the variability in numbers due to enrolment strategies and so may be imprecise; (7) Lastly population denominators were only available for one large urban hospital site, making it difficult to generalize the findings to other sites in the country; (8) The adjustment factors used in our incidence calculation are based on a number of assumptions and this uncertainty in not captured in the confidence intervals for our estimates of incidence; (9) It is possible that health seeking behaviour is different by age and HIV status which could affect our estimation of disease incidence; (10) The true burden of RSV-associated respiratory tract infection is not complete without an estimation of outpatient burden, these data are not as yet published in our setting.

Conclusion

RSV-associated SARI is commonly detected in HIV-infected individuals. In the elderly RSV infection is associated with severe illness. An RSV vaccine if available should target high risk groups such as the elderly (≥65 years) and possibly HIV-infected individuals to prevent hospitalization with RSV-associated SARI in this setting.

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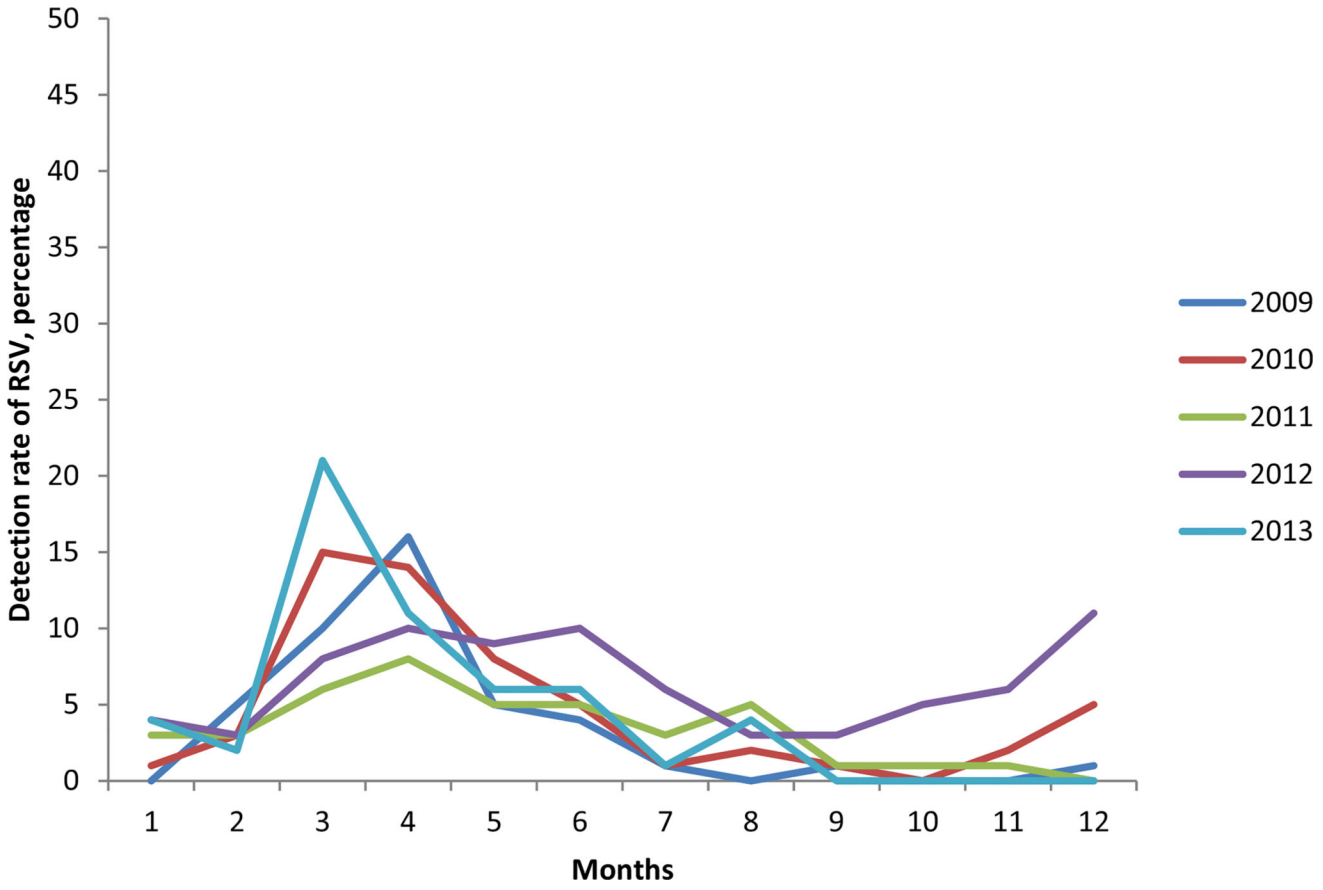

Figure 1.

Detection rate of RSV in patients admitted with SARI by month and year, South Africa 2009 to 2013.

Table 1

Demographic and clinical characteristic of individuals ≥18 years admitted with RSV-associated severe acute respiratory tract infection (SARI), South Africa 2009 to 2013.

Characteristics		RSV-associated LRTI n/N (%)
Age group (years)	18 to 44	217/329 (66)
	45 to 64	93/329 (28)
	≥65	19/329 (6)
Female		209/329 (64)
Black African race		314/329 (95)
Presenting symptoms and underlying medical conditions		
Duration of symptoms prior to admission (days), median (range)		4 (0–7)
HIV infection[a]		228/285 (80)
CD 4 + T cell count in those HIV infected	<200 cell/mm^3	58/90 (64)
	>200 cell/mm^3	32/90 (36)
Any underlying medical condition excluding HIV and TB[b]		40/329 (12)
Infectious agents identified		
RSV single virus infection		224/329 (68)
Pneumococcal infection[c]		25/304 (8)
Started on tuberculosis treatment during admission		32/324 (10)
Influenza (any type)		21/3296
Adenovirus		50/32815
Enterovirus		7/3292
Rhinovirus		52/32916
Human metapneumovirus		4/3291
Parainfluenza virus 1		3/3291
Parainfluenza virus 2		2/3291
Parainfluenza virus 3		5/3292
Clinical course		
Oxygen required		155/329 (48)
Admitted/transferred to intensive care unit		2/325 (1)
Mechanical ventilation		2/325 (1)
Duration of hospitalisation (days) median (range)		6 (1–41)
Duration of hospitalization	<2 days	13/317 (4)
	2–7 days	195/317 (62)
	8+ days	109/317 (34)
Case-fatality ratio	29/314 (9)	

[a] HIV – human immunodeficiency virus.

[b] Asthma, other chronic lung disease, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), diabetes mellitis, immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions) or pregnancy. Comorbidities were considered absent in cases for which the medical records stated that the patient had no underlying medical condition or when there was no direct reference to that condition.

[c]Presence of *Streptococcus pneumoniae* infection identified by *lyt A* PCR or on blood culture.

Table 2

Demographic and clinical characteristics of HIV-infected and HIV-uninfected individuals ≥18 with RSV-associated severe acute respiratory tract infection (SARI).

Characteristics		HIV-infected n/N (%)	HIV-uninfected n/N (%)	Univariate analysis		Multivariable analysis	
				OR (95% CI)[a]	p	OR (95% CI)[a]	p
Demographic characteristics							
Age group (years)	18 to 44	166/228 (73)	33/57 (42)	25.4 (6.6–97.5)	<0.001	26.3 (6.2–112.1)	<0.001
	45 to 64	59/59/228 (26)	22/57 (39)	9.83 (2.5–38.6)		11.4 (2.6–50.0)	
	≥65	3/228 (1)	11/57 (19)	Reference		Reference	
Female		154/228 (68)	28/57 (49)	2.2 (1.2–3.9)	0.012	2.7 (1.4–5.4)	<0.001
Black African race		221/228 (97)	52/57 (91)	3.0 (0.9–9.9)	0.08		
Underlying medical conditions							
Underlying medical condition excluding HIV and TB HIV[b]		18/228 (8)	15/57 (26)	0.2 (0.1–0.5)	<0.001	0.3 (0.1–0.7)	<0.001
Co-infections							
Pneumococcal infection[c]		20/221 (9)	4/56 (7)	1.3 (0.4–3.9)	0.643		
Started on tuberculosis treatment during admission		25/225 (11)	3/55 (5)	2.2 (0.6–7.5)	0.181		
Influenza (any type)		15/228 (7)	2/57 (4)	1.9 (0.4–8.7)	0.353		
Adenovirus		34/227 (15)	5/57 (9)	1.8 (0.7–4.9)	0.203		
Enterovirus		6/228 (2)	1/57 (2)	1.3 (0.1–11.0)	0.833		
Rhinovirus		32/228 (14)	22/57 (19)	0.7 (0.3–1.5)	0.333		
Human metapneumovirus		4/228 (2)	0/57 (0)				
Parainfluenza virus 1		2/228 (1)	0/57 (0)				
Parainfluenza virus 2		2/228 (1)	0/57 (0)				
Parainfluenza virus 3		3/228 (1)	1/57 (2)	0.7 (0.1–7.3)	0.807		
Clinical presentation and course							
Symptom duration prior to hospitalisation, days	<2	21/228 (9)	14/57 (25)	Reference	0.014	Reference	
	2 to <5	102/228 (45)	21/57 (37)	3.2 (1.4–7.4)		4.3 (1.7–11.0)	
	5–7	105/228 (46)	22/57 (38)	3.1 (1.4–7.2)		4.2 (1.6–10.4)	
Oxygen required		106/224 (47)	32/55 (58)	0.6 (0.4–1.2)	0.148		
Duration of hospitalisation (days) excludes deaths	<2	9/196 (5)	1/47 (2)	2.5 (0.3–20.9)	0.330		

Characteristics		HIV-infected n/N (%)	HIV-uninfected n/N (%)	Univariate analysis		Multivariable analysis	
				OR (95% CI)[a]	p	OR (95% CI)[a]	p
	2–7	116/196 (59)	33/47 (70)	Reference			
	8+	71/196 (36)	13/47 (28)	1.6 (0.8–3.1)			
Case-fatality ratio	21/218 (9)	5/53 (9)	1.0 (0.4–2.9)	0.965			
Median time in days to death		6 (4–9)	5 (4–8)				
		Range 0 to 47	Range 1–65				
Time to death (days)	<3	3/21 (14)	2/5 (40)	Ref	0.442		
	3 to <10	10/21 (48)	2/5 (40)	3.3 (0.3–34.8)			
	10 to <20	8/21 (38)	1/5 (20)	5.3 (0.3–82.8)			

[a]OR: Odds ratio, CI: 95% confidence interval.

[b]Asthma, other chronic lung disease, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), diabetes mellitis, immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions) or pregnancy. Comorbidities were considered absent in cases for which the medical records stated that the patient had no underlying medical condition or when there was no direct reference to that condition.

[c]Presence of *Streptococcus pneumoniae* infection identified by *lyt A* PCR or on blood culture.

Table 3

Incidence rates of RSV-associated SARI in HIV-infected and HIV-uninfected individuals aged ≥18 years per 100 000 population and relative-risk of hospitalisation with RSV-associated SARI by year and HIV status, Chris Hani Baragwanath Academic Hospital Gauteng Province.

Year	Age in years	Number of RSV cases adjusted for non enrolment	HIV prevalence in cases	Incidence rate[a] (95% CI[b]) Total population	HIV prevalence in population	Incidence rate (95% CI[b]) HIV-infected	Incidence rate (95% CI[b]) HIV-uninfected	Relative risk HIV-infected vs HIV-uninfected (95% CI[b])
2010	18– 44	190	87%		26%	106 (90–124)	6 (4–8)	19 (12–30)
	45–64	58	68%		13%	141 (100–193)	9 (6–15)	15 (8–28)
	≥65	16	21%		1%	390 (80–1134)	19 (10–33)	21 (4–78)
	Total Incidence			30 (26–34)				
	Age adjusted							18 (13–24)
2011	18–44	116	82%		26%	60 (48–74)	5 (3–7)	12 (8–22)
	45–64	61	62%		13%	137 (97–188)	12 (7–18)	11 (6–20)
	≥65	16	9%		1%	102 (25–569)	21 (11–35)	5 (0.2–32)
	Total Incidence			22 (19–25)				
	Age adjusted							12 (8–16)
2012	25–44	170	84%		26%	90 (76–106)	6 (4–9)	15 (10–34)
	45–64	90	65%		13%	198 (151–256)	16 (11–23)	12 (8–20)
	≥65	20	26%		1%	482 (156–1124)	19 (11–33)	25 (7–73)
	Total Incidence			30 (27–34)				
	Age adjusted							14 (11–19)

[a] Incidence rate/100 000 population.

[b] 95% confidence interval.