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RESEARCH ARTICLE

Mortality in children aged <5 years with severe acute respiratory illness in a high HIV-prevalence urban and rural areas of South Africa, 2009–2013

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Abstract

Background

Severe acute respiratory illness (SARI) is an important cause of mortality in young children, especially in children living with HIV infection. Disparities in SARI death in children aged <5 years exist in urban and rural areas.

Objective

To compare the factors associated with in-hospital death among children aged <5 years hospitalized with SARI in an urban vs. a rural setting in South Africa from 2009–2013.

Methods

Data were collected from hospitalized children with SARI in one urban and two rural sentinel surveillance hospitals. Nasopharyngeal aspirates were tested for ten respiratory viruses

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and blood for pneumococcal DNA using polymerase chain reaction. We used multivariable logistic regression to identify patient and clinical characteristics associated with in-hospital death.

Results

From 2009 through 2013, 5,297 children aged <5 years with SARI-associated hospital admission were enrolled; 3,811 (72%) in the urban and 1,486 (28%) in the rural hospitals. In-hospital case-fatality proportion (CFP) was higher in the rural hospitals (6.9%) than the urban hospital (1.3%, p<0.001), and among HIV-infected than the HIV-uninfected children (9.6% vs. 1.6%, p<0.001). In the urban hospital, HIV infection (odds ratio (OR):11.4, 95% confidence interval (CI):5.4–24.1) and presence of any other underlying illness (OR: 3.0, 95% CI: 1.0–9.2) were the only factors independently associated with death. In the rural hospitals, HIV infection (OR: 4.1, 95% CI: 2.3–7.1) and age <1 year (OR: 3.7, 95% CI: 1.9–7.2) were independently associated with death, whereas duration of hospitalization ≥5 days (OR: 0.5, 95% CI: 0.3–0.8) and any respiratory virus detection (OR: 0.4, 95% CI: 0.3–0.8) were negatively associated with death.

Conclusion

We found that the case-fatality proportion was substantially higher among children admitted to rural hospitals and HIV infected children with SARI in South Africa. While efforts to prevent and treat HIV infections in children may reduce SARI deaths, further efforts to address health care inequality in rural populations are needed.

Introduction

Pneumonia is a leading cause of death in children <5 years of age globally, accounting for over 900,000 deaths annually and largely occurring in low- and middle-income countries (LMICs) [1]. Sub-Saharan Africa (SSA) is disproportionately affected, accounting for more than half of pneumonia deaths globally [1].

In South Africa, pneumonia and influenza together comprised the second leading cause of death in children aged <5 years in 2013, and was responsible for about 10% of deaths in this age group [2]. Reducing mortality in children aged <5 years to 25 per 1,000 live births is a target of the Sustainable Development Goal (SDG) [3]; however, reducing the burden of severe acute respiratory illness (SARI) remains a major challenge in Africa [1]. Possible approaches include improved access to vaccines such as pneumococcal conjugate vaccine (PCV), *Haemophilus influenzae* type b vaccine, reduction in HIV-mother to child transmission (MTCT), integrated management of childhood illness (IMCI), indoor air pollution reduction, and improved hospital care [4]. Despite improvements in patient survival and advances in the development of new antimicrobials and vaccines, pneumonia is still associated with high morbidity and mortality burden in children especially those living with HIV [5]. Previous analysis of surveillance data from South Africa and other LMICs suggested that SARI mortality is higher in rural compared to urban settings [6–9], possibly due to differences in access to public health services and facilities [10,11], underlying HIV prevalence and health conditions. Studies have shown that rural residents are more likely to travel more than 15 minutes to reach their health facilities compared with urban residents (62% vs. 24%, respectively) [11].

Studies on mortality among children aged <5 years hospitalized with SARI have been conducted in South Africa, but none have examined the differences in risk factors for SARI-related in-hospital death in urban and rural areas with high HIV prevalence [6,12]. We aimed to compare the in-hospital case fatality proportion and factors associated with in-hospital mortality among children aged <5 years hospitalized with SARI in a rural vs. an urban area with high HIV prevalence in South Africa from 2009 to 2013.

Materials and methods

Health care system in South Africa

In South Africa, there are four levels of the health care referral system. Level one is comprised of three steps: primary health care clinic (first step), community health care centre (second step), and district hospitals (third step). The regional hospital is the second level. Regional hospitals receive referrals and provide specialist treatment to district hospitals. The provincial tertiary hospital is the third level while the national central hospitals serve as the fourth level of referral [13,14].

Study setting

We used SARI programme data from February 2009 through December 2013. Since 2009, the active, hospital-based SARI programme has been ongoing in three of South Africa's nine provinces. For the present study, we limited our analysis to children aged <5 years enrolled in three of the four participating hospitals: one urban hospital (Chris Hani-Baragwanath Academic Hospital [CHBAH]) in Gauteng Province, and two rural hospitals (Matikwana and Mapulaneng Hospitals) in Mpumalanga Province. The fourth hospital was excluded because of its location in a peri-urban area and to allow direct comparison between the rural and urban settings.

CHBAH is a level 2 regional hospital with approximately 3200 beds, including 408 paediatric beds and approximately 32 paediatric and neonatal intensive care unit (ICU) beds. Mapulaneng Hospital is also a regional hospital with 297 beds and 3 ICU beds; none are specifically dedicated to paediatric admissions. Matikwana Hospital is a level 1 district hospital with 178 beds and no paediatric ICU beds [15]. Children admitted to Matikwana Hospital that require ICU facilities are referred to the provincial tertiary hospitals once the Mapulaneng Hospital ICU beds are fully occupied.

Case definition

A case of SARI was defined as a hospitalized child aged <5 years with illness onset within 7 days of hospitalization meeting age-specific inclusion criteria as follows: children aged two days to ≤ 3 months with a physician's diagnosis of acute lower respiratory tract infection (ALRTI) or sepsis, children aged 3 months to < 5 years with a physician's diagnosis of ALRTI (which included pneumonia, bronchitis, pleural effusion and bronchiolitis). For the main analysis we excluded children admitted to the urban hospital short-stay ward for less than 48 hours because the two rural hospitals did not have a comparable short stay wards. Patients admitted to the short-stay ward are usually less severe than those admitted to the medical wards, potentially introducing biases if included in the main analysis.

Study procedures

The SARI programme methods have been published previously [16]. Briefly, hospitalized individuals residing in the hospital's catchment area admitted between Mondays through Friday

during the study period were screened for enrolment. Beginning in January 2013, enrolment was limited to only two days per week at CHBAH to conserve resources. The number of hospitalized children meeting the study case definition was documented throughout the surveillance period. From enrolled children, data on socio-demographic factors, clinical presentation, and underlying conditions were obtained through hospital record review and structured interviews were conducted by trained research staff within two days of admission. Beginning in 2012, child weight, height and mid upper arm circumference were collected to assess malnutrition. Based on the WHO weight-for-age z-score, we considered children with a z-score $<$ -2 standard deviation as underweight [17].

Laboratory methods

Whole blood and nasopharyngeal aspirates (NPA) specimens were collected from enrolled children and transported to the National Institute for Communicable Diseases (NICD) within 72 hours of collection. Multiplex real-time reverse-transcription PCR (RT-PCR) assays were used to test the NPAs for 10 respiratory viruses (influenza A and B viruses, adenovirus, parainfluenza virus 1, 2 and 3, enterovirus, respiratory syncytial virus (RSV), human metapneumovirus and rhinovirus) [18]. Blood was tested for *S.pneumoniae* using a single-target (*lytA*) quantitative real-time-PCR assay. If clinician initiated, HIV testing was performed according to the standard protocol [19]. Otherwise, dried blood spot specimens were tested by PCR for children aged $<$18 months and by ELISA for children aged $\geq$18 months. Clinician-requested CD4+ T-lymphocyte counts were determined by flow cytometry [20]. During 2009–2011, tuberculosis testing used sputum smear microscopy and culture. In 2011, GeneXpert was introduced for the diagnosis of pulmonary tuberculosis as part of the national tuberculosis programme [21].

Statistical analysis

Race was defined as blacks vs. others, others being white, mixed race or Asian. Type of housing was categorized as brick, iron sheeting and others (mud, thatched); 2 or more doses of pneumococcal vaccine was labelled as "Yes" or "No" based on the number of doses of pneumococcal vaccine received. Yes "2 or more doses" while No "$<$2 doses". We defined any other underlying illness as any of chronic lung disease, asthma, renal disease, heart disease, neurological disease and diabetes. The outcome of interest was in-hospital death which we interpreted as death during hospital admission vs. those that did not die during hospital admission.

Univariate analyses. Characteristics between children admitted at the urban and rural hospitals were compared using the Pearson's Chi squared test. The comparison of children hospitalized at the urban and rural hospitals was repeated to include children admitted to the short stay-ward as a sensitivity analysis. Characteristics between HIV-infected and HIV-uninfected children were compared using chi squared test and univariate logistic regression analysis. We analysed the difference in percentage of HIV infected children by receipt of antiretroviral therapy (ART) by hospital site and year using Pearson Chi squared test. HIV-infected children were categorized into two immunosuppression categories: (i) mild immunosuppression (CD4+ T-lymphocytes $\geq$200/mm^3 or equivalent age-appropriate CD4+ percentage for children aged $<$5 years), or (ii) severe immunosuppression (CD4+ T-lymphocytes $<$200/mm^3 or equivalent age-appropriate CD4+ percentage for children aged $<$5 years) [22].

Multivariable analyses. We assessed factors associated with in-hospital death using multivariable logistic regression models, starting with all variables that were significant at $p<0.1$ on univariable analysis and dropping non-significant factors with stepwise backward selection. All pairwise interactions of factors significant at the final multivariable additive model were

evaluated. Two-sided p-values <0.05 were considered significant. For each univariable analysis, we used all available case information. In the multivariable model, patients with missing data for included variables were dropped from the model.

To compare the characteristics of children who died at the urban hospital with those who died at the rural hospitals, we used a multivariable logistic regression model restricted to children that died. Similar to the in-hospital death analysis, factors significant in univariate analysis were included in the model. For all logistic regression analyses, tuberculosis infection, pneumococcus *lytA* PCR results on blood and malnutrition were evaluated only on univariate analysis due to the elevated number of missing data.

Survival analysis. Survival estimates were compared between those who died, looking at the interval from symptom onset to hospitalization, and date of hospitalization to date of death in the rural and urban hospitals using the Kaplan-Meier survival estimates with a log-rank test for equality of survival function. All analyses were performed using Stata version 14 (StataCorp Limited, College Station, Texas, United States of America).

Ethical consideration. The study was approved by the University of the Witwatersrand Human Research Ethics Committee (Medical) in December 2015 (Reference number: M151030). The protocol for SARI surveillance was approved by Ethics committee of University of the Witwatersrand. Annual recertification was obtained from the Ethics committee (Reference number: M140824). This surveillance was deemed non-research by the US Centers for Disease Control and Prevention (non-research determination number: 2012–6197). Written informed consent was obtained from parents, primary care givers or legal guardians of the children before enrolment.

Results

From February 2009 through December 2013, 14,901 patients were enrolled into the SARI surveillance program in urban and rural hospitals. Of these, 8069 children who met SARI criteria were screened for enrolment; 6583/8069 (81.6%) were enrolled in the urban hospital and 1486/8069 (18.4%) in the rural hospitals. We excluded 2772 (42.1%) children admitted in the short stay ward of the urban hospital. A total of 5297 children were included in the main analysis, including 3811 (71.9%) from the urban hospital and 1486 (28.1%) from the rural hospitals (Fig 1). The characteristics of children admitted to the rural hospitals individually are shown in S1 Table.

Characteristics of children hospitalized in the urban and rural hospitals

Demographic characteristics and clinical presentation. The urban hospital had a higher proportion of children hospitalized with SARI aged <1 year compared to the rural hospitals (74.9% vs. 58.8%, p<0.001) (Table 1). The majority of children were male (57.3%) and black race (98.2% in urban hospital vs. 99.5% in rural hospitals). The overall case-fatality proportion (CFP) was 2.9% and differed significantly by hospital; 103 (6.9%) children died in the rural hospitals compared with 51 (1.3%) in the urban hospitals (p<0.001). Differences in treatment were also observed with 53.7% receiving supplemental oxygen therapy in the urban hospital compared with 21.2% in the rural hospitals. Among children with pneumococcal vaccination data available, 1032/1386 (74.5%) at the urban hospital had received 2 or more doses of pneumococcal vaccine compared to 551/855 (64.4%) at the rural hospitals (p<0.001) (Table 1). A total of 1914 (36.1%) of the children were <14 weeks of age and were not eligible to receive 2 or more doses of pneumococcal vaccine. On sensitivity analysis, including all children admitted to the short stay ward at CHBAH, the case-fatality proportion was 0.8% (54/6583) at the urban hospital vs. 6.9% (103/1486) at the rural hospitals (p<0.001) (S2 Table).

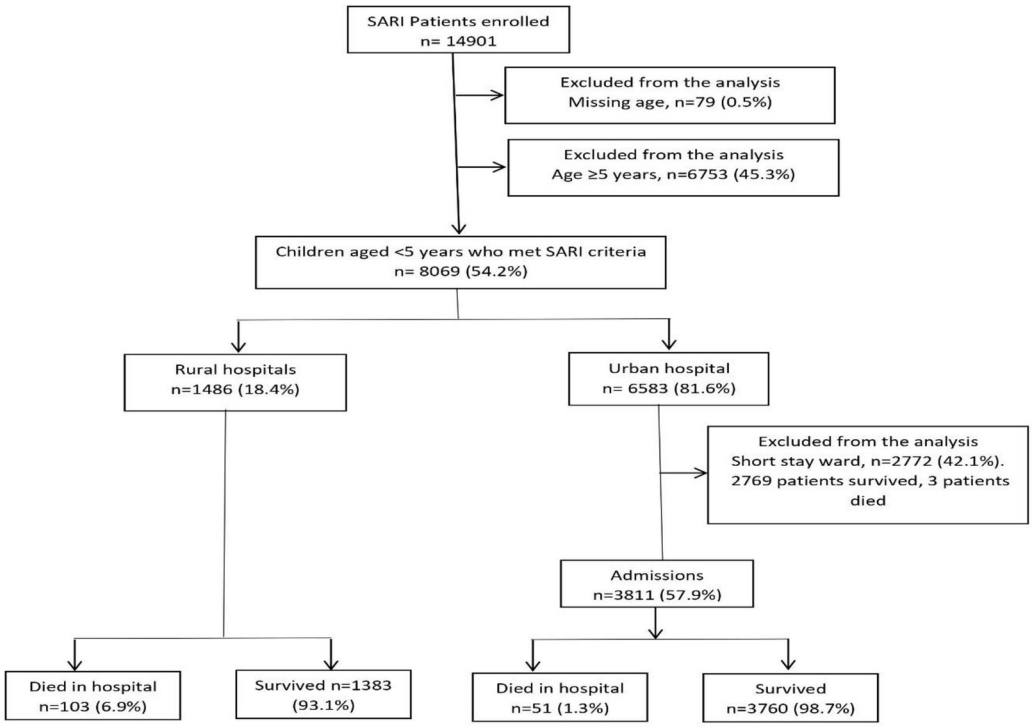


Fig 1. Flow chart of children enrolled in the South African severe acute respiratory illness (SARI) surveillance program at urban and rural hospitals in South Africa, 2009 to 2013.

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Underlying medical conditions. Information on HIV infection status was available for 2493 (65.4%) and 1126 (75.8%) of children from the urban and rural hospitals, respectively. Overall, 13.5% of children were HIV-infected and HIV infection was significantly higher among children admitted in the rural hospitals (20.7%) compared with the urban hospital (10.3%, p<0.001) (Table 1). A similar percentage of children were diagnosed with tuberculosis at the urban hospital compared to the rural hospitals (85/815 (10.4%) vs. 7/123 (5.7%), p = 0.100). A similar percent of children were reported as malnourished at the urban and rural site (26/3806 (0.7%) vs. 7/1482 (0.5%), p = 0.382). We were able to assess malnutrition for 1235/1795 (68.8%) of individuals enrolled during 2012–2013 using the z-score, among which 24.9% were underweight. A significantly higher proportion of children were underweight at the urban site as compared to the rural site (26.9% vs. 21.6%, p = 0.035) (Table 1).

Respiratory pathogens. A total of 5135 (96.9%) children were tested for respiratory viruses but, there was no significant difference between urban and rural hospitals for infection with any respiratory virus (77.6% in urban versus 75.9% in rural sites, p = 0.189). Overall, 2803 (52.9%) of children were tested for pneumococcal *lytA* in blood of which a significantly higher proportion tested positive at the urban site compared to the rural site (113/1592 (7.1%) vs. 53/1211 (4.4%), p = 0.002) (Table 1).

HIV infection

Overall, 13.5% of children were HIV-infected (Table 1). Compared with HIV-uninfected children hospitalized for SARI, HIV-infected children were more likely to present for admission ≥2 days of symptom onset (odds ratio [OR]: 1.31; 95% confidence interval [95% CI]: 1.08–1.59, p = 0.006), to be admitted for ≥5 days (OR: 2.40, 95% CI: 1.95–2.95, p<0.001) and die in

Table 1. Comparison of the demographic characteristics, clinical presentation and respiratory pathogens detected among children aged <5 years hospitalized with SARI at urban and rural hospitals, South Africa 2009–2013.

Characteristics		Total	Urban hospital	Rural hospitals	P value
		N = 5297 (%)	N = 3811 (%)	N = 1486 (%)	
Socio-demographics					
Age group (years)	< 1	3729 (70.4)	2855 (74.9)	874 (58.8)	<**0.001**
	1–4	1568 (29.6)	956 (25.1)	612 (41.2)	
Sex	Female	2260 (42.7)	1619 (42.5)	641 (43.1)	0.666
	Male	3037 (57.3)	2192 (57.5)	845 (56.9)	
Race	Black	5203 (98.2)	3724 (97.7)	1479 (99.5)	<**0.001**
	Other	94 (1.8)	87 (2.3)	7 (0.5)	
2 or more doses of pneumococcal vaccine	Yes	1583 (70.6)	1032 (74.5)	551 (64.4)	<**0.001**
	No	658 (29.4)	354 (25.5)	304 (35.6)	
Type of housing	Bricks	4099 (77.4)	2680 (70.3)	1419 (95.5)	<**0.001**
	Iron sheeting	1086 (20.5)	1079 (28.3)	7 (0.5)	
	Others	112 (2.1)	52 (1.4)	60 (4.0)	
Number of people sleeping in a room	>2	4961 (94.8)	3511 (93.2)	1450 (99.0)	<**0.001**
	≤2	271 (5.2)	256 (6.8)	15 (1.0)	
Clinical presentation and course					
Symptoms prior to admission (days)	≥2	2885 (54.9)	2217 (58.6)	668 (45.3)	<**0.001**
	<2	2373 (45.1)	1567 (41.4)	806 (54.7)	
Antibiotics prescribed on admission	Yes	4915 (95.1)	3446 (93.5)	1469 (99.3)	<**0.001**
	No	251 (4.9)	241 (6.5)	10 (0.7)	
Supplementary oxygen therapy	Yes	2337 (44.5)	2025 (53.7)	312 (21.2)	<**0.001**
	No	2909 (55.5)	1747 (46.3)	1162 (78.8)	
Duration of hospitalization (days)	<5	2522 (48.2)	1800 (47.8)	722 (49.2)	0.336
	≥5	2712 (51.8)	1968 (52.2)	744 (50.8)	
In-hospital death	Yes	154 (2.9)	51 (1.3)	103 (6.9)	<**0.001**
	No	5143 (97.1)	3760 (98.7)	1383 (93.1)	
Co-infections and underlying medical conditions					
HIV status	Positive	490 (13.5)	257 (10.3)	233 (20.7)	<**0.001**
	Negative	3129 (86.5)	2236 (89.7)	893 (79.3)	
Tuberculosis infection	Yes	92 (9.8)	85 (10.4)	7 (5.7)	0.100
	No	846 (90.2)	730 (89.6)	116 (94.3)	
Malnutrition (reported)	Yes	33 (0.6)	26 (0.7)	7 (0.5)	0.382
	No	5255 (99.4)	3780 (99.3)	1475 (99.5)	
Malnutrition (Underweight)	Yes	308 (24.9)	209 (26.9)	99 (21.6)	**0.035**
	No	927 (75.1)	567 (73.1)	360 (78.4)	
*Any other underlying illness	Yes	256 (4.8)	195 (5.1)	61 (4.1)	0.126
	No	5033 (95.2)	3612 (94.9)	1421 (95.9)	
Respiratory pathogens					
Any respiratory virus	Yes	3960 (77.1)	2878 (77.6)	1082 (75.9)	0.189
	No	1175 (22.9)	831 (22.4)	344 (24.1)	
Pneumococcal infection on lytA PCR	Yes	166 (5.9)	113 (7.1)	53 (4.4)	**0.002**

(*Continued*)

Table 1. (Continued)

Characteristics		Total	Urban hospital	Rural hospitals	P value
		N = 5297 (%)	**N = 3811 (%)**	**N = 1486 (%)**	
	No	2637 (94.1)	1479 (92.9)	1158 (95.6)	

• Column percentage were calculated as a percent of all those with available data for the variables (i.e. not including missing).

• Variables statistically significant at p< 0.05 presented in boldface.

• *Any other underlying illness (any of chronic lung disease, asthma, renal disease, heart disease, neurological disease, diabetes).

• Missing values for covariates were as follows: 2 or more doses of pneumococcal vaccine (n = 3056), Number of people sleeping in a room (n = 65), Symptoms prior to admission (days) (n = 39), Antibiotics prescribed on admission (n = 131), Supplementary oxygen therapy (n = 51), Duration of hospitalization (days) (n = 63), HIV (n = 1678), Tuberculosis infection (n = 4359), Malnutrition (reported) (n = 9), Malnutrition (Underweight) (n = 4062), Any other underlying illness (n = 8), Any respiratory virus (n = 162), Pneumococcal infection on lytA PCR (n = 2494).

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the hospital (OR: 6.67, 95% CI: 4.42–10.07, P<0.001) (Table 2). Infection with tuberculosis was not different by rural vs. urban (Table 1), and not different by HIV status in rural hospitals, but significantly different by HIV status in the urban hospital (S3 Table).

HIV-infected children and highly active antiretroviral therapy (HAART). The HIV prevalence amongst hospitalized children decreased over the surveillance period from 19% in 2009 to 8% in 2013; however, the prevalence was consistently higher at the rural site compared to the urban site (Table 3). On sensitivity analysis, assuming that all the children with missing data on HIV status were HIV-uninfected, the prevalence of HIV amongst hospitalized children with SARI also decreased over the study period at both sites and was consistently higher at the rural site compared to the urban site (S4 Table). The percentage of HIV-infected children receiving antiretrovirals increased over the study period and was higher in the urban site initially. Only 129 (26.3%) HIV-infected children had available CD4+ T-lymphocyte data, of whom 83 (75.5%) in the urban and 9 (47.4%) in the rural hospitals had severe immunosuppression (CD4+ T-lymphocytes <200/mm3 or equivalent age-appropriate CD4+ percentage for children aged <5 years) (Table 3).

Factors associated with in-hospital death

In the urban hospital, HIV infection (odds ratio (OR):11.4, 95% confidence interval (CI):5.4–24.1) and presence of any other underlying illness (OR: 3.0, 95% CI: 1.0–9.2) were the only factors independently associated with death. In the rural hospitals, HIV infection (OR: 4.1, 95% CI: 2.3–7.1) and age <1 year (OR: 3.7, 95% CI: 1.9–7.2) were independently associated with death, whereas duration of hospitalization ≥5 days (OR: 0.5, 95% CI: 0.3–0.8) and any respiratory virus detection (OR: 0.4, 95% CI: 0.3–0.8) were negatively associated with death (Table 4).

Comparison of children who died at the rural hospitals vs. the urban hospital

In our comparison of urban and rural hospitals among children who died in-hospital, we found that children at the rural hospitals were more frequently of black race (99% vs. 88% in urban hospital, p = 0.002) and had antibiotics prescribed on admission (98% compared with 90% in the urban hospital, p = 0.025). We further found that children who died during hospitalization in the rural hospital (60%) were hospitalized for < 5 days compared to children from the urban hospital (41%), p = 0.029 (Table 5).

Survival estimates among children who died in the rural and urban sites

Among children that died, the median duration of reported onset of symptoms to hospital admission was similar in the urban and rural hospitals (Fig 2A). The interval from date of

Table 2. Demographics and clinical characteristics of HIV-infected and HIV-uninfected children aged <5 years hospitalized with SARI at urban and rural hospitals, South Africa 2009–2013.

Characteristics		Total	HIV-infected	HIV-uninfected	Univariate analysis	P value
		N = 3619 (%)	N = 490 (%)	N = 3129 (%)	OR (95% CI)	
Socio-demographics						
Hospital	Urban	2493 (68.9)	257 (52.4)	2236 (71.5)	Reference	**<0.001**
	Rural	1126 (31.1)	233 (47.6)	893 (28.5)	2.27 (1.87–2.75)	
Age group (years)	<1	2536 (70.1)	313 (63.9)	2223 (71.0)	0.72 (0.59–0.88)	**0.001**
	1–4	1083 (29.9)	177 (36.1)	906 (29.0)	Reference	
Sex	Male	2087 (57.7)	248 (50.6)	1839 (58.8)	Reference	**0.001**
	Female	1532 (42.3)	242 (49.4)	1290 (41.2)	1.39 (1.14–1.68)	
Black	Others	57 (1.6)	8 (1.6)	29 (1.6)	Reference	0.912
	Black	3562 (98.4)	482 (98.4)	3080 (98.4)	0.96 (0.45–2.04)	
2 or more doses of pneumococcal vaccine	No	475 (29.2)	79 (35.6)	396 (28.1)	Reference	**0.023**
	Yes	1154 (70.8)	143 (64.4)	1011 (71.9)	0.71 (0.53–0.96)	
Number of people sleeping in a room	≤2	191 (5.3)	22 (4.5)	169 (5.5)	Reference	0.387
	>2	3381 (94.7)	464 (95.5)	2917 (94.5)	1.22 (0.78–1.93)	
Clinical presentation and course						
Symptoms prior to admission (days)	<2	1627 (45.2)	192 (39.5)	1435 (46.1)	Reference	**0.006**
	≥2	1969 (54.8)	294 (60.5)	1675 (53.9)	1.31 (1.08–1.59)	
Antibiotics prescribed on admission	No	158 (4.5)	11 (2.3)	147 (4.8)	Reference	**0.012**
	Yes	3379 (95.5)	471 (97.7)	2908 (95.2)	2.16 (1.16–4.02)	
Supplementary oxygen therapy	No	2024 (56.4)	255 (52.7)	1769 (57.0)	Reference	0.078
	Yes	1566 (43.6)	229 (47.3)	1337 (43.0)	1.19 (0.98–1.44)	
Duration of hospitalization (days)	<5	1690 (47.2)	142 (29.4)	1548 (49.9)	1.00 (Reference)	**<0.001**
	≥5	1893 (52.8)	341 (70.6)	1552 (50.1)	2.40 (1.95–2.95)	
In-hospital death	No	3523 (97.3)	443 (90.4)	3080 (98.4)	Reference	**<0.001**
	Yes	96 (2.7)	47 (9.6)	49 (1.6)	6.67 (4.42–10.07)	
Co-infections and underlying medical conditions						
Tuberculosis infection	No	624 (89.8)	95 (81.9)	529 (91.4)	Reference	**0.002**
	Yes	71 (10.2)	21 (18.1)	50 (8.6)	2.34 (1.34–4.07)	
Malnutrition (reported)	No	3595 (99.4)	482 (98.6)	3113 (99.6)	Reference	**0.005**
	Yes	20 (0.6)	7 (1.4)	13 (0.4)	3.48 (1.38–8.76)	
Malnutrition (Underweight)	No	639 (75.2)	45 (54.9)	594 (77.3)	Reference	**<0.001**
	Yes	211 (24.8)	37 (45.1)	174 (22.7)	2.81 (1.76–4.48)	
*Any other underlying illness	No	3441 (95.2)	462 (94.5)	2979 (95.3)	Reference	0.450
	Yes	175 (4.8)	27 (5.5)	148 (4.7)	1.18 (0.77–1.79)	
Respiratory pathogens						
Any respiratory virus	No	791 (22.1)	157 (32.4)	634 (20.5)	Reference	**<0.001**
	Yes	2792 (77.9)	328 (67.6)	2464 (79.5)	0.54 (0.44–0.66)	
Pneumococcal infection on lytA PCR	No	2257 (94.2)	322 (90.2)	1935 (94.9)	Reference	**<0.001**
	Yes	139/2396 (5.8)	35/357 (9.8)	104/2039 (5.1)	2.02 (1.35–3.02)	

• Column percentage were calculated as a percent of all those with available data for the variables (i.e. not including missing).

• Variables statistically significant at $p < 0.05$ presented in boldface. ORs unadjusted.

• *Any other underlying illness (any of chronic lung disease, asthma, renal disease, heart disease, neurological disease, diabetes).

• Missing values for covariates were as follows: 2 or more doses of pneumococcal vaccine (n = 1990), Number of people sleeping in a room (n = 47), Symptoms prior to admission (days) (n = 23), Antibiotics prescribed on admission (n = 82), Supplementary oxygen therapy (n = 29), Duration of hospitalization (days) (n = 36), Tuberculosis infection (n = 2924), Malnutrition (reported) (n = 4), Malnutrition (Underweight) (n = 2769), Any other underlying illness (n = 3), Any respiratory virus (n = 36), Pneumococcal infection on lytA PCR (n = 1223).

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Table 3. Percentage of children that are HIV-infected, those receiving ARV and those having low CD4 count by year among children aged <5 years hospitalized with SARI at urban and rural hospitals, South Africa 2009–2013.

	HIV-infected children				HIV-infected children on ARV			Low CD4 count		
Year	Total	Urban site N = 3811	Rural site N = 1486	P value	Urban site N = 257	Rural site N = 233	P value	Urban site N = 110	Rural site N = 19	P value
		n/N (%)	n/N (%)		n/N (%)	n/N (%)		n/N (%)	n/N (%)	
2009	155/821 (19)	102/655 (16)	53/166 (32)	<0.001	34/78 (44)	5/26 (19)	0.001	31/40 (78)	1/1 (100)	0.162*
2010	135/765 (18)	62/503 (12)	73/262 (28)		16/37 (43)	9/28 (32)		20/26 (77)	2/4 (50)	
2011	72/733 (10)	37/513 (7)	35/220 (16)		7/23 (30)	7/13 (54)		9/15 (60)	0/2 (0)	
2012	90/818 (11)	44/559 (8)	46/259 (18)		13/26 (50)	13/23 (57)		16/20 (80)	4/7 (57)	
2013	38/482 (8)	12/263 (5)	26/219 (12)		5/8 (63)	10/18 (56)		7/9 (78)	2/5 (40)	
Overall	490/3619 (14)	257/2493 (10)	233/1126 (21)		75/172 (44)	44/108 (41)		83/110 (75)	9/19 (47)	
Missing data	1678	1318	360		85	125		62	89	

*Fisher's exact test.

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hospitalization to death amongst those that died was shorter in the rural site (median 3 days (IQR 2–7)) compared to the urban site (median 5 days (IQR 3–11), p = 0.013) (Fig 2B).

Discussion

We found that there was a substantially higher in-hospital mortality among children with SARI at the rural hospitals (6.9%) compared to the urban hospital (1.3%) in South Africa. HIV-infection was higher in the rural hospitals than the urban hospital, death was more common in HIV-infected children and correspondingly death was higher in the rural hospitals. HIV infection and presence of underlying illness were the factors associated with death. At the rural site, we found that HIV and younger age were independently associated with increased odds of death while individuals hospitalized for ≥ 5 days or with any respiratory virus detected were less likely to die. Survival function in terms of hospitalization to death amongst those who died was shorter at the rural site compared to the urban site.

While the 2.9% overall CFP reported in our study was higher than 1.7% reported in a case-series study among hospitalized children aged <5 years with SARI from 8 countries in Africa, the CFP estimate of our urban hospital is consistent [23]. Findings from the national demographic surveillance system in China and Bangladesh also recorded mortality that was 4.9 and 1.4 fold higher, **respectively**, in rural area compared to urban areas [24,25].

The difference in risk factors between urban and rural hospitals could be due to lower power to detect a significant difference for some factors in the urban area because of fewer deaths recorded. Higher mortality among children in rural hospitals could be due to several factors, including differences in standards of living, availability of or access to public health facilities and services [26]. Children in rural areas possibly present with more severe illness due to delayed hospitalization related to remoteness of rural villages and quality of in-hospital care [11,27]. In addition, it is possible that patients have earlier access to high-quality care even before admission, in the urban site, so reducing the impact of these factors on outcome [28]. However, delay in presentation to the hospital as a contributor to higher mortality in the rural site was not supported by the data because patients from the rural site reported a similar interval between symptom onset and hospitalization, but a shorter interval from hospitalization to

Table 4. Factors associated with in-hospital death among children aged <5 years hospitalized with SARI at urban and rural hospitals, South Africa 2009–2013.

	Urban hospital				Rural hospitals			
Characteristics	**Hospitalized case fatality proportion (%)**	**Univariate analysis OR (95%CI)**	**Multivariable analysis OR (95% CI)**	**P value**	**Hospitalized case fatality proportion (%)**	**Univariate analysis OR (95%CI)**	**Multivariable analysis OR (95% CI)**	**P value**
Age group (years)								
<1	42/2855 (1.5)	1.6 (0.8–3.2)			82/874 (9.4)	**2.9 (1.8–4.8)**	**3.7 (1.9–7.2)**	**<0.001**
1–4	9/956 (0.9)	Reference			21/612 (3.4)	Reference	Reference	
Sex								
Male	25/2192 (1.1)	Reference			43/845 (5.1)	Reference	NS	
Female	26/1619 (1.6)	1.4 (0.8–2.5)			60/641 (9.4)	**1.9 (1.3–2.9)**		
Race								
Other	6/87 (6.9)	Reference			1/7 (14.3)	Reference		
Black African	45/3724 (1.2)	**0.2 (0.1–0.4)**	NS		102/1479 (6.9)	0.4 (0.1–3.7)		
2 or more doses of pneumococcal vaccine								
No	7/354 (2.0)	Reference			26/304 (8.6)	Reference		
Yes	18/1032 (1.7)	0.9 (0.4–2.1)			31/551 (5.6)	0.6 (0.4–1.1)		
Number of people sleeping in a room								
≤ 2 people	4/256 (1.6)	Reference			1/15 (6.7)	Reference		
>2 people	46/3511 (1.3)	0.8 (0.3–2.3)			100/1450 (6.9)	1.0 (0.1–8.0)		
Clinical presentation and course								
Duration of symptoms prior to admission								
<2 days	17/1567 (1.1)	Reference			51/806 (6.3)	Reference		
≥2 days	33/2217 (1.5)	1.4 (0.8–2.5)			51/668 (7.6)	1.2 (0.8–1.8)		
Antibiotics prescribed on admission								
No	5/241 (2.1)	Reference			2/10 (20%)	Reference		
Yes	45/3446 (1.3)	0.6 (0.2–1.6)			101/1469 (6.9%)	0.3 (0.1–1.4)		
Supplemental oxygen therapy								
No	7/1747 (0.4)	Reference	Omitted		20/1162 (1.7)	Reference	Omitted	
Yes	43/2025 (2.1)	**5.4 (2.4–12.0)**			83/312 (26.6)	**20.7 (12.4–34.3)**		
Duration of hospitalization (days)								
<5	21/1800 (1.2)	Reference			61/722 (8.5)	Reference	Reference	**0.008**
≥5	30/1968 (1.5)	1.31 (0.7–2.3)			41/744 (5.5)	**0.6 (0.4–1.0)**	**0.5 (0.3–0.8)**	
Co-infection and underlying medical conditions								
HIV status								
Negative	13/2236 (0.6)	Reference	Reference	**<0.001**	36/893 (4.0)	Reference	Reference	**<0.001**
Positive	17/257 (6.6)	**12.1 (5.8–25.2)**	**11.4 (5.4–24.1)**		30/233 (12.9)	**3.5 (2.1–5.8)**	**4.1 (2.3–7.1)**	
Tuberculosis infection								
No	13/730 (1.8)	Reference			6/116 (5.2)	Reference	Omitted	
Yes	2/85 (2.4)	1.3 (0.3–6.0)			2/7 (28.6)	**7.3 (1.2–45.9)**		
Malnutrition (reported)								

(*Continued*)

Table 4. (Continued)

	Urban hospital				Rural hospitals			
Characteristics	**Hospitalized case fatality proportion (%)**	**Univariate analysis OR (95%CI)**	**Multivariable analysis OR (95% CI)**	**P value**	**Hospitalized case fatality proportion (%)**	**Univariate analysis OR (95%CI)**	**Multivariable analysis OR (95% CI)**	**P value**
No	49/3780 (1.3)	Reference	Omitted		99/1475 (6.7)	Reference	Omitted	
Yes	1/26 (3.9)	3.0 (0.4–22.9)			3/7 (42.9)	**10.4 (2.3–47.2)**		
Malnutrition (Underweight)								
No	2/567 (0.4)	Reference	Omitted		15/360 (4.2)	Reference	Omitted	
Yes	3/209 (1.4)	4.1 (0.7–24.8)			12/99 (12.1)	**3.2 (1.4–7.0)**		
*__Any other underlying illness__								
No	44/3612 (1.2)	Reference	Reference	**0.048**	94/1421 (6.6)	Reference	NS	
Yes	6/195 (3.1)	**2.6 (1.1–6.1)**	**3.04 (1.0–9.2)**		8/61 (13.1)	**2.1 (1.0–4.6)**		
Respiratory pathogens								
Any respiratory virus								
No	17/831 (2.1)	Reference	NS		35/344 (10.2)	Reference	Reference	**0.003**
Yes	33/2878 (1.2)	**0.6 (0.3–1.0)**			55/1082 (5.1)	**0.5 (0.3–0.7)**	**0.4 (0.3–0.8)**	
Pneumococcal infection on lytA PCR								
No	15/1479 (1.0)	Reference	Omitted		66/1158 (5.7)	Reference	Omitted	
Yes	1/113 (0.9)	0.9 (0.1–6.7)			8/53 (15.1)	**2.9 (1.3–6.5)**		

• Abbreviations: OR (Odds ratio), CI (Confidence interval), NS (Not significant).

• OR (95% CI) statistically significant at $p < 0.1$ on univariate and $p<0.05$ on multivariable logistic regression analysis presented in boldface.

• Tuberculosis infection, Malnutrition (reported, underweight), Pneumococcal infection on lytA PCR omitted from the multivariable logistic regression analysis due to lack of data.

• Use of supplementary oxygen therapy omitted due to collinearity with in-hospital death.

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death. Factors such as underlying medical conditions and quality of care delivered at each site could affect the CFP. However, there was no significant difference in the prevalence of other underlying conditions apart from HIV between the urban and rural hospitals, but in the urban hospital, other underlying illness was found to be associated with in-hospital death which is in keeping with studies that have shown that children with underlying chronic diseases are more likely to die in-hospital [29,30]. We were not able to assess quality of care in this study.

At both urban and rural hospitals, HIV was a risk factor for death. HIV-infected individuals had 11 times greater odds of in-hospital mortality than HIV-uninfected children in the urban hospital while in the rural hospitals HIV-infected individuals had 3 times greater odds of in-hospital mortality than HIV-uninfected children. This finding from our urban hospital was consistent with other studies carried out in South Africa, which estimated approximately 10 times elevated mortality risk in HIV-infected children and with global estimates [5,31]. Amongst those that died at the urban site, 57.7% were HIV-infected while at the rural area 45.5% were HIV-infected. There have been studies showing that reduction in SARI is associated with availability of ARV but despite these studies a high incidence of SARI is still reported in HIV-infected children on ARV [32–34].

While the HIV prevalence declined at both urban and rural hospitals over the study period, the prevalence at the rural hospitals was consistently twice that of the urban hospital (Table 3), reflecting the underlying community prevalence. Goga et al conducted an evaluation of community-specific HIV prevalence which showed a higher prevalence among infants and

Table 5. Factors associated with hospital site (rural vs. urban) among children aged <5 years hospitalized with SARI who died in hospital, South Africa, 2009–2013.

Characteristics		Total	Urban hospital	Rural hospitals	P value
		N = 154 (%)	N = 51 (%)	N = 103 (%)	
Socio-demographics					
Age group (years)	< 1	124 (80.5)	42 (82.4)	82 (79.6)	0.686
	1–4	30 (19.5)	9 (17.6)	21 (20.4)	
Sex	Female	86 (55.8)	26 (51.0)	60 (58.3)	0.392
	Male	68 (44.2)	25 (49.0)	43 (41.7)	
Race	Black	147 (95.5)	45 (88.2)	102 (99.0)	**0.006***
	Other	7 (4.5)	6 (11.8)	1 (1.0)	
2 or more doses of pneumococcal vaccine	Yes	49 (59.8)	18 (72.0)	31 (54.4)	0.134
	No	33 (40.2)	7 (28.0)	26 (45.6)	
Type of housing	Bricks	132 (85.7)	35 (68.6)	97 (94.2)	**<0.001***
	Iron sheeting	14 (9.1)	14 (27.5)	0 (0.0)	
	Others	8 (5.2)	2 (3.9)	6 (5.8)	
Number of people sleeping in a room	>2	146 (96.7)	46 (92.0)	100 (99.0)	**0.041***
	≤2	5 (3.3)	4 (8.0)	1 (1.0)	
Clinical presentation and course					
Symptoms prior to admission (days)	≥2	84 (55.3)	33 (66.0)	51 (50.0)	0.062
	<2	68 (44.7)	17 (34.0)	51 (50.0)	
Antibiotics prescribed on admission	Yes	146 (95.4)	45 (90.0)	101 (98.1)	**0.025***
	No	7 (4.6)	5 (10.0)	2 (1.9)	
Supplementary oxygen therapy	Yes	126 (82.4)	43 (86.0)	83 (80.6)	0.410
	No	27 (17.6)	7 (14.0)	20 (19.4)	
Duration of hospitalization (days)	<5	82 (53.6)	21 (41.2)	61 (59.8)	**0.029**
	≥5	71 (46.4)	30 (58.8)	41 (40.2)	
Co-infections and underlying medical conditions					
HIV status	Positive	47 (49.0)	17 (56.7)	30 (45.5)	0.308
	Negative	49 (51.0)	13 (43.3)	36 (54.5)	
Tuberculosis infection	Yes	4 (17.4)	2 (13.3)	2 (25.0)	0.589*
	No	19 (82.6)	13 (86.7)	6 (75.0)	
Malnutrition (reported)	Yes	4 (2.6)	1 (2.0)	3 (2.9)	1.000*
	No	148 (97.4)	49 (98.0)	99 (97.1)	
Malnutrition (Underweight)	Yes	15 (46.9)	3 (60.0)	12 (44.4)	0.645*
	No	17 (53.1)	2 (40.0)	15 (55.6)	
*Any other underlying illness	Yes	14 (9.2)	6 (12.0)	8 (7.8)	0.405
	No	138 (90.8)	44 (88.0)	94 (92.2)	
Respiratory pathogens					
Any respiratory virus	Yes	88 (62.9)	33 (66.0)	55 (61.1)	0.566
	No	52 (37.1)	17 (34.0)	35 (38.9)	
Pneumococcal infection on lytA PCR	Yes	9 (10.0)	1 (6.2)	8 (10.8)	1.000*
	No	81 (90.0)	15 (93.8)	66 (89.2)	

• Column percentage were calculated as a percent of all those with available data for the variables (i.e. not including missing).

• Variables statistically significant at p< 0.05 presented in boldface, p value* (Fisher's exact test).

• *Any other underlying illness (any of chronic lung disease, asthma, renal disease, heart disease, neurological disease, diabetes).

• Missing values for covariates were as follows: 2 or more doses of pneumococcal vaccine (n = 72), Number of people sleeping in a room (n = 3), Symptoms prior to admission (days) (n = 2), Antibiotics prescribed on admission (n = 1), Supplementary oxygen therapy (n = 1), Duration of hospitalization (days) (n = 1), HIV (n = 58), Tuberculosis infection (n = 131), Malnutrition (reported) (n = 2), Malnutrition (Underweight) (n = 122), Any other underlying illness (n = 2), Any respiratory virus (n = 14), Pneumococcal infection on lytA PCR (n = 64).

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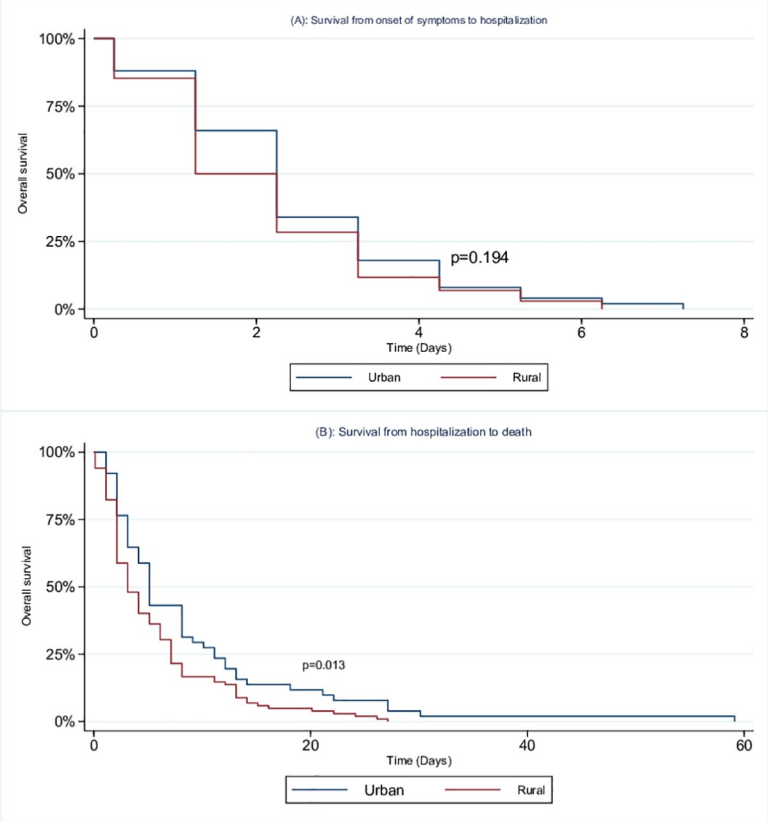


Fig 2. Kaplan-Meier survival estimates among children aged <5 years who died with SARI in urban and rural sites, South Africa, 2009 to 2013. (A) Survival from onset of symptoms to hospitalization (B) Survival from hospitalization to death.

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pregnant women, and higher rates of mother to child transmission in Mpumalanga Province (rural hospitals) (5.7%, 95% CI 4.1–7.3) compared to Gauteng Province (urban hospital) (2.5%, 95% CI 1.5–3.6) [35].

We demonstrated that in our rural hospitals children aged <1 year had a higher CFP compared to children aged 1–4 years. Several studies have found higher all-cause mortality in children aged <1 year mainly due to their immature immune system and vulnerability to infections [12,36–39]. We found that in our rural hospitals, children hospitalized for 5 or more days were less likely to die compared to those hospitalized for <5 days. A study carried out in a developing country also found that over 50% of death among children with pneumonia occurred within the first four days of hospitalization [40]. This finding is a contrasting finding compared to several other studies which show that there is higher probability of dying from a wide range of diseases including influenza, covid-19 and heart failure with a longer hospital stay [41–43]. Detection of a respiratory virus was significantly associated with lower mortality. A multi-country African similarly study found lower CFP in patients testing influenza positive [23], and further studies have associated bacterial aetiologies more commonly with death as these are often severe [44–46]. Similar to these studies, among children tested with pneumococcal lytA PCR, CFP was higher among those with versus those without pneumococcal infection (5% vs. 3%); however, this difference was not statistically significant.

Detection of pneumococcus by *lytA* PCR of a blood sample was low at both sites (7.1% in our rural site and 4.4% in our urban site), likely related to lower sensitivity of available

diagnostic assays for pneumococcal pneumonia, infection with pneumococcus was not evaluated in the multivariable model due to high number of missing data. However, studies from South Africa, India, global estimates, and systemic reviews have reported positive associations of pneumococcal infection with death in children with SARI [6,44,45,47]. In our study, vaccination with 2 or more doses of PCV was significantly higher in the urban site compared to the rural site. Despite advances in preventing SARI caused by *S. pneumoniae* with the introduction of PCV into the Expanded Program on Immunization (EPI) in 2009, pneumococcus remains a relatively common cause of death in children with SARI in South Africa.

Our study has limitations. First, cases from only three hospitals were used for this study; therefore, our findings might not be generalizable to other rural and urban hospitals. Second, our study enrolment could not account for children who died at home, or died too soon after presentation to be enrolled, which might lead to underestimation of mortality. Third, though our enrolment forms account for many common factors associated with in-hospital death, we were unable to collect data on some possible confounders, such as indoor air pollution, socio-economic status and type of feeding. Fourth, we were not able to assess the quality of care at each hospital including one rural hospital which is a district hospital. Lastly, malnutrition, CD4+ T-lymphocyte count, and ART use were inconsistently collected and could not be included in our model.

In conclusion, our study suggests a higher mortality in children hospitalized with SARI at two rural hospitals compared to an urban hospital. Without question, HIV remains a major risk factor for SARI mortality, and wider availability of MTCT services is needed to help reduce the disease burden. But further studies are urgently needed to identify the causal factors leading to an inherently higher risk of mortality in our rural hospitals, such as differences in treatment or access to care and health care inequality.

Supporting information

S1 Table. Comparison of the demographic characteristics, clinical presentation and respiratory pathogens detected among children aged <5 years hospitalized with SARI at rural hospitals (Mapulaneng and Matikwana), South Africa 2009–2013.
(DOCX)

S2 Table. Comparison of the demographic characteristics, clinical presentation and respiratory pathogens detected among children aged <5 years with SARI in urban and rural hospitals, South Africa 2009–2013. Sensitivity analysis including children admitted in the stay over ward.
(DOCX)

S3 Table. Demographics and clinical characteristics of HIV-infected and HIV-uninfected children aged <5 years hospitalized with SARI by hospital site, South Africa 2009–2013.
(DOCX)

S4 Table. Percentage of children HIV-infected by year compared with sensitivity analysis (assuming all those with missing data were HIV-uninfected) amongst children aged <5 years hospitalized with SARI in urban and rural hospital sites, South Africa, 2009–2013.
(DOCX)

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References

1. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet (London, England). 2016; 388(10063):3027–35. https://doi.org/10.1016/S0140-6736(16)31593-8 PMID: 27839855.
2. Statistics South Africa. Mortality and causes of death in South Africa, 2013: Findings from death notification. http://www.statssa.gov.za/publications/P03093/CoD_2013_presentation.pdf, last accessed 17 Aug 2020.
3. World Health Organization. Sustainable Development Goals 3: Ensure healthy lives and promote well-being for all at all ages. https://www.who.int/sdg/targets/en/. Last accessed 17 Aug 2020.
4. Lozano R, Wang H, Foreman KJ, Rajaratnam JK, Naghavi M, Marcus JR, et al. Progress towards Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. The Lancet. 2011; 378(9797):1139–65.

5. Gray DZH. Community-acquired pneumonia in HIV-infected children: a global perspective. Curr Opin Pulm Med. 2010; 16::208–16. https://doi.org/10.1097/MCP.0b013e3283387984 PMID: 20375782

6. Cohen C, Walaza S, Moyes J, Groome M, Tempia S, Pretorius M, et al. Epidemiology of Viral-associated Acute Lower Respiratory Tract Infection Among Children <5 Years of Age in a High HIV Prevalence Setting, South Africa, 2009–2012. The Pediatric Infectious Disease Journal. 2015; 34(1):66–72. https://doi.org/10.1097/INF.0000000000000478 PMC4276570. PMID: 25093972

7. Kang L, He C, Miao L, Liang J, Zhu J, Li X, et al. Geographic disparities in pneumonia-specific under-five mortality rates in Mainland China from 1996 to 2015: a population-based study. International Journal of Infectious Diseases. 2017; 59:7–13. https://doi.org/10.1016/j.ijid.2017.03.014 PMID: 28342801

8. Million Death Study Collaborators. Causes of neonatal and child mortality in India: a nationally representative mortality survey. The Lancet. 2010; 376(9755):1853–60. https://doi.org/10.1016/S0140-6736(10)61461-4 PMID: 21075444

9. Rodrigues FE, Tatto RB, Vauchinski L, Leães LM, Rodrigues MM, Rodrigues VB, et al. Pneumonia mortality in Brazilian children aged 4 years and younger. Jornal de pediatria. 2011; 87(2):111–4. https://doi.org/10.2223/JPED.2070 PMID: 21243180

10. Yaya S, Uthman OA, Okonofua F, Bishwajit G. Decomposing the rural-urban gap in the factors of under-five mortality in sub-Saharan Africa? Evidence from 35 countries. BMC Public Health. 2019; 19(1):616. https://doi.org/10.1186/s12889-019-6940-9 PMID: 31113395

11. Spasojevic N, Vasilj I, Hrabac B, Celik D. RURAL—URBAN DIFFERENCES IN HEALTH CARE QUALITY ASSESSMENT. Mater Sociomed. 2015; 27(6):409–11. https://doi.org/10.5455/msm.2015.27.409-411 PMID: 26937222.

12. Cohen C, Moyes J, Tempia S, Groome M, Walaza S, Pretorius M, et al. Mortality amongst Patients with Influenza-Associated Severe Acute Respiratory Illness, South Africa, 2009–2013. PLoS ONE. 2015; 10(3):e0118884. https://doi.org/10.1371/journal.pone.0118884 PMID: 25786103

13. Department of Health. Province of Kwazulu-Natal, Referral System: Levels of Health Care. http://www.kznhealth.gov.za/Referral-system.htm. Last accessed 17 Aug 2020.

14. Odufuwa OA. Referral of patients between Primary and Secondary levels of health care in the Port Elizabeth Metropole: Stellenbosch: Stellenbosch University; 2010. PMID: 22314909

15. Mpumalanga Department of Health. Report of the Integrated Support Team. http://section27.org.za/wp-content/uploads/2010/09/Mpumalanga.pdf. Last accessed 17 Aug 2020.

16. Cohen C, Moyes J, Tempia S, Groom M, Walaza S, Pretorius M, et al. Severe Influenza-associated Respiratory Infection in High HIV Prevalence Setting, South Africa, 2009–2011. Emerging Infectious Diseases. 2013; 19(11):1766–74. https://doi.org/10.3201/eid1911.130546 PMC3837669. PMID: 24209781

17. World Health Organization. Global Database on Child Growth and Malnutrition, https://www.who.int/nutgrowthdb/about/introduction/en/index4.html. Last accessed 17 Aug 2020.

18. Pretorius MA, Madhi SA, Cohen C, Naidoo D, Groome M, Moyes J, et al. Respiratory viral coinfections identified by a 10-plex real-time reverse-transcription polymerase chain reaction assay in patients hospitalized with severe acute respiratory illness—South Africa, 2009–2010. J Infect Dis. 2012; 206 Suppl 1:S159–65. Epub 2012/11/28. https://doi.org/10.1093/infdis/jis538 PMID: 23169964.

19. Singh E, Cohen C, Govender N, Meiring S. A description of HIV testing strategies at 21 laboratories in South Africa. Communicable Diseases Surveillance Bulletin. 2008; 6:16–7.

20. Glencross D, Scott LE, Jani IV, Barnett D, Janossy G. CD45-assisted PanLeucogating for accurate, cost-effective dual-platform CD4+ T-cell enumeration. Cytometry Part A. 2002; 50(2):69–77. https://doi.org/10.1002/cyto.10068 PMID: 12116348

21. Stevens W, editor GeneXpert implementation in South Africa public sector. One year later. . . lessons learnt. 4th annual GLI meeting/consultation of the SRL network/early implementers meeting on Xpert MTB/RIF roll out Veyrierdu-Lac, France: World Health Organization/Fondation Mérieux; 2012.

22. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Available at: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf. Last accessed April 2018. 2007.

23. McMorrow ML, Wemakoy EO, Tshilobo JK, Emukule GO, Mott JA, Njuguna H, et al. Severe acute respiratory illness deaths in sub-Saharan Africa and the role of influenza: a case series from 8 countries. The Journal of infectious diseases. 2015; 212(6):853–60. https://doi.org/10.1093/infdis/jiv100 PMID: 25712970

24. He C, Kang L, Miao L, Li Q, Liang J, Li X, et al. Pneumonia mortality among children under 5 in China from 1996 to 2013: an analysis from National Surveillance System. PloS one. 2015; 10(7):e0133620. https://doi.org/10.1371/journal.pone.0133620 PMID: 26186717

25. National Institute of Population ResearchTraining—NIPORT/Bangladesh, Mitra and Associates/Bangladesh, and ORC Macro,. Bangladesh Demographic and Health Survey 2004. Dhaka, Bangladesh: NIPORT, Mitra and Associates, and ORC Macro, 2005.

26. Susuman AS. Child mortality rate in Ethiopia. Iran J Public Health. 2012; 41(3):9. PMID: 23113145

27. Ashworth A, Chopra M, McCoy D, Sanders D, Jackson D, Karaolis N, et al. WHO guidelines for management of severe malnutrition in rural South African hospitals: effect on case fatality and the influence of operational factors. The Lancet. 2004; 363(9415):1110–5. https://doi.org/10.1016/S0140-6736(04)15894-7 PMID: 15064029

28. Maher EJ, Frestedt B, Grace C. Differences in child care quality in rural and non-rural areas. Journal of Research in Rural Education (Online). 2008; 23(4):1.

29. Hardelid P, Dattani N, Gilbert R. Estimating the prevalence of chronic conditions in children who die in England, Scotland and Wales: a data linkage cohort study. BMJ open. 2014; 4(8). https://doi.org/10.1136/bmjopen-2014-005331 PMID: 25085264

30. de Lacerda AF, Gomes B. Trends in cause and place of death for children in Portugal (a European country with no Paediatric palliative care) during 1987–2011: a population-based study. BMC pediatrics. 2017; 17(1):1–11. https://doi.org/10.1186/s12887-016-0759-7 PMID: 28056921

31. Tempia SWS, Viboud C, Cohen AL, Madhi SA, Venter M, et al. Mortality Associated With Seasonal and Pandemic Influenza and Respiratory Syncytial Virus Among Children <5 Years of Age in a High HIV Prevalence Setting—South Africa, 1998–2009. ClinInfectDis. 2014; 58:1241–9.

32. Chiappini E, Galli L, Tovo P-A, Gabiano C, Lisi C, Gattinara GC, et al. Changing patterns of clinical events in perinatally HIV-1-infected children during the era of HAART. Aids. 2007; 21(12):1607–15. https://doi.org/10.1097/QAD.0b013e32823ecf5b PMID: 17630556

33. Granados JMS, Amador JTR, De Miguel SF, Tome MIG, Conejo PR, Vivas PF, et al. Impact of highly active antiretroviral therapy on the morbidity and mortality in Spanish human immunodeficiency virus-infected children. The Pediatric infectious disease journal. 2003; 22(10):863–8. https://doi.org/10.1097/01.inf.0000091282.70253.5f PMID: 14551485

34. de Martino M, Tovo P-A, Balducci M, Galli L, Gabiano C, Rezza G, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Jama. 2000; 284(2):190–7. https://doi.org/10.1001/jama.284.2.190 PMID: 10889592

35. Goga A, Dinh T-H, Jackson D. Evaluation of the effectiveness of the national prevention of mother-to-child transmission (PMTCT) programme on infant HIV measured at six weeks postpartum in South Africa: South African Medical Research Council, National Department of Health South Africa and PEPFAR/US Centers for Disease Control & Prevention. 2012. Available at: http://hdl.handle.net/10566/462. Accessed November 2017.

36. Breiman RCL, Njenga M, Williamson J, Mott J, Katz M,et al Severe acute respiratory infection in children in a densely populated urban slum in Kenya, 2007–2011. BMC Infectious Diseases 2015; 15(95).

37. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. The Lancet. 2010; 375(9725):1545–55. https://doi.org/10.1016/S0140-6736(10)60206-1 PMID: 20399493

38. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. Jama. 2003; 289(2):179–86. https://doi.org/10.1001/jama.289.2.179 PMID: 12517228

39. Zar H, Jeena P, Argent A, Gie R, Madhi S. Diagnosis and management of community-acquired pneumonia in childhood-South African Thoracic Society Guidelines. South African Medical Journal. 2008; 95(12):975–90.

40. Brito RdCCMd Guerra TCM, Câmara LdHLD Mattos JDPGd, Mello MJGd Correia JdB, et al. Clinical characteristics and outcomes of acute community acquired pneumonia in children at a reference public hospital in Pernambuco State, Brazil (2010–2011). Revista Brasileira de Saúde Materno Infantil. 2016; 16:247–57.

41. Rees EM, Nightingale ES, Jafari Y, Waterlow NR, Clifford S, B. Pearson CA, et al. COVID-19 length of hospital stay: a systematic review and data synthesis. BMC Medicine. 2020; 18(1):270. https://doi.org/10.1186/s12916-020-01726-3 PMID: 32878619

42. Awad A, Bader–El–Den M, McNicholas J. Patient length of stay and mortality prediction: a survey. Health services management research. 2017; 30(2):105–20. https://doi.org/10.1177/0951484817696212 PMID: 28539083

43. Nupen TL, Argent A, Morrow B. Characteristics and outcome of long-stay patients in a paediatric intensive care unit in Cape Town, South Africa. South African Medical Journal. 2017; 107(1):70–5.

44. Rudan I, O'brien KL, Nair H, Liu L, Theodoratou E, Qazi S, et al. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. Journal of global health. 2013; 3(1).

45. O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. The Lancet. 2009; 374(9693):893–902. https://doi.org/10.1016/S0140-6736(09)61204-6 PMID: 19748398

46. Wolter N, Cohen C, Tempia S, Madhi SA, Venter M, Moyes J, et al. HIV and influenza virus infections are associated with increased blood pneumococcal load: a prospective, hospital-based observational study in South Africa, 2009–2011. The Journal of infectious diseases. 2014; 209(1):56–65. https://doi.org/10.1093/infdis/jit427 PMID: 23922370

47. Farooqui H, Jit M, Heymann DL, Zodpey S. Burden of severe pneumonia, pneumococcal pneumonia and pneumonia deaths in Indian states: modelling based estimates. PloS one. 2015; 10(6):e0129191. https://doi.org/10.1371/journal.pone.0129191 PMID: 26086700