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Risk Factors for Influenza-Associated Severe Acute Respiratory Illness Hospitalization in South Africa, 2012–2015

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Background. Data on risk factors for influenza-associated hospitalizations in low- and middle-income countries are limited.

Methods. We conducted active syndromic surveillance for hospitalized severe acute respiratory illness (SARI) and outpatient influenza-like illness (ILI) in 2 provinces of South Africa during 2012–2015. We compared the characteristics of influenza-positive patients with SARI to those with ILI to identify factors associated with severe disease requiring hospitalization, using unconditional logistic regression.

Results. During the study period, influenza virus was detected in 5.9% (110 of 1861) and 15.8% (577 of 3652) of SARI and ILI cases, respectively. On multivariable analysis factors significantly associated with increased risk of influenza-associated SARI hospitalization were as follows: younger and older age (<6 months [adjusted odds ratio {aOR}, 37.6], 6–11 months [aOR, 31.9], 12–23 months [aOR, 22.1], 24–59 months [aOR, 7.1], and ≥65 years [aOR, 40.7] compared with 5–24 years of age), underlying medical conditions (aOR, 4.5), human immunodeficiency virus infection (aOR, 4.3), and *Streptococcus pneumoniae* colonization density ≥1000 deoxyribonucleic acid copies/mL (aOR, 4.8). Underlying medical conditions in children aged <5 years included asthma (aOR, 22.7), malnutrition (aOR, 2.4), and prematurity (aOR, 4.8); in persons aged ≥5 years, conditions included asthma (aOR, 3.6), diabetes (aOR, 7.1), chronic lung diseases (aOR, 10.7), chronic heart diseases (aOR, 9.6), and obesity (aOR, 21.3). Mine workers (aOR, 13.8) and pregnant women (aOR, 12.5) were also at increased risk for influenza-associated hospitalization.

Conclusions. The risk groups identified in this study may benefit most from annual influenza immunization, and children <6 months of age may be protected through vaccination of their mothers during pregnancy.

Keywords. HIV; hospitalization; influenza; risk factors; severe acute respiratory illness; South Africa.

Data on risk factors for influenza-associated severe disease are key to guide targeted influenza vaccination. This is particularly important in resource-limited settings where influenza vaccine availability is limited.

However, in 2012 the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization highlighted that risk groups for influenza-associated severe disease in low- and middle-income countries are not well defined [1], and a systematic review reported a gap of knowledge on the impact of coinfections and comorbidities prevalent in Africa on influenza-associated severe illness [2]. Moreover, a systematic review conducted in 2013 reported that the level of evidence to support risk factors for influenza-associated complications is low overall and some well accepted risk factors could not be confirmed [3], highlighting the need to generate additional evidence.

Studies conducted in South Africa estimated that approximately 47 000 episodes of influenza-associated severe acute respiratory illness (SARI) [4] and approximately 9500 influenza-associated all-cause deaths occur annually in the country [5, 6]. Factors associated with increased risk of influenza-associated mortality have been partially described in South Africa and include *Streptococcus pneumoniae* coinfection, extremes of age,

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human immunodeficiency virus infection (HIV), underlying medical conditions, and pregnancy [5–8]. In South Africa in 2013, it was estimated that 12% of the population of approximately 53 million people were infected with HIV [9], 1.6% were asthmatic, 7% suffered from chronic heart or lung diseases, and 6% were diabetic [10]. The annual birth cohort and hence the number of pregnant women was approximately 1.1 million [11]. Children aged <5 years and persons aged ≥65 years accounted for 10% and 5% of the population, respectively [11]; 6% of children aged <3 years were malnourished, and 8% of live births were preterm [10].

Since 2009, approximately 1 million doses of influenza vaccine have been made available in the South Africa public sector every year for high-risk groups, which include young children, the elderly, pregnant or postpartum women, and persons of any age with underlying medical conditions such as heart and lung diseases and HIV infection [12]. Approximately the same number of doses is available annually in the private sector.

Nevertheless, the annual number of available doses of influenza vaccine is insufficient to cover the targeted risk groups in the country. A better understanding of the factors associated with increased risk of influenza-associated severe disease in our setting could assist to refine current target groups, better prioritize interventions, and potentially advocate for increased coverage among highly vulnerable populations. In this study, we aimed to assess the risk factors for influenza-associated SARI hospitalization in South Africa from 2012 through 2015.

METHODS

Description of the Surveillance Programs

We conducted prospective, hospital-based surveillance for SARI at 3 public hospitals in 2 provinces of the country (Edendale Hospital in a periurban area of KwaZulu-Natal Province, and Klerksdorp and Tshepong Hospitals [the Klerksdorp-Tshepong Hospital Complex] in a periurban area of North West Province) from May 2012 through April 2015.

In addition, we conducted prospective surveillance for cases presenting with influenza-like illness (ILI) at 2 outpatient clinics (Edendale Gateway Clinic, KwaZulu-Natal Province, and Jouberton Clinic, North West Province) located in the same catchment area to the above-mentioned hospitals during the same study period.

A case of SARI was defined as a hospitalized person who had illness onset within 7 days of admission and who met age-specific clinical inclusion criteria. A case in children aged 2 days to <3 months included any hospitalized patient with diagnosis of suspected sepsis or physician-diagnosed acute lower respiratory tract infection irrespective of signs and symptoms. A case in children aged 3 months to <5 years included any hospitalized patient with physician-diagnosed acute lower respiratory tract infection, including bronchitis, bronchiolitis, pneumonia, and pleural effusion. A case in individuals aged ≥5 years included any hospitalized patient presenting with manifestation of acute lower respiratory tract infection with fever (≥38°C) or history of fever and cough or sore throat and shortness of breath or difficult breathing with or without clinical or radiographic findings of pneumonia [13]. An ILI case was defined as an outpatient of any age presenting with either temperature ≥38°C or history of fever and cough of duration of ≤7 days [13].

The procedures of these programs have been previously described [14–16]. In brief, study staff completed case report forms for all enrolled patients with SARI or ILI. In addition, for SARI cases, the patient's hospital records were reviewed to assess disease progression and outcome (ie, discharge, transfer, or in-hospital death). Referral to hospital was recorded for all enrolled patients with ILI.

Patients enrolled at the outpatient clinics that were referred to hospital after consultation were excluded as ILI cases. These patients were included as SARI cases if they were enrolled at the hospitals conducting SARI surveillance. In addition, we excluded ILI cases that were not referred to hospital after outpatient consultation but were subsequently enrolled as SARI cases within 7 days from the time of consultation at the clinics.

Laboratory Procedures

Upper respiratory tract specimens collected from patients with SARI or ILI were tested for influenza virus, parainfluenza virus types 1–3, respiratory syncytial virus, adenovirus, rhinovirus, human metapneumovirus, enterovirus, *S pneumoniae*, *Haemophilus influenzae* type B, *Bordetella pertussis*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella* spp. In addition, blood samples and induced sputa were collected from patients with SARI and tested for the detection of *S pneumoniae* and *Mycobacterium tuberculosis*, respectively. All test were implemented using polymerase chain reaction assays with the exception of tuberculosis, whereby a combination of tests was used. Sample collection and laboratory procedures are detailed in the Supplementary Material.

Statistical Analysis

The χ^2 test or the Fisher exact test were used for comparison of categorical variables. We used unconditional logistic regression to assess factors associated with influenza-associated SARI hospitalization by comparing the characteristics of influenza-positive SARI cases (cases) to those of influenza-positive ILI cases (comparison group). For the multivariable model, we assessed all variables that were significant at $P < .2$ on univariate analysis, and we dropped nonsignificant factors ($P \geq .05$) with manual backward elimination. Pairwise interactions were assessed by inclusion of product terms for all variables remaining in the final multivariable additive model. This analysis was implemented for all ages as well as among children aged <5 years and persons aged ≥5 years separately.

We also implemented a subanalysis among women of childbearing age (15–49 years) to specifically assess the association of pregnancy with influenza-associated SARI hospitalization. In

addition, we reported the progression of illness among patients hospitalized with SARI and influenza-associated SARI. The statistical analysis was conducted using STATA version 13.1 (StataCorp, College Station, TX).

Ethical Approval

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. The ILI protocol was approved by HREC and BREC protocol numbers M120133 and BF080/12, respectively. This surveillance was deemed nonresearch by the US Centers for Disease Control and Prevention (NRD5621XJ).

RESULTS

Study Population

From May 2012 through April 2015, we enrolled 5607 patients, 5534 (98.7%) of whom had available influenza results and were included for further analysis. Of these, 1861 (33.6%) were SARI cases and 3673 (66.4%) were initially classified as ILI cases. Of the latter, 20 (0.5%) were referred to hospital after outpatient consultation, and 1 (<0.1%) was not referred to hospital after outpatient consultation but was subsequently enrolled as a SARI case within 7 days from the time of consultation at the clinic. These patients were excluded as ILI cases, and therefore 3652 ILI cases were retained for the analysis; 9.5% (2 of 21) of the excluded patients were influenza positive. Among persons with known age, children <5 years of age accounted for 73.2% (1358 of 1855) and 28.0% (1023 of 3651) of SARI and ILI cases, respectively. The HIV serostatus was known for 80.5% (1498 of 1861) of SARI cases and 87.5% (3194 of 3652) of ILI cases. Among individuals with known HIV serostatus, the HIV prevalence was 27.0% (405 of 1498) among SARI cases and 29.8% (952 of 3194) among ILI cases. Among SARI and ILI cases, the HIV prevalence was lowest among infants <1 years of age (SARI 10.6% [75 of 710] vs ILI 2.4% [7 of 295]) and highest among persons 25–44 years of age (SARI 90.0% [171 of 190] vs ILI 59.0% [594 of 1006]).

Influenza virus was detected in 687 (12.5%) specimens. Of these, 329 (47.9%) were influenza A(H3N2), 99 (14.4%) were influenza A(H1N1)pdm09, 247 (35.9%) were influenza B, and 12 (1.7%) were influenza A not subtyped. Influenza B predominated in 2012 (61.7% [166 of 269]), influenza A(H1N1)pdm09 predominated in 2013 (47.1%; 90 of 191), and influenza A(H3N2) predominated in 2014 (78.8% [179 of 227]) (Figure 1).

Risk Factors for Influenza-Associated Severe Acute Respiratory Illness Hospitalization Among Persons of Any Age

During the study period, influenza virus was detected in 5.9% (110 of 1861) and 15.8% (577 of 3652) of SARI and ILI cases, respectively. Among influenza-positive patients with SARI with available results, 5.4% (3 of 55) were tuberculosis-positive on induced sputum, 16.8% (17 of 101) were *S pneumoniae lytA*-positive on blood, and 73.6% (81 of 110) were *lytA*-positive on nasopharyngeal specimens. Of those with pneumococcal colonization, 77.8% (63 of 81) had colonization density ≥1000 deoxyribonucleic acid (DNA) copies/mL. The *lytA*-positivity in blood was 5.9% (1 of 17) and 25.4% (16 of 63) among patients with colonization density <1000 and ≥1000 DNA copies/mL, respectively ($P = .041$). *Legionella* spp were not detected among influenza-positive cases with SARI or ILI during the

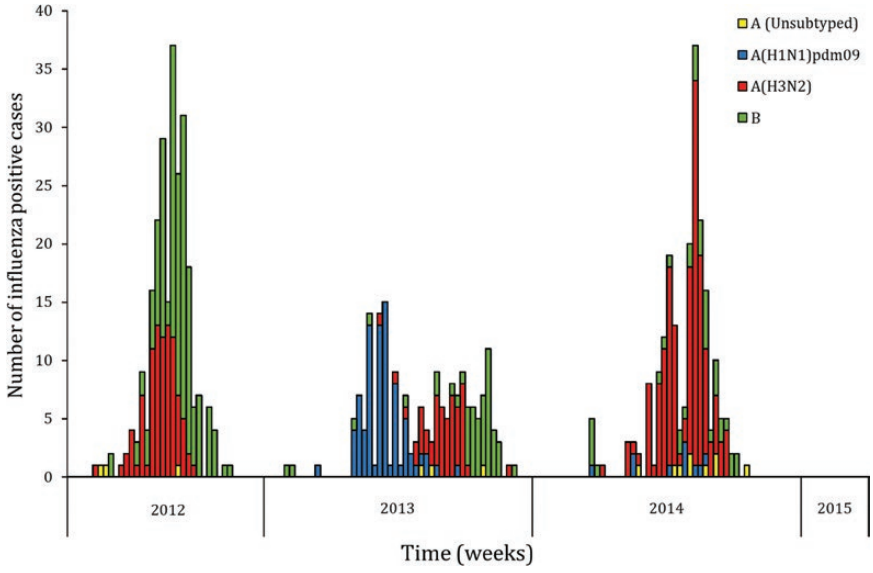

Figure 1. Number of influenza-positive severe acute respiratory illness and influenza-like illness cases by week, Klerksdorp and Pietermaritzburg, South Africa, May 2012–April 2015.

study period. Of the 588 of 687 (85.6%) influenza-positive SARI and ILI cases with available HIV results, 169 (28.7%) were infected with HIV. Of these, 148 (87.6%) had $CD4^+$ T-cells counts available.

On multivariable analysis adjusting for duration of symptoms, factors associated with increased risk of influenza-associated SARI hospitalization were as follows: (1) extremes of age (<6 months [aOR, 37.6; 95% confidence interval {CI}, 8.3–106.4], 6–11 months [aOR, 31.9; 95% CI, 9.1–111.8], 12–23 months [aOR, 22.1; 95% CI, 6.9–70.9], 24–59 months [aOR, 7.1; 95% CI, 2.4–21.5], and ≥65 years [aOR, 40.7; 95% CI, 6.4–256.9] compared with 5–24 years of age); (2) underlying medical conditions excluding HIV infection (aOR, 4.5; 95% CI, 2.4–8.4); (3) HIV infection (aOR, 3.3; 95% CI, 1.4–7.7); and (4) *S pneumoniae* colonization density ≥1000 DNA copies/mL (aOR, 4.8; 95% CI, 2.4–9.8) compared with colonization density <1000 DNA copies/mL (Table 1). No increased risk of severe disease was observed among patients that were not colonized and those that had colonization density <1000 DNA/mL (aOR, 1.0; 95% CI, 0.5–2.2). On a multivariable analysis conducted among patients with available $CD4^+$ T-cells counts, HIV-infected individuals with mild (aOR, 3.7; 95% CI, 1.3–10.2) or severe immunosuppression (aOR, 11.0; 95% CI, 2.9–41.9) were at increased risk of influenza-associated SARI hospitalization when compared with HIV-uninfected individuals. HIV-infected individuals with severe immunosuppression were 3.0 (95% CI, 1.1–8.7) times at increased odds of influenza-associated SARI hospitalization compared with HIV-infected individual with mild immunosuppression (Table 1).

Risk Factors for Influenza-Associated Severe Acute Respiratory Illness Hospitalization Among Children <5 Years of Age

During the study period, children <5 years of age accounted for 66.4% (73 of 110) of influenza-positive SARI cases and 25.8% (149 of 577) of influenza-positive ILI cases. Among children <5 years of age, influenza virus was detected in 5.4% (73 of 1358) and 14.6% (149 of 1023) of SARI and ILI cases, respectively. Among influenza-positive children <5 years of age with SARI with available results, 3.3% (1 of 30) were tuberculosis-positive on induced sputum, 12.3% (8 of 65) were *S pneumoniae lytA*-positive on blood, and 75.3% (55 of 73) were *lytA*-positive on nasopharyngeal specimens.

On multivariable analysis comparing influenza-positive SARI cases to influenza-positive ILI cases, factors associated with increased risk of influenza-associated SARI hospitalization were as follows: (1) young age (<6 months [aOR, 5.8; 95% CI, 2.2–15.2], 6–11 months [aOR, 4.7; 95% CI, 1.9–11.8], and 12–23 months [aOR, 3.0; 95% CI, 1.3–6.9] compared with 24–59 months of age); (2) asthma (aOR, 22.7; 95% CI, 2.8–∞); (3) malnutrition (aOR, 2.4; 95% CI, 1.1–5.6); (4) prematurity (aOR, 4.8; 95% CI, 1.1–21.6); (5) HIV infection (aOR, 3.1; 95% CI, 1.2–8.1); and (6) *S pneumoniae* colonization density ≥1000 DNA copies/mL (aOR, 5.5; 95% CI, 2.2–13.7) compared with colonization density <1000 DNA copies/mL (Table 2).

Risk Factors for Influenza-Associated Severe Acute Respiratory Illness Hospitalization Among Persons ≥5 Years of Age

During the study period, among persons ≥5 years of age, influenza virus was detected in 7.4% (37 of 497) and 16.3% (428 of 2628) of SARI and ILI cases, respectively. Among influenza-positive patients ≥5 years of age with SARI with available results, 8.0% (2 of 25) were tuberculosis-positive on induced sputum, 25.0% (9 of 36) were *S pneumoniae lytA*-positive on blood, and 70.3% (26 of 37) were *lytA*-positive on nasopharyngeal specimens. On multivariable analysis comparing influenza-positive SARI cases to influenza-positive ILI cases and adjusting for duration of symptoms, factors associated with increased risk of influenza-associated SARI hospitalization were as follows: (1) age ≥65 years compared 5–24 years (aOR, 36.2; 95% CI, 5.4–242.3); (2) asthma (aOR, 3.6; 95% CI, 1.2–6.1); (3) diabetes (aOR, 7.1; 95% CI, 1.1–51.4); (4) chronic lung diseases (aOR, 10.7; 95% CI, 1.1–108.7); (5) chronic heart diseases (aOR, 9.6; 95% CI, 1.1–86.5); (6) obesity (aOR, 21.3; 95% CI, 1.3–359.2); (7) other underlying medical conditions excluding HIV infection (aOR, 7.9; 95% CI, 1.1–60.3); (8) working in mines (aOR, 13.8; 95% CI, 1.8–104.3); (9) HIV infection (aOR, 6.2; 95% CI, 2.0–19.8); and (10) *S pneumoniae* colonization density ≥1000 DNA copies/mL (aOR, 3.3; 95% CI, 1.1–11.6) compared with colonization density <1000 DNA copies/mL (Table 3).

Risk Factors for Influenza-Associated Severe Acute Respiratory Illness Hospitalization Among Women of Childbearing Age

Women of childbearing age (15–49 years) accounted for 14.5% (16 of 110) of influenza-positive SARI cases and 29.8% (172 of 577) of influenza-positive ILI cases. Of these, 12.5% (2 of 16) and 1.7% (3 of 172) were pregnant among SARI and ILI cases, respectively (OR, 8.0; 95% CI, 1.2–52.2). On multivariable analysis, adjusting for duration of symptoms, age, underlying medical conditions, HIV infection, and pneumococcal colonization density, pregnancy remained significantly associated with increased risk of influenza-associated SARI hospitalization (aOR, 12.5; 95% CI, 1.2–126.5). The characteristics of the influenza-positive pregnant women are provided in Supplementary Table S1.

Progression of Illness Among Patients Hospitalized With Severe Acute Respiratory Illness

Among the 1861 SARI cases with available influenza results, information on progression of illness was available for 1817 (97.6%) individuals, 981 (54.0%) of whom received oxygen support, 59 (3.2%) were admitted to the intensive care unit (ICU), and 57 (3.1%) died during hospitalization. Influenza-positive cases accounted for 4.3% (42 of 981), 6.8% (4 of 59), and 7.0% (4 of 57) of patients who received oxygen support, were admitted to ICU, or died during hospitalization, respectively.

Table 1. Risk Factors For Influenza-Associated Severe Acute Respiratory Illness Hospitalization Among Persons of Any Age, Klerksdorp and Pietermaritzburg, South Africa, May 2012–April 2015[a]

			Univariate Analysis		Multivariable Analysis	
Variables	Influenza-Associated ILI n/N (%)	Influenza-Associated SARI n/N (%)	Odds Ratio (95% CI)	*P*	Adjusted Odds Ratio (95% CI)	*P*
Demographic and Clinical Characteristics						
Age						
<6 months	12/577 (2.1)	16/110 (14.5)	39.0 (13.9–109.0)	<.001	37.6 (8.3–106.4)	<.001
6–11 months	15/577 (2.6)	17/110 (15.4)	33.1 (912.3-89.1)	<.001	31.9 (9.1–111.8)	<.001
12–23 months	31/577 (5.4)	21/110 (19.1)	19.8 (8.1–48.5)	<.001	22.1 (6.9–70.9)	<.001
24–59 months	91/577 (15.8)	19/110 (17.3)	6.1 (2.6–14.4)	<.001	7.1 (2.4–21.5)	<.001
5–24 years	234/577 (40.5)	8/110 (7.3)	Reference	-	Reference	-
25–44 years	145/577 (26.7)	17/110 (15.4)	3.2 (1.4–7.7)	<.001	1.0 (0.3–3.4)	.997
45–64 years	36/577 (6.2)	8/110 (7.3)	6.5 (2.3–18.4)	<.001	2.7 (0.7–10.7)	.161
≥65 years	4/577 (0.7)	4/110 (3.6)	29.2 (6.2–138.5)	<.001	40.7 (6.4–256.9)	<.001
Sex (female vs male)	336/571 (58.8)	57/110 (51.7)	0.7 (0.5–1.1)	.173		
Site (Klerksdorp vs Pietermaritzburg)	115/577 (19.9)	29/110 (26.3)	1.6 (1.1–2.6)	.048		
Crowding (≥5 vs <5 of people/room)	37/569 (6.5)	10/106 (9.4)	1.5 (0.7–3.1)	.279		
Duration of symptoms (≥4 vs <4 days)	79/569 (13.9)	33/106 (31.1)	2.8 (1.7–4.5)	<.001	2.7 (1.5–5.2)	.002
Underlying Medical Conditions and Behavioral/Occupational Risks						
Underlying medical conditions[b]	58/568 (10.2)	38/110 (34.5)	4.6 (2.9–7.5)	<.001	4.5 (2.4–8.4)	<.001
Tobacco smoking	38/577 (6.6)	6/110 (5.4)	0.8 (0.3–2.0)	.657		
Alcohol consumption	45/577 (7.8)	5/110 (4.5)	0.6 (0.2–1.4)	.235		
Working in mines	5/577 (0.9)	4/110 (3.6)	4.3 (1.1–16.3)	.031	9.4 (1.7–51.0)	.009
HIV	143/488 (29.3)	26/100 (26.0)	0.8 (0.5–1.4)	.506	4.3 (1.7–10.6)	.002
Negative[c]	345/469 (73.6)	74/98 (75.5)	Reference	-	Reference	-
Positive (no/mild immunosuppression)[c]	106/469 (22.6)	16/98 (16.3)	0.7 (0.4–1.3)	.237	3.7 (1.3–10.2)	.011
Positive (severe immunosuppression)[c]	18/469 (3.8)	8/98 (8.2)	2.1 (0.8–4.9)	.101	11.0 (2.9–41.9)	<.001
Negative[c]	345/469 (73.6)	74/98 (75.5)	1.4 (0.8–2.5)	.237	0.3 (0.1–0.7)	.011
Positive (no/mild immunosuppression)[c]	106/469 (22.6)	16/98 (16.3)	Reference	-	Reference	-
Positive (severe immunosuppression)[c]	18/469 (3.8)	8/98 (8.2)	2.9 (1.1–7.9)	.032	3.0 (1.1–8.7)	.041
Influenza Virus Types/Subtypes						
Influenza types (A vs B)	365/577 (63.2)	75/110 (68.2)	1.2 (0.8–1.9)	.335		
Influenza subtypes						
B	212/566 (37.5)	35/107 (32.7)	Reference	-		
A(H1N1)pdm09	82/566 (14.5)	17/107 (15.9)	1.2 (0.7–2.3)	.481		
A(H3N2)	272/566 (48.1)	55/107 (51.4)	1.2 (0.8–1.9)	.388		
Viral Coinfections						
RSV	13/577 (2.2)	6/110 (5.4)	2.5 (0.9–6.7)	.069		
hMPV	10/577 (1.7)	2/110 (1.8)	1.0 (0.2–4.8)	.950		
Parainfluenza virus (types 1–3)	13/577 (2.2)	1/110 (0.9)	0.4 (0.1–3.1)	.377		
Rhinovirus	39/577 (6.7)	13/110 (11.8)	1.8 (0.9–3.6)	.070		
Adenovirus	63/577 (10.9)	14/110 (12.7)	1.2 (0.6–2.2)	.582		
Enterovirus	13/577 (2.2)	2/110 (1.8)	0.8 (0.2–3.6)	.775		
Any viral confection	129/577 (22.3)	26/110 (23.6)	1.1 (0.7–1.7)	.769		
Bacterial Coinfections						
Streptococcus pneumoniae						
Not colonized	244/577 (42.3)	29/110 (26.4)	1.4 (0.8–2.6)	.252	1.0 (0.5–2.2)	.886
Colonized (<1000 DNA copies/mL)	217/577 (37.6)	18/110 (16.4)	Reference	-	Reference	-
Colonized (≥1000 DNA copies/mL)	116/577 (20.1)	63/110 (57.3)	6.5 (3.7–11.6)	<.001	4.8 (2.4–9.8)	<.001
Haemophylus influenzae type B	3/577 (0.5)	2/110 (1.8)	3.5 (0.6–21.4)	.169		
Bordetella pertussis	3/577 (0.5)	2/110 (1.8)	3.5 (0.6–21.4)	.169		
Mycoplasma pneumoniae	3/577 (0.5)	2/110 (1.8)	3.5 (0.6–21.4)	.169		
Chlamydophila pneumoniae	3/577 (0.5)	0/110 (0.0)	0.6 (0.0–12.7)[d]	.845		

Abbreviations: CI, confidence interval; DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus; hMPV, human metapneumovirus; ILI, influenza-like illness; RSV, respiratory syncytial virus; SARI, severe acute respiratory illness.

[a]The characteristics of influenza-positive patients with SARI (cases) were compared with those of patients with ILI (controls).

[b]Evaluated underlying medical conditions included the following: asplenia, including asplenia or sickle cell anemia; chronic illness, including chronic lung, renal, liver or cardiac disease, diabetes mellitus, and asthma; other immunocompromising conditions (excluding HIV), including organ transplant, primary immunodeficiency, immunotherapy, and malignancy; neurological disorders; burns; obesity; malnutrition and prematurity.

[c]Analysis implemented on a subset of patients with available $CD4^+$ T-cells counts. The multivariable model was adjusted for the same factors reported in the table above. No or mild immunosuppression: $CD4^+$ T-lymphocytes ≥200/mm^3 or equivalent age-appropriate $CD4^+$ percentage for children aged <5 years. Severe immunosuppression: $CD4^+$ T-lymphocytes <200/mm^3 or equivalent age-appropriate $CD4^+$ percentage for children aged <5 years.

[d]Estimated using exact logistic regression.

Table 2. Risk Factors For Influenza-Associated Severe Acute Respiratory Illness Hospitalization Among Children <5 Years of Age, Klerksdorp and Pietermaritzburg, South Africa, May 2012–April 2015[a]

Variables	Influenza-Associated ILI n/N (%)	Influenza-Associated SARI n/N (%)	Univariate Analysis Odds Ratio (95% CI)	Univariate Analysis *P*	Multivariable Analysis Adjusted Odds Ratio (95% CI)	Multivariable Analysis *P*
Demographic and Clinical Characteristics						
Age (in months)						
<6	12/149 (8.0)	16/73 (21.9)	6.4 (2.6–15.7)	<.001	5.8 (2.2–15.2)	<.001
6–11	15/149 (10.1)	17/73 (23.3)	5.4 (2.3–12.7)	<.001	4.7 (1.9–11.8)	.001
12–23	31/149 (20.8)	21/73 (28.8)	3.2 (1.5–6.8)	.002	3.0 (1.3–6.9)	.008
24–59	91/149 (61.1)	19/73 (26.0)	Reference	-	Reference	-
Sex (female vs male)	60/147 (40.8)	31/73 (42.5)	1.1 (0.6–1.9)	.815		
Site (Klerksdorp vs Pietermaritzburg)	38/149 (25.5)	27/73 (36.9)	1.7 (0.9–3.2)	.077		
Crowding (≥5 vs <5 of people/room)	8/146 (5.5)	9/71 (12.7)	2.5 (0.9–6.8)	.072		
Duration of symptoms (≥4 vs <4 days)	18/147 (12.2)	22/70 (31.4)	3.3 (1.6–6.6)	.001		
Underlying Medical Conditions						
Asthma	0/145 (0.0)	6/73 (8.2)	17.3 (2.4-∞)[e]	.002	22.7 (2.8-∞)[e]	.002
Malnutrition[b]	16/135 (11.8)	21/73 (28.8)	3.0 (1.4–6.2)	.003	2.4 (1.1–5.6)	.039
Prematurity[c]	4/147 (2.7)	8/73 (10.9)	4.4 (1.3–15.1)	.019	4.8 (1.1–21.6)	.038
HIV	6/145 (4.1)	7/70 (10.0)	2.6 (0.8–7.9)	.101	3.1 (1.2–8.1)	.031
Other medical conditions[d]	0/145 (0.0)	2/73 (2.7)	4.8 (0.4-∞)[e]	.222		
Influenza Virus Types/Subtypes						
Influenza types (A vs B)	96/149 (64.4)	56/73 (76.7)	1.8 (0.9–3.4)	.066		
Influenza Subtypes						
B	53/147 (36.1)	17/71 (23.9)	Reference	-		
A(H1N1)pdm09	21/147 (14.3)	14/71 (19.7)	2.1 (0.9–4.9)	.099		
A(H3N2)	73/147 (49.7)	40/71 (56.3)	1.7 (0.9–3.3)	.116		
Viral Coinfections						
RSV	6/149 (4.0)	4/73 (5.5)	1.4 (0.4–5.0)	.625		
hMPV	6/149 (4.0)	2/73 (2.7)	0.7 (0.1–3.4)	.631		
Parainfluenza virus (types 1–3)	4/149 (2.7)	1/73 (1.4)	0.5 (0.1–4.6)	.543		
Rhinovirus	16/149 (10.7)	11/73 (15.1)	1.5 (0.6–3.4)	.356		
Adenovirus	29/149 (19.46)	13/73 (17.8)	0.9 (0.4–1.8)	.767		
Enterovirus	10/149 (6.7)	2/73 (2.7)	0.4 (0.1–1.8)	.234		
Any viral confection	55/149 (36.9)	22/73 (30.1)	0.7 (0.4–1.3)	.320		
Bacterial Coinfections						
Streptococcus pneumoniae						
Not colonized	65/149 (43.6)	18/73 (24.7)	1.4 (0.6–3.2)	.443	1.1 (0.4–2.8)	.817
Colonized (<1000 DNA copies/mL)	55/149 (36.9)	11/73 (15.1)	Reference	-	Reference	-
Colonized (≥1000 DNA copies/mL)	29/149 (19.5)	44/74 (60.3)	7.6 (3.4–16.9)	<.001	5.5 (2.2–13.7)	<.001
Haemophylus influenzae type B	0/149 (0.0)	1/73 (1.4)	2.0 (0.1–∞)[e]	.658		
Bordetella pertussis	2/149 (1.3)	1/73 (1.4)	1.0 (0.1–11.4)	.987		
Mycoplasma pneumoniae	2/149 (1.3)	2/73 (2.7)	2.1 (0.3–15.0)	.471		
Chlamydophila pneumoniae	1/149 (0.7)	0/73 (0.0)	0.2 (0.0–79.6)	.945		

Abbreviations: CI, confidence interval; DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus; hMPV, human metapneumovirus; ILI, influenza-like illness; RSV, respiratory syncytial virus; SARI, severe acute respiratory illness.

[a]The characteristics of influenza-positive patients with SARI (cases) were compared with those of patients with ILI (controls).

[b]Malnutrition was classified as weight-for-age Z score less than −2 (World Health Organization child growth standards 2009) and/or nutritional edema.

[c]Prematurity was classified as birth before 37 weeks of gestation as reported on the road-to-health card.

[d]Other evaluated underlying medical conditions included the following: asplenia, including asplenia or sickle cell anemia; chronic illness, including chronic lung, renal, liver or cardiac disease, and diabetes mellitus; other immunocompromising conditions (excluding HIV), including organ transplant, primary immunodeficiency, immunotherapy, and malignancy; neurological disorders; burns and obesity.

[e]Estimated using exact logistic regression.

Information on the progression of illness was available for 96.4% (106 of 110) of influenza-positive SARI cases. Of these, 39.6% (42 of 106) received oxygen support, 3.8% (4 of 106) were admitted to ICU, and 3.8% (4 of 106) died during hospitalization. The median length of hospitalization was 4 days (range, 1–18 days). The characteristics of the influenza-positive SARI cases that died are provided in Supplementary Table S2.

Table 3. Risk Factors For Influenza-Associated Severe Acute Respiratory Illness Hospitalization Among Persons ≥5 Years of Age, Klerksdorp and Pietermaritzburg, South Africa, May 2012–April 2015[a]

			Univariate Analysis		Multivariable Analysis	
Variables	Influenza-Associated ILI n/N (%)	Influenza-Associated SARI n/N (%)	Odds Ratio (95% CI)	*P*	Adjusted Odds Ratio (95% CI)	*P*
Demographic and Clinical Characteristics						
Age (in years)						
5–24	234/428 (54.7)	8/37 (21.6)	Reference	-	Reference	-
25–44	154/428 (36.0)	17/37 (45.9)	3.2 (1.4–7.6)	.008	0.4 (0.1–1.7)	.221
45–64	36/428 (8.4)	8/37 (21.6)	6.5 (2.3–18.4)	<.001	1.8 (0.4–7.9)	.417
≥65	4/428 (1.0)	4/37 (10.8)	29.2 (6.2–138.5)	<.001	36.2 (5.4–242.3)	<.001
Sex (female vs male)	276/424 (65.1)	26/37 (70.3)	1.3 (0.6–2.6)	.526		
Site (Klerksdorp vs Pietermaritzburg)	77/428 (18.0)	4/37 (10.8)	0.5 (0.1–1.6)	.269		
Crowding (≥5 vs <5 of people/room)	29/423 (6.9)	1/35 (2.9)	0.4 (0.1–2.0)	.374		
Duration of symptoms (≥4 vs <4 days)	61/422 (14.5)	11/36 (30.6)	2.6 (1.2–5.6)	.013	3.9 (1.4–10.8)	.010
Underlying Medical Conditions and Behavioral/Occupational Risks						
Asthma	13/423 (3.1)	4/37 (10.8)	3.8 (1.2–12.4)	.025	3.6 (1.2–6.1)	.033
Diabetes	5/423 (1.2)	3/36 (8.3)	7.6 (1.7–33.2)	.007	7.1 (1.1–51.4)	.041
Chronic lung diseases[b]	5/423 (1.2)	2/37 (5.4)	4.8 (0.9–25.5)	.067	10.7 (1.1–108.7)	.045
Chronic cardiac diseases[c]	5/423 (1.2)	2/37 (5.4)	4.8 (0.9–25.5)	.067	9.6 (1.1–86.5)	.044
Obesity[d]	2/427 (0.5)	2/37 (5.4)	12.1 (1.6–88.8)	.014	21.3 (1.3–359.2)	.034
Other medical conditions[e]	12/423 (2.8)	4/37 (10.8)	4.1 (1.2–13.6)	.019	7.9 (1.1–60.3)	.047
Tobacco smoking	38/428 (8.9)	6/37 (16.2)	2.0 (0.8–5.1)	.150		
Alcohol consumption	45/428 (10.5)	5/37 (13.5)	1.3 (0.5–3.6)	.573		
Working in mines	5/428 (1.2)	4/37 (10.8)	10.2 (2.6–40.0)	.001	13.8 (1.8–104.3)	.011
HIV	137/343 (39.9)	19/30 (63.3)	2.6 (1.2–5.6)	.016	6.2 (2.0–19.8)	.002
Influenza Virus Types/Subtypes						
Influenza types (A vs B)	269/427 (63.0)	19/37 (51.3)	0.6 (0.3–1.2)	.164		
Influenza Subtypes						
B	159/419 (37.9)	18/36 (50.0)	Reference	-		
A(H1N1)pdm09	199/419 (47.5)	15/36 (41.7)	0.4 (0.1–1.5)	.194		
A(H3N2)	61/419 (14.6)	3/36 (8.3)	0.7 (0.3–1.4)	.226		
Viral Coinfections						
RSV	7/428 (1.6)	2/37 (5.4)	3.4 (0.7–17.2)	.133		
hMPV	4/428 (0.9)	0/37 (0.0)	0.8 (0.0–17.9)[f]	.917		
Parainfluenza virus (types 1–3)	9/428 (2.1)	0/37 (0.0)	0.9 (0.0–5.9)[f]	.941		
Rhinovirus	23/428 (5.4)	2/37 (5.4)	1.0 (0.2–4.4)	.993		
Adenovirus	34/428 (7.9)	1/37 (2.7)	0.3 (0.1–2.4)	.271		
Enterovirus	3/428 (0.7)	0/37 (0.0)	0.9 (0.0–28.4)[f]	.934		
Any viral confection	74/428 (17.3)	4/37 (16.8)	0.6 (0.2–1.7)	.317		
Bacterial Coinfections						
Streptococcus pneumoniae						
Not colonized	179/428 (41.8)	11/37 (29.7)	1.4 (0.5–3.7)	.477	0.9 (0.3–3.2)	.955
Colonized (<1000 DNA copies/mL)	162/428 (37.8)	7/37 (18.9)	Reference	-	Reference	-
Colonized (≥1000 DNA copies/mL)	87/428 (20.3)	19/37 (51.3)	5.1 (2.0–12.5)	<.001	3.3 (1.1–11.6)	.047
Haemophylus influenzae type B	3/428 (0.7)	1/37 (2.7)	3.9 (0.4–38.8)	.241		
Bordetella pertussis	1/428 (0.2)	1/37 (2.7)	11.8 (0.7–193.6)	.083		
Mycoplasma pneumoniae	1/428 (0.2)	0/37 (0.0)	0.2 (0.0–451.1)[f]	.956		
Chlamydophila pneumoniae	2/428 (0.5)	0/37 (0.0)	0.3 (0.0–62.2)	.976		

Abbreviations: CI, confidence interval; DNA, deoxyiribonucleic acid; HIV, human immunodeficiency virus; hMPV, human metapneumovirus; ILI, influenza-like illness; RSV, respiratory syncytial virus; SARI, severe acute respiratory illness.

[a]The characteristics of influenza-positive patients with SARI (cases) were compared with those of patients with ILI (controls).

[b]Chronic lung diseases included the following: chronic obstructive pulmonary disease and emphysema.

[c]Chronic cardiac diseases included the following: chronic heart disease, valvular heart disease, and coronary artery diseases (except hypertension).

[d]Obesity was defined as body mass index ≥30.

[e]Other evaluated underlying medical conditions included the following: asplenia or sickle cell anemia; chronic renal and liver disease; other immunocompromising conditions (excluding HIV), including organ transplant, primary immunodeficiency, immunotherapy, and malignancy; neurological disorders; and burns.

[f]Estimated using exact logistic regression.

DISCUSSION

We provide case-based estimates of risk factors for influenza-associated SARI hospitalizations in a high HIV prevalence setting in Africa. Our study design allows the assessment of risk factors for influenza-associated hospitalization in settings where epidemiological and virological influenza surveillance is conducted among patients with ILI and SARI. The results of this study add to the available literature on populations more vulnerable to severe influenza-associated illness focusing on conditions prevalent in low- and middle-income countries, such as malnutrition, HIV-infection, high pregnancy rates, and a young population.

In this study, we identified risk factors for severe influenza-associated illness, such as extremes of age, pregnancy, asthma, chronic lung and heart diseases, diabetes, obesity, and HIV infection, as previously described [5, 6, 14, 17–25]. Even mildly immunosuppressed HIV-infected individuals remained more vulnerable to influenza-associated severe illness. An ecological study estimated an increased risk of influenza-associated mortality among HIV-positive individuals even after the widespread introduction of highly active antiretroviral treatment in the United States of America [26]. Conditions such as pregnancy, young age, and some underlying medical conditions including immunosuppression could not be confirmed as risk factors for seasonal influenza-associated hospitalization in a systematic review conducted in 2013 [3], but these were associated with an increased risk of influenza-associated SARI hospitalization in our study, highlighting the importance of generating additional data in this domain.

Although conditions such as prematurity and malnutrition have been described as risk factors for pneumonia [27], data on the specific effects of these conditions on severe influenza-associated disease are limited [2]. In our study, mine workers were at increased risk for influenza-associated SARI hospitalization, even after adjusting for comorbidities and coinfections. Conditions related to occupational hazards such as silicosis are underdiagnosed in South Africa [28, 29] and may be responsible for the increased risk of influenza-associated SARI hospitalization observed among mine workers in this study. In addition, a high prevalence of tuberculosis infection has been reported among South African mine workers [30, 31], and this may also independently contribute to the increased risk of influenza-associated SARI hospitalization observed among this category of workers; however, these hypotheses could not be verified.

Complications of viral infections due to superinfection with bacteria including the synergistic effect of influenza virus and *S pneumoniae* on severe illness are well described in the literature [16, 32–34]. In this study, we used elevated pneumococcal colonization density as a proxy for bacteremic pneumococcal pneumonia (BPP). Colonization densities ≥1000 DNA copies/mL have been reported to be associated with increased risk of BPP among hospitalized patients with SARI [35, 36], and this association was also observed in this study, indicating that BPP could complicate influenza-associated illness. Coinfections with the other viral and bacterial pathogens evaluated in this study were not associated with increased risk of influenza-associated SARI hospitalization; however, the detection rate of bacterial pathogens other than *S pneumoniae* was low in this study.

Although our study provides estimates of risk factors for influenza-associated severe illness in a middle-income setting, more data on vulnerable populations should be generated from other low- and middle-income countries where this information is limited [1, 2]. The WHO recommends the implementation of influenza surveillance among patients with SARI and ILI [13], and such surveillance has been established in several African countries in the past decade [37]. If validated in other countries and settings, our risk factors assessment approach could be used to identify risk groups for influenza-associated SARI hospitalizations (as well as risk groups for other pathogens included in routine surveillance) in countries where SARI and ILI surveillance is implemented. Furthermore, if SARI and ILI surveillance are adequately sized, such an approach could provide a platform for the rapid assessment of risk groups during influenza pandemics.

Our study has limitations that warrant discussion. First, although we collected data on visit outcomes from ILI patients and we assessed their enrollment as SARI cases subsequent to outpatient consultation, we did not follow up directly on progression of illness, and the development of undetected severe illness after consultation from some patients cannot be excluded. Second, this study was not powered to assess the individual risk of comorbidities such as chronic renal and liver diseases, neurological disorders, and malignancy because the prevalence of these conditions was low in our study population. Third, although increased risk of influenza-associated severe illness has been reported among women in their 2nd or 3rd trimester of pregnancy or postpartum women [17, 25], such risk could not be evaluated in our study because this information was not available. Fourth, we were underpowered to assess risk factors for influenza-associated mortality given the low number of deaths in our study. Nevertheless, all identified fatal cases had 1 or more conditions that were identified in this study as risk factors for influenza-associated SARI hospitalization, including extremes of age, HIV infection, diabetes, or malnutrition. Last, we used pneumococcal colonization density as a proxy for BPP; however, the effect of non-BPP could not be evaluated. In addition, upper respiratory tract specimens may not be optimal for the detection of some of the bacterial pathogens evaluated in this study, such as *Legionella* spp. We also did not collect induced sputa from patients with ILI, which hindered our ability to evaluate the association of *M tuberculosis* infection with severe illness.

CONCLUSIONS

In conclusion, our study adds to the current knowledge of risk factors associated with influenza-associated severe illness and reports some risk factors poorly described in the literature, such as prematurity, malnutrition, working in mines, and the effect of $CD4^+$ T-cells counts among HIV-infected individuals. The risk groups identified in this study may benefit most from annual influenza immunization, and children <6 months of age may be protected through the vaccination of their mothers during pregnancy [38, 39]. Nonetheless, the availability of influenza vaccine in Africa including South Africa is limited [40], and it is not sufficient to cover all identified risk groups. The prioritization of vaccination in resource-limited settings should consider the following: (1) the burden of influenza-associated illness among identified risk groups, (2) the prevalence of such conditions in the general population, (3) the magnitude of the identified risk, (4) the feasibility to reach the target groups with immunization programs, and (5) the effectiveness of the available influenza vaccines in the target populations. Cost-effectiveness models could then be implemented to evaluate the impact and benefit of different vaccination strategies.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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