

**Title**

Risk factors associated with hospitalisation for influenza-associated severe acute respiratory illness in South Africa: a case-population study

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AT: Contributed to data collation, analysis and discussions.

AS: Contributed to data interpretation and critical revision of the study

ST: Participated in data analysis

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

## **Abstract**

### *Background*

Influenza is a common cause of severe respiratory illness, but risk factors for hospitalization in low income settings with a high HIV prevalence are not well described. We aimed to assess risk factors associated with influenza-associated severe acute respiratory illness (SARI) hospitalisation in South Africa.

### *Methods*

We conducted a case-population study using data on risk conditions in patients hospitalised with SARI and the national prevalence of these conditions. Data on hospitalised cases were from the national SARI surveillance program while data on the referent population were from the latest national census or health and demographic surveillance surveys.

### *Findings*

From 2009 to 2012, we identified 3,646 (7.9%) of 46,031 enrolled cases of SARI that were associated with influenza infection. Risk factors associated with hospitalisation included previous history of smoking [case-population ratio (CPR) 3.82, 95% confidence interval (CI) 3.5-4.16], HIV infection (CPR 3.61, 95% CI 3.5-3.71), asthma (CPR 2.45, 95% CI 2.19-2.73), previous history of hospital admission in the past 12 months (CPR 2.07, 95% CI 1.92-2.23), and tuberculosis (CPR 1.85, 95% CI 1.68-2.02). When stratified by age, there is increased risk of hospitalization in those  $\leq 5$  years of age (CPR 3.07, 95% CI 2.93-3.21) and among those 35 years of age and above (CPR 1.23, 95% CI 1.28-1.18). Male sex (CPR 0.85, 95% CI 0.82-0.88) and completion of pneumococcal conjugate vaccination schedule in children  $< 5$  years of age (CPR 0.74, 95% CI 0.71-0.77) were associated with decreased risk of hospitalisation.

### *Conclusion*

These results identify groups at high-risk for severe influenza who should be considered potential targets for influenza vaccination in South Africa and similar settings.

### **Keywords:**

Influenza, risk factors, hospitalisation, vaccine.

## **BACKGROUND**

Influenza is a vaccine-preventable viral infection which can present with significant morbidity and mortality (1). Globally, there are an estimated 3-5 million severe cases and 300,000-500,000 deaths annually, of which the majority occur in low and middle income countries (2, 3). South Africa is a middle-income country with high incidence of HIV and tuberculosis. These underlying factors play a significant role in the presentation of seasonal influenza and its morbidity in Southern Africa.

National surveillance for influenza-associated hospitalizations in South Africa has estimated that 44% of patients admitted with acute respiratory infections testing positive for influenza are HIV-infected; in contrast, the national prevalence of HIV is 12% (4, 5). Studies from South Africa have suggested that high HIV prevalence in South Africa is associated with higher numbers of severe influenza-associated illness and thus more hospitalized cases (5-8).

Though data are considered insufficient to allow prioritization of strategies for influenza prevention and control in most Sub-Saharan African countries (3), the South Africa government provides influenza vaccination free for those 6 months – <5 years of age, >65 years of age, all pregnant women, healthcare workers and carers, and anyone >6 months of age with certain chronic underlying medical conditions (9, 10). Despite the existence of this policy for many years, procurement in the public immunization program is low and coverage remains approximately 5% (11). Other than HIV, most known risk conditions for influenza-associated hospitalisation, such as extremes of age and smoking, are derived from studies in developed countries with different health demographics or disease burden than sub-Saharan countries. The objective of this study was to identify risk factors and conditions which are associated with increased morbidity from influenza-associated severe respiratory illnesses in South Africa, a country with a background of high HIV endemicity, to guide influenza vaccination policy.

## **METHODS**

### **Study design**

This study uses a case-population design to evaluate risk factors for influenza-associated hospitalisation using data from the Severe Acute Respiratory Illness (SARI) surveillance programme and health and demographic surveillance in South Africa from 2009 to 2012.

### **Determination of risk factors among cases**

The SARI surveillance programme has been previously described (5). Briefly, SARI surveillance started in 2009 at 4 sentinel sites in South Africa located in 3 provinces: Gauteng Province (Chris Hani Baragwanath Academic Hospital, CHBAH), KwaZulu-Natal Province (Edendale Hospital), and Mpumalunga Province (Mapulaneng and Matikwana Hospitals). In 2010, one additional surveillance site was introduced in North West Province at Klerksdorp-Tshepong Hospital Complex (KTHC). A case of SARI was defined as a hospitalized person who had illness onset within 7 days of admission and met age-specific clinical inclusion criteria. These included children aged 2 days through <3 months who had physician-diagnosed sepsis or acute lower respiratory tract infection (LRTI); children aged 3 months through <5 years with physician-diagnosed LRTI (e.g., bronchitis, bronchiolitis, pneumonia, or pleural effusion), and persons >5 years of age who met the World Health Organization (WHO) case definition for severe acute respiratory infection: an acute respiratory illness with a history of fever or measured fever of  $\geq 38^{\circ}\text{C}$  and cough, with onset within the past 10 days, requiring hospitalization (12).

Every patient with the above criteria, admitted on any weekday, was eligible for enrollment; however, adult patients at the sentinel site in Gauteng Province were enrolled only on 2 out of 5 weekdays due to the large number of admissions and limited resources. All eligible patients were approached for inclusion into the study.

Consenting patients were enrolled by completing a structured questionnaire on demographic characteristics and current and past medical history through interview and review of medical records. Nasopharyngeal and oropharyngeal swabs (for patients >5 years of age) or nasopharyngeal aspirates (for those <5 years of age) were collected and transported in viral transport media at  $4-8^{\circ}\text{C}$  to the National Institute for Communicable Diseases (NICD) within 72 hours. Specimens were tested using the reverse transcription real-time polymerase chain reaction (RT-PCR) for influenza A and B viruses. HIV infection status was determined from results of testing undertaken as part of standard of care or through anonymized linked dried blood spot specimen testing by HIV PCR for children <18 months of age and by enzyme-linked immuno-sorbent assay (ELISA) for persons >18 months of age. Enrolled patients were followed until discharge or death.

For our study, cases included all enrolled hospitalised SARI patients who tested positive for influenza by RT-PCR.

### **Determination of risk factors among referent population**

Data on risk factors from South African national surveys were used for comparison and included the following (Table 1):

1. The National Census, 2011 (13): This is the most recent national census with an estimated population of 51,770,560 individuals.
2. South African National Health and Nutrition Examination Survey (SANHANES), 2013 (4): This was a national cross-sectional study conducted to provide critical information on the emerging epidemics of Non-Communicable Diseases (NCDs) in South Africa and to analyse social, economic, behavioural and environmental determinants of NCDs.
3. South African National HIV Prevalence, Incidence and Behavioural Survey (SABSSM) 2008 & 2012 (14): This was a multi-staged stratified cluster survey involving individuals of all ages living in South African households with statistical data on socio-behavioural and structural aspects that contribute to the spread of HIV infections in the population.
4. District Health Information System (DHIS), 2012 (15): This is a system where the National Department of Health routinely collects health information from all the primary health care clinics throughout South Africa.
5. Risk Equalisation Fund for 2007 (16): This study was done following the approval of the Social Health Insurance (SHI) policy by the South African National Department of Health to provide a baseline for cost evaluation of health policies and interventions.

Several risk factors are known to affect the risk of hospitalisation from influenza-associated SARI. The risk conditions evaluated for this study are limited to those which are prevalent in Africa and South Africa and for which we had data available; they are listed in Tables 1 & 2.

### **Statistical analysis**

The case-population study consists of comparing exposure to a condition or risk factor in patients presenting with a given disease or symptom (cases) with the exposure rate to this factor in the whole cohort or in the source population of cases (17). Similar to the case-control approach, the case-population approach measures the disproportionality of exposure between cases of a given disease and those exposed in a referent population, expressed as the case population ratio (CPR) (17). Our study compared the prevalence of demographic and medical conditions of cases enrolled in SARI surveillance with the national prevalence of these conditions to derive the age-specific and overall age-adjusted case-population ratios.

To estimate the actual number of influenza-associated SARI cases, the total number of enrolled SARI cases was adjusted for refusal to participate and non-enrolment in 3 of 5 adult wards at CHBAH by age group using study logs that tracked all SARI cases (enrolled and not enrolled) admitted at the sentinel sites. We assumed that the prevalence of influenza-associated cases and the prevalence of the exposure variables evaluated in this study among the influenza-associated cases were the same among enrolled and non-enrolled SARI cases. Using study logs, this adjustment (ranging from 1-7.8) was implemented because the proportion of cases enrolled varied each year by surveillance site depending on the age groups.

Cases were defined as patients hospitalised with SARI who tested positive for influenza as part of the SARI surveillance programme. The comparison population was the entire population of South Africa, identified from surveys and national health and demographic surveillance data. The exception to this was our analysis of the risk of influenza-associated hospitalization from mining; since all of those who reported a history of mining were working age adults from Gauteng Province, the comparison population for this potential risk factor was the Gauteng working population 15-65 years of age. The case-population ratio for factors associated with influenza-associated hospitalization was estimated as follows:

***Case-population ratio*** (CPR) =  $(a/x)/(b/y)$

Where

**a:** number exposed in the cases

**b:** number exposed in referent population

**x:** total number of cases

**y:** total number of referent population

Under the null hypothesis, the ratio of the number exposed to the risk condition of interest to the total number of individual cases ( $a/x$ ) should be the same as that in the source-population ( $b/y$ ), or CPR=1. A positive CPR suggests a positive association between the risk condition and increased hospitalisation due to influenza-associated SARI and vice versa. The age-specific and age-adjusted CPR [with associated 95% confidence interval (CI)] for each exposure variable assessed in the study was estimated using log-binomial regression. The statistical analysis was implemented using STATA version 13.1 (Stata Corporation, College Station, Texas, USA).

### **Ethical considerations**

The protocol of the SARI surveillance programme was approved by the University of the Witwatersrand Human Research Ethics Committee, Johannesburg, South Africa, Reference R14/41 Cohen and was deemed not to be research by the U.S. Centers for Disease Control and

Prevention, Atlanta, USA. Data from national health and demographic surveys were publicly available.

## **FINDINGS**

### **Description of patients enrolled in the SARI programme**

Between February 2009 and December 2012, a total of 18,590 patients were eligible and enrolled into SARI surveillance, of which 1425 (7.6%) tested positive for influenza virus. This was adjusted for age-specific differences in non-enrollment as described in the Methods to yield a total of 46,031 patients. After age-adjustment, the overall influenza detection rate was 7.9% (3646/46,031) with the highest detection rate in the 5-14 year age group (10.6%, 119/1124) and the lowest in the 45-54 year age group (6.9%, 395/5652; Table 2). There was no significant change in age distribution in the different influenza seasons.

### **Factors associated with influenza hospitalisation**

#### *Age*

The risk of hospitalization for influenza was elevated in children <5 years of age (CPR 3.07; 95% CI 2.93-3.21) and adults ≥35 years of age (CPR 1.23, 95% CI 1.28-1.18; Table 2 and 3, Figure 1) when compared to children aged 5-14 years.

#### *Social and economic factors*

Among those aged 15 years and above, previous history of smoking, i.e., stopping use of all tobacco more than 4 weeks prior to presentation, was much more common among the influenza-associated SARI patients than in the referent population (CPR 3.82; 95% CI 3.50-4.16). Current alcohol use or within the past one month among adults (>15years) did not suggest any increase in risk of hospitalisation (CPR 0.51, 95% CI 0.47-0.55). Similarly, the prevalence of adults with a history of mining was higher among hospitalised influenza-associated SARI cases compared with the Gauteng working population (CPR 1.34: 95% CI 1.07-1.67).

#### *Co-morbidities*

Influenza-associated SARI patients were twice as likely to have been hospitalized in the past 12 months compared to the general population (CPR 2.07: 95% CI 1.92-2.23; Table 2 and 3). HIV was found to be 4 times more prevalent among the influenza-associated SARI cases when compared to the general South African population (CPR 3.56; 95% CI 3.50-3.72). Furthermore, HIV co-infected influenza cases identified in SARI were more likely to be on highly active anti-retroviral therapy (HAART) than the referent HIV-infected population.

A history of active tuberculosis and a history of asthma were each twice as common among the influenza-associated SARI cases compared to the referent population (CPR 1.85; 95% CI 1.68-2.02 and CPR 2.45; 95% CI 2.19-2.73, for tuberculosis and asthma, respectively). Among children



aged <5 years, the proportion of children among SARI cases who completed the 3<sup>rd</sup> dose of PCV was less than the proportion seen in the general population (CPR 0.74; 95% CI 0.71-0.77). Malnutrition was not associated with increased risk of hospitalization for influenza in our study population.

## DISCUSSION

Based on the strength of the associations we found in our analysis, we can classify the risk conditions into high risk (CPR >2) or low risk (CPR ≤2). We can also classify risk conditions by their public health importance: high population prevalence (>20%) and low population prevalence (<20%). As shown in Table 3, the results of this study are consistent with current influenza vaccination policy in South Africa, which recommends influenza vaccination for children <5 years, adults >65 years and those with underlying medical conditions such as HIV (9). Other risk groups that may be considered for influenza vaccination based on these results are those with asthma, those with a previous history of hospital admission in last 1 year, and those with a previous history of smoking of cigarettes. In addition, there may be benefit to targeted vaccination among miners and those with tuberculosis, but it may yield a smaller public health benefit compared with the other risk conditions. Sex, use of alcohol and malnutrition do not seem to be contributory factors to influenza-associated hospitalisations in severe respiratory infections in South Africa.

The increased prevalence of children (especially those <5 years) among influenza-associated hospitalised patients found in this study is similar to findings in studies from the U.S., the Philippines, Spain, China, Thailand and other European countries (18-23). In a global pooled analysis, the risk of infection and hospitalisation was also found to be highest in children (24). This evidence has been the basis for consistent inclusion of these risk groups in the WHO recommended vaccination groups (3).

As has been shown in previous studies of this influenza surveillance data from South Africa, there is also an increase in prevalence among adults (>35 years) with increases at 35-44 years and >65 years (5). The increased prevalence among young adults may be due to a high prevalence of HIV infection, which suggests that vaccinating HIV-infected adults and children as well as the elderly may be a good strategy.

HIV is the most common underlying risk condition among the SARI cohort. In contrast to HIV non-endemic countries like United States (26) and Spain (27), HIV has been implicated as a risk factor for influenza hospitalisation and severe disease in highly endemic settings like South Africa (5) and Kenya (28). Cohen, *et al.*, demonstrated that HIV-infected patients had a 4-8 times greater hospitalisation incidence, longer inpatient hospital admission by 2-7 days and more deaths when compared to HIV-uninfected patients (5). HIV infection is also associated with increased magnitude and prolonged duration of influenza viral shedding (29). Unexpectedly, we found that more HIV-influenza co-infected hospitalised patients were on HAART compared to

HIV-infected individuals in the general population. This could be from confounding factors like staging of HIV infection or non-adherence to treatment, which we did not have data for in this analysis. It could also be due to under-reporting of HAART utilisation in the general population compared with the SARI cohort.

This study found a 4-fold higher prevalence of previous smoking among hospitalised SARI patients than in the general population. Other studies have also identified smoking as a risk factor for increased influenza severity (30) but many were not statistically significant after adjusting for confounders (27, 31). Our findings could be explained by the fact that most of the SARI patients are female, who are more likely to be HIV-infected, and patients may quit smoking once sick, prior to hospital admission. In many studies, rates of hospitalization from seasonal influenza viruses seem to be higher in males than females (32-36). The reverse was found in this study, which could be as a result of high HIV infection prevalence among females (70% of SARI cases) predisposing them to influenza infection and hospitalisation. Our study suggested that consumption of alcohol currently or within the past month was associated with a reduction in risk of hospitalisation from influenza. There are few studies on seasonal influenza and alcohol use to explain this finding, and we were unable to adjust for duration and intensity of alcohol consumption which may affect these findings.

The increased risk associated with mining in this study is similar to a U.S. study from the 1918 pandemic which estimated that coal-miners with influenza-associated pneumonia had a 44% mortality rate compared to a 30% overall death rate among all males aged 15 years and over in Ohio (37). Mining has been associated with tuberculosis in South Africa (38, 39), and active tuberculosis may be a risk factor for increased influenza severity (40). Our results show that history of diagnosis with active tuberculosis was almost double within the SARI cohort compared to the expected national estimate, which is consistent with other studies from South Africa (41).

As we found in our study, a study in Netherlands showed that previous history of hospitalisation in the past year is an independent risk factor for influenza-associated respiratory hospitalisation (42). Likewise, among the elderly in Manitoba, Canada, approximately 40% of all those discharged for influenza-associated conditions and approximately 65% of those who died had been discharged from hospital during the previous vaccination season (43). Malnutrition does not attain a statistically significant CPR in our study consistent with mixed results reported by others (44-48).

Our data suggests a 25% decrease in prevalence of influenza-associated respiratory hospitalizations among children who completed their pneumococcal vaccination compared to the referent. This is consistent with a double blind, randomised placebo-controlled trial in South Africa which showed that pneumococcal vaccination in children not only prevents invasive pneumococcal diseases but also prevents 31% of pneumonias associated with respiratory viruses in children in hospital (49). This is likely due to the well-described increased risk of pneumococcal disease following influenza infection, which could be prevented by influenza vaccination.

This study has some limitations. Firstly, the SARI cohort may not be a geographically and racially representative sample of the entire South African population, which is what was available as the referent population from the national surveys. CHBAH is one of the four sentinel surveillance sites in this study and contributed 62% of the entire SARI data. Secondly, the use of an ecological referent comparison did not allow for control of individual level confounding to derive an unbiased effect estimate of each risk factor, as we are restricted to basic socio-demographic variables like sex and age. Thirdly, data in SARI and South African population surveys were obtained using different methodologies. Clinical data among SARI cases was obtained through oral interviews and review of hospital records, whereas the national health surveys were carried out without access to participant's hospital records. This review of the medical records could have led to identification of more risk conditions in the SARI cohorts causing overestimation between the two groups, such as with HAART. Since our comparison data were derived for demographic surveys which are reported and summarised in certain age groups of relevance, analysis into smaller age groups were not be possible which could yield more specific groups at highest risk for prioritization of the limited available vaccine. Lastly, pregnant women have been demonstrated in several studies to have increased severity of influenza disease and rate of hospitalisation (5, 24, 50). Since few pregnant women were enrolled in our study because review of admissions to maternity wards during recruitment was not always consistent, no risk analysis was carried out in this risk group in our study.

Despite these limitations, our results were consistent with existing medical literature from other contexts in identifying age, previous smoking history, HIV, tuberculosis, asthma, mining and previous history of hospital admission as factors influencing influenza-associated hospitalisation.

In conclusion, the findings from this study can potentially help policy-makers make evidence-based decisions on how to target influenza treatment and prevention programs, such as

vaccination, and can lead to more effective allocation of resources within countries like South Africa with a high prevalence of HIV.

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Table 1: Sources of data on the prevalence of risk factors in South African referent population

Risk factor	Definition of risk factor	Referent population source					
		Census	SANHANES <sup>1</sup>	SABSSM <sup>2</sup>	DHIS <sup>3</sup>	REF <sup>4</sup>	Age category (years) <sup>5</sup>
<b>Age</b>	Number in years	+	-	-	-	-	5
<b>Sex</b>	Sex designation	+	-	-	-	-	5
<b>Alcohol</b>	Alcohol use in the past one month	-	-	+	-	-	4 (>15 years)
<b>Previous smoking</b>	Number who quit smoking more than 4 weeks prior to presentation	-	+	-	-	-	20 (>15 years)
<b>History of mining</b>	Number who have ever worked in a mine	+	-	-	-	-	Unadjusted for age
<b>History of hospital admission in past 1 year</b>	Number who were admitted in the hospital in the last 12 months prior to presentation	-	+	-	-	-	20 (>15 years)
<b>HIV</b>	Number infected with HIV virus	-	+	+	-	-	15
<b>Highly Active Anti-Retroviral Therapy (HAART)</b>	Number on HIV treatment	-	+	-	-	-	15
<b>Tuberculosis</b>	History of past or present diagnosis of active tuberculosis	-	+	-	-	-	10
<b>Asthma</b>	History of diagnosis with bronchial asthma	-	-	-	-	+	5
<b>Malnutrition</b>	Underweight for age less than 2 standard deviations from Z-score	-	+	-	-	-	Unadjusted for age
<b>3rd dose of pneumococcal conjugate vaccine (PCV)</b>	Completion of 3 <sup>rd</sup> dose of PCV	-	-	-	+	-	Unadjusted for age

<sup>1</sup>SANHANES: South African National Health and Nutrition Examination Survey<sup>2</sup>South African National HIV Prevalence, Incidence and Behavioural Survey<sup>3</sup>DHIS: District Health Information System<sup>4</sup>REF: Risk Equalisation Fund<sup>5</sup>This shows the age intervals each risk factor was obtained stratified in the source population. Example History of hospital admission in past 1 year: 20 (>15years) implies that from SANHANES, the number of people who were admitted to hospital in the past 1 year where categorised in intervals of 20 years starting from those above 15 years.

Table 2: Comparison of prevalence of potential risk factors among patients hospitalised with influenza-associated severe acute respiratory illness (SARI) at 4 sites in South Africa from 2009 to 2012 with the prevalence in the South African population

		Un-adjusted SARI cases	Adjusted SARI (cases)			South African Population (comparison group)			Case Population Ratio (CPR) = (x/y)				
			Exposed (n)	Total (n)	Proportion (x)	Exposed (n)	Total (n)	Proportion (y)					
											95% Confidence interval		
	Demographic factors									CPR <sup>i</sup>	Lower	Upper	p value
Age in years	<5	634	NA	1229	0.34	NA	5685452 <sup>a</sup>	0.11	3.07	2.93	3.21	<0.001	
	5-14	69	NA	119	0.03	NA	9414637 <sup>a</sup>	0.18	0.18	0.15	0.21	<0.001	
	15-24	76	NA	227	0.06	NA	10378019 <sup>a</sup>	0.20	0.31	0.27	0.35	<0.001	
	25-34	186	NA	579	0.16	NA	9088327 <sup>a</sup>	0.18	0.9	0.84	0.97	<0.001	
	35-44	207	NA	575	0.16	NA	6416385 <sup>a</sup>	0.12	1.27	1.18	1.37	<0.001	
	45-54	104	NA	395	0.11	NA	4838572 <sup>a</sup>	0.09	1.16	1.06	1.27	<0.001	
	55-64	75	NA	275	0.08	NA	3183176 <sup>a</sup>	0.06	1.23	1.09	1.37	<0.001	
	65+	74	NA	245	0.07	NA	2765992 <sup>a</sup>	0.05	1.27	1.12	1.43	<0.001	
	Total	1425	NA	3646	1.01	NA	51770560 <sup>a</sup>	0.99	0.97 <sup>ii</sup>	0.94	1.00	0.054	
Male sex			1492	3646	0.41	25188791 <sup>a</sup>	51770560 <sup>a</sup>	0.49	0.85	0.82	0.88	<0.001	
Lifestyle factors													
Alcohol (>15years)		328			2298	0.14	3830 <sup>b</sup>	13828 <sup>b</sup>	0.28	0.51	0.47	0.55	<0.001
Previous smoking(>15years)		371			2298	0.16	615 <sup>c</sup>	15372 <sup>c</sup>	0.04	3.82	3.50	4.16	<0.001
Occupational history of mining (15-65 years)		74			1634	0.05	98125 <sup>a</sup>	2894777 <sup>a</sup>	0.03	1.34	1.07	1.67	0.011
Comorbidities													
History of hospital admission in past 1 year (15 years)													
		655			3646	0.29	670 <sup>c</sup>	7361 <sup>c</sup>	0.09	2.07	1.92	2.23	<0.001

<i>HIV</i>	<b>1703</b>	<b>3646</b>	<b>0.47</b>	<b>3459<sup>d</sup></b>	<b>28685<sup>d</sup></b>	<b>0.12</b>	<b>3.61</b>	<b>3.50</b>	<b>3.72</b>	<0.001
<i>Highly Active Anti-Retroviral Therapy</i>	<b>639</b>	<b>1703</b>	<b>0.53</b>	<b>1995000<sup>d</sup></b>	<b>6405000<sup>d</sup></b>	<b>0.31</b>	<b>1.62</b>	<b>1.49</b>	<b>1.76</b>	<0.001
<i>Tuberculosis</i>	<b>260</b>	<b>2298</b>	<b>0.11</b>	<b>881<sup>c</sup></b>	<b>15029<sup>c</sup></b>	<b>0.06</b>	<b>1.85</b>	<b>1.68</b>	<b>2.02</b>	<0.001
<i>Asthma</i>	<b>151</b>	<b>3646</b>	<b>0.04</b>	<b>821809<sup>e</sup></b>	<b>51770560<sup>e</sup></b>	<b>0.02</b>	<b>2.45</b>	<b>2.19</b>	<b>2.73</b>	<0.001
<i>Malnutrition {Underweight for age (0-3 years)}</i>	<b>31</b>	<b>672</b>	<b>0.05</b>	<b>64<sup>c</sup></b>	<b>1090<sup>c</sup></b>	<b>0.06</b>	<b>0.78</b>	<b>0.52</b>	<b>1.19</b>	0.258
<i>3rd dose of Pneumococcal Conjugate Vaccine (&lt;5)</i>	<b>854</b>	<b>1229</b>	<b>0.69</b>	<b>5355696<sup>f</sup></b>	<b>5685452<sup>f</sup></b>	<b>0.94</b>	<b>0.74</b>	<b>0.71</b>	<b>7.00</b>	<0.001

i: All CPRs given are crude unless otherwise indicated

ii: age-adjusted CPR

Data source for South African population

a: National Census 2011

c: SANHANES 2013

e: REF: Risk Equalisation

b: South African National HIV Prevalence, Incidence and Behavioural Survey 2008

d: South African National HIV Prevalence, Incidence and Behavioural Survey 2012

f: District Health Information System (DHIS) 2012

Table 3: Identification of priority conditions for influenza vaccination based on the strength of association and population prevalence of the various risk conditions identified in this study

Prevalence in the general population			
		Low <10%	High >10%
Case population ratio (CPR)	Low <2.0	Tuberculosis (Prevalence 6%, CPR 1.85)  History of mining (3%, 1.34)  Elderly 65+ years (5%, 1.27)	
	High 2.0	Previous history of smoking (>15 years) (4%, 3.82)  Asthma (4%, 2.45)  Previous history of admission in the past 1year (9%, 2.07)	HIV (12%, 3.61)  Children <5 years (11%, 3.07)

Figure 1: Case Population Ratio and 95% Confidence Intervals by age group of influenza-associated SARI patients compared to South African population.

