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

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ABSTRACT

Background: Influenza is a common cause of severe respiratory illness, but risk factors for hospitalisation 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 3646 (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 hospitalisation in those ⩽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.

1. 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 hospitalised cases [5–8].

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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.

2. Methods

2.1. 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.

2.2. 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 Mpumalanga 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 hospitalised 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 $\geqslant$38 °C and cough, with onset within the past 10 days, requiring hospitalisation [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 °C to the National Institute for Communicable Diseases (NICD) within 72 h. 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.

2.3. 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 and 2.

2.4. 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-enrollment 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 to 7.8) was implemented because the

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