Influenza-associated morbidity and mortality in South Africa

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of

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Declaration

I, Cheryl Cohen, declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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28th day of October 2014

Publications directly contributing to this thesis and role of the student in these studies

This thesis consists of two components. The first two papers are analyses of national vital statistics data aiming to estimate the excess mortality associated with influenza in South Africa. The last three papers include analyses of data from a surveillance programme for severe acute respiratory illness (SARI) and influenza.

For the first two papers I conceived the analyses, obtained the data, conducted the analyses, and drafted and revised the manuscripts. For the final three papers I wrote the initial surveillance protocol in 2009 and was principal investigator for the grant that funded the surveillance. I hired the team of staff needed to implement and manage the surveillance programme and oversaw all aspects of initial and ongoing implementation. This surveillance programme provided the data used in the final three manuscripts contributing to this PhD.

1. **Cohen C**, Simonsen L, Kang J, Miller M, McAnerney J, Blumberg L, Schoub B, Madhi S, Viboud C. Elevated Influenza-Related Excess Mortality in South African Elderly Individuals, 1998–2005. Clinical Infectious Diseases 2010; 51(12):1362–1369
2. **Cohen C**, Simonsen L, Sample J, Kang J, Miller M, Madhi SA, Campsmith M, Viboud C. Influenza-related mortality among adults age 25-54 years with AIDS in South Africa and the United States of America. Clinical Infectious Diseases 2012; 55(7), 996-1003.
3. **Cohen C**, Walaza S, Moyes J, Groome M, Tempia S, Pretorius M, Hellferscee O, Dawood H, Chhagan M, Naby F, Haffejee S, Variava E, Kahn K, Nzenze S, Tshangela A, von Gottberg A, Wolter N, Cohen AL, Kgokong B, Venter M, Madhi SA. Epidemiology of viral-associated acute

lower respiratory tract infection amongst children aged <5 years in a high HIV prevalence setting, South Africa, 2009-2012. Pediatric Infectious Diseases Journal 2014 (In press).

4. **Cohen C**, Walaza S, Moyes J, Groome M, Tempia S, Pretorius M, Hellferscee O, Dawood H, Haffejee S, Variava E, Kahn K, Tshangela A, von Gottberg A, Wolter N, Cohen AL, Kgokong B, Venter M, Madhi SA. Epidemiology of severe acute respiratory illness (SARI) among adults and children ≥5 years age in a high HIV-prevalence setting, 2009-2012. Submitted.

5. **Cohen C**, Moyes J, Tempia S, Groome M, Walaza S, Pretorius M, Dawood H, Chhagan M, Haffejee S, Variava E, Kahn K, Tshangela A, von Gottberg A, Wolter N, Cohen AL, Kgokong B, Venter M, Madhi SA. Severe influenza-associated respiratory infection in high HIV prevalence setting, South Africa, 2009-2011. Emerging Infectious Diseases 2013; Nov;19(11):1766-74.

Abstract

Introduction

Data on the burden of influenza-associated hospitalisation and mortality in relation to other aetiologies of pneumonia as well as risk groups for severe and complicated disease are important to guide influenza prevention policy.

Materials and methods

We estimated influenza-related deaths as excess mortality above a model baseline during influenza epidemic periods from monthly age-specific mortality data using Serfling regression models. For individuals aged ≥65 years from South Africa and the United States of America (US) we evaluated influenza-related deaths due to all causes, pneumonia and influenza (P&I) and other influenza-associated diagnoses for 1998-2005. For adults with acquired immune deficiency syndrome (AIDS) aged 25-54 years in South Africa (1998-2005) and the US (pre-highly active antiretroviral therapy (HAART) era: 1987-1994; HAART era: 1997-2005) we estimated deaths due to all-causes and P&I.

We prospectively enrolled individuals with severe acute respiratory illness (SARI) at six hospitals in four provinces of South Africa from 2009-2012. Using polymerase chain reaction, respiratory samples were tested for ten respiratory viruses and blood for pneumococcal DNA. Cumulative annual SARI incidence was estimated at one site with available population denominators.

Results

Age-standardised excess mortality rates amongst seniors were higher in South Africa than in the US (545 vs. 133 per 100,000 for all-causes, p<0.001; 63 vs. 21 for P&I, p=0.03). The mean percent of winter deaths attributable to influenza was 16% in South Africa and 6% in the US, p<0.001. For all respiratory causes, cerebrovascular disease and diabetes age-standardised excess death rates were 4- to 8-fold greater in South Africa than in the US, and the percent increase in winter deaths attributable to influenza was 2- to 4-fold higher.

In the US pre-HAART, influenza-related mortality rates in adults with AIDS were 150- (95% confidence interval (CI) 49-460) and 208- (95% CI 74-583) times greater than in the general population for all-cause and P&I respectively and 2.5- (95% CI 0.9-7.2) and 4.1- (95% CI 1.4-13) times higher than in seniors. Following HAART introduction, influenza-related mortality in adults with AIDS dropped 3-6 fold but remained elevated compared to the general population (all cause relative risk (RR) 44, 95% CI 16-12); P&I RR 73, 95% CI 47-113). Influenza-related mortality in South African adults with AIDS was similar to that in the US in the pre-HAART era.

From 2009-2012 we enrolled 8723 children age <5 years with SARI. The human immunodeficiency virus (HIV) prevalence among tested children was 12% (705/5964). The overall prevalence of respiratory viruses identified was 78% (6517/8393), which included 26% (n=2216) respiratory syncytial virus (RSV) and 7% (n=613) influenza. The annual incidence of SARI hospitalisation in children age <5 years ranged from 2530-3173 per 100,000 and was 1.1-3-fold greater in HIV-infected than HIV-uninfected children. In multivariable analysis, compared to HIV-uninfected children, HIV-infected children were more likely to be hospitalised >7 days (odds ratio (OR) 3.6, 95% CI 2.8-5.0) and had a 4.2-fold (95% CI 2.6-6.8) higher case-fatality ratio.

From 2009-2012, we enrolled 7193 individuals aged ≥5 years with SARI. HIV-prevalence was 74% (4663/6334) and 9% (621/7067) tested influenza positive. The annual incidence of SARI hospitalisation in individuals age ≥5 years ranged from 325-617 per 100,000 population and was 13 to 19-fold greater in HIV-infected individuals (p<0.001). On multivariable analysis, compared to HIV-uninfected individuals, HIV-infected individuals were more likely to be receiving tuberculosis treatment (OR 2.1, 95% CI 1.3-3.2), have pneumococcal infection (OR 2.2, 95% CI 1.6-2.9), be hospitalised for longer (>7 days rather than <2 days OR 2.4, 95% CI 1.8-3.2) and had a higher case-fatality ratio (8% vs. 5%; OR 1.6, 95% CI 1.2-2.2), but were less likely to be infected with influenza (OR 0.6, 95% CI 0.5-0.8).

Influenza was identified in 9% (1056/11925) of patients of all ages enrolled in SARI surveillance from 2009-2011. Among influenza case-patients, 44% (358/819) were HIV-infected. Age-adjusted influenza-associated SARI incidence was 4-8 times greater in HIV-infected (186-228 per 100,000 population) than HIV-uninfected (26-54 per 100,000 population). On multivariable analysis, compared to HIV-uninfected individuals, HIV-infected individuals with influenza-associated SARI were more likely to have pneumococcal co-infection (OR 2.3, 95% CI 1.0-5.0), influenza type B than type A (OR 1.6, 95% CI 1.0-2.4), be hospitalised for 2-7 days (OR 2.8 95% CI 1.5-5.5) or >7 days (OR 4.5, 95% CI 2.1-9.5) and more likely to die (OR 3.9, 95% CI 1.1-14.1).

Discussion and conclusions

The mortality impact of seasonal influenza in the South African elderly may be substantially higher in an African setting compared to the US. Adults with AIDS in South Africa and the US experience substantially

elevated influenza-associated mortality rates, which although lessened by widespread HAART treatment does not completely abrogate the heightened risk for influenza illness. HIV-infected children and adults also experience substantially elevated incidence of hospitalisation for influenza-associated SARI and have higher case-fatality ratios. Influenza is commonly detected amongst children (7%) and adults (9%) with SARI. Less frequent identification of influenza amongst HIV-infected than -uninfected individuals aged ≥5 years likely reflects increased relative burden and role of other opportunistic pathogens such as pnuemococcus and *Pneumocystis jirovecii*. Improved access to HAART for HIV-infected individuals and vaccination against influenza virus amongst HIV-infected individuals, young children and the elderly, where the influenza burden is great may reduce the high burden of hospitalisations and mortality associated with influenza.

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List of abbreviations

AIDS – Acquired immune deficiency syndrome

ASSA – Actuarial Society of South Africa

CDC – Centers for Disease Control and Prevention

CI - Confidence interval

CVD - Cerebrovascular disease

ELISA – Enzyme-linked immunosorbent assay

HAART – Highly active antiretroviral therapy

HIV – Human immunodeficiency virus

ICD - International Classification of Diseases

ICU – Intensive care unit

IHD - Ischaemic heart disease

OR – Odds ratio

P&I - Pneumonia and influenza

PCR – Polymerase chain reaction

PCV – Pneumococcal conjugate vaccine

PMTCT – Prevention of mother-to-child transmission of HIV

RR – Relative risk

RSV – respiratory syncytial virus

SA – South Africa

SARI – Severe acute respiratory illness

SD – Standard deviation

TIV – Trivalent inactivated influenza vaccine

US – United States of America

WHO – World Health Organization

Chapter 1 Introduction

Pneumonia is the commonest cause of death amongst children aged less than five years globally, and the majority of this disease burden occurs in sub-Saharan Africa and South East Asia.[1-3] In South Africa, pneumonia and influenza (P&I) was the second leading underlying natural cause of death amongst persons aged 0-14 and 15-49 years from 2009-2010[4] and pneumonia is an important cause of morbidity and mortality in human immunodeficiency virus (HIV)-infected adults and children.[5;6] Influenza is an important cause of pneumonia and approximately 8-10% of all cases of pneumonia test positive for influenza.[7]

1.1 Influenza virology, clinical manifestations and seasonality

The influenza virus is a negative stranded RNA virus with a segmented genome. There are 3 types of influenza virus: A, B and C, but only influenza A and B cause widespread outbreaks.[8] Influenza A viruses are divided into subtypes based on antigenic differences of the haemaglutinin and neuraminidase surface glycoproteins. There have been more than 14 haemaglutinin and more than 8 neuraminidase subtypes recovered from birds but only 3 haemaglutinin subtypes (H1, H2 and H3) and two neuraminidase subtypes (N1 and N2) have circulated stably in the human population. Influenza B has only one subtype but two antigenically distinct lineages (Victoria and Yamagata) which co-circulate globally. Circulating influenza viruses evolve constantly by accumulating point mutations in the surface glycoproteins. This evolution is known as “antigenic drift” and may allow the virus to evade immune recognition and contributes to annual influenza epidemics. This antigenic drift is the reason why seasonal influenza vaccines need to be updated each year. Influenza virus A subtypes may also be generated by a major genetic reassortment (known as “antigenic shift”) which gives rise to a virus that is

substantially antigenically different from viruses that have caused infection in humans over the previous years and have the potential to cause a pandemic.[9;10]

The most recent influenza pandemic virus was influenza A(H1N1)pdm09 which emerged globally in April 2009. The virus was first identified in Mexico and the US but rapidly spread to the rest of the world with the first case detected in South Africa on 14 June 2009.[11-13] Initial reports suggested that the novel virus was associated with high case-fatality ratios. Later studies estimated the mortality burden of the virus to be similar to that of seasonal influenza but characterised by a substantially younger age distribution of cases, leading to greater years of life lost than a typical influenza season.[14]

Influenza causes a wide range of clinical illness ranging from asymptomatic infection to severe hospitalised disease and death.[8] Influenza typically presents with sudden onset of fever accompanied by headache, sore throat, myalgia, malaise anorexia and dry cough.[9] Symptoms may be atypical in young children and the elderly. The commonest complication of influenza is pneumonia which may be a primary viral pneumonia or secondary bacterial pneumonia, most commonly causes by *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae* and *Streptococcus pyogenes.* A wide range of other complications may occur less commonly, including neurologic, cardiac and musculoskeletal disease.

Disease due to influenza is highly seasonal in temperate countries where epidemics generally occur each year with minimal virus circulation between epidemics.[8] In tropical countries influenza may circulate throughout the year with one or two annual peaks which may be related to the rainy season or other climatic events.[15]

1.2 Risk groups for severe influenza

There are a number of established risk groups for severe influenza.[16;17;17;18] Risk groups include individuals at the extremes of extremes of age (≥65 years and <2 years), pregnant women and individuals with underlying chronic illness such as cardiac, respiratory and renal disease, diabetes and metabolic disorders and immunosuppression. An additional risk group which came to prominence during the 2009 influenza pandemic was persons with obesity. In addition, pregnancy which had been an established risk group prior to the 2009 pandemic was identified as a major risk factor for severe pandemic influenza.[19;20]

In 2012, the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunisation (SAGE) published an updated position paper on influenza vaccines.[17] In this paper, 5 main groups were recommended to be targeted for influenza vaccination: pregnant women (highest priority), children aged 6-59 months, the elderly, individuals with specific chronic medical conditions and healthcare workers. The paper also emphasised the need for country-specific information about risk groups, disease burden and cost-effectiveness to aid local decision making about target groups and timing of vaccination.

In sub-Saharan Africa and South Africa, HIV-infected individuals are a group of particular importance due to the extremely high burden of underlying HIV in the region. It is estimated that there are more than 5 million HIV-infected individuals living in South Africa.[21;22] In South Africa in 2009, the HIV prevalence amongst antenatal attendees was 29%.[23;24] The interaction between HIV and influenza is discussed in Chapter 4 and 7. Children aged <5 years and particularly those aged <1 year as well as the elderly aged ≥65 years are another important risk group for severe influenza outcomes.[17;25]

It has been suggested that the mortality burden associated with the 1918 and 2009 influenza pandemics was greatest in low-income countries.[14;26;27] Possible contributing factors include high baseline mortality rate, poor nutritional status, high prevalence of comorbid conditions, young age distribution of population, poverty and poor access to health care.[27] While there are numerous published studies evaluating seasonal influenza-related mortality in more affluent northern hemisphere and tropical countries,[28-30] only 2 studies provide information on mortality associated with influenza in Africa and they are geographically and temporally limited.[31;32]

1.3 Influenza in Africa

A systematic review of research published from 1980 to 2009 on seasonal influenza epidemiology in sub-Saharan Africa identified only 49 articles.[33] While a fair amount of data was available on the proportion of patients with acute respiratory illness testing positive for influenza from different settings, data were lacking in many other areas. Particular gaps identified included representative data on influenza seasonality, data on influenza incidence and burden, data on case-fatality ratios amongst patients with influenza, data on the contribution of influenza to acute respiratory illness amongst hospitalised adults, economic burden data and data on the interaction between influenza and prevalent disorders in Africa such as HIV, tuberculosis and malaria. The authors concluded that data from sub-Saharan Africa were insufficient to allow most countries to prioritise strategies for influenza prevention and control.

Concern about the poor capacity for surveillance and detection of influenza in Africa, coupled with outbreaks of influenza A(H5N1) on the African continent from 2006 have led to an increasing international interest in strengthening the capacity for influenza surveillance in the African region.[34-37]

Technical and financial support has been provided to various African countries by a number of partners including the WHO, the United States of America (US) Centers for Disease Control and Prevention (CDC), other US government agencies, the international network of the Institute Pasteur and the National Institute for Communicable Diseases in South Africa.[35] In addition, a number of African networks and initiatives focusing on influenza surveillance and research have been established, these include the Africa Flu Alliance, the African Network for Influenza Surveillance and Epidemiology (ANISE) and the Strengthening Influenza Sentinel Surveillance in Africa (SISA) project.[34;35;38-40] These initiatives have led to an unprecedented expansion of influenza surveillance activities in the African region. More than 25 countries now contribute influenza specimens to WHO and more than 6000 specimens are contributed each year.[40;41] As many of these programmes are largely supported by external funds, critical challenges now exist regarding the sustainability of these networks. In 2012, a supplement to the Journal of Infectious Diseases entitled "Influenza in Africa" was published including 25 articles from 16 African countries. These articles begin to address some of the data gaps within the region and include descriptions of the 2009 influenza pandemic in the region.[35] While the supplement addresses some of the data gaps, data still remain limited on influenza burden, mortality, interaction with underlying conditions prevalent in Africa and economic impact.

1.4 Influenza surveillance and control in South Africa

South Africa has operated a sentinel surveillance network for influenza-like illness (ILI), the "Viral Watch" programme, since 1984.[42] This programme has provided valuable data on the timing of the influenza season and circulating influenza virus strains each year. The system does, however, have a number of limitations, including lack of data from patients with more severe respiratory illness, lack of data on burden and severity of influenza and inability to provide data on risk groups for severe influenza. In order to address these gaps, the severe acute respiratory illness (SARI) surveillance

programme was established in 2009.[43] Details of this programme are described in Chapter 2 Methods Section 2.2.

Influenza virus circulation in South Africa in highly seasonal and occurs mainly during the Southern Hemisphere winter.[42] South Africa has published annual recommendations for influenza vaccination since 2005.[44] In addition, since 2009, a more comprehensive guideline for the prevention and management of influenza has been published online and updated annually.[45] Groups recommended to receive influenza vaccine in South Africa include pregnant women, persons (adults or children) at increased risk of complications of influenza due to the presence of underlying medical conditions (including HIV infection), residents of chronic care facilities, medical and nursing staff and persons aged >65 years. Trivalent inactivated influenza vaccine (TIV) distribution in the private sector in South Africa varies each year but has averaged approximately 1 million doses each year from 2006 through 2012 (B. Greenblatt, personal communication). TIVs have been available to a limited extent (<40 000 doses each year) through the public health system since 1996, from 2005-2009 annual doses distributed in the public sector ranged from 128,000 to 205,000 each year (B. Greenblatt and W. Ramkrishna, personal communication). In 2010, 1,022,000 TIV doses were distributed and these were supplemented with approximately 3,5 million doses of monovalent influenza A(H1N1)pdm09 vaccine donated by the WHO. Since 2010, TIV distribution in the public sector has dropped somewhat, and was estimated at 850,000 doses in 2012 (W. Ramkrishna, personal communication). The population of South Africa was estimated to be 51,770,560 in 2011[46] with an estimated 70% accessing initial care in the public sector in 2010.[47] Using these data, in 2007 <3% of the South African population received influenza vaccination. In contrast, ~33% of the US general population had received the annual influenza vaccine in the 2008-09 season, while coverage in US seniors have remained at ~65% since the mid 1990s.[48] Oseltamivir

treatment is made available free of charge through the public health sector in South Africa, although challenges in procurement and distribution may limit practical availability.

1.5 Justification for the research and statement of the problem

There are few published estimates of influenza-associated severe morbidity and mortality in Africa. A contributing factor is the fact that such studies are difficult to conduct in a low- or middle-income country setting. Direct estimates of hospitalisation and mortality rates require resource-intensive surveillance programmes, while indirect estimates require high quality vital statistics or other routine surveillance data sources. The perception that influenza does not cause substantial mortality in Africa may contribute to the underutilisation of influenza vaccines, antivirals and other control measures in this setting.[49]

Estimates of seasonal influenza hospitalisation and mortality burden are useful to identify groups at elevated risk of mortality and to identify geographical high risk areas. Data on risk groups for severe hospitalised influenza and mortality, as well as data on the relative contribution of influenza to the syndrome of pneumonia in relation to other pathogens are important to guide decision-making around seasonal and pandemic influenza prevention and control measures including vaccination in South Africa and other countries in Africa. In addition, it is important to obtain baseline seasonal estimates of morbidity and mortality burden, to allow comparison against the impact of the influenza A(H1N1)pdm09 2009 pandemic.

1.6 Aims and Objectives

Introduction

Aims: To evaluate the burden of hospitalisations and mortality associated with influenza in South Africa, the relative contribution of influenza to the syndrome of SARI in relation to other respiratory viruses and the epidemiologic characteristics of patients with influenza-associated SARI. These data will inform policy on preventive strategies such as influenza vaccination as well as facilitate planning for future influenza pandemics in South Africa.

Objectives:

1. To estimate the excess mortality associated with influenza in South African adults ≥65 years of age from 1998 through 2005 and compare these estimates to those from the US for the same period
2. To estimate the excess mortality associated with influenza in South African young adults with acquired immune deficiency syndrome (AIDS) aged 25-54 years of age from 1998 through 2005 and compare these estimates to those from the US from 1987 through 2005
3. To describe the epidemiologic characteristics of HIV-infected and -uninfected children aged <5 years with SARI in South Africa from 2009 through 2012
4. To describe the epidemiologic characteristics of HIV-infected and -uninfected individuals aged ≥5 years with SARI in South Africa from 2009 through 2012
5. To estimate the incidence of hospitalisation for influenza-associated SARI and describe the epidemiologic characteristics and clinical course of illness in HIV-infected and -uninfected individuals of all ages in South Africa from 2009 through 2011

Chapter 2 Materials and Methods

This thesis consists of two separate components; a primary analysis of existing vital statistics data which addresses objectives 1 and 2 and a prospective surveillance study to address objectives 3, 4 and 5. A summary of the project is outlined in figure 2.1.

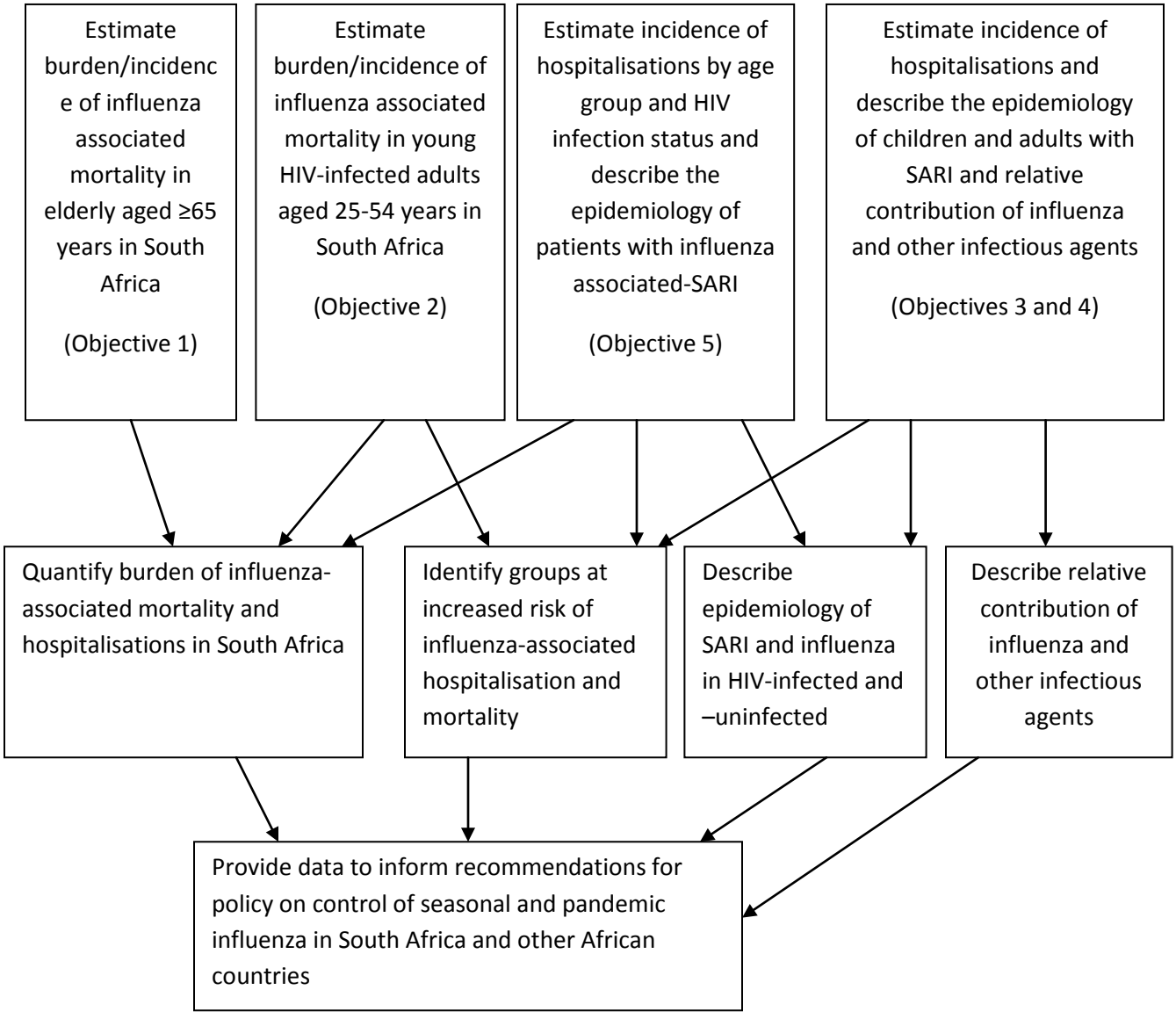

Figure 2.1 Overview of thesis objectives and public health relevance

SARI – Severe acute respiratory illness, HIV – Human immunodeficiency virus

2.1 Primary mortality data analysis (Objectives 1 and 2, Chapters 3 and 4)

2.1.1 Overview

The mortality burden of influenza cannot be measured directly, as influenza diagnoses are generally not confirmed in the laboratory and many influenza-related deaths are not coded as such in death certificates but are attributed to other co-morbid conditions or secondary complications of infection.[50] Instead, indirect statistical regression methods are used to quantify the seasonal increase in mortality above a baseline of expected mortality for broad disease categories occurring during influenza activity periods, termed "excess mortality".[30;51-54] We applied statistical regression models to monthly US and South African mortality statistics by age and cause of death, combined with country-specific estimates of population sizes and deaths, as detailed below and in Chapter 3 and Chapter 4.

2.1.2 Sources of data

2.1.2.1 Mortality data

Data on underlying causes of death were obtained from Statistics South Africa[55-57] from 1998-2005 and from the US National Centre for Health Statistics from 1987-2005 (http://www.cdc.gov/nchs/nvss.htm). Data included age group, month and year of death, and underlying causes of death. For South Africa it is estimated that from 1998 to 2005 the completeness of reporting of deaths increased from 73% to 90% for males and 63% to 88% for females.[56] Causes of death were manually coded and verified by trained coders and coding practices were consistent over the study period.[55-57] Data were not adjusted to account for under-reporting and thus represent a minimum estimate of mortality.

We used the International Classification of Diseases (ICD) versions 9 and 10 to compile monthly mortality time series for all causes and underlying causes of death as specified in Chapter 3 and 4. For the US, we adjusted for the conversion from ICD-9 to ICD-10 in 1999, by multiplying the reported number of P&I deaths in 1998 by published comparability ratios.[58] Estimation of deaths in persons with AIDS is described in Chapter 4.

2.1.2.2 Population denominators

We obtained annual population estimates for South Africa from Statistics South Africa (http://www.statssa.gov.za/publications/populationstats.asp) or the Actuarial Society of South Africa (ASSA) model as described in Chapter 3 and 4. We obtained annual population estimates for the US from the US Census Bureau (http://www.census.gov/popest/national/national.html). For South Africa from 1998-1999, age-specific denominators were unavailable and were estimated by linear interpolation from data available from 2000 onwards. Determination of denominators by HIV status is described in Chapter 4.

2.1.3 Estimation of influenza-related excess mortality

To determine influenza-related excess mortality we compared the mortality observed during influenza epidemic periods to a seasonal model baseline of "expected" mortality, separately for each population group and mortality outcome. First, we identified influenza epidemic periods separately for each winter and country by applying a linear seasonal regression model to influenza-specific deaths for all ages (ICD-9 code 487-488, ICD-10 code J9-J10), excluding winter months (December-March in the US, May-August in South Africa) and estimating the expected mortality in the absence of influenza circulation. We

defined “epidemic months” as the months for which reported influenza-specific deaths exceeded the upper 95% confidence limit of that predicted by the model (the “epidemic threshold”), separately for each winter. This has been shown to accurately estimate the timing of influenza virus circulation in the US.[51;59;60] To estimate influenza-related excess mortality we used a Serfling-type linear regression approach in the elderly as described in Chapter 3 and a spline model in adults with AIDS, young adults and the elderly as described in Chapter 4.

Non-demographic differences between countries, such as access to health care, socioeconomic factors, and coding practices (for cause-specific deaths), may also affect baseline and influenza-related mortality rates and bias geographical comparisons. To adjust for differences in baseline mortality, we estimated the proportion of deaths attributable to influenza, estimated as the excess deaths divided by the model predicted baseline of deaths in summer and/or winter respectively, as used in past research and as described in Chapter 3 and 4.[59;60]

2.2 Prospective SARI surveillance (Objectives 3, 4 and 5, Chapters 5, 6 and 7)

2.2.1 Description of the surveillance programme

From February 2009, active, prospective, hospital-based surveillance (the SARI programme) was implemented in three of the nine provinces of South Africa (Chris Hani-Baragwanath Academic Hospital (CHBAH) in Gauteng Province, Edendale Hospital in KwaZulu-Natal Province and Matikwana and Mapulaneng Hospitals in Mpumalanga Province). In June 2010, an additional surveillance site was introduced at Klerksdorp and Tshepong Hospitals in the Northwest Province (Figure 2.2). CHBAH is situated in an urban area close to the economic hub of Johannesburg, serves a population of

approximately 1,3 million people and has a temperate climate. Edendale hospital is situated in a peri-urban area, serves a population of approximately 600,000 and has a sub-tropical climate. Matikwana and Mapulaneng Hospitals are situated in a rural area, serve a population of approximately 500,000 and have a sub-tropical climate. Klerksdorp and Tshepong Hospitals are situated in a peri-urban area, serve a population of approximately 550,000 people and have a temperate climate.

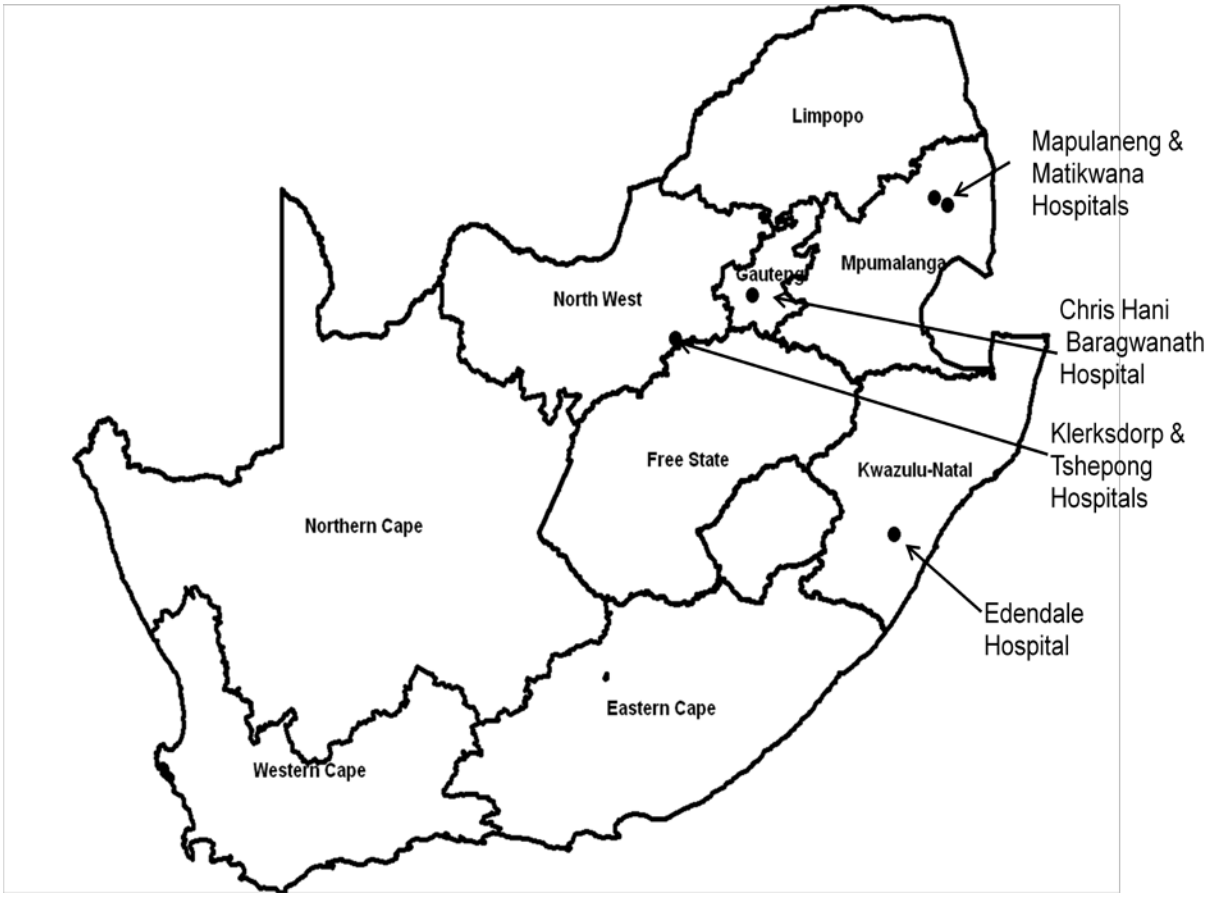

Figure 2.2 Map showing the nine provinces of South Africa and the geographic locations of the four sentinel surveillance sites

2.2.2 Case definition

A case of SARI was defined as a hospitalised individual with illness onset within seven days of admission meeting age-specific clinical inclusion criteria. We included children aged two days through <3 months with physician-diagnosed sepsis or lower respiratory tract infection, children aged 3-59 months with physician-diagnosed lower respiratory tract infection (including, for example bronchitis, bronchiolitis, pneumonia and pleural effusion) and patients aged ≥5 years meeting the WHO case definition for SARI:(1) sudden onset of fever (>38°C) or reported fever, (2) cough or sore throat, and (3) shortness of breath, or difficulty breathing.[61]

2.2.3 Study procedures

All patients admitted during Monday through Friday were eligible, except for adult patients at CHBAH where enrolment occurred for two of every five working days (selected days varied systematically) per week due to large patient numbers and limited resources. Numbers of patients admitted, numbers meeting study case definitions and numbers enrolled were collected. Study staff completed case report forms until discharge and collected respiratory (nasopharyngeal and throat swabs from patients aged ≥5 years or nasopharyngeal aspirates from patients aged <5 years) and blood specimens from consenting patients within 48 hours following admission. All decisions on medical-care, including whether patients should be admitted to hospital, mechanical ventilation, intensive care unit (ICU) admission and other investigations such as blood, cerebrospinal fluid or pleural fluid bacterial culture, testing for *Mycobacterium tuberculosis* and CD4+ T-lymphocyte counts was undertaken at the discretion of the attending-physician. At CHBAH, occasionally children with SARI, but without WHO signs of severe SARI and who did not require supplemental- oxygen treatment were admitted to a short stay observational

ward for one to two days, following which they were either discharged or admitted to the general paediatric wards. Children in the short stay wards were included in this study.

2.2.4 Laboratory methods

Respiratory specimens were immersed in viral transport medium and transported at 4-8°C to the National Institute for Communicable Diseases within 72 hours of collection. Respiratory specimens were tested by multiplex real-time reverse-transcription polymerase chain reaction (PCR) assay for 10 respiratory viruses (influenza A and B viruses, parainfluenza virus 1, 2 and 3; respiratory syncytial virus (RSV); enterovirus; human metapneumovirus; adenovirus and human rhinovirus).[43] All influenza A viruses were further subtyped as either H1 or H3 using primers and probe sets that target the HA genes of each virus as recommended by the WHO and CDC using the standard CDC subtyping kit [Influenza Virus Real-time RT-PCR Influenza A (H1/H3/H1pdm09) Subtyping panel, Cat# FluRUO-04 (CDC, Centres for Disease control and Prevention, Atlanta, USA available from [62])]. Due to challenges with availability of reagents, we did not test for adenovirus from August-October 2009. *S. pneumoniae* was identified by quantitative real-time PCR detecting the *lytA* gene from whole blood specimens.[63] Blood culture specimens were undertaken at the discretion of the attending physician and processed at study hospitals using automated blood culture systems and standard microbiologic procedures for organism identification. Specimens for *M. tuberculosis* identification were also submitted at the discretion of the attending-physician and examined by light microscopy for the presence of acid fast bacilli and culture performed using the BACTEC MGIT automated culture system (Becton Dickinson, Franklin Lakes, New Jersey).

2.2.5 Definitions

Underlying medical conditions were defined as asthma, other chronic lung disease, chronic heart disease, liver disease, renal disease, diabetes mellitis, immunocompromising conditions (excluding HIV infection) or neurological disease and were considered absent if indicated in medical records or when there was no direct reference to that condition. For analyses of risk factors for influenza, pregnancy was included as an underlying condition, but pregnancy was not considered an underlying condition in the analysis of risk factors for SARI. Pneumococcal conjugate vaccine (PCV) vaccination was defined as receipt of all age-appropriate doses of PCV (scheduled doses at 6 weeks, 14 weeks and 9 months of age). Invasive bacterial isolates were defined as a bacterial pathogen isolated from blood or pleural fluid from a specimen taken within 48 hours of hospitalisation in Chapter 5 and 6; organisms viewed as likely contaminants were excluded. In Chapter 7 bacterial pathogens isolated from cerebrospinal fluid were also included as we wanted to identify any severe co-infections with influenza. In Chapter 7, current tuberculosis was defined as patients with either a laboratory-confirmed diagnosis of tuberculosis or receiving or initiated on anti-tuberculosis treatment during the current admission based on clinical assessment.

2.2.6 Evaluation of HIV sero-status

HIV-infection status data was obtained based on testing undertaken as part of standard-of-care,[64] or through anonymised linked dried blood spot specimen testing by HIV PCR for children aged <18 months and by enzyme-linked immunosorbent assay (ELISA) for individuals aged ≥18 months.[65] CD4+ T-cell counts were determined by flow cytometry using the PanLeucogating method.[66] Patients were categorised into two immunosuppression categories: (1) mild immunosupression (CD4+ T-lymphocytes ≥200/mm^3 or equivalent age-appropriate CD4+ percentage for children aged <5 years), or (2) severe immunosuppression (CD4+ T-lymphocytes <200/mm^3 or equivalent age-appropriate CD4+ percentage for children aged <5 years).[67] We included any patient with a known HIV-status result whether it was

obtained through clinician testing or anonymised HIV-testing as described above. Age-specific HIV prevalence findings were not significantly different when only patients tested through anonymised linked testing were included for all SARI and for patients with influenza-associated SARI (results not shown).

2.2.7 Calculation of incidence

Calculation of incidence was conducted at one surveillance site (CHBAH) where population denominator data were available. This hospital is the only public hospital serving a community of about 1,3 million black African persons in 2012 (about 120,000 children age <5 years) amongst whom <10% have private medical insurance.[68] The vast majority (>80%) of uninsured individuals and approximately 10% of insured individuals seek care at public hospitals, consequently the majority of individuals requiring hospitalisation from this community are admitted to CHBAH. We estimated the incidence of hospitalisations per 100,000 individuals, using the number of SARI hospitalisations, adjusting for non-enrollment (refusal to participate and non-enrollment during weekends and in three of five adult wards) by age groups and HIV status divided by the mid-year total population estimates for each year, multiplied by 100,000.[69] To estimate the incidence of influenza hospitalisations per 100,000 individuals we utilised the number of SARI hospitalisations testing positive for influenza virus. HIV prevalence in the study population was estimated from the projections of the Actuarial Society of South Africa AIDS and Demographic model.[23] We assumed that the HIV prevalence by age group and influenza sub-type amongst patients not tested for HIV was the same as that amongst those tested. For 14 patients from whom influenza A virus subtyping was not performed, we imputed the influenza subtype based on the date of specimen collection and circulating influenza subtypes for estimation of incidence by influenza subtype.

Confidence intervals for incidence estimates were calculated using the Poisson distribution. Age-specific and overall age-adjusted risk of SARI and influenza hospitalisation in HIV-infected and -uninfected persons was determined using log-binomial regression. To explore the possible effect of missing data on estimates of HIV-specific incidence, a sensitivity analysis was conducted in which all cases not tested for HIV were assumed to be HIV uninfected. This scenario was chosen because our main question of interest was to estimate the excess hospitalisation risk in HIV-infected as compared to HIV-uninfected individuals. Exploring a scenario in which all untested individuals were assumed to be HIV-uninfected would bias towards a lower excess risk in HIV-infected individuals.

2.2.8 Analysis of factors associated with HIV-positive serostatus and death

To identify factors associated with HIV infection and death, we included both potential determinants for, as well as outcomes or characteristics of, the primary endpoints of the analysis. Univariate and multivariable analyses were performed with Stata version 9 (StataCorp Limited). Multivariable logistic regression models were evaluated, starting with all variables that were significant at $p<0.1$ on univariate analysis, and dropping non-significant factors with stepwise backward selection. All pairwise interactions of factors significant in the final multivariable additive model were evaluated. Two-sided p values <0.05 were considered significant throughout. For each univariate analysis, we used all available case information. In the multivariable model, patients with missing data for included variables were dropped from the model. Age group, hospital, duration of hospitalisation and year were defined as categorical variables in multiple levels. All other variables were defined as the presence or absence of the attribute excluding missing data. To explore possible bias, patients tested for HIV were compared to those not tested.

2.3 Ethics

Ethical approval for the mortality analyses was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical), South Africa. The US census and national HIV surveillance system data do not contain personal identifiers and their use in this report does not require human subjects oversight. The SARI surveillance protocol was approved by the Research Ethics Committees of the Universities of the Witwatersrand and KwaZulu-Natal. SARI surveillance was deemed non-research by the US CDC and human subjects review by that institution was deferred to the South African Ethics Committees.

2.4 Funding

Funding for travel to Bethesda for Dr Cohen to learn influenza mortality modelling statistical techniques was provided by the Fogarty International Centre.

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Chapter 3 Elevated influenza-related excess mortality in South African seniors, 1998-2005

3.1 Introduction

Influenza infection is associated with substantial global mortality each winter season, with the greatest burden experienced in seniors ≥65 years of age.[70] The incidence of influenza-related mortality in seniors ranges from 80-150 deaths/100,000 for all causes and 16-22/100,000 for P&I in the US and Europe.[29;30;51] Studies from high-income tropical locations such as Hong Kong and Singapore have found similar rates of excess deaths in the elderly to temperate northern hemisphere countries.[71;72] To our knowledge there are no published studies estimating seasonal influenza-associated mortality amongst the elderly from Africa.

Mortality is greatest in seasons where the more severe A(H3N2) influenza virus subtype predominates as compared to the milder A(H1N1) or B viruses.[51] Seasonal increases associated with influenza virus circulation have been demonstrated for a number of mortality outcomes in the elderly including all-cause mortality, P&I, diabetes, cerebrovascular disease (CVD) and ischaemic heart disease (IHD).[30;53;71;72] By contrast, cancer deaths show no clear seasonality.[53]

Here, we aimed to compare the influenza mortality burden between South Africa and the US, using multiple years of data, 1998-2005, and focusing on seniors ≥65 years of age.

3.2 Materials and Methods

3.2.1 Sources of data

3.2.1.1 Mortality data

Data on underlying causes of death for individuals aged ≥65 years were obtained from Statistics South Africa[55-57] from 1998-2005 and from the US National Centre for Health Statistics from 1997-2005 (http://www.cdc.gov/nchs/nvss.htm) as described in Methods section 2.1.2.1. Data included age group by 5-year age bands (65-69 years, 70-74 years, 75-79 years and ≥ 80 years), month and year of death, and underlying causes of death. We used the ICD versions 9 and 10 to compile monthly mortality time series for P&I, all respiratory diseases, diabetes, ischaemic heart disease (IHD), cardiovascular disease (CVD), cancer, and all causes (Table 3.1).

3.2.1.2 Population denominators

We obtained annual population estimates in individuals aged ≥65 years for South Africa and the US from Statistics South Africa (http://www.statssa.gov.za/publications/populationstats.asp) and the US Census Bureau (http://www.census.gov/popest/national/national.html) respectively as described in Methods section 2.1.2.2.

3.2.1.3 Influenza viral isolation data

The climate in South Africa ranges from temperate to sub-tropical, and influenza virus circulation is seasonal.[73] Data on number, timing and subtype of influenza virus isolates in South Africa was obtained from laboratory-based sentinel surveillance for influenza-like illness.[73] Total annual numbers of influenza virus isolates varied markedly between study years due to changes in the surveillance methodology over the study period, and do not represent the true influenza burden. To confirm the validity of the mortality data as an indicator of influenza timing in South Africa, we compared the timing of peak viral isolation data with the timing of peak influenza mortality, as in past research.[74] We considered an

influenza subtype (A(H3N2), A(H1N1) or B) to be dominant during the influenza season when it accounted for at least 50% of circulating viruses.

3.2.2 Estimation of influenza-related excess mortality

Influenza-related excess mortality was estimated for each of the 8 influenza seasons and 4 age groups for South Africa (winters 1998-2005) and the US (winters 1997/1998 through 2004/2005). To model the expected level of mortality in the absence of influenza virus activity, we used a Serfling-type linear regression approach, which includes harmonic terms to model seasonality and terms for time trends.[51;59] First, we identified influenza epidemic periods separately for each winter and country as described in Methods section 2.1.3. We then applied the seasonal regression model to monthly mortality rates for broader death categories and specific age groups, after standardising for month length and excluding data from winter months. Rates of monthly excess mortality were calculated as the observed minus predicted mortality rate for all "epidemic months". Seasonal excess mortality was estimated as the sum of the monthly excess mortality after adjusting for true month length. All model terms included were statistically significant ($p<0.001$), but additional terms were not ($p>0.05$). Overall, excess mortality regression models fitted the South African data for persons aged ≥65 years well, especially for P&I (R^2=0.82). For other influenza-associated causes of death (all causes, all respiratory causes, diabetes, IHD and CVD) R^2 ranged from 0.68-0.77.

To control for differences in the population age structure between the US and South Africa, we adjusted estimates for each 5-year age band to the US population in 2000. To adjust for differences in baseline mortality as described in Methods section 2.1.3, we calculated two measures of the proportion of deaths attributable to influenza, estimated as the excess deaths divided by the model predicted baseline of deaths in summer and winter respectively, as used in past research.[59;60] We used negative binomial

regression models to compare annual excess mortality rates between countries and logistic regression to compare percentage excess deaths.

3.3 Results

3.3.1 Description of mortality data in South Africa and the US

In South Africa, there were 3,831,176 deaths reported over the study period and age data was available for 3,808,121 (99%). Twenty-six percent of deaths (992,020) were in individuals aged ≥65 years; the annual number of reported deaths in the elderly increased by 18% over the study period (Tables 3.1 and 3.2). The proportion of deaths coded as P&I, all respiratory causes, CVD and diabetes was similar between South Africa and the US, but a larger proportion of elderly deaths in the US were due to IHD and cancer (Table 3.1).

Table 3.1: Comparison of causes of death in persons aged ≥65 years, South Africa (SA) vs. United States of America (US), 1998-2005

Cause of death	ICD 9 code	ICD 10 code	US n (%)	SA n (%)
All causes	Any	Any	14,321,704 (100)	992,020 (100)
All respiratory causes	460-519	J00.0-J99.0	1,627,057 (11)	126,729 (13)
Pneumonia and influenza	480-487	J10.0-J18.9	479,390 (3)	50,461 (5)
Cerebrovascular disease	430 – 438	I60.0-I69.8	1,117,140 (8)	104,296 (11)
Diabetes mellitus	250	E10.0-E14.9	426,094 (3)	69,338 (7)
Ischaemic heart disease	410 – 414	I20.0-I25.9	3,247,033 (23)	55,503 (6)
Cancer	140 – 209	C00.0-C97	3,118,900 (22)	109,391 (11)

Table 3.2: Annual excess pneumonia and influenza (P&I) and all-cause deaths in individuals aged ≥65 years, South Africa, 1998-2005

Year	Predominant influenza subtype	Population ≥65 years	Annual all cause deaths	Excess P&I deaths		Excess all cause deaths	
				Number	per 100,000 population	Number	per 100,000 population
1998	H3N2	1,750,648	113,248	1583	90	10,987	628
1999	B	1,825,544	111,694	603	33	4680	256
2000	H1N1	1,900,440	116,926	418	22	6075	320
2001	H3N2	1,975,337	124,163	1239	63	7441	377
2002	B	2,050,997	127,629	559	27	4175	204
2003	H3N2	2,130,051	135,644	1040	49	9700	455
2004	H3N2	2,211,678	129,031	465	21	5462	247
2005	H1N1	2,295,512	133,685	705	31	5381	234
Mean		2,017,526	124,003	827	42	6738	340

3.3.2 Timing of viral activity and mortality, South Africa

In South Africa, laboratory-based sentinel surveillance demonstrates that influenza causes seasonal outbreaks during May-August (Figure 3.1).[73] During the study period, timing of peak viral activity coincided with peak P&I and all-cause mortality in 6 of 8 years (0 month difference), and there was a 1-month delay in peak mortality in 2 years (1998 and 2000 for P&I, 2000 and 2004 for all causes). For comparison, influenza A/H3N2 was the predominant subtype in 4 of 8 seasons in South Africa (Figure 1) and 6 of 8 seasons in the United States (1997/1998,1998/1999, 1999/2000, 2001/2002, 2003/2004, and 2004/2005)(www.cdc.gov/flu).

The mean rate of excess P&I and all cause deaths in seasons where influenza A H3N2 predominated was elevated compared to seasons when influenza A H1N1 or B predominated for all diagnoses evaluated, however this difference was not statistically significant (data not shown) due to the small number of observations available for comparison (Table 3.2).

3.3.3 Comparison of influenza-related excess death rates, South Africa and US

Rates of excess P&I and all-cause mortality in seniors were higher in South Africa than in the US (42 and 387 per 100 000 respectively in South Africa as compared to 22 and 112 in the US, p=0.08 for P&I and p<0.001 for all-cause) (Table 3.3). For all diagnoses evaluated, except cancer, the estimated influenza-associated excess mortality increased with age and the age-specific influenza-related excess mortality rates were higher in South Africa as compared to US (Table3. 4).

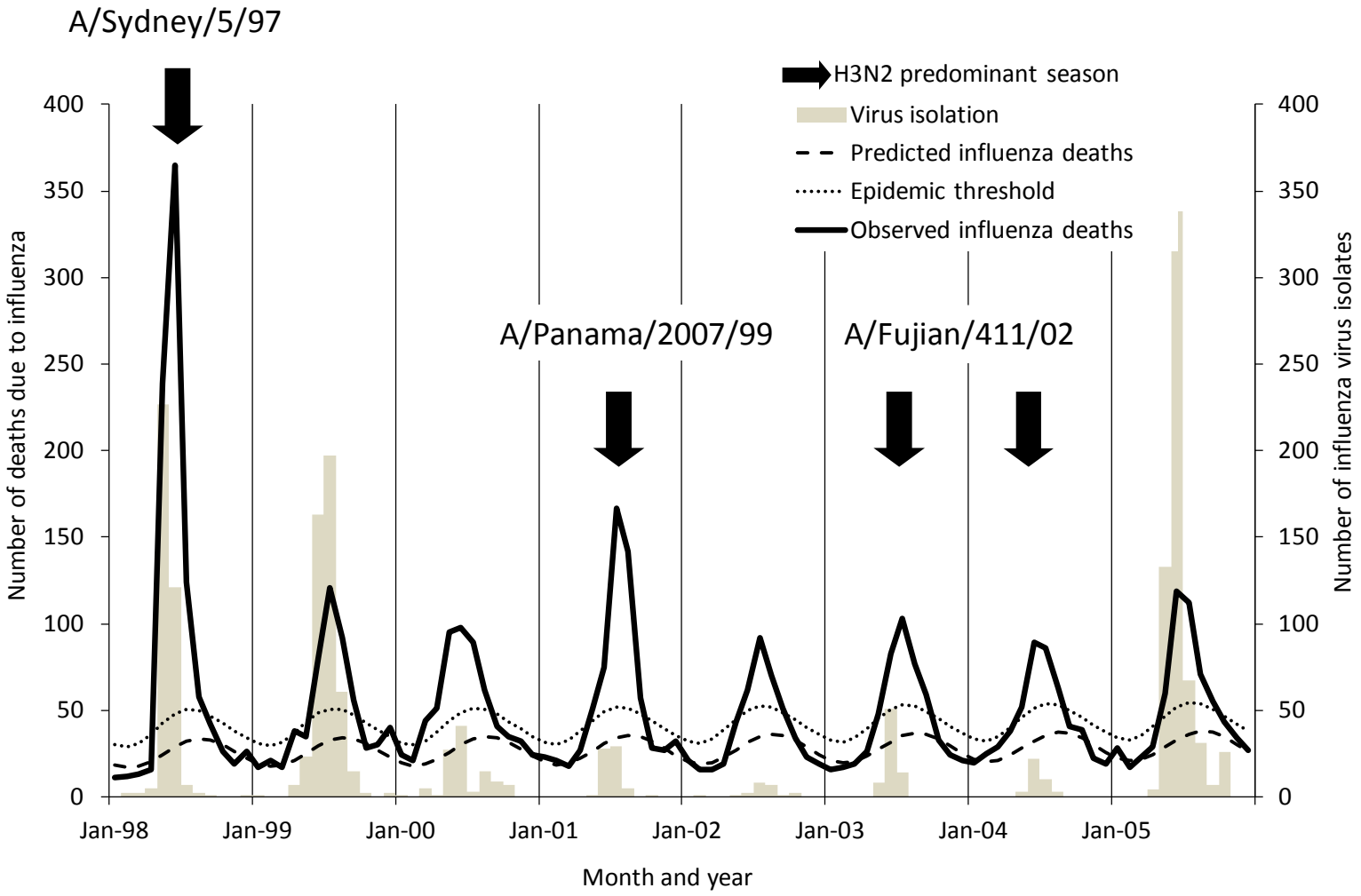


Figure 3.1 Observed and predicted* deaths in persons aged ≥65 years by month, 1998-2005, South Africa

Figure 3.1A: Reported influenza deaths, predicted* deaths and epidemic threshold; and number of influenza viral isolations (all ages)

Jan – January. *Number of deaths predicted assuming that influenza viruses were not circulating

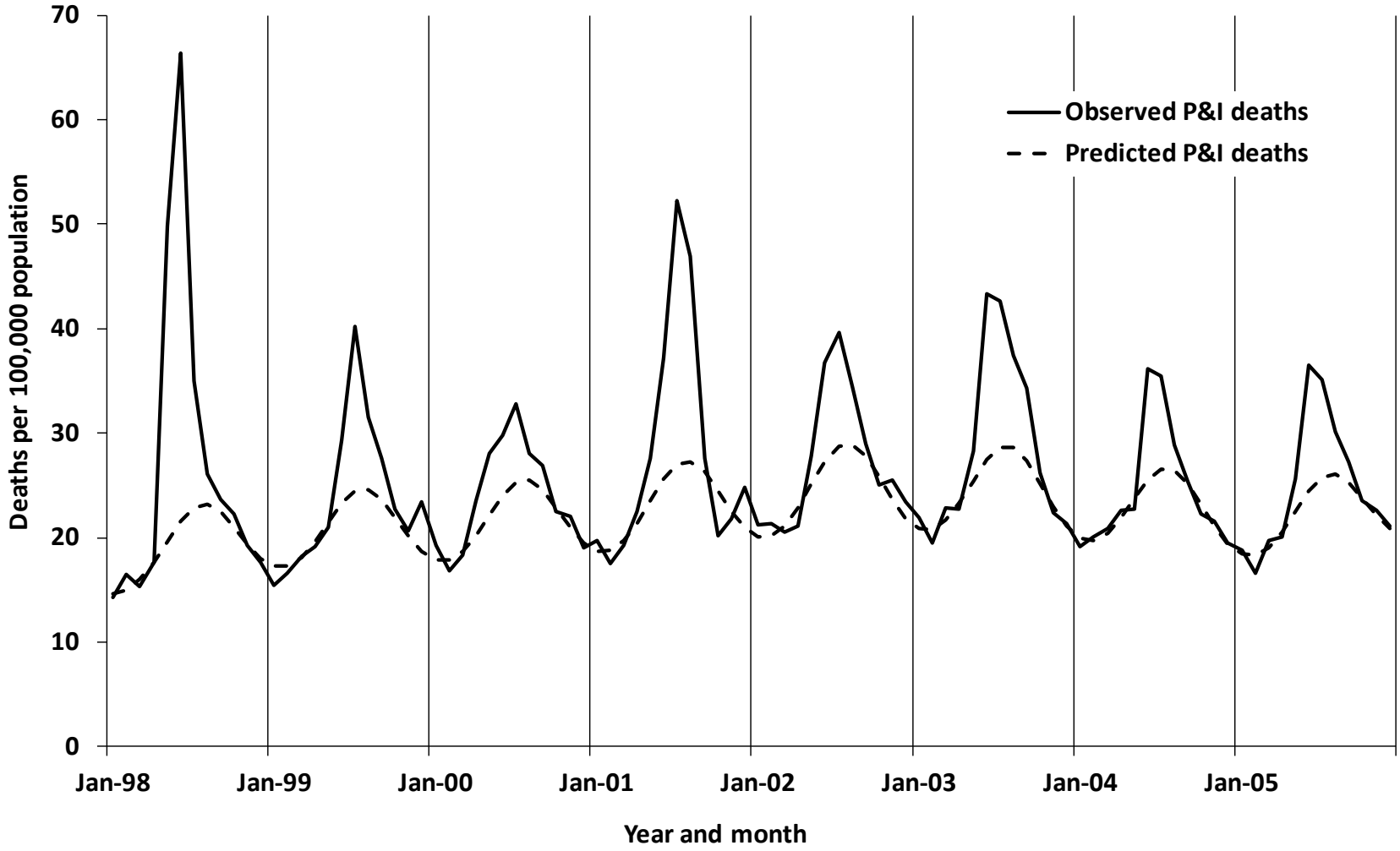


Figure 3.1B: Pneumonia and influenza (P&I) deaths

Jan – January. *Number of deaths predicted assuming that influenza viruses were not circulating

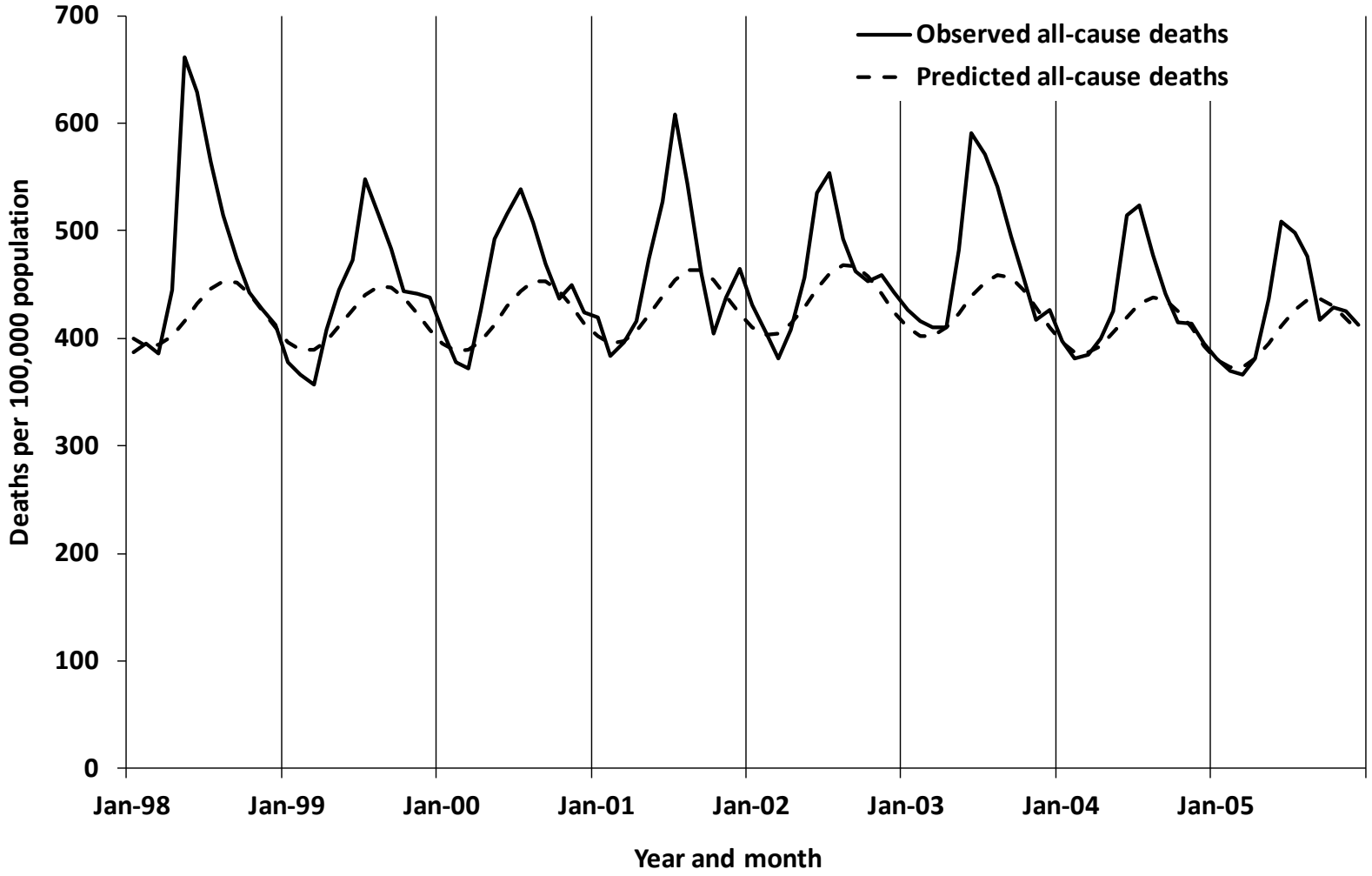


Figure 3.1C: All cause deaths

Jan – January. *Number of deaths predicted assuming that influenza viruses were not circulating

Table 3.3: Comparison of mean seasonal estimates of influenza-related excess mortality in individuals aged ≥65 years in South Africa for 1998-2005 (SA) and the United States of America (US) for 1997/1998 to 2004/2005 seasons

	Crude deaths per 100,000 (SD)			Age standardised deaths per 100,000 (SD)*			Percent excess deaths over summer baseline (SD) **			Percent excess deaths over expected winter deaths (SD) ***		
Cause of death	SA	US	P[+]	SA	US	P[+]	SA	US	P[++]	SA	US	P[++]
All-cause	387 (203)	112 (62)	<0.001	545 (190)	133 (79)	0.01	19 (9)	8 (4)	<0.001	16 (6)	6 (3)	<0.001
All respiratory causes	87 (45)	35 (21)	0.008	124 (62)	35 (21)	0.02	38 (23)	26 (13)	<0.001	25 (11)	14 (8)	<0.001
Pneumonia & Influenza	42 (21)	22 (13)	0.08	63 (35)	21 (13)	0.03	50 (36)	44 (25)	<0.001	29 (14)	20 (11)	<0.001
Cerebrovascular disease	40 (14)	7 (5)	<0.001	54 (20)	7 (5)	<0.001	18 (5)	6 (4)	<0.001	16 (4)	4 (3)	<0.001
Diabetes	20 (5)	3 (2)	<0.001	25 (6)	3 (2)	<0.001	14 (3)	8 (3)	<0.001	13 (3)	5 (3)	<0.001
Ischaemic heart disease	12 (4)	25 (20)	0.036	15 (6)	24 (20)	0.40	10 (4)	8 (6)	<0.001	9 (3)	6 (4)	<0.001
Cancer	3 (4)	7 (4)	0.221	6 (5)	7 (4)	0.83	1 (2)	2 (1)	<0.001	1 (2)	2 (1)	<0.001

Data are rate per 100,000 population or percent and standard deviation of annual estimates (SD)

* Standardised to the US population in 2000

**Percentage excess deaths over the baseline summer mortality rate for the relevant year (January, February, November, December - South Africa and May to August – US)

*** Excess mortality expressed as percentage increase over the winter baseline (ratio of excess deaths during epidemic months divided by the baseline expected deaths from the seasonal model).

+ Negative binomial regression

++Logistic regression

Table 3.4: Age-specific estimates of influenza-related excess mortality rates per 100,000 population aged ≥65 years, South Africa (SA) and United States (US)

Diagnosis	Country	Age group (years)			
		65 to 69	70 to 74	75 to 79	≥ 80
All cause	SA	156 (49)	243 (99)	429 (193)	1326 (438)
	US	22 (14)	40 (24)	85 (49)	377 (225)
All respiratory	SA	30 (17)	54 (32)	104 (68)	305 (136)
	US	9 (5)	15 (9)	27 (16)	86 (54)
Pneumonia and influenza	SA	10 (8)	30 (15)	32 (32)	175 (87)
	US	3 (2)	5 (3)	11 (7)	64 (39)
Cardiovascular disease	SA	18 (4)	31 (14)	40 (22)	126 (49)
	US	1 (1)	2 (1)	4 (1)	19 (15)
Diabetes	SA	17 (9)	8 (5)	31 (12)	44 (13)
	US	1 (1)	2 (1)	3 (2)	5 (3)
Ischaemic heart disease	SA	7 (4)	6 (4)	24 (9)	27 (15)
	US	5 (6)	9 (9)	14 (13)	68 (54)
Malignant disease	SA	1 (2)	9 (6)	8 (9)	5 (11)
	US	2 (1)	4 (3)	7 (4)	14 (8)

Data are rate per 100,000 population and standard deviation of annual estimates

After standardising for population age structure, the differences in the rates of excess P&I and all-cause mortality per 100,000 population increased between the two countries ($p=0.03$ for P&I and $p=0.01$ for all cause mortality; Table 3.3). When standardising for coding practices and baseline mortality, the differences in influenza-related excess mortality were reduced but South African mortality estimates remained significantly higher. In addition, the proportion of all winter deaths attributable to influenza was higher in South Africa than in the US on average (16% vs. 6%, $p<0.001$, Table 3.3). Similarly, the percent of all deaths attributable to influenza standardised by the summer baseline was higher in South Africa (19% vs. 8%, $p<0.001$, Table 3.3).

Rates of excess deaths due to all respiratory causes, CVD and diabetes were generally greater in South Africa than in the US and differences remained when standardised for demographics, death-coding practices and baseline mortality differences. Excess mortality rates for IHD were not significantly different between the US and South Africa. In both countries, deaths due to cancer had little seasonal variation that could be attributed to influenza.

3.4 Discussion

This was the first nationally representative study from Africa to estimate seasonal influenza-associated excess mortality. Overall, rates of seasonal influenza-related excess mortality in South African adults ≥65 years of age were substantially greater than those observed in the US. These patterns were consistent for a variety of death outcomes which have been used in the past as indicators of influenza disease burden including all-cause, P&I, all respiratory diseases, CVD and diabetes.[30;53;71] Standardisation for demographics, as well as proxies of death-coding practices and baseline health accounted for some, but not all of these differences. These data support increased efforts for control of seasonal influenza in seniors in South Africa and other low- and middle-income countries, where the excess seasonal mortality burden could be greater than previously thought.

Studies from several northern hemisphere temperate countries, as well as urbanised tropical areas such as Hong Kong and Singapore, have yielded remarkably similar estimates of influenza-related excess mortality in the elderly to those from the US.[29;30;51;71;72;75;76] By contrast, severe outbreaks of A(H3N2) influenza occurred in Madagascar and the Democratic Republic of Congo in 2002, suggesting that populations in African countries may experience increased risk of severe outcomes following influenza infection.[32;77] Case-fatality ratios in these outbreaks were high, possibly due to limited access to medical care, high prevalence of underlying illness and malnutrition and crowded living conditions. Remote areas with less frequent influenza virus activity could experience higher influenza-related mortality,[32;77] although serological studies suggest that rural African populations may be exposed to influenza each season.[78;79] While there are several published reports describing influenza circulation from various

locales in Africa, surveillance remains limited especially in rural areas, thus the epidemiology and seasonality of inter-pandemic influenza virus activity remains unclear in this region.[80;81]

A previous study evaluated influenza-associated excess mortality in the elderly occurring at a single South African hospital between 1997-1999 and found lower excess mortality rates than ours (82-221/100,000 population ≥65 years).[31] Given that only 50% of deaths occur in the hospital, this study may have substantially underestimated the influenza mortality burden.[31;57] In addition, the hospital study only covered a short period and was conducted in an urban community with relatively good access to health care, limiting the generalisability of the findings.[31]

Our study had several potential limitations. Some deaths in South Africa were not registered,[57] however this improved over the study period and under-reporting is unlikely to vary with season. About 14% of deaths in South Africa were non-specifically coded, which is higher than in the US (0.8%-1.2%). If anything, this should lead to underestimation of the excess mortality in South Africa, especially for disease-specific mortality indicators. Standardisation for baseline should account for difference in coding practices or baseline mortality between settings, and did not eliminate differences in excess death rate between countries. There was a slight increase in the proportion of deaths not specifically coded in winter in South Africa (≤1%). However given that the seasonal component only explained 9% of the variance in the data (P=0.01), we did not further adjust for this factor. We also note that our analyses of all-cause mortality are not prone to biases in the proportion of non-specific codes.

All-cause excess mortality is less likely to be subject to differences in coding practices and the most pronounced and consistent differences between South Africa and the US were for this mortality outcome. We also found similar between-country differences for other diagnoses, such as P&I, all respiratory deaths, CVD and diabetes. Although not significant due to small sample size, we found elevated excess mortality in seasons when H3N2 viruses predominated in South Africa, as has been seen in previous studies.[51] These patterns support the hypothesis that excess deaths were due to influenza, and not other causes such as temperature variation. Moreover, the observation of elevated mortality in South Africa is robust because our study period saw fewer A(H3N2)-dominated seasons in South Africa (4 of 8 seasons) compared with the US (6 of 8 seasons).[51] Overall, this suggests that our estimates of excess mortality for South African seniors are valid and that South African populations experience similar risk factors to other countries, including older age and that impact is worse in seasons dominated by the A(H3N2) subtype.

This study highlights that seasonal influenza-related excess mortality in Africa is likely greater than that observed in wealthier countries. Possible contributing factors may include socioeconomic differences as well as variability in the contributing role of co-circulating viral and bacterial respiratory pathogens. Studies have suggested that much of the morbidity and mortality associated with influenza infection may be due to secondary bacterial infection, particularly *S. pneumoniae.*[82;83] In addition, the relative contribution of other respiratory viruses such as RSV to excess mortality in the elderly has been debated in the literature. The type of modelling we have used in this study is thought to account for the relatively constant year-to-year mortality from RSV in the baseline.[30;84] Our approach cannot however evaluate the relative contribution of secondary bacterial infections or other viruses to influenza mortality in the US and South Africa, and this should be explored in further studies.

The observed differences in excess mortality are not explained by differences in influenza vaccination coverage between the US (approximately 65%) and South African elderly (15% of insured population in one study), because influenza associated mortality in the US elderly has remained constant since the 1980s despite increased vaccination coverage.[51;85] HIV/AIDS co-morbidity is also probably not a contributing factor in persons over 65 years, unless high HIV prevalence in younger populations is associated with increased intensity of influenza transmission in the community. It has been suggested that pandemic influenza-related mortality may be greater in lower socioeconomic settings.[27] In 2001, it was estimated that >40% of South Africans resided in a rural setting and >50% were living in poverty.[86;87] Although it is difficult to predict how representative estimates from South Africa are of the situation elsewhere in Africa; it is likely that non-specific factors related to poverty may have contributed at least in part to the observed increased excess mortality.

The mortality burden in the 2009 A(H1N1) pandemic differed from that of seasonal influenza, with highest apparent mortality risk in younger adults with underlying health conditions.[11;88] We have demonstrated elevated influenza-associated mortality in the South African elderly. Our study is consistent with the concept that African populations in general may be at higher risk for severe mortality from pandemic influenza,[27] which may be confirmed as more robust data become available from the African continent. Future studies are needed to estimate influenza disease burden in younger African populations and evaluate the impact of underlying host susceptibility, socioeconomic factors and co-circulating bacterial and viral pathogens. Such data are key to predict the potential impact of influenza pandemics and provide support for influenza vaccination programs and other control

measures in developing countries. The model presented here could be applied to any near-real time data available from South Africa, to estimate the burden in each wave as the pandemic progresses.

Chapter 4 Influenza-related mortality among adults age 25-54 years with AIDS in South Africa and the US

4.1 Introduction

There are approximately 30 million persons infected with HIV worldwide, including 5 million in South Africa and 1.2 million in the US.[21;22] The burden of influenza in HIV-infected persons remains poorly studied, particularly in sub-Saharan Africa where HIV burden is greatest.[89] Further, data are limited on the impact of widespread use of highly active anti-retroviral therapy (HAART) on mitigating severe influenza outcomes.[90] There have been no population-based studies evaluating influenza-associated mortality in adults with AIDS from sub-Saharan Africa and none following the introduction of HAART in the US.

During the US pre-HAART era, adults with AIDS were reported to experience higher influenza-related mortality rates compared to the general population and similar to those aged ≥65 years.[91] Following the introduction of HAART in the mid-1990s,[22] rates of influenza-related cardiopulmonary hospitalisations declined among US adults with AIDS but remained similar to those in other high-risk groups.[90] In South Africa, hospital-based studies have shown an elevated risk of influenza hospitalisation and a potentially increased case-fatality ratio in HIV-infected children.[89;92]

In this study, we compared influenza-related mortality rates in young adults (defined as age 25-54 years) with AIDS in South Africa and the US during the pre-HAART era. Further, we evaluated trends in influenza-related mortality rates in young adults with AIDS following the widespread introduction of HAART in the US and compared estimates with those from reference population groups.

4.2 Materials and Methods

4.2.1 Mortality data

Data on underlying and contributing causes of death were obtained from Statistics South Africa from 1998-2005[55-57] and from the US National Center for Health Statistics from 1987-2005 (*http://www.cdc.gov/nchs/nvss.htm*) as described in Methods section 2.1.2.1. We used the ICD versions 9 and 10 to compile monthly numbers of P&I and all cause deaths, outcomes which have been used traditionally to measure influenza mortality burden in the US, South Africa and elsewhere.[51;93] We focused on the age-group 25-54 years because this was the age group most affected by AIDS (Table 4.2). For comparison purposes, we also considered a similar age group in the general population, as well as seniors age 65 and older.[55-57;94]

4.2.2 Population denominators

For South Africa, we obtained annual age-specific population size estimates for the general population and individuals living with AIDS for 1998-2005 from the ASSA AIDS and Demographic model.[21;23] For the US we obtained age-specific population denominators from for the general population from the US Census Bureau *(http://www.census.gov/popest/national/national.html)*. We obtained annual population

size estimates for persons age 25-54 years living with AIDS in the US based on HIV surveillance data reported to the CDC, Atlanta, Georgia through June 30, 2010 ([22] and CDC unpublished data).

4.2.3 Estimation of deaths in persons with AIDS

South Africa Estimates: In South Africa, it is estimated that 80%-90% of adult deaths were registered in 2000.[95] A diagnosis of AIDS is rarely coded on the death certificate (less than 2% of deaths in 2002),[96] although the estimated percentage of deaths due to AIDS in persons age 25-54 years increased from 28% to 72% during 1998-2005, reflecting the increasing burden of the AIDS epidemic.[21] To get around this coding issue, we compiled monthly deaths due to P&I (as the underlying or contributing cause) and total deaths in persons age 25-54 years. To estimate the monthly number of deaths in young adults with AIDS we multiplied the total monthly numbers of all-cause and P&I deaths in young adults by the proportion of all deaths associated with AIDS in this age group and year, as estimated by the ASSA AIDS and Demographic model (http://aids.actuarialsociety.org.za/ASSA2003-Model-3165.htm). This is a validated model which compares favorably with other sources of HIV data in South Africa.[21;97]

***US* estimates:** To estimate deaths in young adults with AIDS in the US we included all deaths in persons aged 25-54 years with AIDS listed either as an underlying or contributing cause (an estimated ~90% of US patients deceased with AIDS).[98] To estimate P&I deaths in young adults with AIDS we included all deaths that had both AIDS and P&I listed anywhere on the death certificate.

4.2.4 Estimation of influenza-related excess mortality

To determine influenza-related excess mortality we compared the mortality observed during influenza epidemic periods to a seasonal model baseline of "expected" mortality. First, we identified influenza epidemic periods separately for each winter and country as described in Methods section 2.1.3. Next, to obtain seasonal baselines for all-cause and P&I mortality, we fitted spline models to monthly mortality data for each outcome and population subgroup, after exclusion of influenza epidemic months). In this approach, the seasonal baseline represents the expected number of deaths in the absence of influenza virus circulation and therefore observed data during winter months are set to missing (May-October in South Africa and November-April in the US). The model followed $y(t)=\alpha+\beta*t+\chi*\sin(2Pi*t/12)+\delta*\cos(2Pi*t/12)$, where y(t) is the monthly observed influenza deaths at month t, α and β are coefficients for linear time trends to be estimated from the data, and χ and δ are estimated coefficients representing annual seasonal cycles. Influenza periods were identified as the months where observed influenza-specific deaths exceeded the upper limit of 95% confidence interval of the seasonal baseline.[51;59;93]

Next, a seasonal baseline for monthly all-cause and P&I deaths was established by fitting a spline model including linear terms for time trends and annual sine and cosine terms for seasonality, after exclusion of observed deaths during influenza periods. We chose to use spline models instead of linear regression to accommodate the steep increase in HIV/AIDS deaths seen in the pre-HAART era. Separate models were fitted to different population age subgroups, time periods (pre-HAART, HAART era in the US), cause of death (P&I and all-cause), and country.

Monthly influenza-related excess deaths were estimated as the difference between observed and baseline P&I or all-cause deaths during influenza periods. Seasonal excess deaths were estimated as the sum of the monthly excess deaths for each winter. Influenza-related excess mortality deaths were

calculated by dividing the total excess deaths in the influenza season by the population size of the relevant country, year, age and HIV-status group. We derived 95% confidence intervals (CI) on seasonal excess mortality rate estimates based on the 95% CI of the monthly seasonal baseline model.

We estimated influenza-related excess mortality for 8 winter seasons (1998-2005) in South Africa, and for 7 winter seasons in the pre-HAART era (1987/1988-1993/1994) and 8 seasons in the HAART era (1997/1998-2004/2005) in the US. We excluded US seasons from 1994/1995-1996/1997 as both HAART coverage and baseline mortality were changing rapidly.

To adjust for differences in baseline mortality between countries, we calculated the proportion of winter deaths attributable to influenza as the winter-season excess deaths divided by baseline expected deaths during influenza epidemic months.[59;60] These proportions were compared between different population subgroups using logistic regression. To obtain an estimate of the relative risk (RR) of influenza-related mortality associated with AIDS, we compared seasonal excess mortality rates in young adults with AIDS in the US and South Africa with rates in reference population groups (seniors, age-peers), using negative binomial regression.

4.2.5 Sensitivity analysis

We conducted a sensitivity analysis using a simple additive method for the estimation of influenza-associated excess mortality relative to a peri-influenza baseline, as described previously.[91] We defined the peri-influenza season baseline period as the 2 month period preceding and following the influenza season (rather than the period preceding the season only, as has been done previously).[91] Using months

in the pre and post-influenza activity period allows fitting a stable baseline in periods of rapidly increasing mortality, such as in the pre-HAART era.

4.3 Results

4.3.1 Overall trends and seasonality of deaths among persons with AIDS

In South Africa between 1998 and 2005, there was a greater than 8-fold increase in the estimated number of young adults aged 25-54 yrs living with AIDS and a greater than 4-fold increase in annual deaths in young adults with AIDS (Table 4.1, Figure 4.1). In the US, the annual number of deaths in young adults with AIDS increased 2-fold during the pre-HAART era, 1987-1994, and decreased more than 2-fold in the HAART era (Table 4.1, Figure 4.2). Over 80% of all adult deaths due to AIDS in South Africa and the US throughout the study period were in persons age 25-54 years (young adults). The mean age at which people died increased over this period (Table 4.2).

Influenza seasons occurred between May and September in South Africa and November and March in the US, averaging 4 months duration. All-cause and P&I deaths among young adults with AIDS were particularly winter seasonal in South Africa, and seasonality increased over time (Figure 4.1). Mortality in US young adults with AIDS was less seasonal, especially in the pre-HAART era (Figure 4.2).

Table 4.1 Estimated population size and number of annual deaths among adults age 25-54 years with AIDS - South Africa and United States of America (US)

	Year	Estimated adults age 25-54 living with AIDS	Estimated all-cause deaths in adults age 25-54 with AIDS	Estimated pneumonia & influenza deaths in adults age 25-54 with AIDS
South Africa	1998	63,923	37,912	3,979
South Africa	2005	583,371	205,042	32,485
US pre-HAART	1987	26,249	12,996	1,894
US pre-HAART	1994	167,462	41,925	6,050
US post-HAART	1997	224,437	17,600	2,573
US post-HAART	2005	350,316	11,365	1,591

AIDS – Acquired immunodeficiency syndrome, HAART – Highly active antiretroviral therapy

Source of data: US: US National Center for Health Statistics from 1987-2005 (*http://www.cdc.gov/nchs/nvss.htm*); South Africa: Actuarial Society of South Africa (ASSA) AIDS and Demographic model http://www.actuarialsociety.org.za/Models-274.aspx and Statistics South Africa [55-57]

Table 4.2 Age distribution of deaths amongst persons with AIDS—United States of America (US) and South Africa

AIDS deaths by age group in years	South Africa pre-HAART 1998	South Africa pre-HAART 2005	US pre-HAART 1987	US pre-HAART 1994	US HAART era 1997	US HAART era 2005
13-14	0%	0%	0%	0%	0%	0%
15-24	9%	5%	4%	2%	2%	1%
25-44	79%	76%	74%	72%	66%	43%
45-54	10%	16%	14%	19%	23%	36%
55-64	2%	3%	6%	6%	7%	14%
>=65	0%	0%	3%	2%	3%	5%
Total number	51,417	300,821	14,808	46,051	19,901	14,244

AIDS – Acquired immunodeficiency syndrome, HAART – Highly active antiretroviral therapy

Source of data: US: US National Center for Health Statistics from 1987-2005 (*http://www.cdc.gov/nchs/nvss.htm*); South Africa: Actuarial Society of South Africa (ASSA) AIDS and Demographic model http://www.actuarialsociety.org.za/Models-274.aspx and Statistics South Africa [55-57]

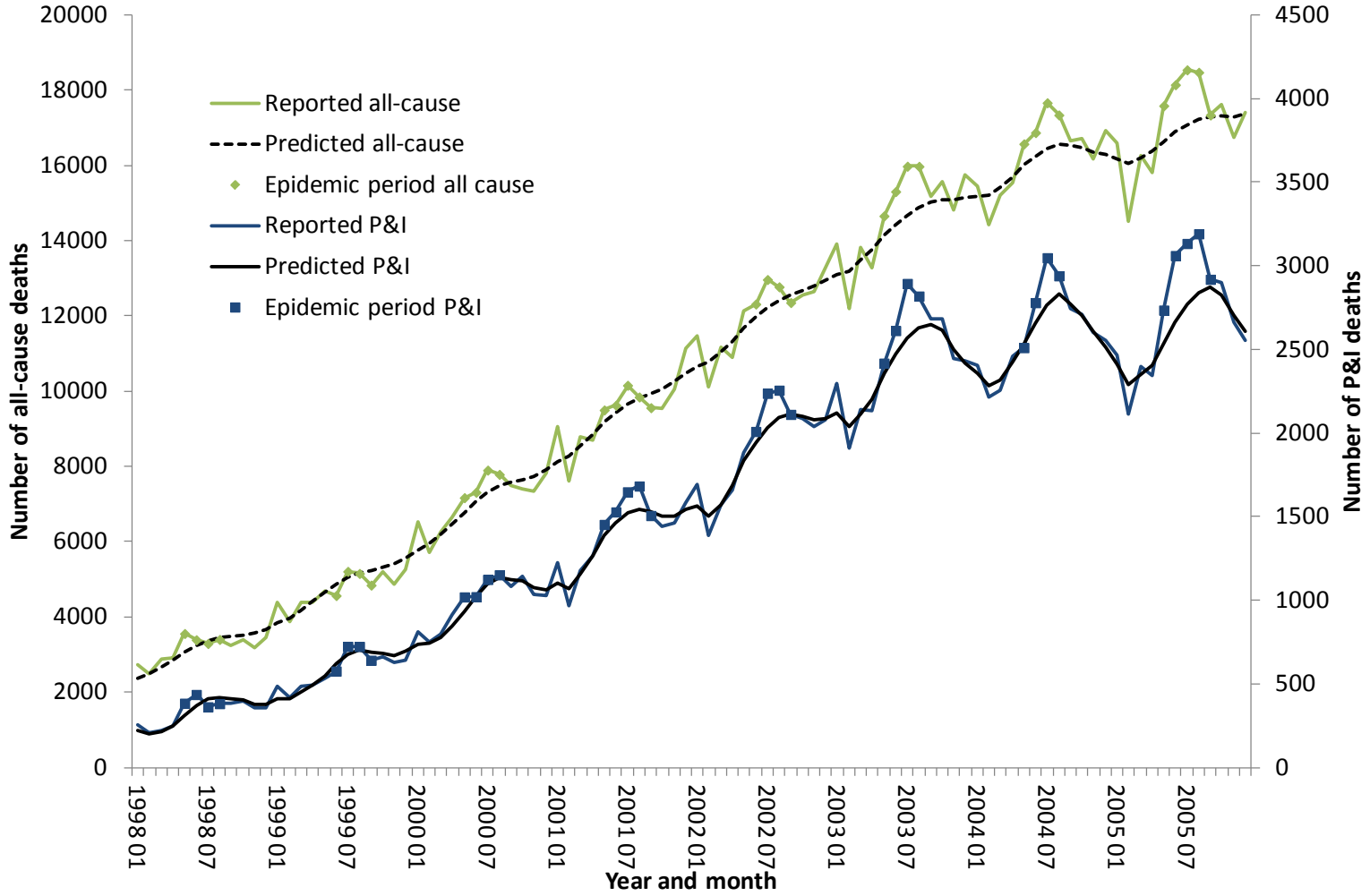


Figure 4.1 Monthly number of reported and predicted baseline all-cause and pneumonia and influenza (P&I) deaths in adults age 25-54 years with AIDS and influenza epidemic periods, South Africa, 1998-2005. Influenza epidemic periods were identified based on influenza-specific monthly mortality patterns.

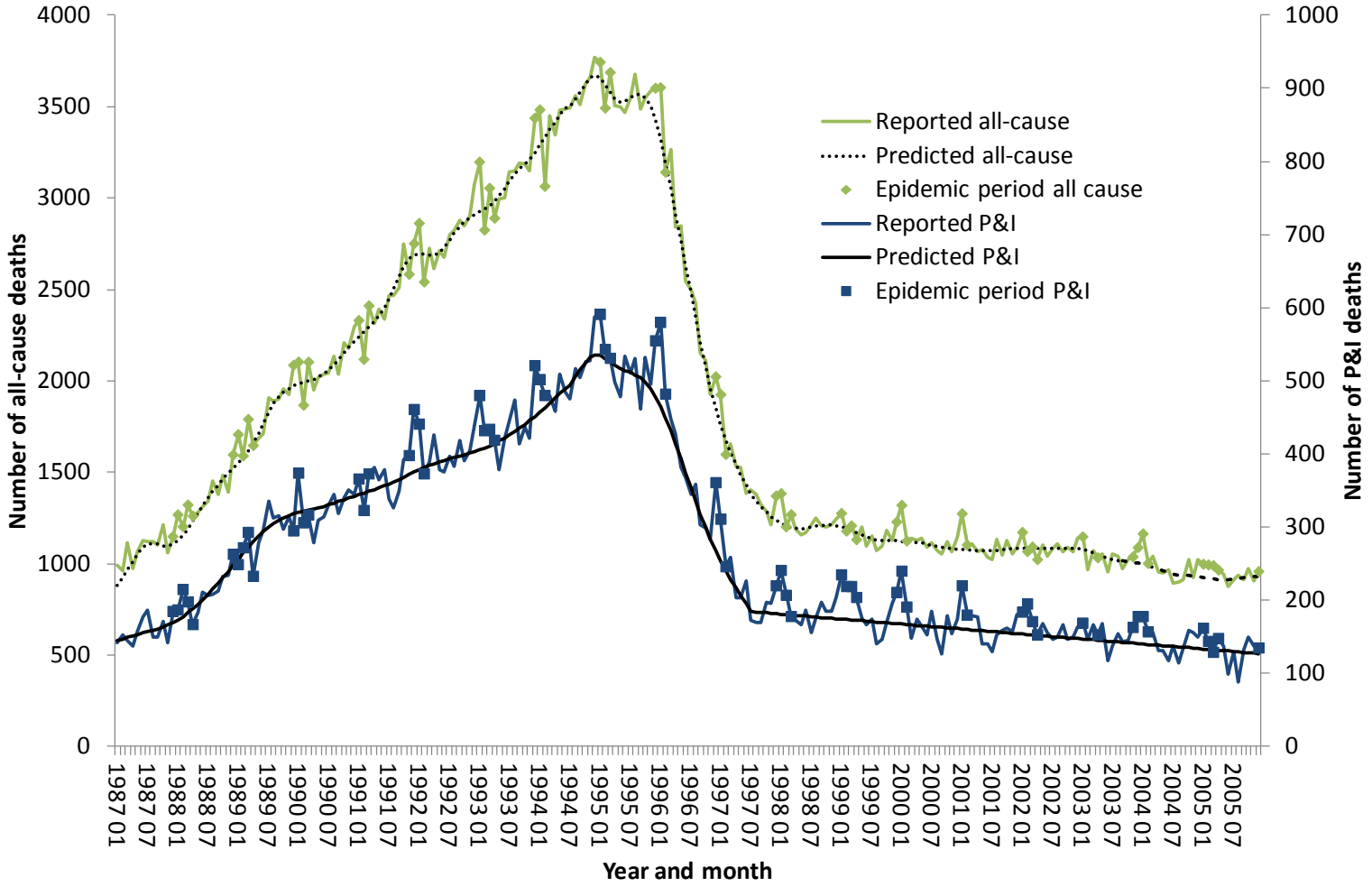


Figure 4.2 Monthly number of reported and predicted baseline all-cause and pneumonia and influenza (P&I) deaths in adults age 25-54 years with AIDS and influenza epidemic periods, United States of America, 1987-2005. Influenza epidemic periods were identified based on influenza-specific monthly mortality patterns.

4.3.2 Estimates of influenza-related excess mortality in adults with AIDS, South Africa

Influenza-related seasonal excess mortality rates in young adults with AIDS were estimated at 574 and 127 per 100,000 for all-cause and P&I (Table 4.3). These excess mortality rates were 2.2-fold (95% CI 1.0-5.1) and 3.8-fold (95% CI 2.2-6.6) greater than those in seniors over 65 years for the same time period (Table 4.4). In contrast, the proportion of winter deaths attributable to influenza was lower in young adults with AIDS as compared to seniors (all-cause 5% vs. 17%; P&I 7% vs. 43%, p<0.001) (Table 4.3).

4.3.3 Trends in influenza-related excess mortality in young adults with AIDS and HAART, US

In the US, in the pre-HAART era, young adults with AIDS experienced an average of 431 and 103 influenza-related excess all-cause and P&I deaths per 100,000 population respectively (Table 4.3). Excess mortality rates declined by 3-6 fold with the widespread use of HAART (Table 4.4). In the pre-HAART era, influenza-related excess mortality rates in young adults with AIDS were similar to or greater than those in seniors, and 150-200 times greater than the experience in the general population aged 25-54 years. In the HAART era, influenza-related excess mortality rates in young adults with AIDS became similar to those experienced in seniors (RR not different from 1) but still remained substantially elevated when compared to their age peers (RR~40-70).

Similar to South Africa, the influenza contribution to winter deaths in the pre-HAART era was lower in young adults with AIDS than in seniors (all-cause 2% vs. 5%; P&I 5% vs. 18%, p<0.001, Table 4.3).

Interestingly, while the absolute rate of influenza-related excess mortality declined from the pre- to the post-HAART era in young adults with AIDS, the percentage of winter deaths attributable to influenza increased over this period (from 2% to 5% of all-cause deaths, and from 5% to 17% of P&I deaths, $p<0.001$).

Influenza-related mortality rates in South African young adults with AIDS in recent years were similar to those in the US in the pre-HAART era (RR not different from 1.0, Table 4.4)

4.3.4 Results of sensitivity analysis using a different approach to estimate excess mortality

Results using a simple additive model to estimate excess mortality[91] are presented in table 4.5. Comparisons of influenza-related excess mortality rates between different age and HIV-status groups yielded similar results to those obtained using the more conservative spline model.

Table 4.3 Estimated influenza-related seasonal excess mortality rates in different population groups and time periods in South Africa and United States of America (US). Rates are based on excess all-cause and pneumonia and influenza (P&I) mortality derived from a seasonal regression modeling approach.

	South Africa		US					
	Persons with AIDS age 25-54 years	General population age ≥65 years	Persons with AIDS age 25-54 years		General population age 25-54 years		General population age ≥65 years	
	Pre-HAART	Pre-HAART	Pre-HAART	HAART	Pre-HAART	HAART	Pre-HAART	HAART
Mean seasonal excess all cause deaths per 100 000 population (95% CI)	574 (321-827)	264 (252-276)	431 (271-591)	77 (66-88)	3 (2.8-3.2)	2 (1.7-2.3)	104 (92-116)	96 (87-105)
Mean percent winter all cause deaths attributable to influenza* (95% CI)	5 (3-7)	17 (12-22)	2 (0-4)	5 (2-8)	3 (2-4)	2 (1-3)	5 (3-7)	5 (3-7)
Mean seasonal excess P&I deaths per 100 000 population (95% CI)	127 (65-189)	34 (33-35)	103 (73-133)	40 (39-41)	0.5 (0-1)	0.5 (0-1)	40 (38-42)	43 (41-45)
Mean percent winter P&I deaths attributable to influenza* (95% CI)	7 (5-9)	43 (22-64)	5 (2-8)	17 (13-21)	9 (6-12)	13 (10-16)	18 (11-25)	22 (14-30)

CI-confidence interval, HAART - Highly active anti-retroviral therapy, AIDS – Acquired immunodeficiency syndrome

Pre-HAART period US 1987-1994, HAART era US 1997-2005, pre-HAART period South Africa 1998-2005

*Excess mortality expressed as percentage increase over the baseline (ratio of excess deaths during influenza epidemic months divided by baseline expected deaths during influenza epidemic months)

Table 4.4 Relative risk (RR) of influenza-related excess death rates in adults age 25-54 years with AIDS, as compared with reference population groups and periods, South Africa and the United States of America (US)

	South African adults age 25-54 years with AIDS		US adults age 25-54 years with AIDS				
Mortality outcome	vs. South African general population age ≥65 years	vs. US adults age 25-54 years with AIDS in the pre-HAART	Pre-HAART vs HAART era	vs. general population age 25-54 years in the pre-HAART era	vs. general population age ≥65 years in the pre-HAART era	vs. general population age 25-54 years in the HAART era	vs. general population age ≥65 years in the HAART era
RR* of influenza-related excess all cause death rate (95% CI)	2.2 (1.0-5.1)	1.3 (0.3-5.3)	5.6 (1.3-24)	150 (49-460)	4.1 (1.4-13)	44 (16-121)	0.8 (0.2-3.3)
RR* of influenza-related excess P&I death rate (95% CI)	3.8 (2.2-6.6)	1.2 (0.4-3.5)	2.6 (0.9-7.1)	208 (74-583)	2.5 (0.9-7.2)	73 (47-113)	0.9 (0.5-1.7)

HAART - Highly active anti-retroviral therapy, P&I – pneumonia and influenza, AIDS – Acquired immunodeficiency syndrome

*Negative binomial regression, data are relative risks (RR) and 95% confidence intervals

All estimates given for South Africa are considered to predate the HAART era in this country.

Table 4.5 Relative risk (RR) of influenza-related excess death rates in adults with AIDS, as compared with reference population groups, South Africa and United States of America (US) – use of an additive model with peri-influenza season baseline to estimate influenza related excess mortality

	South African adults age 25-54 years with AIDS		US adults age 25-54 years with AIDS				
Mortality outcome	vs. US adults age 25-54 years with AIDS in the pre-HAART	vs. South African general population age ≥65 years	Pre-HAART vs HAART era	vs. general population age 25-54 years in the pre-HAART era	vs. general population age ≥65 years in the pre-HAART era	vs. general population age 25-54 years in the HAART era	vs. general population age ≥65 years in the HAART era
RR* of influenza-related excess all cause death rate (95% CI)	5.9 (1.3-26.0)	2.7 (1.8-3.9)	4.0 (0.8-20.1)	183.6 (22.1-1522.7)	1.3 (0.3-5.5)	30.4 (13.3-69.6)	0.3 (0.2-0.7)
RR* of influenza-related excess P&I death rate (95% CI)	4.9 (2.5-9.3)	4.0 (2.8-5.6)	2.9 (1.3-6.7)	101.6 (52.2-197.6)	1.4 (0.7-2.7)	34.0 (17.4-66.6)	0.5 (0.3-1.01)

HAART - Highly active anti-retroviral therapy, P&I – pneumonia and influenza, AIDS – Acquired immunodeficiency syndrome

*Negative binomial regression, data are relative risks (RR) and 95% confidence intervals

All estimates given for South Africa are considered to predate the HAART era in this country.

4.4 Discussion

This study evaluated influenza-related excess mortality both among adults with AIDS in South Africa and the US in the pre-HAART era and in the US during the HAART era. Our data suggest that in the absence of HAART, adults age 25-54 years with AIDS experienced a substantially elevated risk of influenza-associated death, 150 to 200-fold higher than the general population of the same age, and 2-4-fold higher than seniors age 65 and over. This is consistent with the overall dramatic increase in total risk of death in patients with AIDS. In the US, influenza-related mortality rates in young adults with AIDS declined following the widespread introduction of HAART around 1995 but still remained approximately 40-70 fold higher than those of their age peers and similar to those of seniors.[22] The risk of influenza-related mortality in untreated young adults with AIDS was similar in South Africa and the US. These findings suggest that AIDS remains a substantial risk factor for severe influenza-related disease in developed and developing world settings and support the ongoing importance of influenza prevention measures in persons with AIDS.

Studies from South Africa have reported an approximately 8-fold elevation of influenza-associated hospitalisation rates and possible elevated case-fatality ratios in HIV-infected children.[89;92] A US study set in the pre-HAART era[91] reported an average excess P&I mortality rate of 122 per 100,000 and a 100-fold mortality risk elevation in adults with AIDS aged ≥ 13 years relative to their age peers, which is the same order of magnitude as our estimates. Limitations of the previous study include the lack of adjustment for rapidly increasing background mortality in individuals with AIDS before HAART, which may have resulted in overestimation of excess mortality, and the inclusion of only 3 influenza seasons. Another US study in the pre-HAART era has shown that HIV-infected women experienced excess rates of

cardiopulmonary hospitalisation 50-75 times greater than their age peers.[99] Our study suggests even higher influenza-related excess mortality risks in persons with AIDS.

Our results suggest that the introduction of HAART in the mid 1990s in the US substantially decreased influenza-related excess mortality in young adults with AIDS, coinciding with an overall mortality rate decline in this group. Similarly, a population-based study demonstrated that influenza-associated hospitalisations in adults with AIDS age 15-50 years decreased after the introduction of HAART, although only one year of pre-HAART data was available for comparison.[90] Overall, our study is more robust than earlier population-based studies in the US, as we compare 8 pre-HAART seasons to 7 post-HAART seasons, and confirm that the introduction of HAART has decreased the mortality burden of influenza among young adults with AIDS. Unfortunately, we were unable to evaluate the effect of HAART on influenza-related mortality in South Africa. Although a national treatment programmefor HIV-infected individuals was initiated in 2004 in this country, only an estimated 25% of those requiring treatment had been initiated on HAART by the end of our study period in 2005.[100]

On average 11.6% (range 10.8%-12.1%) of deaths in South African adults age 25-54 were non-specifically coded (ICD 10 R0-99) compared to 2.0% (range 1.6%-2.7%) in the US. This may have led to underestimation of excess mortality risk for P&I in South Africa. In the US, clinicians may be more or less likely to report P&I as an underlying cause of death in persons with AIDS as compared to the general population. Similarly they may be more likely to seek an AIDS diagnosis or record AIDS as a cause of death in persons with pneumonia. The proportion of non-coded deaths in South Africa does not show substantial seasonal variation and should not affect between-group comparisons.[93] In addition, our analyses of all-cause mortality are not prone to such biases in coding.

Our study is subject to several limitations. We used different methodologies for estimating mortality rates among persons with AIDS in South Africa and the US given differences in coding of deaths. While in the US, the majority of deaths in persons with AIDS receive an AIDS diagnosis on the death certificate,[98] this is not the case in South Africa.[96] For this reason we estimated deaths in young South African adults with AIDS by multiplying total deaths in young adults by an estimated proportion of deaths due to AIDS in this age group, derived from a validated model.[21;23] This method relies on the assumption that the proportion of deaths due to AIDS does not vary seasonally or by cause of death. Our methodological approach to estimate AIDS-related mortality in South Africa produced annual numbers of deaths approximately 20% lower than those presented by the ASSA model.[21] This is expected because the ASSA model adjusts for unregistered deaths, which we did not do. Similarly, our estimates of excess mortality in persons with AIDS in the US likely represent a minimum estimate as we only included persons with AIDS-specific ICD codes if it was indicated anywhere on the death certificate. Compared to the annual estimates of deaths among persons with AIDS from the CDC AIDS surveillance reports (which includes deaths from all causes), the numbers of deaths in our series were approximately 8% lower, possibly due to failure to record an AIDS diagnosis on the death certificate and the fact that CDC estimates are adjusted for delays in case and death reporting.[98;101] Overall the underestimation of the number of deaths among persons with AIDS would tend to underestimate influenza-related excess death rates in this population. This, in addition to findings from sensitivity analyses comparing our mortality estimates with those published by other sources and evaluating the impact of deaths with no specific code of death, suggests that our estimates of the relative risk associated with AIDS are conservative.

Several internal and external consistency checks suggest the validity of our findings. Most importantly perhaps, we found similar levels of influenza-related excess mortality rates in untreated young adults with AIDS in South Africa and the US. Further, influenza-related mortality rate estimates were consistently 2-4 times greater in young adults with AIDS as compared with seniors in both countries. Further, our excess mortality approach to measure influenza burden produced estimates within 10% of those previously published for US seniors.[30;93] The numbers of US AIDS deaths in our series was also within 10% of annual estimates of deaths among persons with AIDS from the CDC AIDS surveillance reports.[98;101] Additionally, the increasingly strong winter seasonality of P&I and all-cause mortality in all South African young adults, at a time of rapidly increasing AIDS mortality burden, suggests a robust association between winter respiratory mortality and AIDS. Finally, we conducted a sensitivity analysis using a simple and less conservative method for the estimation of influenza-associated excess mortality [91] While there was some variation in the absolute estimates of excess mortality between the two methodologies and in relation to previously published estimates,[30;51;93] our main results remain valid. In particular, influenza-related excess mortality risk was elevated in untreated young adults with AIDS, as compared with seniors, and influenza-related excess mortality declined with HAART. Taken together, these comparisons and sensitivity analyses suggest that our modeling approach is robust and specific of influenza.

An important caveat of our study is related to the unknown contribution of winter respiratory pathogens co-circulating with influenza. Our excess mortality approach assumes that all winter deaths occurring above a seasonal baseline during influenza activity periods are attributable to influenza. However, influenza-related mortality may be in part associated with secondary bacterial infection, particularly *S. pneumoniae,*[82;102] and this may be even more marked in persons living with AIDS. In

addition, the relative contribution of other respiratory viruses such as RSV and the interaction between influenza and common AIDS-associated pathogens such as *Pneumocystis jirovecii* is unknown and may have caused us to over- or under-estimate influenza-associated mortality. We did not have access to data on these other pathogens, but this is an important area for future research.

Surprisingly, although the absolute rate of influenza-related deaths in young US adults with AIDS declined with the introduction of HAART, the percent of winter deaths attributable to influenza increased 2-3 fold over this period. This suggests that as the background rate of mortality decreases in treated AIDS patients, together with the absolute influenza burden, the etiological fraction of influenza among total mortality may increase. Our study suggests that HAART may be less effective in reducing mortality risk from influenza than from other causes, leading to an increase in the relative contribution of influenza to winter mortality in the HAART era. In addition, our study is ecological, therefore changes in the uptake of interventions other than HAART (such as influenza or pneumococcal vaccination) could have impacted mortality trends although this effect would likely have been small. Indeed, observational cohorts show a very steep uptake in HAART coverage from 0% before 1995, when protease inhibitors were not available, to approximately 80% in 1997,[103] coinciding with a 200-300% decline in influenza-related mortality. In contrast, influenza vaccination coverage increased by about 10-15% from about 29% to 42% during 1990-2002 in HIV-infected individuals,[104] inconsistent with the level of decline seen in influenza-related mortality. Further, the major mortality reductions reported in our study predate by several years the introduction of the PCV in the US.[105]

Recent US vaccination guidelines recommend influenza vaccination for all persons aged ≥ 6 months and identify persons with HIV and AIDS as a high risk group for influenza complications.[10] This is in line with

our results showing that AIDS remains a risk factor for influenza-related death in the US. TIV is protective against laboratory-confirmed symptomatic influenza in persons with moderate or asymptomatic HIV infection.[106-108] Effectiveness amongst persons with advanced HIV disease and low CD4+ T cell counts is however unclear. Very few sub-Saharan African countries have routine influenza vaccination programmes and high HIV-burden countries have to balance conflicting health priorities with limited available resources.[37] A recommendation for state-sponsored influenza vaccination of HIV-infected persons would have substantial economic and logistic cost,[109] while our data suggest that HAART has a great impact in reducing influenza-related mortality risk.

The 2009 influenza A(H1N1)pdm pandemic has highlighted the dearth of influenza-related mortality risk estimates in persons with underlying conditions, which are key to guide international guidelines for influenza vaccination and treatment. Our findings support the recommendation for vaccination of HIV-infected individuals in the US in the HAART era. HIV-infected persons hospitalised with suspected or confirmed influenza infection should receive early influenza antiviral therapy. In addition, the US experience suggests that more widespread access to HAART in sub-Saharan Africa may substantially reduce influenza-related mortality in this region.

Chapter 5 Epidemiology of viral-associated acute lower respiratory tract infection amongst children aged <5 years in a high HIV prevalence setting, South Africa, 2009-2012

5.1 Introduction

In 2010, an estimated 1.4 million children died due to pneumonia and an estimated 11.9 million were hospitalised.[1;3] HIV infection is associated with increased severity of pneumonia and higher case-fatality ratios in children.[110-112] The relative contribution of viral and bacterial aetiologies to the syndrome of childhood pneumonia also varies by HIV status.[6;89] Data from Europe and North America suggest that even in the presence of widespread availability of HAART the incidence of pneumonia remains elevated in HIV-infected children.[113;114]

There are limited data on the burden, aetiology and epidemiology of SARI in HIV-infected and -uninfected children in sub-Saharan Africa in the era of HAART availability. In South Africa among children age <5 years in 2011, the estimated HIV prevalence was 4% and coverage with HAART approximately 26%.[23] *H. influenzae* type b conjugate vaccine was introduced into the South African immunisation programme in 1999 and PCV in 2009.[115] As bacterial aetiologies decline due to vaccination, respiratory viral causes of SARI may gain greater prominence. We aimed to describe the incidence, aetiology and factors associated with death amongst HIV-infected and -uninfected children aged <5 years hospitalised with SARI in South Africa from 2009 through 2012.

5.2 Materials and Methods

Case definitions, study procedures, laboratory methods, definitions, evaluation of HIV serostatus and calculation of incidence are described in Chapter 2 Methods section 2.2.

5.3 Results

5.3.1 Demographic and clinical characteristics

From February 2009 through December 2012, 13,815 children <5 years age fulfilling the SARI case definition were screened for study enrolment, of whom 8723 (63%) were enrolled (Figure 5.1). The most common reasons for non-enrolment were study refusal (n=1209, 24%) or unavailability of a legal guardian (n=1452, 29%). Of the children enrolled, 64% (5603) were <12 months age, and 69% (6024) were enrolled at CHBAH (Table 5.1).

HIV infection status was determined in 5964 (68%) enrolled children (Figure 5.1). The proportion of children with available HIV results increased from 48% in 2009 to 77% in 2012 ($p<0.001$; Table 5.2). The proportion of children with available HIV results also differed by study site and duration of hospitalisation. The overall HIV prevalence was 12% (705/5964) and varied by age group: 10% (249/2565) in those <6 months, 13% (163/1290) in 6-11 months, 10% (125/1201) in 12-23 months and 19% (168/908) in 24-59 months ($p<0.001$). HIV prevalence varied by hospital: 8% (322/3893) at CHBAH, 23% (206/906) at Matikwana and Mapulaneng, 14% (118/850) at Edendale and 19% (59/315) at Klerksdorp ($p<0.001$). At CHBAH the HIV prevalence amongst children admitted to the short stay ward was 5% (97/1965) compared to 12% (225/1928) amongst those admitted to the general paediatric wards ($p<0.001$).

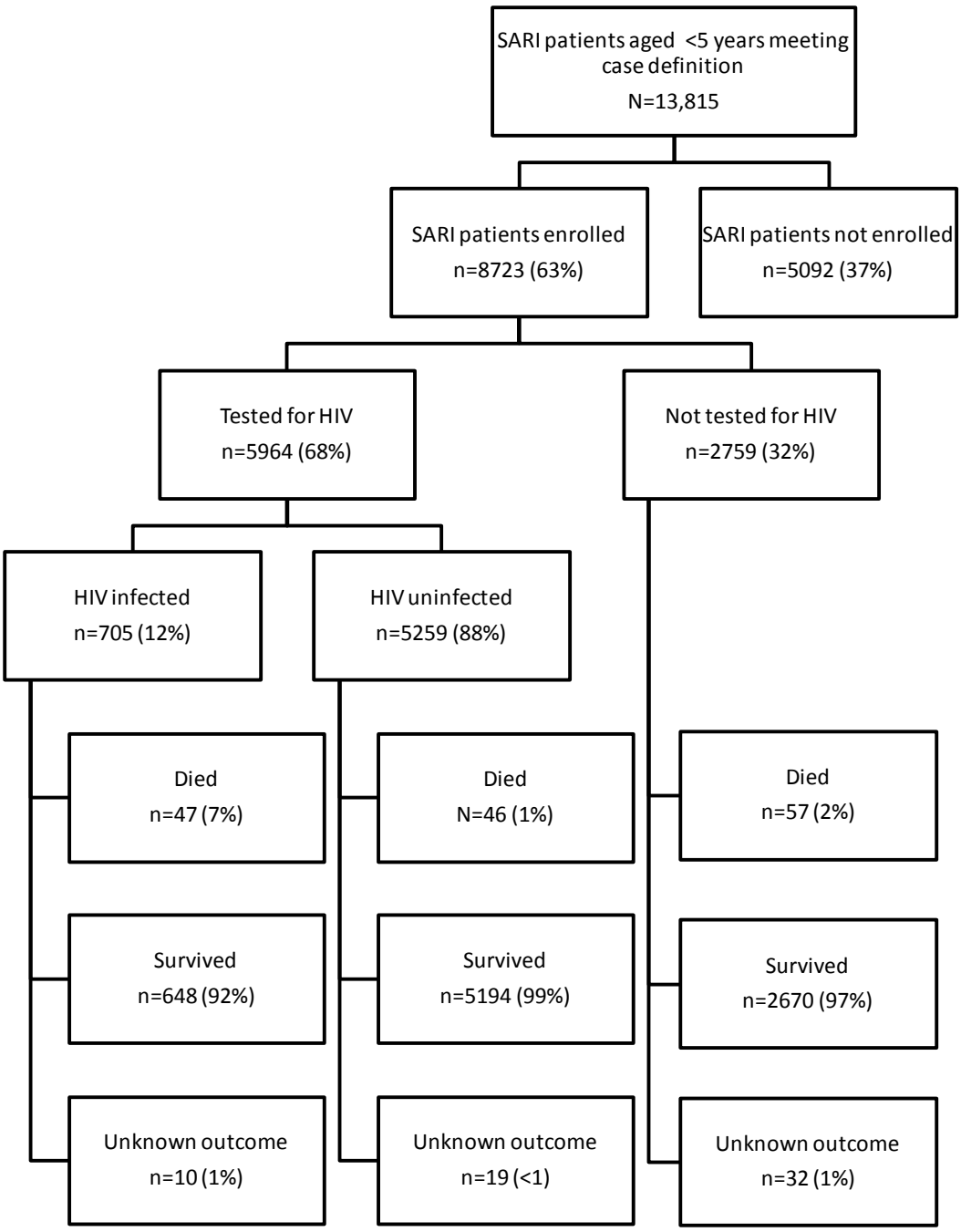


Figure 5.1 Flow chart of patients aged <5 years included in the study

SARI – Severe acute respiratory illness, HIV – Human immunodeficiency virus

Table 5.1 Clinical and epidemiologic characteristics of HIV-infected and -uninfected children <5 years hospitalised with severe acute respiratory illness (SARI) at four sentinel surveillance sites, South Africa, 2009-2011

Characteristics		All patients n/N (%)	HIV-infected n/N (%)	HIV-uninfected n/N (%)	Univariate analysis~ OR(95% CI)	p	Multivariable analysis*** OR (95% CI)	p
Demographic characteristics								
Age group	<12	5603/8723 (64)	412/705 (58)	3443/5259 (65)	Reference	<0.001	Reference	<0.001
(months)	12-23	1747/8723 (20)	125/705 (18)	1076/5259 (20)	1.0 (0.8-1.2)		1.1 (0.9-1.4)	
	24-59	1373/8723 (16)	168/705 (24)	740/5259 (14)	1.9 (1.6-2.3)		2.1 (1.7-2.7)	
Female		3708/8723 (43)	334/705 (47)	2189/5259 (42)	1.3 (1.1-1.5)	0.004	1.3 (1.1-1.5)	0.010
Black African race		8551/8709 (98)	693/704 (98)	5167/5253 (98)	1.0 (0.6-2.0)	0.883		
Year	2009	2191/8723 (25)	180/705 (26)	869/5259 (17)	Reference	<0.001	Reference	<0.001
	2010	2004/8723 (23)	204/705 (29)	1190/5259 (23)	0.8 (0.7-1.0)		0.8 (0.6-1.0)	
	2011	2350/8723 (27)	153/705 (22)	1697/5259 (32)	0.4 (0.3-0.5)		0.4 (0.3-0.6)	
	2012	2178/8723 (25)	168/705 (24)	1503/5259 (29)	0.5 (0.4-0.7)		0.5 (0.4-0.6)	
Site	CHBAH	6024/8723 (69)	322/705 (46)	3571/5259 (68)	Reference	<0.001	Reference	<0.001
	Matikwana and	1190/8723 (14)	206/705 (29)	700/5259 (13)	3.2 (2.7-4.0)		2.8 (2.2-3.6)	

	Mapulaneng					
	Edendale	1071/8723 (12)	118/705 (17)	732/5259 (14)	1.8 (1.4-2.2)	1.7 (1.3-2.2)
	Klerksdorp	438/8723 (5)	59/705 (8)	256/5259 (5)	2.6 (1.9-3.5)	2.4 (1.7-3.4)
Underlying medical conditions						
Underlying medical condition excluding HIV*		198/8713 (2)	15/704 (2)	133/5259 (3)	0.8 (0.5-1.4)	0.524
2 or more doses of PCV (eligible children <5 years) (vs. <2 doses)		1745/3765 (46)	131/321 (41)	1269/2643 (48)	0.7 (0.6-0.9)	0.015
Infectious agents identified						
Invasive bacterial infection on culture†		75/3196 (2)	12/311 (4)	51/2092 (2)	1.6 (0.8-3.0)	0.164
Pneumococcal infection**		238/5094 (5)	42/524 (8)	168/3982 (4)	2.0 (1.4-2.8)	<0.001
Any virus identified		6517/8393 (78)	466/688 (68)	4098/5160 (79)	0.5 (0.4-0.6)	<0.001
>1 virus identified		2760/8393 (33)	190/688 (28)	1733/5160 (34)	0.8 (0.6-0.9)	0.002
Influenza (any type)		613/8394 (7)	49/688 (7)	362/5161 (7)	1.0 (0.7-1.4)	0.917
Influenza A		434/8394 (5)	32/688 (5)	243/5161 (5)	1.0 (0.7-1.4)	0.947
Influenza B		171/8394 (2)	17/688 (2)	112/5161 (2)	1.1 (0.7-1.9)	0.614

Adenovirus	2061/7799 (26)	198/628 (32)	1298/4837 (27)	1.3 (1.0-1.5)	0.013		
Enterovirus	877/8393 (10)	56/688 (8)	513/5160 (10)	0.8 (0.6-1.1)	0.135		
Human rhinovirus	3115/8393 (37)	245/688 (36)	1952/5160 (39)	0.9 (0.8-1.1)	0.259		
Human metapneumovirus	504/8393 (5)	26/688 (4)	357/5160 (7)	0.5 (0.4-0.8)	0.002	0.5 (0.3-0.7)	<0.001
Parainfluenzavirus 1	161/8392 (2)	12/688 (2)	93/5160 (2)	1.0 (0.5-1.8)	0.914		
Parainfluenzavirus 2	116/8392 (1)	11/688 (2)	64/5159 (1)	1.3 (0.7-2.5)	0.434		
Parainfluenzavirus 3	535/8392 (6)	39/688 (6)	344/5159 (7)	0.8 (0.6-1.2)	0.320		
Parainfluenzavirus 1,2 or 3	789/8393 (9)	62/688 (9)	486/5160 (9)	1.0 (0.7-1.3)	0.731		
Respiratory syncytial virus	2216/8393 (26)	88/688 (13)	1412 /5160 (27)	0.4 (0.3-0.5)	<0.001	0.5 (0.4-0.6)	<0.001
Any aetiology identified	6635/8723 (76%)	486/705 (69)	4164/5259 (79)	0.6 (05-0.7)	<0.001		
Clinical presentation and course							
Symptoms ≥ 2 days prior to admission	4754/8620 (55)	425/693 (61)	2841/5196 (55)	1.3 (1.1-1.5)	0.001	1.4 (1.2-1.7)	<0.001
Admission to intensive care††	109/8634 (1)	14/697 (2)	67/5228 (1)	1.6 (0.9-2.8)	0.120		
Mechanical ventilation ††	95/8635 (1)	14/698 (2)	49/5228 (1)	2.2 (1.2-3.9)	0.010		
Supplementary oxygen required	3042/8637 (35)	328/698 (47)	1796/5229 (34)	1.7 (1.4-2.0)	<0.001	1.3 (1.1-1.7)	0.006
Antibiotics prescribed on	7893/8471 (93)	675/690 (98)	4758/5120 (93)	3.4 (2.0-5.8)	<0.001		

admission								
Duration of hospitalisation (days)	<2	3239/8616 (38)	116/692 (17)	1983 (5213 (38)	Reference	<0.001	Reference	<0.001
	2-7	4011/8616 (47)	245/692 (50)	2525/5213 (48)	2.3 (1.9-2.9)		1.4 (1.1-1.8)	
	>7	1366/8616 (16)	231/692 (33)	705/5213 (14)	5.6 (4.4-7.1)		3.8 (2.8-5.0)	
Duration of hospitalisation (days) (median, interquartile range)		3 (1-15)	6 (1-23)	3 (1-13)		<0.001		
Case-fatality ratio		150/8512 (2)	47/695 (7)	46/5240 (1)	8.2 (5.4-12.4)	<0.001	4.2 (2.6-6.8)	<0.001

OR – Odds ratio, CI – confidence interval, HIV – human immunodeficiency virus, PCV-pneumococcal conjugate vaccine

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

**Detected on *lytA* PCR

~Comparing HIV-infected vs. HIV-uninfected

***Odds ratios and p values shown for all variables included in the multivariable model. Hosmer-Lemeshow goodness of fit test for the final multivariable model p=0.611.

† Invasive isolates were defined as a bacterial pathogen isolated from blood or pleural fluid from a specimen taken within 48 hours of hospitalisation; organisms viewed as likely contaminants were excluded. Four percent (12/311) of HIV-infected patients had a positive blood culture (six *Staphylococcus aureus*, four *Streptococcus pneumoniae*, one *Klebsiella pneumoniae* and one *Haemophilus influenzae*). Two percent (51/2092) of HIV-uninfected patients had a positive blood culture (25 *S. aureus*, 13 *S. pneumoniae*, five *K. pneumoniae*, three *Neisseria meningitidis,* one *H. influenzae*, two *Streptococcus agalactiae* and two *Escherischia coli*). Two percent (12/793) of HIV-unknown patients had a positive blood culture (seven *S. aureus*, two *Salmonella* species, one *S. pneumoniae,* one *K. pneumoniae* and one *H. influenzae*). This variable was not evaluated on multivariable analysis due to a large proportion of missing data

††62 of 109 patients admitted to ICU received mechanical ventilation, an additional 33 patients were ventilated outside of the ICU

Table 5.2 Percent of children tested for HIV by characteristic among children <5 years hospitalised with severe acute respiratory illness (SARI) at four sentinel surveillance sites, South Africa, 2009-2011

Characteristics		Tested for HIV n/N (%)	p
Age group (months)	<12	3855/5603 (69)	0.220
	12-23	1201/1752 (69)	
	24-59	908/1368 (66)	
Sex	Male	3441/5015 (69)	0.570
	Female	2523/3708 (68)	
Race	Other race	97/158 (61)	0.056
	Black African	5860/8551 (69)	
Year	2009	1049/2191 (48)	<0.001
	2010	1394/2004 (70)	
	2011	1850/2350 (79)	
	2012	1671/2178 (77)	
Site	CHBAH	3893/6024 (65)	<0.001
	Matikwana and Mapulaneng	906/1190 (76)	
	Edendale	850/1071 (79)	
	Klerksdorp	315/438 (72)	
Underlying medical condition excluding HIV*	No	5815/8515 (68)	0.053
	Yes	148/198 (75)	
Duration of symptoms prior to admission	< 2 days	2623/3866 (68)	0.398
	≥ 2 days	3266/4754 (69)	
ICU admission	No	5844/8525 (69)	0.198
	Yes	81/109 (74)	
Mechanical ventilation	No	5863/8540 (69)	0.625
	Yes	63/95 (66)	
Supplementary oxygen therapy	No	3803/5595 (68)	0.077
	Yes	2124/3042 (70)	
Duration of hospitalisation (days)	<2	2099/3239 (65)	<0.001
	2-7	2870/4011 (72)	

	>7	936/1366 (69)	
Died	No	5842/8512 (69)	0.083
	Yes	93/150 (62)	

ICU – intensive care unit

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

Only 2% of children reported an underlying medical condition other than HIV-infection (Table 5.1). The case-fatality ratio was 2% (150/8512) and 1% (109/8634) were admitted to the ICU. Supplemental oxygen was administered to 35% (3042/8637) of children (63%, 277/437 at Klerksdorp; 62%, 661/1062 at Edendale; 21%, 246/1181 at Matikwana and Mapulaneng; 59%, 1746/2932 in the CHBAH general paediatric wards and 4%, 115/3025 at the CHBAH short stay ward). Data on presence or absence of WHO criteria for clinical severity of pneumonia[116] were only available for 44% (3841/8723) of children, of whom 23% (900/3841) would be classified as having pneumonia, 23% (894/3841) as severe pneumonia and 53% (2047/3841) very severe pneumonia. Patients with very severe pneumonia (8%; 156/1969) were more likely to test positive for influenza than those with non-severe pneumonia (6%; 48/859) or only severe pneumonia (6%; 51/862; p=0.03). All children were eligible to receive *H. influenzae* type b conjugate vaccine and 5292 to receive PCV. Coverage of *H. influenzae* type b conjugate vaccine was 78% (4477/5719) and PCV coverage was 46% (1745/3765) amongst eligible children with available data. Only 6 patients reported having received the influenza vaccine.

5.3.2 Incidence of hospitalisation in HIV-infected and -uninfected patients

The annual incidence of SARI hospitalisation amongst children <5 years at CHBAH ranged from 2530-3173/100,000 population, being highest in infants (annual range: 8446-10532 per 100,000 population; Table 5.3). Additionally, the incidence was higher in children <4 months age (15573-21752 per 100,000 population) than those age 4-11 months (5424-6792 per 100,000 population) (Table 5.4).

HIV-infected children had up to 3-fold greater incidence of SARI, although the risk of hospitalisation among HIV-infected individuals decreased in later years (Table 5.3). On sensitivity analysis, assuming that all patients not tested for HIV were HIV-uninfected, the trend toward a higher incidence of SARI hospitalisations in HIV-infected children remained in most age groups and most years, but relative risks were lower in more recent years. The overall incidence of SARI hospitalisation decreased from 2009 to 2012 amongst children <5 years (3173/100,000 to 2530/100,000; $p<0.001$) and children <1 year (9965/100,000 to 8446/100,000; $p<0.001$) although elevated incidences were noted in all age groups in 2011.

Table 5.3 Incidence of severe acute respiratory illness (SARI) hospitalisations per 100,000 population by year and HIV status among children <5 years at Chris Hani-Baragwanath Academic Hospital, South Africa

Year	Age group (months)	% with HIV result (n/N)	HIV prevalence %	IR (95% CI) All patients	IR (95% CI) HIV infected	IR (95% CI) HIV uninfected	RR (95% CI) HIV infected vs. HIV uninfected	RR (95% CI) HIV infected vs. HIV uninfected sensitivity analysis∫
2009	<12	53 (573/1090)	15	9965 (9572-10373)	36745 (32970-40747)	8857 (8480-9251)	**4.1 (3.7-4.6)**	**2 (1.7-2.3)**
	12-23	43 (155/357)	9	3189 (2971-3420)	5753 (4486-7246)	3054 (2835-3287)	**1.9 (1.5-2.4)**	0.8 (0.5-1.1)
	24-59	40 (133/332)	17	978 (909-1052)	3522 (2947-4206)	850 (783-920)	**4.2 (3.4-5.0)**	**1.5 (1.1-2.0)**
	All	48 (861/1779)	14	3173 (3075-3275)	9502 (8725-9251)	2862 (2767-2961)	**3.7 (3.4-4.0)**	**1.6 (1.5-1.8)**
2010	<12	66 (611/930)	9	8861 (8478-9258)	23038 (19723-26701)	8372 (7994-8765)	**2.7 (2.3-3.2)**	**1.7 (1.4-2.1)**
	12-23	66 (189/286)	10	2645 (2443-2865)	5508 (4218-7052)	2500 (2295-2715)	**2.2 (1.7-2.9)**	**1.4 (1.0-1.9)**
	24-59	55 (103/189)	13	563 (510-621)	1508 (1137-1997)	516 (465-574)	**2.9 (2.2-3.9)**	**1.5 (1.0-2.2)**
	All	64 (903/1405)	9	2561 (2471-2655)	5431 (4826-6101)	2427 (2337-2520)	**2.7 (2.4-3.0)**	**1.6 (1.4-1.9)**

2011	<12	75 (804/1071)	4	10532 (10123-10952)	13309 (10890-16181)	10438 (10024-10863)	**1.3 (1.0-1.5)**	0.9 (0.7-1.2)
	12-23	84 (260/309)	5	3009 (2796-3239)	3375 (2299-4691)	2993 (2774-3225)	1.1 (0.8-1.6)	0.9 (0.6-1.4)
	24-59	74 (114/154)	11	494 (444-548)	1146 (813-1577)	463 (414-516)	**2.5 (1.7-3.5)**	**1.8 (1.2-2.6)**
	All	77 (1178/1534)	5	2972 (2876-3072)	3434 (2943-3984)	2952 (2853-3052)	**1.4 (1.2-1.6)**	1.0 (0.9-1.2)
2012	<12	72 (625/870)	6	8446 (8083-8821)	16893 (14088-20021)	8167 (7805-8543)	**2.1 (1.7-2.5)**	**1.5 (1.2-1.8)**
	12-23	77 (188/245)	4	2375 (2186-2579)	2512 (1585-3681)	2370 (2174-2575)	1.1 (0.7-1.6)	0.8 (0.5-1.3)
	24-59	72 (139/193)	8	618 (563-679)	1150 (817-1614)	595 (538-655)	**2 (1.4-2.8)**	1.4 (0.9-2.1)
	All	73 (952/1307)	6	2530 (2442-2622)	3936 (3395-4536)	2472 (2382-2564)	**1.8 (1.6-2.1)**	**1.3 (1.1-1.6)**

IR – Incidence rate, RR – relative risk, CI – confidence interval, HIV – Human immunodeficiency virus

*Significant value at p<0.05 are in bold ∫Assuming that all patients not tested for HIV are HIV-negative

Table 5.4 Incidence of severe acute respiratory illness (SARI) hospitalisations per 100,000 population by year and HIV status among children <1 years at Chris Hani-Baragwanath Academic Hospital, South Africa

Year	Age group (months)	IR (95% CI) All patients	IR (95% CI) HIV infected	IR (95% CI) HIV uninfected
2009	<4	20,955 (19,813-22,140)	49,966 (41,455-59,787)	19,754 (18,619-20,927)
	4-11	6302 (5944-6681)	34,152 (30,0719-38,758)	5149 (4817-5497)
2010	<4	19,171 (18,047-20,345)	47,724 (38,291-58,532)	18,185 (17,076-19,354)
	4-11	5424 (5081-5787)	14,685 (11,659-18,147)	5105 (4767-5465)
2011	<4	21,752 (20,583-22,972)	27,336 (20,570-35,920)	21,565 (20,378-22,796)
	4-11	6792 (6414-7184)	8628 (6409-11384)	6730 (6347-7127)
2012	<4	15,573 (14,598-16,609)	31,576 (24,176-40,599)	15,044 (14,068-16,078)
	4-11	6071 (5719-6444)	12021 (9288-15108)	5874 (5520-6244)

IR – Incidence rate, CI – confidence interval, HIV – Human immunodeficiency virus

5.3.3 Aetiologic agents identified

Overall, 78% (6517/8393) of SARI episodes were associated with a viral infection, including 37% (3115/8393) for human rhinovirus, 26% (2216/8393) for RSV, 26% (2061/7799) for adenovirus, 10% (877/8393) for enterovirus and other individual viruses in <10% of children (Table 5.1). Thirty-three percent (2893/8723) of patients (311 HIV-infected, 2092 HIV-uninfected, 793 HIV-unknown) had sterile site specimens (2890 blood culture, two pleural fluid culture and one blood and pleural fluid culture) submitted for bacterial culture. Two percent (75/3196) of patients had a positive bacterial culture (Table 5.1). Only 37 patients had laboratory-confirmed tuberculosis. Five percent (238/5094) of children had pneumococcal infection. Amongst patients testing positive for pneumococcus on *lyt*A PCR, 78% (179/230) also tested positive for at least one respiratory virus, similar to the percent testing positive for respiratory viruses among pneumococcus-negative patients (78%, 3721/4764). The only virus with a significantly different prevalence amongst pneumococcal-positive compared to -negative children was influenza (13%, 29/230 detection amongst pneumococcus-positive vs. 7%, 344/4764 amongst pneumococcus-negative children, p=0.002). Patients with very severe pneumonia were more likely to test positive for influenza (6% [48/859] vs. 6% [51/862] vs. 8% [156/1969] in pneumonia, severe and very severe pneumonia respectively, p=0.03). There was no association between pneumonia severity and any other pathogen tested.

When the proportion of patients testing positive for different pathogens was analysed by age group, the prevalence of infection increased with increasing age for influenza, adenovirus, enterovirus and human rhinovirus, while RSV was most common in the 0-3 month age- group (Table 5.5). The proportion of patients testing positive for individual or any respiratory viruses did not differ by pneumococcal

vaccination status (results not shown). SARI cases were enrolled throughout the year with peaks in late summer and autumn concomitant with RSV circulation and winter and spring associated with influenza circulation (Figure 5.2).

5.3.4 Characteristics of HIV-infected children and factors associated with HIV infection

Compared to children without HIV infection, using multivariable analysis controlling for year and hospital, HIV-infected children were more likely to be in the older 24-59 month age-group (odds ratio (OR) 2.1, 95% CI 1.7-2.7 vs. <12 months), have symptoms ≥2 days prior to admission (OR 1.4, 95% CI 1.2-1.7), require supplementary-oxygen (OR 1.3, 95% CI 1.1-1.7), be hospitalised for longer duration (>7 days OR 3.8, 95% CI 2.8-5.0, 2-7 days OR 1.4, 95% CI 1.1-1.8 vs. <2 days) and to die (OR 4.2, 95% CI 2.6-6.8) (Table 5.1). In contrast, they were less likely to be infected with RSV (OR 0.5, 95% CI 0.4-0.6) or human metapneumovirus (OR 0.5, 95% CI 0.3-0.7).

Only 25% (174/705) of HIV-infected patients had available CD4+ T-lymphocyte data, of whom 64% had severe immunosuppression.[67] Forty-four percent (96/217) of those with available data reported currently receiving HAART and 30% (207/690) reported receiving prophylaxis with trimethoprim-sulfamethoxazole.

5.3.1 Factors associated with in-hospital mortality among children hospitalised with SARI

The unadjusted case-fatality ratio was seven-fold greater amongst HIV-infected (47/695, 7%) compared to HIV-uninfected (46/5240, 1%) children. On multivariable analysis, controlling for year and site, HIV-positivity (OR 3.8, 95% CI 2.1-6.8), pneumococcal co-infection (OR 3.1, 95% CI 1.3-7.4), receipt of mechanical ventilation (OR 9.1, 95% CI 3.1-27.0) and receipt of supplementary-oxygen (OR 32.8, 95% CI 14.7-72.1) were independent risk factors associated with death, while case-fatality ratio was lower in children who tested RSV-positive (OR 0.5, 95% CI 0.3-0.9) (Table 5.6). The case-fatality ratio was not significantly different between patients with (8%, 9/112) and without (3%, 2/61) severe

immunosuppression, (p=0.221) or patients receiving (3%, 3/95) and not receiving (8%, 9/118) HAART (p=0.160) although numbers were small.

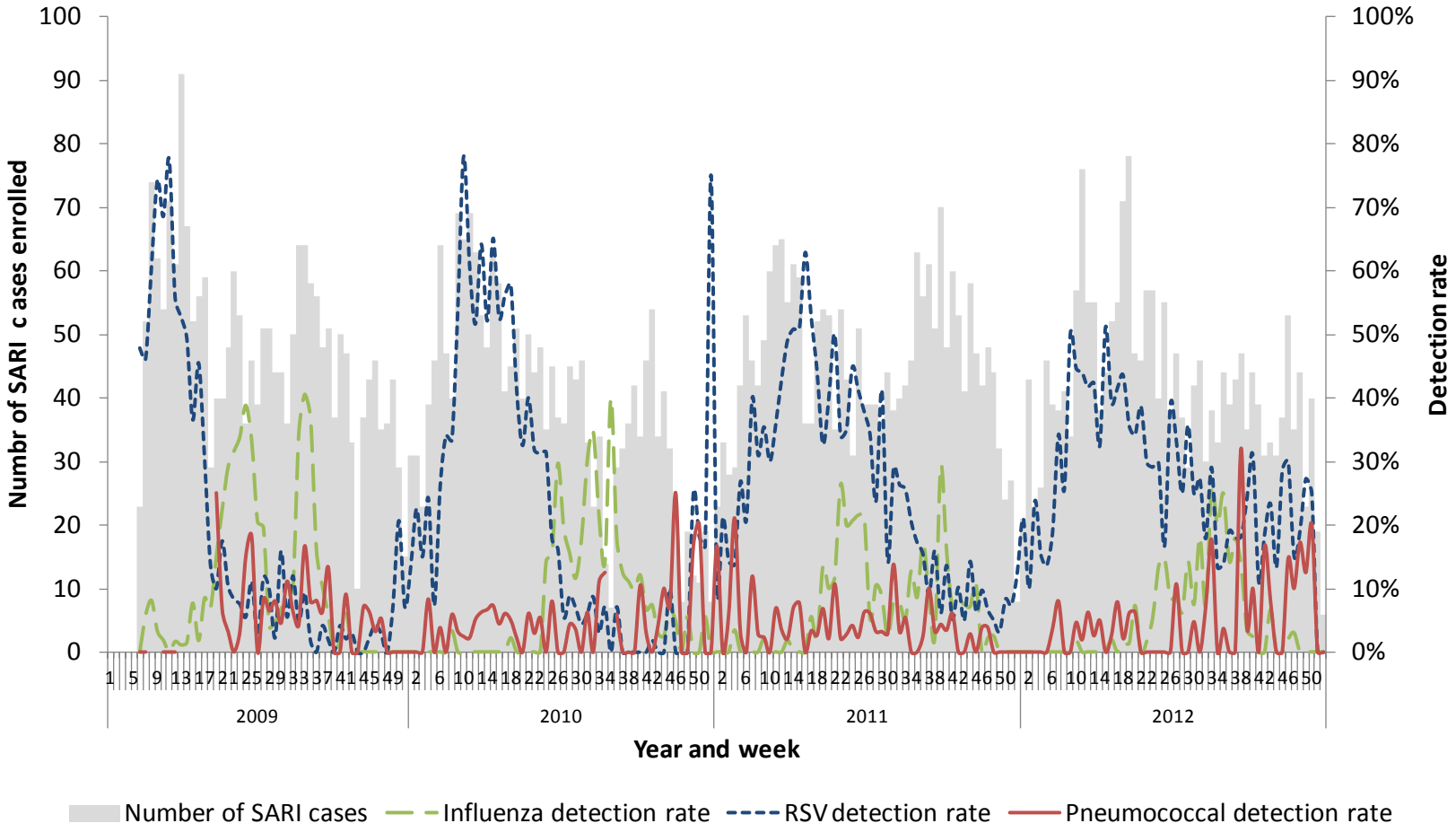
Table 5.5 Percentage of patients testing positive for viral and bacterial pathogens by age group amongst children <5 years hospitalised with severe acute respiratory illness (SARI) at four sentinel surveillance sites, South Africa, 2009-2012

Age group	0-3 months n/N (%)	4-11 months n/N (%)	12-23 months n/N (%)	24-59 months n/N (%)	P**
Influenza	109/2726 (4)	201/2637 (8)	153/1703 (9)	150/1328 (11)	<0.001
Adenovirus	298/2558 (12)	646/2448 (26)	600/1559 (38)	517/1234 (42)	<0.001
Enterovirus	207/2725 (8)	245/2637 (9)	249/1703 (15)	176/1328 (13)	<0.001
Human rhinovirus	816/2725 (30)	1027/2637 (39)	677/1703 (40)	595/1328 (45)	<0.001
Human metapneumovirus	129/2725 (5)	211/2637 (8)	97/1703 (6)	67/1328 (5)	<0.001
Parainfluenzavirus 1	28/2725 (1)	54/2637 (2)	46/1703 (3)	33/1328 (2)	<0.001
Parainfluenzavirus 2	21/2725 (1)	42/2637 (2)	27/1703 (2)	26/1328 (2)	0.007
Parainfluenzavirus 3	136/2725 (5)	229/2637 (9)	126/1702 (7)	44/1328 (3)	<0.001
Respiratory syncytial virus	897/2725 (33)	717/2637 (27)	374/1703 (22)	228/1328 (17)	<0.001
Any respiratory virus	1883/2725 (69)	2146/2637 (81)	1410/1703 (83)	1078/1328 (81)	<0.001
>1 respiratory virus	602/2725 (22)	932/2637 (35)	676/1703 (40)	550/1328 (41)	<0.001
Invasive bacterial infection on culture	32/1440 (2)	19/876 (2)	14/499 (3)	13/381 (3)	0.503
Pneumococcal infection*	67/1470 (5)	56/1086 (5)	44/852 (5)	71/1685 (4)	0.597

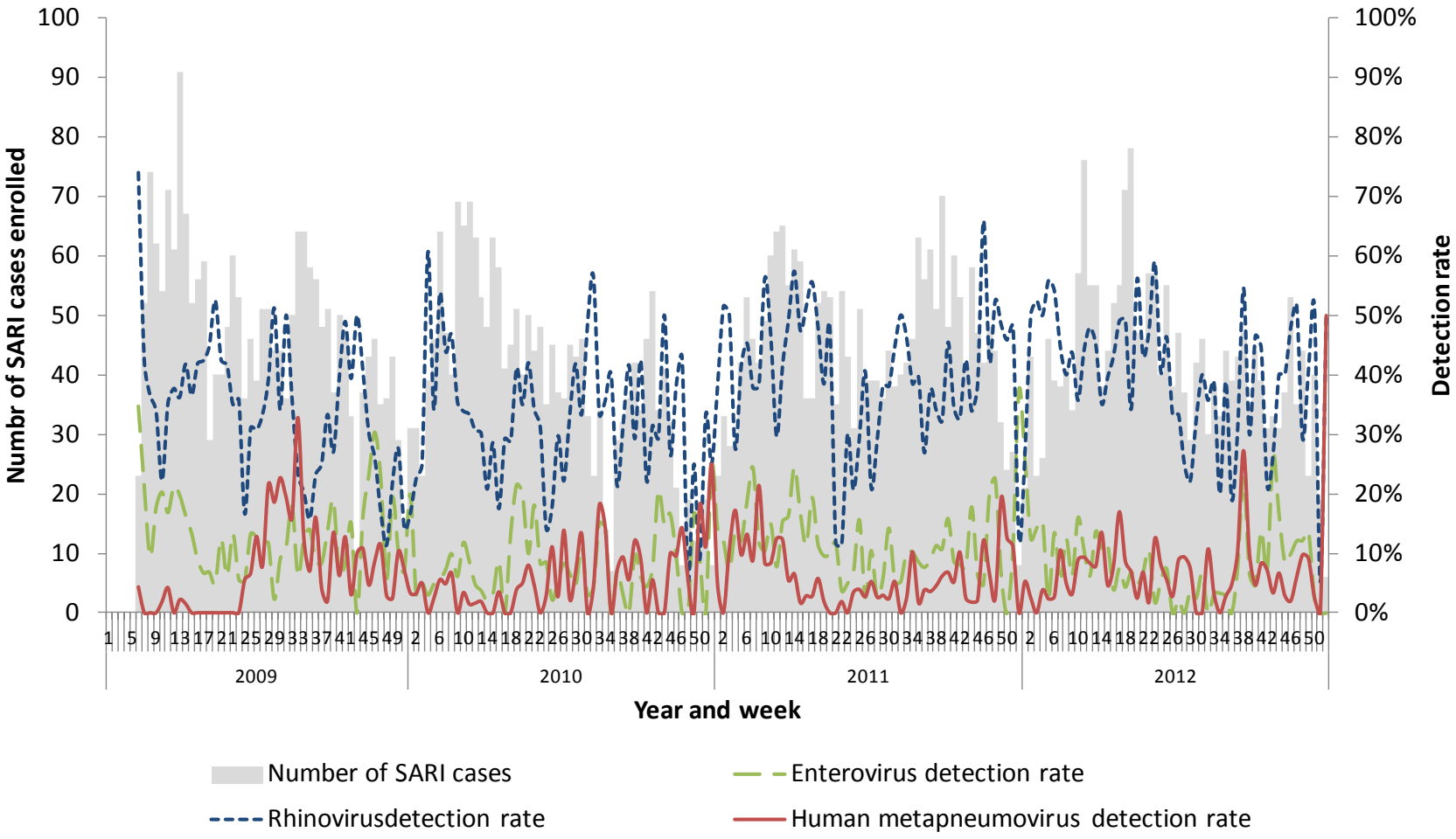
*Detected on *lytA* PCR **For heterogeneity between age groups

Figure 5.2 Number of children aged <5 years enrolled with severe acute respiratory illness (SARI) and detection rates by epidemiologic week and year at four sentinel surveillance sites, South Africa, 2009-2012

A Influenza, respiratory syncytial virus (RSV) and pneumococcal detection rates



B Enterovirus, human rhinovirus and human metapneumovirus detection rates



C Adenovirus and parainfluenza virus 1,2 and 3 detection rates

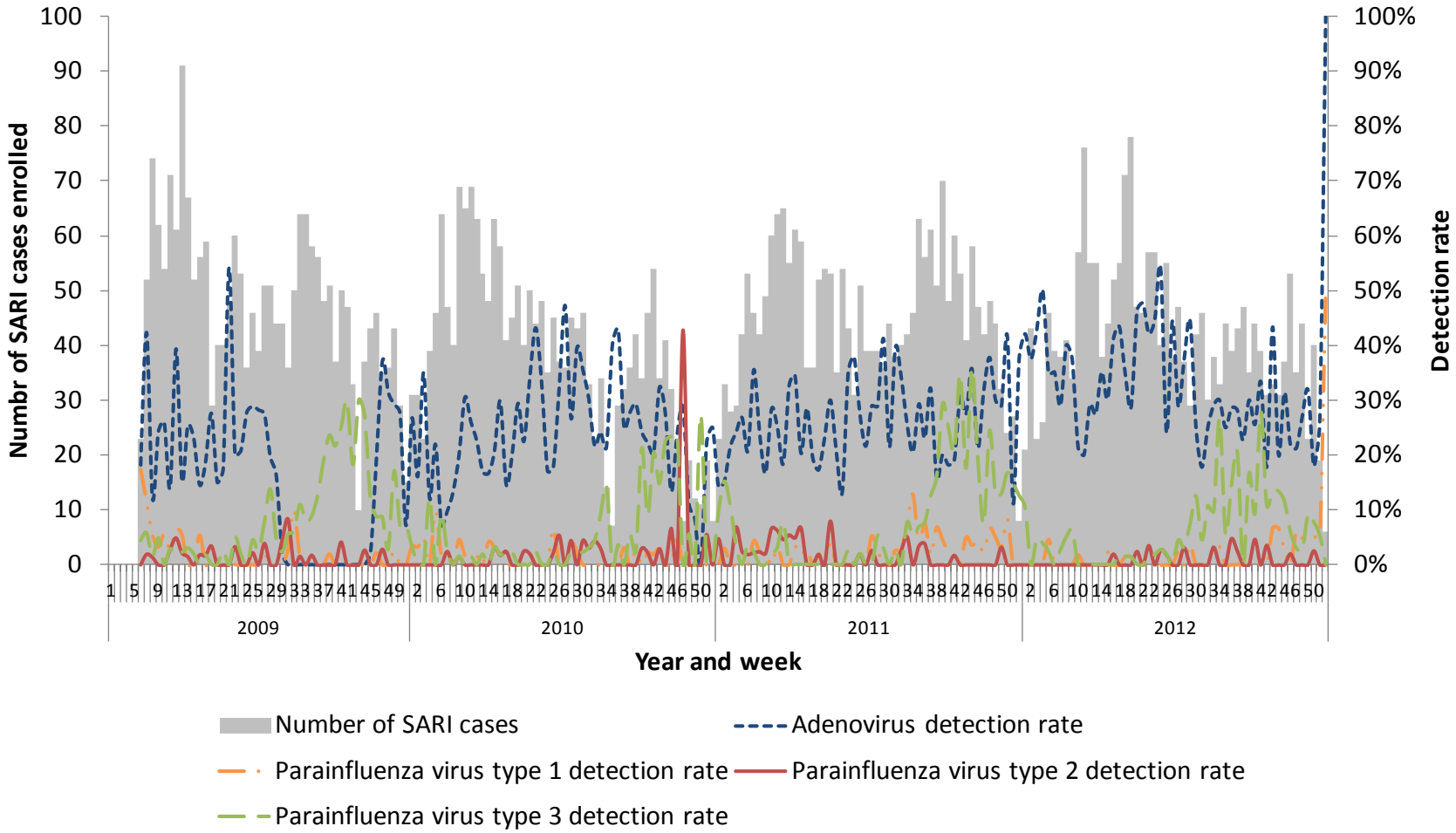


Table 5.6 Factors associated with death amongst children <5 years hospitalised with severe acute respiratory illness (SARI) at four sentinel surveillance sites, South Africa, 2009-2012

Characteristics		Case-fatality ratio (%)	Univariate analysis OR (95% CI)	p	Multivariable analysis† OR (95% CI)	p
Demographic characteristics						
Age group (months)	<12	118/5560 (2)	Reference	<0.001		
	12-23	18/1742 (1)	0.5 (0.3-0.8)			
	24-59	14/1360 (1)	0.5 (0.3-0.8)			
Sex	Male	69/4977 (1)	Reference	0.004		
	Female	81/3685 (2)	1.6 (1.2-2.2)			
Race	Other race	5/158 (3)	Reference	0.164		
	Black African	144/8490 (2)	0.5 (0.2-1.3)			
Year	2009	34/2175 (2)	Reference	0.001	Reference	0.001
	2010	55/2003 (3)	1.8 (1.2-2.8)		3.0 (1.2-7.4)	
	2011	35/2331 (2)	1.0 (0.6-1.5)		1.5 (0.6-3.8)	
	2012	26/2153 (1)	0.8 (0.5-1.3)		0.9 (0.3-2.5)	
Site	CHBAH	52/5987 (1)	Reference	<0.001	Reference	<0.001
	Matikwana and Mapulaneng	86/1185 (7)	8.9 (6.3-12.7)		13.4 (6.6-27.5)	
	Edendale	4/1054 (<1)	0.4 (0.2-1.2)		0.4 (0.1-1.2)	

Klerksdorp		8/436 (2)	2.1 (1.0-4.5)		1.2 (0.4-4.0)	
Underlying medical conditions						
HIV status	Negative	46/5240 (1)	Reference	<0.001	Reference	<0.001
	Positive	47/695 (7)	8.2 (5.4-12.4)		3.8 (2.1-6.8)	
Underlying medical	No	143/8458 (2)	Reference	0.352		
condition excluding HIV*	Yes	5/194 (3)	1.5 (0.6-3.8)			
2 or more doses of	No	34/2005 (2)	Reference	0.084		
pneumococcal conjugate	Yes	18/1733 (1)	0.6 (0.3-1.1)			
vaccine (eligible children						
<5 years)						
Infectious agents identified						
Invasive bacterial infection	No	195/4260 (5)	Reference			
on culture	Yes	8/122 (7)	1.5 (0.7-3.0)			
Pneumococcal infection**	No	78/4827 (2)	Reference	0.011	Reference	0.012
	Yes	9/236 (4)	2.4 (1.2-4.9)		3.1 (1.3-7.4)	
Influenza (any type)	No	128/7731 (2)	Reference	0.204		
	Yes	6/609 (1)	0.6 (0.3-1.3)			
Adenovirus	No	94/5698 (2)	Reference	0.299		
	Yes	27/2050 (1)	0.8 (05-1.2)			
Enterovirus	No	120/7468 (2)	Reference	0.999		
	Yes	14/871 (2)	1.0 (0.6-1.7)			

Human rhinovirus	No	98/5245 (2)	Reference	0.014		
	Yes	36/3094 (1)	0.6 (0.4-0.9)			
Human metapneumovirus	No	129/7838 (2)	Reference	0.269		
	Yes	5/501 (1)	0.6 (0.2-1.5)			
Parainfluenzavirus 1	No	130/8179 (2)	Reference	0.369		
	Yes	4/160 (3)	1.6 (0.6-4.3)			
Parainfluenzavirus 2	No	131/8222 (2)	Reference	0.398		
	Yes	3/116 (3)	1.6 (0.5-5.2)			
Parainfluenzavirus 3	No	125/7808 (2)	Reference	0.863		
	Yes	9/530 (2)	1.1 (0.5-2.1)			
Respiratory syncytial virus	No	120/6135 (2)	Reference	<0.001	Reference	0.042
	Yes	14/2204 (1)	0.3 (0.2-0.6)		0.5 (0.3-0.9)	
Clinical presentation and course						
Duration of symptoms	< 2 days	60/3843 (2)	Reference	0.276		
prior to admission	≥ 2 days	88/4716 (2)	1.2 (0.9-1.7)			
ICU admission	No	145/8497 (2)	Reference	0.179		
	Yes	4/109 (4)	2.2 (0.8-6.0)			
Mechanical ventilation	No	128/8512 (2)	Reference	<0.001	Reference	<0.001
	Yes	21/95 (22)	18.6 (11.1-31.1)		9.1 (3.1-27.0)	
Supplementary Oxygen	No	30/5579 (1)	Reference	<0.001	Reference	<0.001
therapy	Yes	119/3029 (4)	7.6 (5.1-11.3)		32.8 (14.7-73.1)	
Antibiotics prescribed on	No	7/576 (1)	Reference	0.322		
admission	Yes	142/7847 (2)	1.5 (0.7-3.2)			

Duration of hospitalisation	<2	22/3238 (1)	Reference	<0.001
(days)	2-7	85/4001 (2)	3.2 (2.0-5.1)	
	>7	42/1362 (3)	4.7 (2.8-7.9)	

OR – Odds ratio, CI – confidence interval, HIV – human immunodeficiency virus, ICU – Intensive care unit

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

** Detected on *lytA* PCR

***Pathogen isolated within 72 hours of hospitalisation from blood or pleural fluid; organisms viewed as likely contaminants were excluded

****Co-infection with at least one of parainfluenza virus 1, 2 and 3; respiratory syncytial virus; enterovirus; human metapneumovirus; adenovirus; human rhinovirus in addition to influenza

†Odds ratios and p values shown for all variables included in the multivariable model. Hosmer-Lemeshow goodness of fit test for the final multivariable model p=0.54.

5.4 Discussion

In South Africa, HIV-infected children have an elevated incidence of SARI hospitalisation, duration of hospitalisation and in-hospital case-fatality ratio compared to HIV-uninfected children. This indicates that underlying HIV-infection remains a major risk factor for pneumonia morbidity and mortality in settings such as ours, even following HAART availability. Of the respiratory viruses with a likely pathogenic role, RSV was identified in more than 25% of children, particularly in infants, and influenza was identified in 7% of children. While pneumococcus was not as commonly identified (4% of cases), likely related to lower sensitivity of available diagnostic assays for pneumococcal pneumonia, infection with pneumococcus was an independent risk factor for death.

The overall incidence of hospitalisation for SARI per 100,000 population in South Africa amongst children <5 years of age (~2500-3000) was similar to that described from Africa in a recent systematic review of global pneumonia burden (~2260, 95% CI 1530-3340).[3] We observed the highest incidence in those aged <12 months (~8000-11000/100,000 population), where incidences were slightly higher than other estimates for Africa (~5080/100,000 population, 95% CI 3360-7690/100,000) but similar to those from some studies from middle-income countries.[3;117 118]

Pneumonia is the most common reason for hospitalisation among African HIV-infected children.[6] In our study, HIV-infected children experienced an elevated incidence of hospitalisation compared to HIV-uninfected children but this excess risk decreased over the study period from 3.7 (95% CI 3.4-4.0) in 2009 to 1.8 (1.6-2.1) in 2012, possibly related to more widespread availability of early HAART over this period.[119;120] Studies have shown that more widespread HAART availability is associated with a reduction in pneumonia incidence in HIV-infected children, albeit HIV-infected children on HAART still have a higher incidence of pneumonia.[110;113;114] We found that HIV-infected children experienced a four times increased risk of death compared to HIV-uninfected children once hospitalised. This is similar to several other studies which reported case-fatality ratios 3-6 times greater in HIV-infected children.[6;89;121;122] The overall case-fatality ratios among HIV-infected children in our study are however lower than has

previously been described in HIV-infected children from South Africa, possibly related to more widespread HAART availability.

Human rhinovirus (37%), RSV (26%) and adenovirus (26%) were the most commonly identified respiratory viruses, while influenza was identified in 7% of patients, similar to what has been found in other studies from Africa using PCR for viral diagnosis.[118;123-125] Challenges remain for the attribution of a causal role for some viruses (including human rhinovirus, adenovirus and enterovirus), which are also identified at high frequency from healthy individuals.[118;123;125] RSV and human metapneumovirus (both thought to have a likely pathogenic role) were identified less frequently in HIV-infected than -uninfected children suggesting that the increased risk of hospitalisation due to HIV-associated immunosuppression is relatively lower for these pathogens than for other aetiologies. Previous studies from South Africa have shown that while the detection rate for viruses may be lower in HIV-infected children, the incidence of hospitalisation is substantially higher in HIV-infected compared to HIV-uninfected children.[89;126] Children with RSV were less likely to die, as has been previously described.[118] This is likely because the relative contribution of viral aetiologies compared with bacterial aetiologies is greater for hospitalised pneumonia than amongst deaths.[127] A high proportion of children were co-infected with multiple respiratory viruses (33%), as has been described previously, although co-infection was not associated with adverse outcome.[7;43;125] HIV-infected children have been described to have an increased risk of polymicrobial infections due to multiple bacterial, viral and fungal pathogens.[110] We were not able to assess this as we did not systematically test for important pathogens in HIV-infected children, particularly tuberculosis, *P. jirovecii* and cytomegalovirus.

Blood cultures were performed in less than half of children, limiting our ability to comment on the proportion with bacteraemic pneumonia, but similar to other studies from South Africa, the pneumococcus and *S. aureus* were the most common bacteria identified. *S. pneumoniae* is an important cause of pneumonia in HIV-infected and uninfected children.[121;122] In our study we identified pneumococcus from 5% of children overall using PCR. These rates are similar to other studies from South Africa prior to PCV introduction which used systematic blood culture collection.[121;122] Failure to observe lower detection rates following PCV introduction may be attributed to our diagnostic technique, real-time PCR, identifying more pneumococcal cases than blood culture in our setting.[128] Notwithstanding this, additional cases of pneumococcal co-infection may still have been missed.[129;130] Pneumococcal DNA in the blood may reflect occult bacteraemia in some individuals.[131-133] Patients

testing positive for pneumococcus had a high prevalence of detection of respiratory viruses although many of these may have been co-incidental viral shedding.[7] Influenza was the only virus to be more commonly detected in patients testing positive for pneumococcus. The association between influenza and pneumococcal infection has been described previously. [82;134]

Our study had potential limitations. HIV status data was only available for ~60% of children. If the characteristics of untested children differed from those of tested children this may have biased findings, however, we did not find any significant differences in epidemiologic characteristics of tested and untested patients. In addition, for the estimation of incidence stratified by HIV status we conducted a sensitivity analysis to explore the scenario if all untested children were HIV-uninfected. Data on access to HAART and CD4+ T cell count were only available for a limited number of HIV-infected children limiting our ability to comment on the effect of HAART and degree of immunosupression on disease incidence and severity. Incidence data were only available for one urban site with available denominator data and thus may not be generalisable to other settings within South Africa. We may have underestimated incidence as not all cases may have sought care at CHBAH hospital. In addition, we did not account for individuals who did not seek care at all. Children who died may have been less likely to consent to inclusion into studies such as ours or may die before or shortly after hospital admission prior to being consented and this may lead to underestimation of case-fatality ratios and potential exclusion of most severely ill children.[123] Therefore our incidence and mortality estimates likely represent a minimum estimate. The denominators for the numbers of HIV-infected and -uninfected children each year were obtained from the 2008 version of the ASSA model. Subsequent to the development of this model, rates of access to interventions for prevention of mother-to-child transmission of HIV (PMTCT) and early HAART amongst children have been more rapid than expected leading to possible overestimation of the numbers of children with AIDS in South Africa, which could have led to an underestimation of the relative risk of hospitalisation in HIV-infected children.[23;119] There were a large number of statistical analyses conducted on these data and corrections were not made for multiple testing.

In conclusion, we have demonstrated a high incidence of hospitalisation for SARI amongst children aged <5 years in South Africa, particularly in children aged <1 year and HIV-infected children. HIV-infected children also experience increased hospitalisation duration and mortality. RSV was an important cause of pneumonia. Vaccines for RSV are currently under development and could be expect to have a

substantial impact on pneumonia burden if they become available. [135] Ongoing reductions in burden of pneumococcal pneumonia may be expected following PCV introduction. Influenza was identified in 7% of children and influenza vaccination is recommended for children <5 years in South Africa but very few children in our study reported being vaccinated.[45] Influenza vaccines are less effective in children <5 years and efficacy has not been demonstrated in HIV-infected children.[136] More widespread access to influenza vaccines could, however, potentially impact on disease burden, particularly if newer formulations such as adjuvanted vaccines are shown to be safe and effective in our setting. HIV remains a major risk factor for SARI and adverse outcome, and more widespread adherence to PMTCT protocols and availability of HAART can be expected to have ongoing impact in reducing disease burden.[6;110]

Chapter 6 Epidemiology of SARI among adults and children ≥5 years age in a high HIV-prevalence setting, 2009-2012

6.1 Introduction

There are few published studies estimating the incidence and aetiology of pneumonia amongst older children and adults from high HIV-prevalence settings in sub-Saharan Africa.[137] Data on the burden, severity and aetiology of SARI amongst HIV-infected and -uninfected older children and adults are necessary to guide the relative prioritisation of prevention and control efforts. In South Africa the HIV prevalence amongst individuals aged 15-49 years, the age group with the highest prevalence of HIV, was estimated to be 17% in 2012.[23] South Africa embarked on a national programme of provision of HAART in 2004.[138] HAART coverage amongst eligible HIV-infected adults (CD4+ T cell count<350/mm3) in South Africa was estimated to be 29% in 2009 and 52% in 2011.[120]

We aimed to describe the incidence, viral aetiology and factors associated with death amongst HIV-infected and -uninfected individuals aged ≥5 years hospitalised with SARI in South Africa from 2009 through 2012.

6.2 Materials and Methods

Case definitions, study procedures, laboratory methods, definitions, evaluation of HIV serostatus and calculation of incidence are described in Chapter 2 Methods section 2.2.

6.3 Results

6.3.1 Demographic, clinical characteristics and aetiology

From February 2009 through December 2012, 7977 individuals ≥5 years of age who fulfilled the SARI case definition were screened for study enrolment, of whom 7193 (90%) were enrolled (Figure 6.1). The most common reasons for non-enrolment were being confused or too ill to consent (55%) and study refusal (11%). Of the 7193 enrollees, 8% (579) were 5-14 years of age, 8% (599) 15-24 years, 53% (3784) 25-44 years, 25% (1778) 45-64 years and 6% (453) ≥65 years (Table 6.1). The majority of subjects were enrolled at CHBAH (76%, 5443/7193), and 61% (4413/7193) were female. Among patients with available information, the overall case-fatality ratio was 7% (514/7154).

HIV-infection status was available for 6334 (88%) of enrolled individuals (Figure 6.1). When comparing patients tested for HIV to those not tested for HIV, controlling for year of test, surveillance site and age group there were no differences in patient epidemiologic characteristics or case-fatality ratios (data not shown). The overall HIV prevalence among persons ≥5 years with available data was 74% (4663/6334) and was highest in the 25-44 year age group 88% (3016/3421) (Table 6.1). Twelve percent of individuals (879/7191) had an underlying medical condition, excluding HIV. Only 14 individuals reported having been vaccinated against influenza in the current year and no subject had received pneumococcal vaccines.

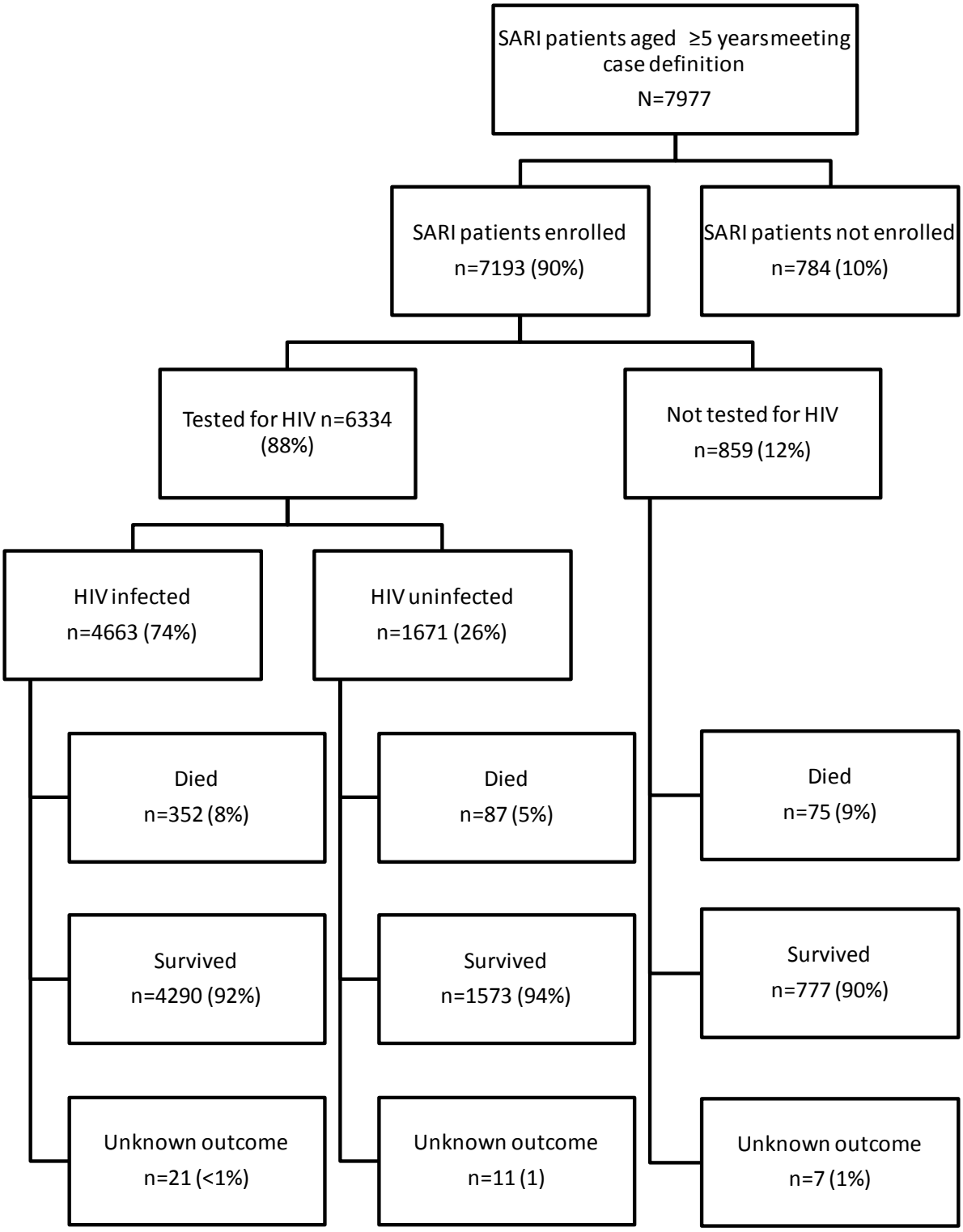


Figure 6.1 Flow chart of patients aged ≥5 years included in the study

SARI - severe acute respiratory illness, HIV - human immunodeficiency virus

Table 6.1 Comparison of the clinical and epidemiologic characteristics of HIV-infected and -uninfected individuals aged ≥5 years hospitalised with severe acute respiratory illness (SARI) at four sentinel surveillance sites, South Africa, 2009-2012

Characteristics		**All patients n/N (%)**	**HIV-infected n/N (%)**	**HIV-uninfected n/N (%)**	**Univariate analysis (HIV-infected vs. uninfected) OR(95% CI)**	**p**	**Multivariable analysis**** **OR (95% CI)**	**p**
Demographic characteristics								
Age group	5-14	579/7193 (8)	191/4663 (4)	185/1671 (11)	Reference	<0.001	Reference	<0.001
(years)	15-24	599/7193 (8)	336/4663 (7)	192/1671 (11)	1.7 (1.3-2.2)		1.1 (0.8-1.6)	
	25-44	3784/7193 (53)	3016/4663 (65)	405/1671 (24)	7.2 (5.7-9.1)		5.4 (4.1-7.2)	
	45-64	1778/7193 (25)	1047/4663 (22)	564/1671 (34)	1.8 (0.4-2.3)		1.6 (1.2-2.1)	
	≥65	453/7193 (6)	73/4663 (2)	325/1671 (19)	0.2 (0.2-0.3)		0.2 (0.1-0.3)	
Female		4413/7193 (61)	3037/4663 (65)	891/1671 (53)	1.6 (0.5-1.87)	<0.001	1.7 (1.5-2.0)	<0.001
Black African race		6998/7185 (97)	4597/4659 (99)	1573/1670 (94)	4.5 (3.3-6.3)	<0.001	3.8 (2.6-5.7)	<0.001
Year	2009	1464/7193 (20)	857/4663 (18)	302/1671 (18)	Reference	<0.001		
	2010	2022/7193 (28)	1407/4663 (30)	423/1671 (25)	1.2 (1.0-1.4)			
	2011	1935/7193 (27)	1291/4663 (28)	544/1671 (33)	0.8 (0.7-1.0)			
	2012	1772/7193 (25)	1108/4663 (24)	402/1671 (24)	1.0 (0.8-1.2)			
Site	CHBAH	5443/7193 (76)	3648/4663 (78)	1230/1671 (74)	Reference	<0.001		
	Matikwana and Mapulaneng	950/7193 (13)	543/4663 (12)	231/1671 (14)	0.8 (0.7-0.9)			

Edendale	565/7193 (8)	348/4663 (7)	123/1671 (7)	1.0 (0.8-1.2)			
Klerksdorp	235/7193 (3)	124/4663 (3)	87/1671 (5)	0.5 (0.4-0.6)			
Underlying medical conditions							
Underlying medical condition excluding tuberculosis and HIV*	879/7191 (12)	345/4663 (7)	433/1671 (26)	0.2 (0.2-0.3)	<0.001	0.3 (0.2-0.4)	<0.001
Underlying tuberculosis (receiving tuberculosis treatment on admission)	276/7167 (4)	217/4646 (5)	28/1668 (2)	2.9 (1.9-4.3)	<0.001	2.1 (1.3-3.2)	0.002
Alcohol use	1175/7174 (16)	729/4650 (16)	344/1667 (21)	0.7 (0.6-0.8)	<0.001	0.6 (0.5-0.7)	<0.001
Smoking	1029/7175 (14)	625/4651 (13)	310/1667 (19)	0.7 (0.6-0.8)	<0.001		
Infectious agents identified							
Pneumococcus**	600/6519 (9)	499/4506 (11)	70/1601(5)	2.7 (2.1-3.5)	<0.001	2.2 (1.6-2.9)	<0.001
>1 virus identified	470/7056 (7)	289/4608 (6)	98/1640 (6)	1.1 (0.8-1.3)	0.669		
Influenza (any type)	621/7067 (9)	350/4609 (8)	185/1650 (11)	0.7 (0.5-0.8)	<0.001	0.6 (0.5-0.8)	<0.001
Influenza A	366/7067 (5)	190/4609 (4)	113/1650 (7)	0.6 (0.5-0.7)	<0.001		
Influenza B	246/7067 (3)	153/4609 (3)	70/1650 (4)	0.8 (0.6-1.0)	0.083		
Adenovirus	613/6453 (10)	394/4206 (9)	132/1509 (9)	1.1 (0.9-1.3)	0.475		
Enterovirus	119/6933 (2)	65/4610 (1)	30/1636 (2)	0.8 (0.5-1.2)	0.230		
Human rhinovirus	1267/7049 (18)	835/4608 (18)	265/1636 (16)	1.1 (1.0-1.3)	0.080		
Human metapneumovirus	124/7052 (2)	88/4610 (2)	23/1636 (1)	1.4 (0.9-2.2)	0.188		
Parainfluenzavirus 1	28/7052 (<1)	20/4610 (<1)	6/1636 (<1)	1.2 (0.5-3.0)	0.718		
Parainfluenzavirus 2	43/7052 (1)	31/4610 (1)	3/1636 (<1)	3.7 (1.1-12.1)	0.031		
Parainfluenzavirus 3	127/7050 (2)	94/4610 (2)	22/1634 (1)	1.5 (1.0-2.4)	0.077		

Parainfluenza virus 1,2 or 3		194/7052 (3)	141/4610 (3)	31/1636 (2)	1.6 (1.1-2.4)	0.014		
Respiratory syncytial virus		321/7052 (5)	209/4610 (5)	60/1636 (4)	1.2 (0.9-1.7)	0.139		
Any virus identified		2279/7056 (32)	1507/4608 (33)	473/1640 (29)	1.2 (1.1-1.4)	0.004		
Any aetiology identified		2951/7193 (41)	2032/4663 (44)	570/1671 (34)	1.5 (1.3-1.7)	<0.001		
Clinical presentation and course								
Symptoms ≥2 days prior to admission		5934/7059 (84)	3998/4576 (87)	1296/1636 (79)	1.8 (1.6-2.1)	<0.001	1.6 (1.3-1.9)	<0.001
Admission to intensive care		11/7165 (<1)	7/4650 (<1)	2/1665 (<1)	1.3 (0.3-6.0)	0.778		
Mechanical ventilation		11/7167 (<1)	5/4651 (<1)	3/1666 (<1)	0.6 (0.1-2.5)	0.480		
Oxygen required		2682/7164 (37)	1788/4649 (38)	641/1666 (38)	1.0 (0.9-1.1)	0.991		
Antibiotics prescribed on admission		6787/7002 (97)	4468/4569 (98)	1549/1630 (95)	2.3 (1.7-3.1)	<0.001	2.5 (1.7-3.6)	<0.001
Duration of hospitalisation (days)	<2	525/7092 (7)	208/4605 (5)	158/1647 (10)	Reference	<0.001	Reference	<0.001
	2-7	4014/7092 (57)	2580/4605 (56)	1016/1647 (62)	1.9 (1.5-2.4)		1.6 (1.2-2.1)	
	>7	2553/7092 (36)	1817/4605 (39)	473/1647 (29)	2.9 (2.3-3.7)		2.4 (1.8-3.2)	
Duration of hospitalisation (days) (median, interquartile range)		6 (1-20)	7 (2-20)	5 (1-19)		<0.001		
Case-fatality ratio		514/7154 (7)	352/4642 (8)	87/1660 (5)	1.5 (1.2-1.9)	0.001	1.6 (1.2-2.2)	0.002

OR – Odds ratio, CI – confidence interval, HIV – human immunodeficiency virus, CHBAH – Chris Hani Baragwanath Academic Hospital

* Asthma, other chronic lung disease, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), diabetes mellitis, immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions) or pregnancy. Comorbidities

were considered absent in cases for which the medical records stated that the patient had no underlying medical condition or when there was no direct reference to that condition.

**Positive on *lytA* PCR

***Infection with at least one of influenza, parainfluenza virus 1, 2 and 3; respiratory syncytial virus; enterovirus; human metapneumovirus ; adenovirus; human rhinovirus in addition to influenza

**** HIV-infected vs. -uninfected. Odds ratios and p values shown for all variables included in the multivariable model

† Not evaluated in multivariable model due to large amount of missing data

Enrolment occurred throughout the year and peaked in the winter months (May-August) (Figure 6.2). Overall, among those tested for respiratory viruses, 18% (1267/7049) were positive for human rhinovirus, 10% (613/6453) for adenovirus and 9% (621/7067) for influenza (Table 6.1). Other respiratory viruses tested positive in less than 5% of individuals. Adenovirus, human rhinovirus and enterovirus were more commonly identified in individuals 5-14 years old than other age groups (Table 6.2). Also, 9% (600/6519) of subjects tested positive for pneumococcus (Table 6.1). The detection of influenza virus-associated SARI peaked during the winter months (Figure 6.2). Although pneumococcus on *lyt*A PCR was detected perennially, there was also a peak in detection during winter months of at least two years (2009 and 2010).

Table 6.2 Percentage of patients testing positive for viral and bacterial pathogens by age group amongst individuals aged ≥5 years hospitalised with severe acute respiratory illness (SARI) at four sentinel surveillance sites, South Africa, 2009-2012

Age group (years)	5-14 n/N (%)	15-24 n/N (%)	25-44 n/N (%)	45-64 n/N (%)	≥65 n/N (%)	p*
Influenza	64/560 (11)	64/590 (11)	306/3715 (8)	139/1756 (8)	48/446 (11)	0.010
Adenovirus	115/489 (24)	49/520 (9)	286/3403 (8)	138/1628 (8)	25/413 (6)	<0.001
Enterovirus	43/550 (8)	12/585 (2)	40/3715 (1)	17/1756 (1)	7/446 (2)	<0.001
Human rhinovirus	189/550 (34)	128/585 (22)	652/3715 (18)	249/1756 (14)	49/446 (11)	<0.001
Human metapneumovirus	13/550 (2)	9/585 (2)	68/3715 (2)	26/1756 (1)	8/446 (2)	0.694
Parainfluenzavirus 1	3/550 (1)	2/585 (<1)	11/3715 (<1)	9/1756 (1)	3/446 (1)	0.599
Parainfluenzavirus 2	8/550 (1)	4/585 (1)	25/3715 (1)	6/1756 (<1)	0/446 (0)	0.021
Parainfluenzavirus 3	7/550 (1)	17/585 (3)	67/3715 (2)	27/1756 (2)	9/446 (2)	0.220
Respiratory syncytial virus	36/550 (7)	21/585 (4)	171/3715 (5)	77/1756 (4)	16/446 (4)	0.118
Any respiratory viral infection	315/550 (57)	209/585 (36)	1159/3715 (31)	491/1756 (28)	105/446 (24)	<0.001
Infection with >1 respiratory virus	108/550 (19)	47/585 (8)	211/3715 (6)	85/1756 (5)	19/446 (4)	<0.001
Pneumococcus**	24/381 (6)	48/553 (9)	348/3507 (10)	166/1655 (10)	14/423 (3)	<0.001

*chi squared test **On *lyt*A PCR or blood culture

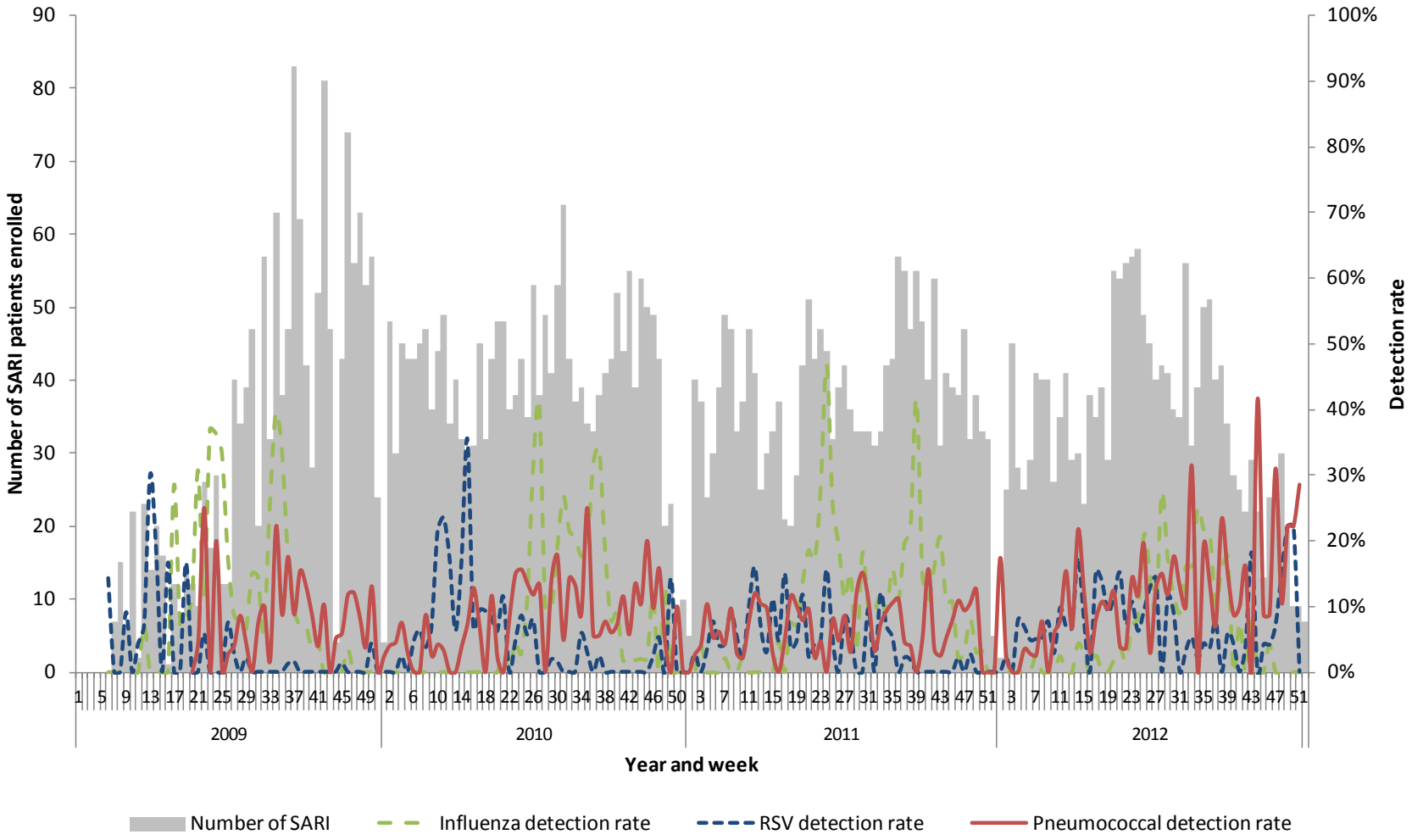


Figure 6.2 Number of patients enrolled with severe acute respiratory illness (SARI) and influenza, pneumococcal and respiratory syncytial virus (RSV) detection rates by epidemiologic week and year at four sentinel surveillance sites, South Africa, 2009-2011

6.3.2 Incidence of hospitalisation in HIV-infected and -uninfected patients

The annual incidence of hospitalisation per 100,000 population for SARI at CHBAH ranged between 325 (95% CI 315-335) in 2012 and 617 (95% CI 603-632) in 2010 and was highest in the 45-64 year age-group; annual range 501 to 1284 (Table 6.3). HIV-infected individuals experienced an age-adjusted increased relative risk of 13 to 19 times for SARI hospitalisation compared to HIV-uninfected individuals. On sensitivity analysis, assuming that all patients not tested for HIV were HIV-uninfected, the trend towards a higher incidence of SARI hospitalisations in HIV-infected individuals remained in all age groups and years.

6.3.3 Characteristics of HIV-infected patients and factors associated with HIV infection

Compared to HIV-uninfected cases, using multivariable analysis, in addition to other factors, HIV-infected subjects were more likely to be receiving tuberculosis treatment at admission (OR 2.1, 95% CI 1.3-3.2), have pneumococcal infection (OR 2.2, 95% CI 1.6-2.9) and had a higher case-fatality ratio (OR1.6, 95% CI 1.2-2.2; Table 6.1). In contrast, HIV-infected subjects were less likely to have an underlying medical condition (OR 0.3, 95% CI 0.2-0.4), or be infected with influenza (OR 0.6, 95% CI 0.5-0.8).

Only 1455 (31%) of 4663 HIV-infected patients had available CD4+ T cell count data, of whom 68% (987) had CD4+ T-lymphocyte cell counts <200/mm3. The case-fatality ratio was significantly higher in HIV-infected subjects with severe immunosuppression (12%, 117/983) than those with CD4+ T-lymphocyte

count of >200/mm3 (5%, 22/462, p<0.001). Of those with available data, 41% (1083/2629) reported currently receiving HAART and 34% (1566/4569) reported receiving prophylaxis with trimethoprim-sulfamethoxazole. The case-fatality ratio was similar in individuals receiving (7%, 80/1075) and not receiving HAART (vs. 8%, 121/1536, p=0.681).

6.3.4 Factors associated with mortality

The overall case-fatality ratio was 7% (514/7154), with a median age of 42 years (interquartile range 23-74) among those who died. The case-fatality ratio was 1.5 times greater amongst HIV-infected (8%) as compared to HIV-uninfected (5%) individuals with SARI (Table 6.4). On multivariable analysis, independent risk indicators associated with death included increasing age group, HIV infection (OR 1.8, 95% CI 1.3-2.4), receipt of mechanical ventilation (OR 6.5, 95% CI 1.3-32.0) and receiving supplementary-oxygen therapy (OR 2.6, 95% CI 2.1-3.2) (Table 6.4).

Table 6.3 Incidence of severe acute respiratory illness (SARI) hospitalisations per 100,000 population by year and HIV status at Chris Hani-Baragwanath Hospital, South Africa

Year	Age group (years)	% with HIV result (n/N)	HIV prevalence %	IR (95% CI) All patients	IR (95% CI) HIV infected	IR (95% CI) HIV uninfected	RR (95% CI) HIV infected vs. HIV uninfected	RR (95% CI) HIV infected vs. HIV uninfected sensitivity analysis∫
2009	5-14	41 (53/129)	36	126 (112-141)	1833 (1496-2227)	82 (71-96)	22.1 (17.2-28.4)	6.9 (4.8-9.6)
	15-24	85 (88/103)	65	283 (261-308)	2005 (1806-2223)	110 (95-126)	18.2 (15.3-21.8)	12.3 (10.4-14.5)
	25-44	89 (553/625)	91	846 (818-875)	2947 (2845-3053)	101 (90-114)	29.0 (25.8-32.8)	11.8 (10.8-12.8)
	45-64	88 (232/263)	62	925 (882-970)	4682 (4403-4973)	400 (370-432)	11.7 (10.6-12.9)	8.7 (7.9-9.5)
	≥65	79 (37/47)	14	624 (562-690)	8777 (6488-1152)	544 (487-608)	16.1 (11.7-21.7)	12.1 (8.5-16.9)
	All (≥5 years)	83 (963/1167)	76	591 (577-606)	3072 (2985-3162)	179 (171-188)	18.1 (17.0-19.3)*	10 (9.8-11.0)*
2010	5-14	53 (41/77)	37	65 (56-76)	876 (670-1126)	42 (35-52)	20.5 (14.7-28.4)	8.4 (5.5-12.5)
	15-24	89 (121/136)	70	206 (187-226)	1665 (149-1858)	67 (56-79)	24.9 (20.3-30.6)	17.5 (14.5-21.3)
	25-44	92 (906/981)	90	753 (727-779)	2576 (248-267)	105 (95-117)	24.3 (21.8-27.3)	13.5 (12.4-14.8)
	45-64	93 (435/468)	69	1284 (1237-1334)	7025 (671-735)	456 (426-488)	15.4 (14.2-16.7)	12.4 (11.4-13.4)

	≥65	92 (85/92)	21	1101 (1022-1185)	19793 (16749-23169)	878 (808-954)	22.5 (18.7-26.9)	20.5 (16.9-24.6)
	All (≥5 years)	91 (1588/1754)	78	617 (603-632)	3175 (3091-3262)	194 (186-203)	19.3 (18.2-20.4)*	13.6 (12.9-14.3)*
2011	5-14	73 (29/40)	31	36 (29-44)	376 (252-541)	25 (20-33)	14.4 (9.0-22.7)	9.4 (5.5-15.5)
	15-24	97 (97/100)	55	150 (134-167)	998 (859-115)	74 (63-87)	13.4 (10.8-16.7)	12.6 (10.1-15.6)
	25-44	98 (755/770)	85	588 (566-611)	1914 (1837-1996)	117 (106-130)	16.3 (14.7-18.3)	14.4 (13.0-16.0)
	45-64	97 (368/379)	62	641 (608-677)	3056 (2854-3269)	282 (259-308)	10.8 (9.7-12.1)	10 (9.0-11.2)
	≥65	96 (71/74)	9	419 (372-470)	2490 (1564-3633)	389 (344-440)	6.3 (3.9-9.5)	6 (3.7-9.2)
	All (≥5 years)	97 (1320/1363)	71	389 (378-401)	1934 (1869-2001)	134 (127-141)	13.1 (12.2-14.0)*	11.9 (11.1-12.7)*
2012	5-14	60 (22/37)	27	33 (26-41)	285 (186-431)	25 (19-32)	11.6 (6.9-18.8)	5.9 (3.1-10.6)
	15-24	82 (75/91)	67	134 (119-149)	1154 (1002-1323)	48 (40-59)	23.8 (18.7-30.5)	14.6 (11.6-18.4)
	25-44	88 (586/665)	86	505 (485-527)	1665 (1592-1741)	94 (84-106)	17.6 (15.6-19.9)	8.9 (8.1-9.8)
	45-64	89 (270/302)	65	501 (472-532)	2448 (2271-2635)	203 (184-225)	12 (10.6-13.6)	9 (8.0-10.2)
	≥65	84 (53/63)	26	337 (296-381)	5260 (4052-6692)	252 (217-291)	20.8 (15.4-27.8)	16.6 (12.1-22.5)
	All (≥5 years)	87 (1006/1158)	75	325 (315-335)	1703 (1642-1766)	99 (93-105)	15.8 (14.7-17.1)*	9.6 (8.9-10.3)*

IR – incidence rate, RR – relative risk, CI – confidence interval, HIV – human immunodeficiency virus

Significant relative risk value at p<0.05 are in bold ∫Assuming that all patients not tested for HIV are HIV negative *Age-adjusted

Table 6.4 Factors associated with death amongst patients aged ≥5 years hospitalised with severe acute respiratory illness (SARI) at four sentinel surveillance sites, South Africa, 2009-2012

Characteristics		Case-fatality ratio (%)	Univariate analysis OR (95% CI)	p	Multivariable analysis† OR (95% CI)	p
Demographic characteristics						
Age group (years)	5-14	12/577 (2)	Reference		Reference	<0.001
	15-24	28/594 (5)	2.3 (1.2-4.6)	<0.001	3.0 (1.2-7.5)	
	25-44	255/3760 (7)	3.4 (1.9-6.2)		3.4 (1.5-7.9)	
	45-64	171/1774 (10)	5.0 (2.8-9.1)		5.9 (2.5-13.7)	
	≥65	48/449 (11)	5.6 (3.0-10.7)		9.1 (3.7-22.2)	
Sex	Male	204/2773 (7)	Reference	0.654		
	Female	310/4381 (7)	1.0 (0.8-1.2)			
Race	Other race	6/187 (3)	Reference	0.038	Reference	0.033
	Black African	508/6959 (7)	2.4 (1.0-5.4)		3.5 (1.1-11.2)	
Year	2009	106/1456 (7)	Reference	0.196		
	2010	164/2018 (8)	1.1 (0.9-1.5)			
	2011	132/1927 (7)	0.9 (0.7-1.2)			
	2012	112/1753 (6)	0.9 (0.7-1.1)			
Site	CHBAH	371/5424 (7)	Reference	0.016	Reference	0.001
	Matikwana and Mapulaneng	77/948 (8)	1.2 (0.9-1.6)		1.8 (1.3-2.6)	

	Edendale	55/554 (10)	1.5 (1.1-2.0)		1.6 (1.1-2.4)	
	Klerksdorp	11/228 (5)	0.7 (0.4-1.3)		0.9 (0.5-1.8)	
Underlying medical conditions						
HIV status	Negative	87/1660 (5)	Reference	0.001	Reference	<0.001
	Positive	352/4642 (8)	1.5 (1.2-1.9)		1.8 (1.3-2.4)	
Underlying medical	No	456/6281 (7)	Reference	0.520		
condition excluding	Yes	58/871 (6)	0.9 (0.7-1.2)			
tuberculosis and HIV*						
Underlying tuberculosis	No	475/6854 (7)	Reference	<0.001	Reference	0.001
(receiving tuberculosis	Yes	36/274 (13)	2.0 (1.4-2.9)		2.0 (1.3-3.0)	
treatment on admission)						
Alcohol	No	447/5963 (8)	Reference	0.018		
	Yes	65/1172 (6)	0.7 (0.6-0.9)			
Smoking	No	461/6108 (8)	Reference	0.003		
	Yes	51/1028 (5)	0.6 (0.5-0.9)			
Infectious agents identified						
Invasive bacterial infection	No	108/994 (11)	1.1 (0.4-3.0)	0.789		
on culture†	Yes	5/41 (12)				
Pneumococcal infection**	No	413/5885(7)	Reference	0.187		
	Yes	50/597 (8)	1.2 (0.9-1.6)			
Laboratory-confirmed	No	132/2951 (4)	Reference	0.003		
tuberculosis†	Yes	30/373 (8)	1.9 (1.2-2.8)			
Influenza (any type)	No	473/6413 (7)	Reference	0.014		

	Yes	29/616 (5)	0.6 (0.4-0.9)			
Influenza A	No	485/6666 (7)	Reference	0.062		
	Yes	17/363 (5)	0.6 (0.4-1.0)			
Influenza B	No	490/6785 (7)	Reference	0.170		
	Yes	12/244 (5)	0.7 (0.4-1.2)			
Adenovirus	No	456/6401 (7)	Reference	0.727		
	Yes	46/613 (8)	1.1 (0.8-1.4)			
Enterovirus	No	495/6895 (7)	Reference	0.586		
	Yes	7/119 (6)	0.8 (0.4-1.7)			
Human rhinovirus	No	413/5747 (7)	Reference	0.856		
	Yes	89/1264 (7)	1.0 (0.8-1.2)			
Human metapneumovirus	No	493 /6890 (7)	Reference	0.965		
	Yes	9/124 (7)	1.0 (0.5-2.0)			
Parainfluenzavirus 1	No	499/6986 (7)	Reference	0.464		
	Yes	3/28 (11)	1.6 (0.5-5.1)			
Parainfluenzavirus 2	No	499/6971 (7)	Reference	0.963		
	Yes	3/43 (7)	1.0 (0.3-3.2)			
Parainfluenzavirus 3	No	496 (6886 (7)	Reference	0.292		
	Yes	6/126 (5)	0.6 (0.3-1.5)			
Respiratory syncytial virus	No	472/6695 (7)	Reference	0.111		
	Yes	30/319 (6)	1.4 (0.9-2.0)			
Clinical presentation and course						
Duration of symptoms	< 2 days	56/1122 (5)	Reference	0.003	Reference	0.039

prior to admission	≥ 2 days	441/5899 (7)	1.5 (1.2-2.0)		1.4 (1.0-2.0)	
ICU admission	No	511/7133 (7)	Reference	0.010		
	Yes	3/11 (27)	4.9 (1.3-18.4)			
Mechanical ventilation	No	510/7135 (7)	Reference	<0.001	Reference	0.022
	Yes	4/11 (36)	7.4 (2.2-25.4)		6.5 (1.3-32.0)	
Oxygen therapy	No	215/4466 (5)	Reference	<0.001	Reference	<0.001
	Yes	299/2677 (11)	2.5 (2.1-3.0)		2.6 (2.1-3.2)	
Antibiotics prescribed on	No	19/215 (9)	Reference	0.349		
admission	Yes	484/6760 (7)	0.8 (0.5-1.3)			
Duration of hospitalisation	<2	39/523 (7)	Reference	0.002	Reference	<0.001
(days)	2-7	252/4011 (6)	0.8 (0.6-1.2)		0.5 (0.3-0.7)	
	>7	219/2552 (9)	1.2 (0.8-1.7)		0.6 (0.4-1.0)	

OR – Odds ratio, CI – confidence interval, HIV – human immunodeficiency virus, CHBAH- Chris Hani Baragwanath Academic Hospital, ICU – Intensive care unit

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

**On *lyt*A PCR

† Not evaluated in multivariable model due to large amount of missing data

6.4 Discussion

More than two thirds (>70%) of individuals aged ≥5 years hospitalised with SARI in South Africa are co-infected with HIV, making this by far the most important underlying risk condition for this syndrome even in the era of widespread availability of HAART. HIV-infected individuals had a 13-19 times greater incidence of SARI hospitalisation than HIV-uninfected individuals and also experienced prolonged hospitalisation and increased risk of death. The spectrum of infectious agents identified from HIV-infected and -uninfected individuals was generally similar, however HIV-infected individuals were more likely to test positive for pneumococcus.

The overall incidence of SARI hospitalisation ranged from 325-617/100,000, somewhat greater than was described for the same age group in another high HIV-prevalence setting in Kenya (229/100,000).[139] The incidence of SARI hospitalisation in HIV-uninfected individuals aged ≥5 years ranged from 99-194/100,000 population each year, similar to what has been described from low HIV-prevalence middle income countries such as Bangladesh (110-130/100,000) and Thailand (incidence in all ages 177-580/100,000) and slightly lower than the incidence in US adults (267/100,000).[117;140;141] Differences in incidence observed in different settings may be related to differences in health-seeking behavior, differing thresholds for hospital admission and case definitions or may reflect real differences. The 13-19 times elevated incidence (1703-3175/100,000) of hospitalised SARI which we observed in HIV-infected individuals was somewhat greater than the 4 times elevated incidence described in HIV-infected adults from Kenya with outpatient and hospitalised acute respiratory illness.[137] Amongst HIV-uninfected individuals, incidence increased with increasing age, similar to that seen in low HIV-prevalence countries.[141]

We identified at least one respiratory virus in approximately one-third of all patients, similar to other studies from adults.[7;142] The prevalence of detection of most respiratory viruses was highest in the 5-14 year age-group and decreased with increasing age. Human rhinovirus and adenovirus were most commonly detected, followed by influenza. While the detection of influenza virus in persons aged ≥5 years with SARI likely reflects an aetiologic role, the clinical relevance of many of the other respiratory viruses is unclear without a comparison to controls.[7;137] Unfortunately we did not have data available on the prevalence of these viruses amongst healthy controls.

Pneumococcus was identified in 9% of individuals overall with the highest detection rate in persons aged 25-64 years, the age group most affected by HIV. While real-time PCR is more sensitive than blood culture for diagnosing pneumococcal SARI, additional cases of pneumococcal co-infection may still have been missed.[130] Sterile specimen cultures for bacteria were performed uncommonly (<15% of patients) and thus we were not able to compare bacterial culture with PCR results. On multivariable analysis pneumococcus was significantly more likely to be detected in HIV-infected than HIV-uninfected individuals, likely reflecting the very high relative risk of hospitalisation for pneumococcal SARI in HIV infected adults.[143] Pneumococcal polysaccharide vaccine is used uncommonly in South Africa, but PCV was introduced into the routine childhood immunisation programme in 2009. This may have impacted on the proportion of patients testing positive for pneumococcus over time as a result of indirect protection conferred to unvaccinated adults.[105;144]

In contrast to pneumococcus, influenza virus was significantly less commonly identified from HIV-infected individuals. We have previously demonstrated, in the same population, that HIV-infected individuals aged 25-44 years have an ~10-20 times increased incidence of hospitalisation for influenza.[134] The relatively lower detection rates in our study likely reflect the fact that HIV-infected individuals have

a substantially elevated risk of other important pathogens such as pneumococcus, *P. jirovecii* and tuberculosis which contribute to a greater proportion of SARI cases in the HIV-infected, rather than an absolute lower risk in HIV-infected individuals. This has been described for respiratory viral infections in HIV-infected children from South Africa.[89]

The overall case-fatality ratio was 7%, similar to other studies from Africa and the US.[137;139;141;145;146] Increasing age was a risk factor for death, similar to that observed in developed country settings.[147] However, the median age at death was 42 years, lower than the median age at death in more developed settings where death is more common in elderly individuals. HIV-infected individuals were 1.5 times more likely to die than HIV-uninfected individuals in contrast to other studies which have found a similar case-fatality ratio in HIV-infected and -uninfected individuals.[145;148;149] Earlier studies included smaller numbers of cases and may have been underpowered to detect the relatively modest increased relative risk of death. In addition, in other studies, HIV-uninfected individuals may have had a higher proportion of elderly or persons with underlying illness than in our study. Receiving tuberculosis treatment on admission was also a risk factor for death. A study among South African gold miners found that underlying lung damage from tuberculosis was a risk factor for SARI mortality.[150] Patients who died had a shorter duration of hospitalisation, suggesting that death occurred early during admission. A longer duration of symptoms prior to hospitalisation was also associated with increased mortality, thus delayed clinical presentation and subsequent delayed treatment initiation may have contributed to mortality in some cases.

Approximately 40% of patients with available data reported receiving HAART on admission, suggesting that even in the presence of HAART, pneumonia remains a common clinical presentation in HIV-infected individuals. More than two thirds of patients with available data had severe immunosuppression on

CD4+ T cell count and a low CD4+ T cell count was associated with increased mortality. Data on receipt of HAART and CD4+T cell counts was unfortunately available for less than half of all HIV-infected patients potentially biasing results.

Additional limitations of our study include that subjects were only tested systematically for ten viruses and pneumococcus. Blood cultures were not performed systematically and we did not test for *P. jirovecii* or tuberculosis, important causes of pneumonia in HIV-infected individuals.[149] Our study may have underestimated mortality because severely ill cases may have been less likely to consent to inclusion or may have died before or shortly after hospital admission prior to being consented.[123] Our estimates of incidence were only obtained from one surveillance hospital and assumed that all individuals in the community accessed care at CHBH hospital. In addition, we did not account for individuals who did not seek care at all. Therefore our incidence and mortality estimates likely represent a minimum estimate. Nevertheless, the estimates of relative risk by HIV status should be robust, unless patients had differential access to care by HIV-infection status.

Efforts to promote earlier diagnosis of HIV infection and earlier HAART initiation as well as more widespread HAART availability may reduce the substantial burden of disease in HIV-infected individuals and improve outcomes in patients with SARI. Pneumococcus and influenza were commonly detected aetiologies. This suggests that more widespread access to vaccination against influenza and pneumococcus as well as indirect protection following the introduction of PCV in children in South Africa could also reduce the burden of SARI.

Chapter 7 Severe influenza-associated lower respiratory tract infection in a high HIV-prevalence setting-South Africa, 2009-2011

7.1 Introduction

There is limited knowledge about influenza epidemiology in HIV-infected individuals, particularly in sub-Saharan Africa where the burden of HIV is greatest.[89;151] Studies from the US suggest that in the absence of HAART, HIV-infected adults have an increased risk of seasonal influenza hospitalisation,[151] mortality[152] and prolonged illness compared to the general population. This risk decreased following the widespread introduction of HAART.[90;152] In 2011 ~52% of eligible HIV-infected adults in South Africa were receiving HAART.[120]

In South Africa, HAART-naïve HIV-infected children had an 8-fold greater risk of hospitalisation for laboratory-confirmed influenza infection, and a trend toward higher case-fatality (8% vs. 2% in HIV-uninfected children).[89;92] South African adults with AIDS experienced similar influenza-associated mortality to US adults with AIDS in the pre-HAART era.[152] In Kenya, HIV-infected adults were at increased risk of influenza-associated pneumonia hospitalisation compared with HIV-uninfected adults.[137;153]

Data from low HIV prevalence countries where most individuals evaluated had access to HAART and influenza antivirals suggest that HIV-infected individuals were more likely to be hospitalised with influenza A(H1N1)pdm09 infection compared to the general population, but did not differ in rates of

ICU admission or death.[151;154] Conversely, a high HIV prevalence (53%) was described amongst patients who died with confirmed influenza A(H1N1)pdm09 infection in South Africa.[12]

We aimed to estimate the incidence of hospitalisation for influenza-associated SARI and describe the clinical course of illness in HIV-infected and -uninfected individuals in South Africa.

7.2 Materials and Methods

Case definitions, study procedures, laboratory methods, definitions, evaluation of HIV serostatus and calculation of incidence are described in Chapter 2 Methods section 2.2.

7.3 Results

7.3.1 Demographic, clinical characteristics, and seasonality of influenza-associated SARI

From February 2009 through December 2011, 14,725 individuals fulfilling the SARI case definition were approached for study enrolment, of whom 2562 (17%) were not enrolled. The commonest reasons for non-enrolment were study refusal (n=779, 30%), unavailable legal guardian (n=758, 30%) and patients being confused or too ill to consent (n=242, 9%). Of 12,163 patients enrolled and meeting the SARI case definition, 11,925 (98%) were tested for influenza and 1056 (9%) tested positive (Figure 7.1). The influenza detection rate varied by age group from 7% (266/4046) in those <1 year, 11% (252/2292) in 1-4 years, 12% (111/934) in 5-24 years, 9% (270/2930) in 25-44 years, 9% (119/1395) in 45-64 years and 12% (38/328) in ≥65 years ($p<0.001$). The overall influenza detection rate was similar amongst HIV-infected (358/4208, 9%) and HIV-uninfected (461/4473, 10%) individuals ($p=0.163$). The majority of patients (8961/12163, 74%) were enrolled at CHBAH.

In 2009, influenza circulation was biphasic with a peak in influenza A(H3N2) (190/386, 49% of annual cases), followed by a second peak of influenza A(H1N1)pdm09 (158/386, 41% of annual cases). In 2010, influenza B was the predominant subtype (172/289, 60% of annual cases) and in 2011 there were again two influenza peaks; influenza A(H1N1)pdm09 predominated (152/381, 40% of annual cases) initially, followed by influenza B and A(H3N2) (129/381, 34% and 100/381, 26% of annual cases respectively) (Figure 7.2).

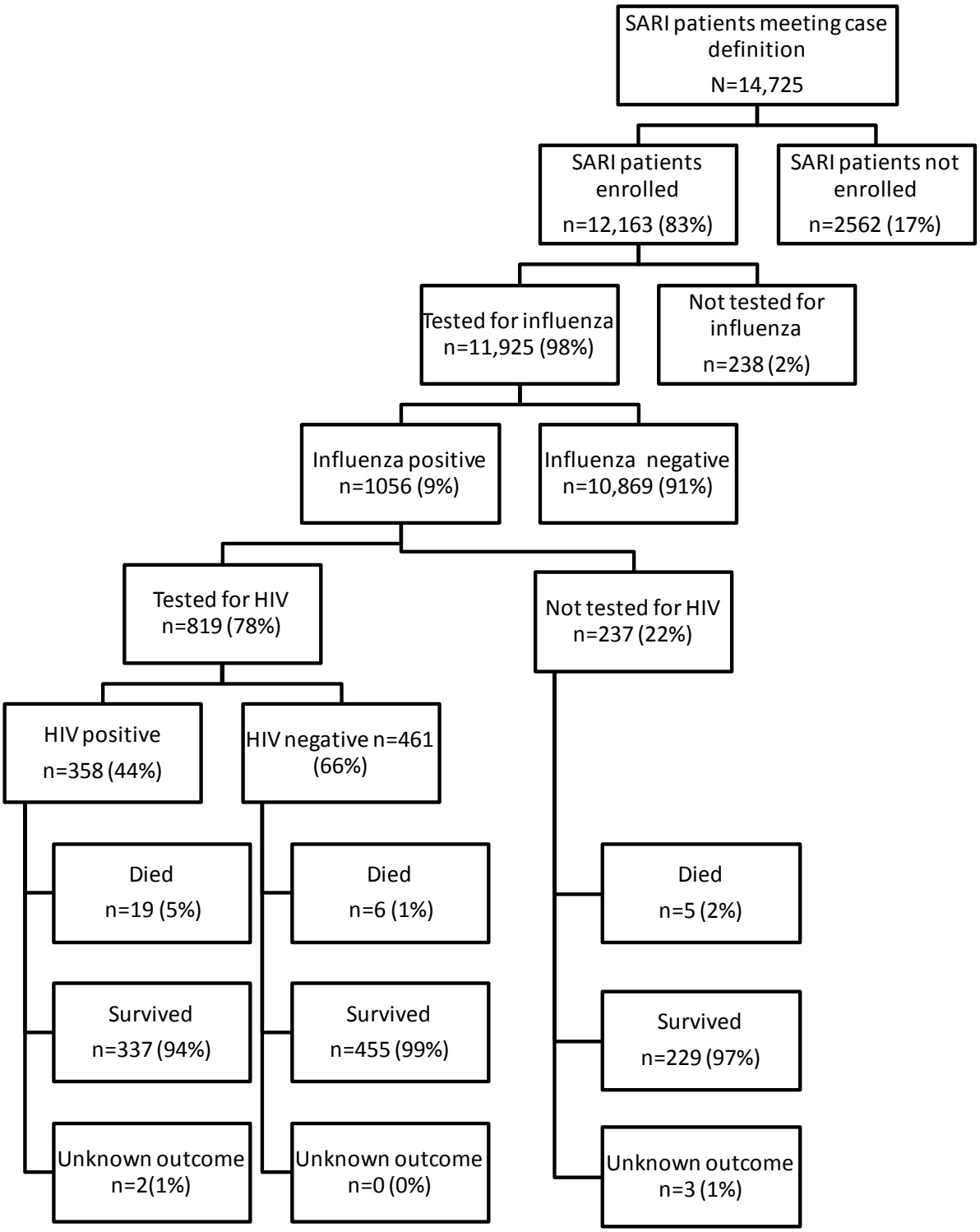


Figure 7.1 Flow chart of patients included in the study

SARI – Severe acute respiratory illness, HIV – human immunodeficiency virus

Influenza-associated SARI epidemiology, South Africa, all ages

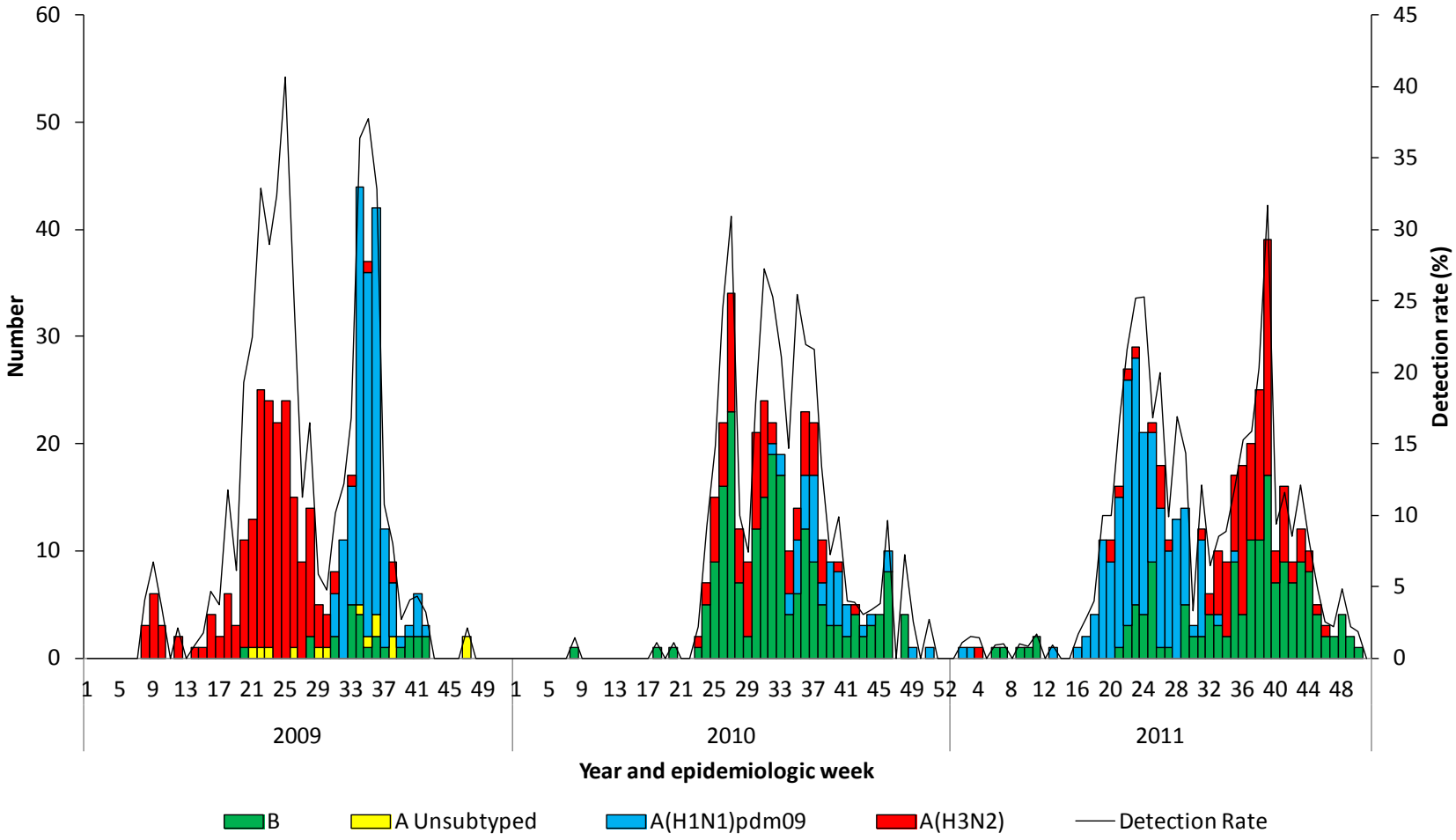


Figure 7.2 Number of patients testing influenza positive by subtype and influenza detection rate by epidemiologic week and year amongst patients with hospitalised pneumonia at four sentinel surveillance sites, South Africa, 2009-2011

Of the 1056 patients testing influenza positive, 819 (78%) had an available HIV-infection status result (597 (73%) on anonymised HIV testing; 83 (10%) tested by ward clinicians; 139 (17%) both anonymous and clinician testing) (Figure 7.1). The proportion of influenza-positive patients with available HIV results increased over the study period from 62% (239/386) in 2009 to 89% (339/381) in 2011 ($p<0.001$); and increased with increasing age from 65% (335/518) among children <5 years to 90% (484/538) amongst persons ≥5 years ($p<0.001$). When comparing patients tested for HIV to those not tested for HIV, controlling for year of test and age group, there were no differences in patient epidemiologic characteristics or case-fatality ratios (data not shown). The proportion of patients tested for HIV and the HIV prevalence amongst tested patients did not differ between surveillance sites (data not shown). The overall HIV prevalence among influenza-positive case-patients was 44% (358/819) and varied by age group: 10% (16/164) in those <1year, 17% (29/171) in 1-4 years, 46% (38/82) in 5-24 years, 84% (212/251) in 25-44 years, 54% (61/113) in 45-64 years and 5% (2/38) in ≥65 years ($p<0.001$).

Amongst patients testing influenza positive, 10% (106/1056) had tuberculosis co-infection, 7% (63/889) had pneumococcal co-infection on *lytA* PCR and 7% (78/1056) had another underlying medical condition. Amongst 106 patients classified as having tuberculosis, only 31 (29%) were laboratory confirmed. There were only three pregnant women identified in this surveillance testing influenza positive, all of whom were HIV infected. No influenza-positive patient reported receiving influenza vaccine or oseltamivir treatment. Forty-eight HIV-infected and 116 HIV-uninfected patients with influenza had sterile site specimens submitted for bacterial culture, amongst which three HIV-infected patients (two *S. pneumoniae* and one *H. influenzae*) and two HIV-uninfected patients (one *Neisseria meningitidis* and one *S. pneumoniae*) tested positive.

7.3.2 Incidence of influenza hospitalisation in HIV-infected and -uninfected patients

The incidence of hospitalisation for influenza-associated SARI amongst patients at CHBAH was highest in patients aged 0-4 years in all study years and for all influenza subtypes with highest incidence in those aged <1 year (Table 7.1, Figure 7.3). Smaller peaks in incidence were observed in the adult (25-54 years) and elderly (≥65 years) age groups each year (Figure 7.3). HIV-infected individuals experienced a four to eight times greater incidence of influenza-associated SARI (age-adjusted RR 4.2 (95% CI 3.6-4.8) in 2009, age-adjusted RR 7.5 (95% CI 6.4-8.8) in 2010 and age-adjusted RR 5.5 (4.7-6.3) in 2011) (Table 7.1). The incidence of hospitalisation amongst HIV-infected as compared to HIV-uninfected individuals was three to five times greater for influenza A(H3N2) (age-adjusted RR 3.3 (95% CI 2.7-4.0) in 2009 and age-adjusted RR 4.9 (3.5-6.5) in 2011), four to six times greater for influenza A(H1N1)pdm09 (age-adjusted RR 4.4 (95% CI 3.6-5.4) in 2009 and 5.6 (95% CI 4.4-7.1) in 2011), and nine times greater for influenza B (age-adjusted RR 8.7 (13.2-38.5) in 2010 and 8.7 (4.4-7.2) in 2011) (Table 7.2). The relative risk of hospitalisation for influenza-associated SARI amongst HIV-infected individuals was elevated in all age groups (generally highest in age group 25-44 years) and for all influenza subtypes however this was not statistically significant in children aged 0-4 years in some analyses (Table 7.1 and Table 7.2). On sensitivity analysis, assuming that all patients not tested for HIV were HIV negative, the trend towards a higher incidence of influenza in HIV-infected individuals remained in all age groups and subtypes except amongst those aged 0-4 years, the group with the lowest proportion of patients tested for HIV.

Table 7.1 Incidence of laboratory-confirmed influenza-associated severe acute respiratory illness (SARI) hospitalisations per 100,000 population by year and HIV status at Chris Hani-Baragwanath Academic Hospital, South Africa

Year	Age group (years)	% with HIV result (n/N)	HIV prevalence %	IR (95% CI) All patients	IR (95% CI) HIV infected	IR (95% CI) HIV uninfected	RR (95% CI) HIV infected vs. HIV uninfected	RR (95% CI) HIV infected vs. HIV uninfected sensitivity analysis∫
2009	0-4	55 (103/188)	11	336 (304-370)	766 (553-1021)	314 (284-349)	**2.4 (1.7-3.3)**	1.3 (0.8-1.9)
	5-24	62 (18/29)	39	27 (23-33)	194 (142-261)	17 (14-22)	**11.0 (7.4-16.1)**	**5.5 (3.5-8.5)**
	25-44	93 (41/44)	88	59 (52-67)	198 (173-227)	9 (7-14)	**20.3 (13.8-31.3)**	**12.7 (9-17.9)**
	≥45	100 (27/27)	41	67 (57-78)	260 (201-331)	44 (36-54)	**5.9 (4.2-8.2)**	**5.9 (4.2-8.2)**
	Total	66 (189/288)	34	78 (73-83)	228 (206-254)	54 (50-60)	**4.2 (3.6-4.8)***	**3.3 (2.9-3.8)***
2010	0-4	64 (54/84)	9	153 (131-177)	317 (187-514)	145 (124-170)	**2.2 (1.3-3.6)**	1.4 (0.7-2.5)
	5-24	68 (15/22)	33	14 (11-18)	89 (57-135)	10 (7-13)	**8.8 (5.2-15.2)**	**5.2 (2.8-9.5)**
	25-44	94 (73/78)	89	60 (53-68)	203 (178-231)	9 (6-13)	**22.9 (15.4-34.7)**	**14.1 (10.1-19.8)**
	≥45	97 (38-39)	55	47 (40-56)	243 (191-307)	24 (18-31)	**10.3 (7.2-14.8)**	**9.7 (6.8-13.9)**
	Total	81 (180/223)	53	49 (45-53)	197 (176-219)	26 (23-29)	**7.5 (6.4-8.8)***	**6.2 (5.3-7.3)***

	0-4	84 (81/96)	6	186 (162-212)	273 (151-463)	182 (159-209)	1.5 (0.8-2.6)	1.3 (0.6-2.3)
	5-24	100 (13/13)	46	8 (6-11)	71 (42-111)	5 (3-7)	**15.4 (7.7-30.3)**	**15.4 (7.7-30.3)**
2011	25-44	99 (88/89)	80	68 (61-76)	206 (180-234)	19 (15-24)	**10.9 (8.2-14.7)**	**10.4 (7.9-14)**
	≥45	98 (42/43)	38	56 (48-65)	192 (146-247)	39 (32-48)	**4.9 (3.5-6.9)**	**4.8 (3.4-6.7)**
	Total	93 (224/241)	43	54 (50-58)	186 (167-207)	34 (31-37)	**5.5 (4.7-6.3)***	**5.3 (4.6-6.2)***

IR – incidence rate, RR – relative risk, CI – confidence interval, HIV – human immunodeficiency virus

Significant relative risk value at p<0.05 are in bold ∫Assuming that all patients not tested for HIV are HIV negative *Age-adjusted

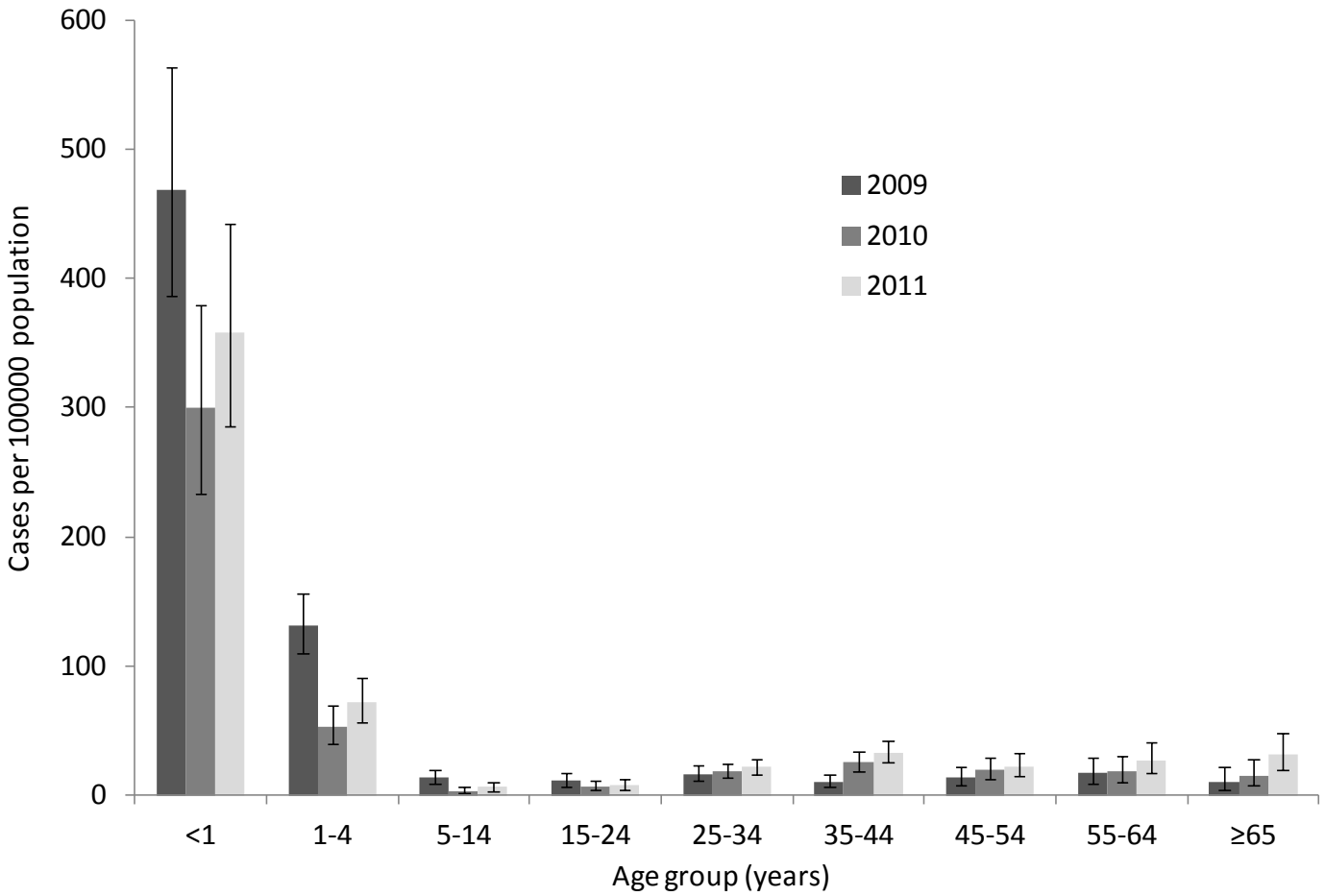


Figure 7.3 Incidence of laboratory-confirmed influenza-associated severe acute respiratory illness (SARI) hospitalisation, per 100,000 population, by year and age group, at Chris Hani-Baragwanath Academic Hospital, South Africa

Table 7.2 Incidence rate (IR) of laboratory-confirmed influenza associated severe acute respiratory illness (SARI) hospitalisation per 100,000 population by year, HIV status and influenza type or subtype at Chris Hani-Baragwanath Hospital, South Africa

Year	Dominant influenza type/subtype	Age group (years)	% with HIV result	HIV prevalence %	IR (95% CI) All patients	IR (95% CI) HIV infected	IR (95% CI) HIV uninfected	RR (95% CI) HIV infected vs. HIV uninfected	RR (95% CI) HIV infected vs. HIV uninfected sensitivity analysis∫
2009	A(H3N2)	0-4	51	8	211 (186-238)	375 (238-576)	202 (178-230)	**1.9 (1.2-2.9)**	0.9 (0.4-1.6)
	A(H3N2)	5-24	53	50	14 (11-18)	129 (88-185)	7 (5-11)	**17.3 (10.1-29.8)**	**6.3 (3.3-11.4)**
	A(H3N2)	25-44	87	100	20 (16-25)	77 (62-96)	0 (0-1)**	**-**	**18.3 (9.6-38.1)**
	A(H3N2)	≥45	100	38	20 (15-26)	71 (42-112)	13 (9-20)	**5.2 (2.7-9.5)**	**5.2 (2.7-9.5)**
	A(H3N2)	Total	57	28	38 (34-41)	94 (80-111)	28 (26-32)	**3.3 (2.7-4.0) ***	**2.2 (1.8-2.8)***
	A(H1N1)pdm09	0-4	61	11	109 (92-129)	251 (145-428)	101 (84-122)	**2.5 (1.4-4.4)**	1.4 (0.7-2.9)
	A(H1N1)pdm09	5-24	77	30	12 (9-16)	67 (40-112)	9 (6-12)	**7.4 (4-14.3)**	**5.2 (2.5-10.1)**
	A(H1N1)pdm09	25-44	96	86	30 (25-36)	97 (87-119)	5 (3-9)	**16.9 (10.2-30.5)**	**12.7 (7.9-21)**
	A(H1N1)pdm09	≥45	100	31	40 (32-48)	118 (80-169)	30 (23-39)	**3.9 (2.4-6.1)**	**3.9 (2.4-6.1)**
	A(H1N1)pdm09	Total	75	36	34 (30-37)	101 (87-119)	23 (20-26)	**4.4 (3.6-5.4)***	**3.8 (3.1-4.7)***
2010	B	0-4	62	6	94 (78-114)	133 (53-272)	93 (76-112)	1.4 (0.6-3)	0.9 (0.2-2.1)
	B	5-24	77	30	8 (6-11)	47 (24-82)	6 (4-9)	**7.6 (3.5-15.3)**	**5.3 (2.1-11)**

	B	25-44	96	92	37 (32-44)	131 (111-154)	4 (2-7)	**30.3 (17.5-56.9)**	**20.2 (12.7-34.4)**
	B	≥45	96	73	28 (22-35)	189 (143-246)	9 (5-13)	**22.1 (13.2-38.5)**	**19 (11.5-32.7)**
	B	Total	81	58	30 (27-33)	129 (113-147)	15 (13-17)	**8.7 (13.2-38.5)***	**7.5 (6.1-9.2)***
2011	A(H3N2)	0-4	65	0	45 (34-58)	0 (0-72)**	47 (35-61)	**0 (0-1.6)**	**0 (0-1.6)**
	A(H3N2)	5-24	25	100	1 (0-2)	12 (2-34)	-	-	**-**
	A(H3N2)	25-44	51	84	15 (11-18)	47 (35-61)	3 (1-6)	**15 (7.7-33.5)**	**15 (7.7-33.5)**
	A(H3N2)	≥45	94	33	19 (15-25)	59 (34-91)	15 (10-20)	**4 (2.1-7)**	**4 (2.1-7)**
	A(H3N2)	Total	63	40	13 (11-15)	42 (34-53)	9 (7-11)	**4.9 (3.5-6.5)***	**4.9 (3.5-6.5)***
	A(H1N1)pdm09	0-4	52	8	85 (70-104)	160 (68-311)	82 (66-100)	2.0 (0.8-3.9)	1.7 (0.7-3.6)
	A(H1N1)pdm09	5-24	67	38	5 (3-7)	35 (16-67)	3 (2-5)	**10.8 (4.2-26.3)**	**10.8 (4.2-26.2)**
	A(H1N1)pdm09	25-44	26	84	25 (208-303)	81 (66-100)	5 (3-9)	**15.2 (8.9-26.1)**	**12.7 (7.9-22.2)**
	A(H1N1)pdm09	≥45	19	46	16 (11-21)	64 (39-99)	10 (6-14)	**6.7 (3.5-12.6)**	**5.7 (2.9-10.5)**
	A(H1N1)pdm09	Total	33	43	21 (19-24)	74 (62-88)	13 (11-15)	**5.6 (4.4-7.1)***	**5.2 (4.1-6.6)***
	B	0-4	81	8	60 (47-75)	133 (43-258)	57 (45-74)	1.4 (0.7-4.7)	1.4 (0.5-4.1)
	B	5-24	100	50	2 (1-4)	23 (9-51)	1 (0-3)	**7.6 (4.8-67.1)**	**7.6 (4.8-67.1)**
	B	25-44	100	73	28 (24-34)	78 (64-97)	10 (7-15)	**30.3 (5.1-11.6)**	**30.3 (5.1-11.6)**
	B	≥45	100	38	21 (16-27)	189 (44-106)	9 (10-20)	**22.1 (2.7-8.3)**	**22.1 (2.7-8.3)**
	B	Total	93	45	20 (18-23)	129 (58-84)	15 (10-15)	**8.7 (4.4-7.2)***	**8.7 (4.3-7.1)***

IR – incidence rate, RR – relative risk, CI – confidence interval, HIV – human immunodeficiency virus

Significant relative risk values at p<0.05 in bold ∫Assuming that all patients not tested for HIV are HIV negative **1 sided

*Age-adjusted

7.3.3 Characteristics of HIV-infected patients and factors associated with HIV infection among influenza virus positive patients

Among influenza virus-positive cases, the case-fatality ratio was four times greater amongst HIV-infected (19/356, 5%) as compared to HIV-uninfected (6/461, 1%) individuals (p=0.002). In each age group except for the elderly the case-fatality ratios were significantly higher in HIV-infected compared to HIV-uninfected individuals (0-4 years 7%, 36/509 vs. 1% 34/3630 RR 7.6, 95% CI 4.7-12.1; 5-24 years 6%, 28/433 vs. 1%, 3/298 RR 6.4, 95% CI 2.0-21.1; 25-44 years 7%, 164/2381 vs. 3%, 8/308 RR 2.7, 95% CI 1.3-5.4; 45-64 years 12%, 100/833 vs. 7%, 34/456 RR 1.6, 95% CI 1.1-2.4; ≥65 years 4%, 2/50 vs. 9%, 23/246 RR 0.4, 95% CI 0.1-1.8).

Compared to patients without HIV infection who were hospitalised with influenza, using multivariable analysis, HIV-infected patients hospitalised with influenza were more likely to be age group 5-24 years (OR 4.4, 95% CI 2.4-8.2), 25-44 years (OR 24.2, 95% CI 14.1-41.7) or 45-64 years (OR 6.2, 95% CI 3.4-11.3), female sex (OR 1.9, 95% CI 1.2-2.8), black African race (OR 4.0, 95% CI 1.1-14.6), co-infected with pneumococcus (OR 2.3, 95% CI 1.0-5.0), have influenza type B (vs. A) infection (OR 1.6 95% CI 1.0-2.4), hospitalised for 2-7 days (OR 2.8 95% CI 1.5-5.5) or >7 days (OR 4.5, 95% CI 2.1-9.5) and more likely to die (OR 3.9, 95% CI 1.1-14.1) (Table 7.3). In contrast they were less likely to have underlying medical conditions other than HIV (OR 0.4, 95% CI 0.2-0.8).

One hundred and eighteen (33%) HIV-infected patients had available CD4+ T cell count data, seven of these were aged <5 years. The majority, (60%, 70/118) had severe immunosuppression (CD4+ T cell counts <200/mm^3 or age-specific equivalent). The case-fatality ratio was not significantly different between patients with (13%, 9/70) and without (6%, 3/47, p=0.258) severe immunosuppression, although numbers were small. The duration of hospitalisation was longer amongst those with (median 7

days, interquartile range (IQR) 2-11 days) than those without (median 5 days, IQR 1-7 days, p=0.02) severe immunosuppression. Fifty-one percent (111/218) of those with available data reported currently receiving HAART and 25% (60/241) reported receiving prophylaxis with trimethoprim-sulfamethoxazole. The case-fatality ratio was similar in patients receiving (7/113, 6%) and not receiving (8/107, 7%) HAART (p=0.706).

Table 7.3 Comparison of the clinical and epidemiologic characteristics of HIV-infected and -uninfected patients hospitalised with influenza-associated severe acute respiratory illness (SARI) at four sentinel surveillance sites, South Africa 2009-2011

Characteristics		HIV-infected n/N (%)	HIV-uninfected n/N (%)	Univariate analysis OR(95% CI)	p	Multivariable analysis**** OR (95% CI)	p
Demographic characteristics							
Age group (years)	<5	45/358 (13)	290/461 (63)	Referent	<0.001	Referent	<0.001
	5-24	38/358 (11)	44/461 (10)	5.6 (3.3-9.5)		4.4 (2.4-8.2)	
	25-44	212/358 (59)	39/461 (8)	35.0 (22.0-55.7)		24.2 (14.1-41.7)	
	45-64	61/358 (17)	52/461 (11)	7.6 (4.7-12.3)		6.2 (3.4-11.3)	
	≥65	2/358 (1)	36/461 (8)	0.4 (0.1-1.5)		0.2 (0.04-0.9)	
Female		253/358 (71)	224/461 (49)	2.5 (1.9-3.4)	<0.001	1.9 (1.2-2.8)	0.003
Black African race		353/358 (99)	445/460 (97)	2.4 (0.9-6.6)	0.096	4.0 (1.1-14.6)	0.036
Year	2009	88/358 (25)	151/461 (33)	Referent	0.002		
	2010	127/358 (35)	114/461 (25)	1.9 (1.3-2.8)			
	2011	143/358 (40)	196/461 (43)	1.3 (0.9-1.8)			
Co-infections and underlying medical conditions							
Underlying medical condition excluding tuberculosis and HIV*		25/358 (7)	47/461 (10)	0.7 (0.4-1.1)	0.109	0.4 (0.2-0.8)	0.008
Smoking (≥12 years)		32/299 (11)	24/151 (16)	0.6 (0.4-1.1)	0.117		
Alcohol (≥12 years)		28/299 (9)	26/151 (17)	0.5 (0.3-0.9)	0.017		

Underlying tuberculosis		60/357 (17)	19/461 (4)	4.7 (2.7-8.0)	<0.001		
Pneumococcal co-infection on PCR **		37/345 (11)	17/389 (4)	2.7 (1.5-5.0)	<0.001	2.3 (1.0-5.0)	0.043
Viral respiratory co-infection***		82/358 (23)	152/456 (33)	0.6 (0.4-0.8)	0.001		
Influenza type B (vs. A)		148/358 (41)	133/461 (29)	1.7 (1.3-2.3)	<0.001	1.6 (1.0-2.4)	0.035
2 or more doses of pneumococcal conjugate vaccine(<5 years)		3/39 (8)	53/242 (22)	0.3 (0.1-1.0)	0.051		
Clinical presentation and course							
Symptoms ≥ 2 days prior to admission		296/358 (83)	295/461 (64)	2.7 (1.9-3.7)	<0.001		
Admission to intensive care		0/357 (0)	6/461 (1)	Undefined	0.031		
Mechanical ventilation		2/357 (1)	4/461 (1)	0.6 (0.1-3.5)	0.612		
Oxygen required		142/357 (40)	141/461 (31)	1.5 (1.1-2.0)	0.006		
Antibiotics prescribed on admission		351/358 (98)	438/460 (95)	2.5 (1.1-6.0)	0.036		
Duration of hospitalisation	<2	20/352 (6)	149/460 (32)	Referent	<0.001	Referent	<0.001
(days)	2-7	217/352 (62)	241/460 (52)	6.7 (4.1-11.1)		2.8 (1.5-5.5)	
	>7	115/352 (33)	70/460 (15)	12.2 (7.0-21.3)		4.5 (2.1-9.5)	
Duration of hospitalisation (days) (median, interquartile range)		6 (4-8)	3 (1-6)	1.1 (1.05-1.13)	<0.001		
Case-fatality ratio		19/356 (5)	6/461 (1)	4.3 (1.7-10.8)	0.002	3.9 (1.1-14.1)	0.038

OR – Odds ratio, CI – confidence interval, HIV – human immunodeficiency virus

* Asthma, other chronic lung disease, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), diabetes mellitis, immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions) or pregnancy. Comorbidities

were considered absent in cases for which the medical records stated that the patient had no underlying medical condition or when there was no direct reference to that condition.

**Three additional cases of *Streptococcus pneumoniae* on blood culture not included

***Co-infection with at least one of parainfluenza virus 1, 2 and 3; respiratory syncytial virus; enterovirus; human metapneumovirus ; adenovirus; human rhinovirus in addition to influenza

**** Odds ratios and p values shown for all variables included in the multivariable model

7.4 Discussion

We have shown that HIV-infected individuals experienced elevated incidence of hospitalisation, prolonged hospitalisation and increased in-hospital mortality due to influenza. In contrast to what is described in most other countries,[154] in our setting, HIV is the commonest underlying risk condition associated with hospitalised influenza (overall >40% of patients with laboratory-confirmed influenza were HIV infected). This results in a W-shaped age-distribution of influenza hospitalisations, with peaks in young children, somewhat in the elderly and an additional peak in young adults associated with HIV infection. These findings highlight the need to target HIV-infected individuals for influenza prevention including vaccination and early influenza antiviral treatment during the influenza season.

Bacterial co-infections may have contributed to some of the hospitalisations and mortality in the HIV-infected group. HIV-infected individuals with influenza-associated SARI had an elevated risk of co-infection with pneumococcus. HIV-infected individuals have an elevated risk of hospitalisation for invasive pneumococcal disease[129] and there is a synergistic relationship between influenza and pneumococcus.[82;102] HIV-infected individuals with influenza-associated SARI were also more likely to have underlying tuberculosis. However, not all cases of tuberculosis were laboratory-confirmed. Tuberculosis was also common in a South African case-series of influenza A(H1N1)pdm09 deaths.[12] An association between tuberculosis and influenza-associated mortality has been suggested, but further studies are needed to evaluate these interactions.[153;155]

The observed prevalence of underlying medical conditions was lower in HIV-infected (7%) than -uninfected individuals (10%) and lower than has been observed in the US (68% of HIV-infected and 74%

of hospitalised HIV-uninfected adults with influenza A(H1N1)pdm09).[154] This could be because these conditions are not well documented or may reflect a true difference in the relative contribution of underlying risk conditions in our setting.

The increased risk of hospitalisation for influenza-associated SARI amongst HIV-infected individuals appeared to be greater for influenza B (~8 times increased risk) than influenza A (~3-4 times increased risk). Reasons for this are unclear. Influenza B severity is intermediate between that of influenza A(H3N2) and A(H1N1). Bacterial superinfection may contribute to mortality in patients (particularly adults) with influenza B, and severe and fatal disease due to influenza B has been described in previously healthy individuals.[156]

Influenza vaccination is safe and efficacious in African HIV-infected adults,[108;157] while the efficacy amongst HIV-infected children is unclear.[136] No patients reported receiving influenza vaccination or antiviral treatment despite national recommendations for influenza vaccination of risk groups and for treatment of individuals with severe illness or underlying risk conditions.[45] TIVs (between 170,000-1,000,000 doses for a population of ~40 million each year) and oseltamivir treatment are made available free of charge through the public health sector in South Africa, although challenges in procurement and distribution may limit practical availability. The low uptake of oseltamivir may be related to clinician perception that antiviral therapy is ineffective when patient presentation to hospital is delayed (>80% of HIV-infected patients reported symptoms for more than 48 hours prior to admission). More data on effectiveness of antivirals from settings similar to ours are needed. An additional contributing factor may be a low index of suspicion for influenza in HIV-infected persons who are at risk of other causes of respiratory disease such as pneumococcus, *P. jirovecii* and tuberculosis.[154] Communication of surveillance data to inform clinicians about the influenza season should increase the clinical index of

suspicion for influenza infection. Maternal immunisation against influenza has been suggested as a strategy to reduce the high burden of influenza in children aged <6 months.[158] Data are needed on the effectiveness of this intervention in HIV-infected women.

Our study has several limitations. The low rate of HIV testing amongst children may have introduced bias if the characteristics of children not tested for HIV differed from those tested. Incidence data were derived from a temperate urban area and may not be representative of more subtropical rural areas, but incidences in HIV-uninfected individuals were similar to what has been described in other developing countries.[25;159] This analysis included the years following the introduction of influenza A(H1N1)pdm09 and thus we cannot comment on age-specific influenza incidence prior to this period. Several studies have suggested that pregnancy is an important risk factor for severe influenza and mortality.[20;160] Very few pregnant women were enrolled in our study, likely because these patients may have been missed as review of admissions to maternity wards was not always consistent. The case definition of physician-diagnosed SARI in children aged three months through <5 years relied on subjective clinician assessment and did not include fever as a criterion because fever reporting may be subjective in this age group. CD4+ T cell count data were only available for a third of HIV-infected patients and CD4+ T cell counts among tested patients may have differed from those in untested patients.

In conclusion, we have demonstrated that in a high HIV-prevalence setting, HIV is an important risk factor for influenza hospitalisation and severe disease. Additional data on the efficacy of newer (adjuvanted, increased dose or intradermal) influenza vaccine strategies in HIV-infected children and adults and children with advanced HIV-associated immunosupression or tuberculosis co-infection are needed. Studies exploring the cost-effectiveness of influenza vaccination strategies in high HIV-

prevalence settings are needed to guide the relative prioritisation of these interventions for HIV-infected individuals in relation to other risk groups and other interventions.

Chapter 8 Conclusions

Using vital statistics data on underlying causes of death for individuals age ≥65 years from South Africa and the US, and Serfling-type linear regression modeling, we have demonstrated that influenza causes substantially greater rates of excess mortality amongst South African compared to the US elderly. These elevated rates of excess mortality were observed for several different underlying causes of death and increased with increasing age group. This challenges the perception held by clinicians and public health officials in many African countries that influenza does not cause substantial mortality in Africa and supports ongoing efforts to expand access to influenza control measures in the region.[33;35;40]

Using a similar approach amongst adults with AIDS aged 25-54 years in South Africa and the US, we were able to demonstrate that in the US, adults with AIDS experienced dramatically (150-200 times) elevated influenza-related mortality rates compared to the general population in the pre-HAART era. These rates declined substantially following widespread HAART availability, but still remained elevated compared to age peers. South African adults with AIDS experienced similar mortality burden in the pre-HAART era to US adults with AIDS. This provides useful data to guide policy in South Africa regarding interventions to control influenza.[161] Specifically, it is likely that more widespread access to HAART will have a substantial impact on influenza-associated mortality in this risk group, however even in the presence of HAART this group will remain important to target for influenza prevention for the foreseeable future.

In order to prioritise influenza control measures in relation to other interventions aimed at reducing the hospitalisation and mortality burden due to SARI in South Africa, it is important to describe the epidemiology of influenza in relation to the syndrome overall and other aetiologic agents. In our analysis of SARI surveillance data amongst children aged <5 years from 2009 through 2012, when considering

viral pathogens with a likely aetiologic role, influenza was less common than RSV (26% of disease) but accounted for 7% of SARI hospitalisations. For comparison, 4% of patients tested positive for pneumococcus, although tests for the diagnosis of pneumococcal pneumonia lack sensitivity (5-20% sensitivity for blood culture) and PCV was introduced into the EPI in 2009.[63;115;130;131;162] Influenza was the only respiratory virus for which detection rate varied by severity of pneumonia, with patients with very severe pneumonia being more likely to test influenza positive as compared to those with pneumonia or severe pneumonia.[116] In addition, the only virus with a significantly different prevalence amongst pneumococcal-positive compared to -negative children was influenza, with the influenza detection rate being approximately two times higher in pneumococcus-positive children. This supports other data demonstrating the synergistic relationship between these two pathogens.[82;102] Amongst children, two seasonal peaks in SARI hospitalisations were observed in most years, the first larger peak coinciding with RSV circulation and the second coinciding with the influenza season, although in some years, peaks coincided with circulation of other respiratory viruses.

Analysis of SARI surveillance data amongst individuals aged ≥5 years, found that HIV-infected individuals were proportionately more likely to be infected with pneumococcus and less likely to be infected with influenza when compared to HIV-uninfected individuals with SARI. However, we have demonstrated that HIV-infected individuals experience a 4-8 times greater incidence of hospitalisation for influenza-associated SARI than HIV-uninfected individuals. The lower influenza detection rate in HIV-infected individuals likely reflects the fact that a greater proportion of SARI in HIV-infected individuals is due to other pathogens such as *P. jirovecii* or tuberculosis, which we did not test for. Amongst adults with SARI, 9% tested positive for influenza, making it the commonest virus detected with a likely aetiologic role. Also, 9% of patients tested positive for pneumococcus although tests for pneumococcal pneumonia may

lack sensitivity and underestimate the true contribution of this pathogen.[63;130;131] Hospitalisations for SARI amongst adults peaked in the winter months coinciding with influenza virus circulation.

Amongst both adult and paediatric patients we detected high prevalences of respiratory viruses such as human rhinovirus and adenovirus. The clinical significance of detection of these viruses amongst patients with SARI is unclear as these viruses may also be identified at high prevealences in control individuals.[123] Since 2012, we have been collecting respiratory specimens from healthy control individuals at our sentinel surveillance sites. Preliminary analyses of these data indicate that on multivariable analysis influenza virus, RSV, human metapneumovirus and human rhinovirus were more commonly identified in patients with SARI and ILI than healthy controls.[163] Simple comparison of the prevalence of respiratory virus detection amongst cases of SARI and ILI as compared to healthy controls does not in itself confirm an aetiologic role. The pneumonia aetiology research for child health (PERCH) project, an international multicentre case-control study (including the CHBAH surveillance site), aiming to determine the aetiology of pneumonia amongst children aged <5 years will hopefully provide additional insight related to this issue.[164]

Using data from active sentinel syndromic surveillance for SARI, we were able to demonstrate that HIV is the most important underlying risk factor for hospitalisation for influenza-associated SARI in our setting (44% of all patients were HIV infected). HIV-infected individuals had 4-8 times elevated incidence of hospitalisation for influenza-associated SARI and experienced prolonged hospitalisations and increased case-fatality ratios. These data complement the above data on influenza-associated mortality in HIV-infected individuals, highlighting the importance of this risk group in South Africa. Children aged <5 years and particularly <1 year of age experienced the highest rates of hospitalisation for influenza-associated SARI, confirming this group as an important risk group for influenza prevention

interventions.[25] Interestingly, population-based surveillance data did not demonstrate a substantial burden of influenza-associated hospitalisations in the elderly, in contrast to the large mortality burden estimated using modelling approaches. This could possibly be related to age-specific differences in health-seeking behaviour, with elderly individuals with SARI being less likely to seek care in hospital compared to other age groups. Data on health seeking behavior in this age group are, however, not available to support this hypothesis. Our ability to evaluate the risk of influenza hospitalisation in pregnant women was limited by the lack of systematic enrolment from maternity wards. This represents a substantial data gap both within South Africa and on the African continent.[33;35] Future studies targeting this specific risk group are needed.

Numbers of adult and paediatric patients enrolled with SARI drop sharply each year around week 1. This is likely as a result of end of year effects (i.e. people are less likely to be hospitalised at this time) although changes in contact patterns and hence risk of infections related to school holidays and closing of many businesses at this time of year could be a contributing factor.

We observed the highest rates of SARI hospitalisations amongst children aged <5 years. More recently we have conducted an analysis of vital statistics data demonstrating the substantial mortality burden (greater than that observed in the US and Europe) associated with influenza and RSV in this age group in South Africa.[165] Additional planned analyses of South African vital statistics data include estimation of the mortality impact of influenza in pregnant women and evaluation of the interaction between influenza and other pathogens such as tuberculosis and pneumococcus.[166;167]

The arrival of the influenza A(H1N1)pdm09 pandemic in 2009 heralded an increased interest in influenza both globally and in Africa.[35] A major limitation of the analyses modelling vital statistics data presented

here, is the inherent delays in data availability (data are released an average of three years after the year of death). This limits the ability to use these methods to provide timeous information on the mortality burden of important public health events such as the 2009 influenza pandemic. Unfortunately due to limitations in data availability we were not able to include an evaluation of the pandemic mortality impact using modelling approaches in this thesis. The year 2009 was the first year of the SARI surveillance programme. In this year we were able to show that the overall incidence of influenza was approximately double that of a typical influenza season. This was mostly because South Africa experienced the equivalent of two influenza seasons in that year with a full H3N2 season preceding the circulation of influenza A(H1N1)pdm09 virus which circulated for a similar duration of time. When we estimated the incidence by subtype the overall incidence of influenza A(H1N1)pdm09 was similar to that of seasonal influenza. Influenza A(H1N1)pdm09 was associated with a substantial increase in rates of SARI hospitalisation in individuals aged <25 years but no obvious difference in rates in young adults. This is similar to findings from other studies from other regions of the world that the greatest increase in incidence was experienced amongst children and adolescents, although some studies have found an increased incidence in young adults.[168] We did not specifically evaluate the epidemiologic characteristics of patients with pandemic as compared to seasonal influenza in our study. However, in a separate analysis comparing characteristics of patients with influenza A(H1N1)pdm09 to those with influenza B and influenza A(H3N2) we found that the only significant difference between subtypes was the age distribution of cases [B, median age 23.7 years (95% CI 0.2-63.2); A(H3N2), median age 2.8 years (95% CI 0.2-64.6); A(H1N1), median age 5.1 years (95% CI 0.3-60.6); p<0.001 by Wilcoxon rank sum test).[169]

More recently, we have conducted updated analyses of South African vital statistics data from 2009 and have estimated a total of 4662 pandemic influenza-associated deaths for all causes of which 93% occurred among individuals <65 years of age.[170] This estimate is similar to the lower-bound estimates for

South Africa from a global influenza A(H1N1)pdm09 mortality study in which country-level data for Africa were interpolated based on data from other regions of the world.[14] Estimates were also similar to but slightly greater than those from a second global study aiming to estimate influenza A(H1N1)pdm09 mortality burden utilizing time-series mortality data.[171] Interestingly, while overall estimates of global number of deaths associated with influenza A(H1N1)pdm09 are similar (100,000–400,000 deaths from respiratory causes during the first year of circulation) between the two studies, estimates of the relative distribution of these deaths vary widely.[14;171] Dawood et al. estimate that the highest rate of mortality was experienced in Africa in contrast to Simonsen et al. who estimated a particularly high impact in the Americas and South East Asia. Because in both analyses there were very few direct estimates of mortality burden from these regions the differences mostly result from the different approaches to interpolation of burden taken in these two papers. Data are lacking on the most important factors determining the between-country variability in influenza associated mortality both for seasonal and for pandemic influenza. To date, estimates of pandemic mortality from South Africa represent the only country-specific estimates of pandemic mortality from the African continent. More studies aiming to estimate influenza-associated mortality both for seasonal and pandemic influenza from Africa are needed although the lack of reliable vital statistics data remains an ongoing challenge.[35] Novel approaches to estimation of influenza-associated mortality using data from verbal autopsy have been described and may have applicability in some African countries.[172]

One of the key objectives of the SARI surveillance programme has been to describe the relative burden and contribution of different pathogens to the burden of SARI in South Africa. A major limitation in achieving this objective has been the focus on viral aetiologies and pneumococcocus and a lack of data for some other important pathogens. In order to address this, since mid 2012 at two sentinel sites, surveillance has been expanded to include the collection of additional clinical specimens (induced

sputum) and testing of specimens expanded to include active testing for *M. tuberculosis*, *P. jirovecii*, *Legionella* spp., *Mycoplasma* spp., *Chlamydophila* spp. and *Bordetella pertussis*. [173] In addition, at these sites patients with milder influenza-like illness and healthy controls are being enrolled, which may assist in addressing outstanding questions related to the aetiologic role of some pathogens detected amongst patients with SARI, as well as the spectrum of illness cause by these pathogens. These data, when available, will be an important supplement to the data presented here. Another limitation of the programme is that we have only been able to generate estimates of incidence from one sentinel site (CHBAH) and for this site we have not had data on health-seeking behaviour in the community. Towards the end of 2012, we conducted health utilisation surveys in Soweto and Klerksdorp. In addition, we conducted a health utilisation survey in the second half of 2013 in the area around Edendale hospital. These surveys, once analysed, should provide more robust incidence estimates for the CHBAH site. In addition, in combination with denominator estimates of the populations serving Klerksdorp-Tshepong and Edendale Hospitals, this should allow for estimation of incidence from additional sites. This should provide insight into the relative influenza burden between different geographic regions and allow for more broadly generalisable estimates of influenza hospitalisation burden for South Africa.

Estimation of the incidence of hospitalisation stratified by HIV status depends on the availability of robust denominator data stratified by HIV status. We obtained these data from the ASSA2008 model which is a widely used validated model aiming to provide demographic data related to the HIV epidemic in South Africa.[23] Data are generally thought to be robust and correlate well with data from other sources.[97] One limitation of the ASSA2008 model is that this model likely overestimates the rate of mother-to-child transmission of HIV in recent years and consequently the size of the population of HIV-infected children.[174] This has likely led to an underestimation of the increased risk of illness experienced in HIV-infected children <5 years, however this model represents the best currently available source of

such data. This limitation is stated in the relevant papers included in this thesis. A new version of the ASSA model is currently under development. Once this is released we may need to generate revised estimates of these risks if revised estimates are found to differ substantially from those published.

An important limitation of ecological approaches to estimate influenza-associated excess mortality, is that the approach used assumes that all winter deaths above the seasonal winter baseline during influenza circulation periods are attributable to influenza, and does not account for the possible contribution of other co-circulating winter pathogens or the contribution of secondary bacterial infection (particularly with pneumococcus). Data from SARI surveillance confirmed that among patients with SARI testing positive for influenza, HIV-infected individuals are significantly more likely to have pneumococcal co-infection than HIV-uninfected individuals. A separate study using data from the SARI surveillance programme has demonstrated that both influenza and HIV co-infection are independent risk factors for elevated pneumococcal blood bacterial load and that pneumococcal bacterial load is an independent risk factor for mortality.[128] Another limitation is that the modelling approach which we have used was not able to directly evaluate the relative contribution of RSV and other viruses to influenza-associated mortality in the elderly. Subsequent to the study included in this thesis we have conducted an analysis utilising more recent data and a different modelling approach (Poisson regression) and have found similar estimates of influenza-associated excess deaths in the South African elderly but noted no RSV-associated deaths in this group, in contrast to publications from some other settings.[30;170]

Data included in this thesis has contributed to policy recommendations related to influenza vaccination and treatment both internationally and locally. The WHO SAGE updated their recommendations on influenza vaccination in 2012.[17] Data on influenza-associated mortality in the elderly in South Africa

were cited in the background documentation justifying the updated recommendations. In addition, unpublished data from SARI surveillance on influenza incidence in children aged <5 years were requested by the SAGE group for consideration in their deliberations. Data on SARI burden in children aged <5 years were also included in an international collaborative paper aiming to estimate global SARI burden amongst children aged <5 years.[3] In 2012, South Africa began a process of development of a draft policy on influenza vaccination for the country.[161] Local mortality and surveillance data are extensively cited in this document and have been utilised to develop local recommendations for risk groups to be targeted through public health vaccination programmes in South Africa.[45] Despite recommendations for influenza vaccination and oseltamivir treatment, as well as free availability through the public sector, data from our surveillance programme suggests that these interventions are not widely utilised in the populations under surveillance.

Challenges for influenza policy and vaccination in South Africa remain substantial. The number of individuals falling into risk groups to be targeted for influenza vaccination identified based in review of international and local data was estimated at more than 20 million individuals in 2011.[161] This includes over 5 million HIV-infected individuals, over 5 million children <5 years, over 6 million individuals with underlying illnesses and just over 800,000 pregnant women. In 2012, <1 million doses of TIV were distributed through the public sector, thus significant challenges remain in order to be able to scale-up influenza vaccination programmes to meet this demand. In addition, there are substantial challenges for influenza vaccine delivery to risk groups over a limited time period preceding the influenza season which lead to wastage of a proportion of the limited available stock.[161] While influenza antivirals are recommended in South Africa for persons at high risk and are freely available through the public sector, uptake is extremely low and no SARI patients with influenza reported receiving oseltamivir treatment.

Data on the effectiveness of oseltamivir treatment from developing and middle-income country settings where patients frequently present late for care may be needed in order to change clinician practices.

In conclusion, using a combination of ecological studies modelling influenza-associated excess mortality as well as individual data from active syndromic surveillance we were able to demonstrate that influenza causes substantial morbidity and mortality in South Africa each year. Important risk groups for influenza-associated hospitalisations and mortality in South Africa include children <5 years, HIV-infected adults and the elderly. TIV vaccine effectiveness is reduced in young children and the elderly.[17] While TIVs are effective in HIV-infected adults with minimal immunosupression,[108] there are no data on efficacy in severely immunosupressed adults and efficacy in HIV-infected children has not been demonstrated.[136] More effective influenza vaccines including vaccines with a longer duration of protection and heterosubtypic protection as well as vaccines which are more effective in risk groups and at an affordable price are needed if routine influenza vaccination is to be included in national routine vaccination policies in African countries.[35] Influenza was one of the commonest causes of SARI amongst both children and adults in South Africa from 2009-2012. Over the next few years in South Africa, interventions such as HAART, PMTCT and PCV can be expected to have a marked impact on the epidemiology of SARI and the relative contribution of influenza in South Africa. Ongoing surveillance will be important to document these changes and guide influenza vaccination and treatment policies.

Chapter 9 Appendices

NATIONAL HEALTH LABORATORY SERVICE
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Severe Acute Respiratory Illness (SARI) Surveillance

Case Investigation Form (CIF)

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 086 723 3569

SO Initials: ☐☐☐

Date completed: ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

SARI Study ID:

? Study ID:

Note: For Edendale Hospital only if patient co-enrolled in TSAP study.

Patient Hospitalised at: CHBH ☐ Selby ☐ Mapulaneng ☐ Matikwana ☐
Edendale ☐ Klerksdorp ☐ Tshepong ☐

Note: surveillance officer to review criteria for all case definitions before making a decision about the case definition/s met

SARI* ☐ SRI** (severe respiratory illness not SARI) ☐ Febrile illness*** (enrolled on TSAP) ☐

**SARI with duration of symptoms ≤ 7 days.*
*** SARI with duration of symptoms > 7 days, SARI/TB or TB (for Edendale and Klerksdorp-Tshepong Hospital Complex only).*
****If patient co-enrolled in the TSAP study (for Edendale Hospital only).*

NB: For Edendale and Klerksdorp-Tshepong Hospital Complex only

Enrolled in shedding study Yes ☐ No ☐

1. Date of birth (DOB): ☐☐/☐☐/☐☐☐☐ If DOB unknown, please enter age:_____Years ☐ Months ☐ Days ☐
2. Gender: Male ☐ Female ☐
3. Race: Asian/Indian ☐ Black ☐ Coloured ☐ White ☐ Other ☐ (Specify) _____
4. What is your house made of: Bricks ☐ Iron sheeting ☐ Mud ☐ Other ☐ (Specify) _____
5. Number of rooms used for sleeping? _____ 5.1 Number of people living in the house? _____
6. What is the interviewee's relationship to the participant? Self ☐ Parent/Caregiver ☐ Other ☐ (Specify) _____
7. Date of admission: ☐☐/☐☐/☐☐☐☐
8. Admission diagnosis: (Tick all that apply) Neonatal Sepsis ☐ Bronchiolitis ☐ Bronchopneumonia/Pneumonia/Lower Respiratory Tract Infection ☐
   TB ☐ Bronchitis ☐ Diarrhoea ☐ Febrile seizures ☐ Meningitis ☐ Sepsis (not neonatal) ☐
   Other ☐ (Specify)_____
9. Date of onset of symptoms: ☐☐/☐☐/☐☐☐☐
9.1 Duration of symptoms: 0-7days ☐ 8-14days ☐ >14days

Note: Complete the signs and symptoms at the time of admission, some of the signs or symptoms may have resolved by the time you interview the patient. This information should be available in the patient records.

10. Maximum recorded temperature within 24hours of admission ____.____C° (##.#C°)
Note: Record the maximum temperature recorded in the clinical notes or a temperature taken by the surveillance officer

within 24 hours of admission if no temperature in the file.

11. Date of maximum temperature recorded: ☐☐/☐☐/☐☐☐☐ Temperature not recorded ☐

12. History of fever? Yes ☐ No ☐ Unk ☐ If yes, date of fever onset: ☐☐/☐☐/☐☐☐☐

13. Respiratory Rate: _____breaths per minute Not recorded ☐

14. Oxygen saturation (room air): _____% Date of O_2 Saturation: ☐☐/☐☐/☐☐☐☐
Recorded on file ☐ Measure by Surveillance Officer within 24h of admission ☐
Not recorded on file and not measured by Surveillance Officer within 24h of admission ☐

15. Patient length (if not recorded, surveillance officer to measure): _____._____cm Percentile (if patient < 5 years) _____ Unk ☐

15.1 Patient weight (if not recorded, surveillance officer to measure): _____._____kg Percentile (if patient < 5 years) _____ Unk ☐

15.2 Mid upper arm circumference (MUAC) (for patients < 5 years of age only) _____ cm

16. Blood pressure on day of admission: _____/_____ Not recorded ☐

17. Mental status of the patient (based on AVPU), within 24 hours of admission
Alert ☐ Disorientated ☐ Stuporous ☐ Comatose ☐ Sedated ☐
Unknown ☐
(responds to verbal commands) (responds to painful stimuli)

Note: If patient is alert report 15/15.

18. Glasgow Coma Score (GCS) _____/15 GCS from medical records: Yes ☐ No ☐
GCS Unk ☐ (if patient not alert and GCS not recorded on medical records)

Note: Complete for patients ≥ 12 years, if patient < 12 years skip to Q 20.

19. Patient oriented to:
Person: Yes ☐ No ☐ Unk ☐ Place: Yes ☐ No ☐ Unk ☐ Time: Yes ☐ No ☐ Unk ☐

Note: Complete the table below for children < 5 years, if patient ≥ 5 years skip to Q 21.

20. Were any of the following signs and symptoms present?

Cough	Y	N	Difficulty breathing	Y	N	Chest in drawing (retraction)	Y	N
Stridor in a calm child	Y	N	Tachypnoea/respiratory distress (2mnth-1yr RR>50, 1-5 RR>40)	Y	N	Diarrhoea (>3 loose stools per day)	Y	N
Unable to drink or breast feed	Y	N	Vomits everything	Y	N	Convulsions	Y	N
Lethargy	Y	N	Unconsciousness	Y	N	Any vomiting	Y	N
Wheezing	Y	N						

Note: Complete the table below for patients ≥ 5 years, if patient < 5 years skip to Q 22.

21. Were any of the following signs and symptoms present?

Sore throat	Y	N	Cough	Y	N	Chest pain	Y	N
Shortness of breath/difficulty breathing	Y	N	Diarrhoea (>3 loose stools per day)	Y	N	Wheezing	Y	N

Note: Complete the table below for all patients.

22. Were any of the following signs and symptoms present?

Chronic cough for 2 weeks or more	Y	N	Fever for more than 2 weeks (14 days)	Y	N	Cough up blood (Hemoptysis)	Y	N
Loss of appetite	Y	N	Night sweats	Y	N	Loss of weight	Y	N
Painless enlarged lymph glands	Y	N	History of close contact with a person with recently active TB (diagnosis ≤ 12 months ago)	Y	N	If yes, is the patient staying in the same house with the TB contact	Y	N

Note: Complete the following questions for patients ≥ 18 years, if patient < 18 years skip to Q 26.

23. Do you drink alcohol? Yes ☐ No ☐ If yes, how many units per week? _____

24. Do you currently smoke? Yes ☐ No ☐ If yes, how many cigarettes do you smoke per day? _____

24.1 If no, have you smoked in the past? Yes ☐ No ☐ If yes, date stopped smoking: ☐☐/☐☐/☐☐☐☐

25. Do you currently or have you ever worked in a mine before? Yes ☐ No ☐ Unk ☐
Note: If no or unknown, skip to Q 26)

25.1 If yes, date started working in the mine: ☐☐/☐☐/☐☐☐☐ Date unknown ☐

25.2 If working in a mine or worked in a mine before, when did you stop working in the mine? ☐☐/☐☐/☐☐☐☐ Ongoing ☐

Date Unknown ☐

25.3 If currently or worked in mine before, what type of mine/s? (tick all that apply)

Gold ☐ Coal ☐ Platinum ☐ Asbestos ☐ Other ☐
(Specify) _____

26. Do you have any underlying illness or condition at the moment? Yes ☐ No ☐
Note: Check patient's notes for details if necessary. If no skip to Q 27

Asthma	Y	N	Other chronic lung disease	Y	N	CVA/Stroke	Y	N
Cirrhosis/Liver failure	Y	N	Chronic renal failure	Y	N	Heart failure	Y	N
Valvular heart disease	Y	N	Coronary artery disease (except H/T)	Y	N	Pregnancy	Y	N
Organ transplant	Y	N	Any immunosuppressive therapy, cortisone, chemotherapy, radiation therapy	Y	N	Sickle cell	Y	N
Splenectomy	Y	N	Diabetes	Y	N	Burns	Y	N
Immunoglobulin deficiency	Y	N	Autoimmune disease, SLE	Y	N	Kwashiorkor/ Marasmus	Y	N
Nephrotic syndrome	Y	N	Spinal cord injury	Y	N	Seizure disorder	Y	N
Prematurity	Y	N	Obesity / BMI >=30	Y	N	COPD/Emphysema	Y	N
Malignancy/Cancer	Y	N	If yes, specify:					
Other	Y	N	If yes, specify:					
Does the patient live in an institution/care facility	Y	N	If yes, name of institution:					

27. Has the patient been admitted to hospital in the last 12months? (prior to this admission) Yes ☐ No ☐ Unk ☐

Note: If no or unknown, skip to Q 28.

27.1 If yes, what was the date that you were discharged from your last hospital admission? ☐☐/☐☐/☐☐☐☐ Date Unk ☐

27.2 Was the patient admitted more than once in the past year? Yes ☐ No ☐ Unk ☐ If yes, how many times? _____

Note: Complete for patients < 5 years, if patient ≥ 5 years skip to Q 29.

28. HIV result during pregnancy (mother of patient): Yes ☐ No ☐ Unk ☐
Note: If no or unk skip to Q 29

28.1 If yes, what was the result? Positive ☐ Negative ☐

28.2 What was the source of the results? RTHC ☐ Laboratory report ☐ Medical records ☐ Verbal ☐ Other ☐ Specify _____

28.3 Was the child exposed to HIV (yes if the mother tested HIV positive during pregnancy) Yes ☐ No ☐ Unk ☐ N/A ☐

29. Has the patient been tested for HIV prior to this admission? Yes ☐ No ☐ Unk ☐
Note: If no or unknown skip to Q 30

29.1 If yes, what was the result? Positive ☐ Negative ☐ Unk ☐
Note: If negative or unknown skip to Q 30

29.2 Currently on ART? Yes ☐ No ☐ Unknown ☐ If yes, date of initiation of ART: ☐☐/☐☐/☐☐☐☐

29.3 Bactrim (contrimoxazole/trimethoprim) prophylaxis taken currently? Yes ☐ No ☐ Unk ☐
Note: If no or unknown skip to Q 29.5

29.4 If yes, how long have you taken Bactrim? _____Years _____Months_____Weeks _____Days

29.5 What is the patient's clinical HIV stage according to WHO criteria (refer to WHO clinical staging information and HIV staging tick box document)
1 ☐ 2 ☐ 3 ☐ 4 ☐

30. Have you ever taken TB prophylaxis? Yes ☐ No ☐ Unk ☐ If yes, date TB prophylaxis initiated: ☐☐/☐☐/☐☐☐
Note: If no or unknown skip to Q 31

30.1 Are you still taking TB prophylaxis? Yes ☐ No ☐ Unk ☐ If no, date TB prophylaxis stopped: ☐☐/☐☐/☐☐☐
Note: If yes skip to Q 32

31. TB treatment in the last 12 months? Yes ☐ No ☐ Unk ☐ If yes, date TB treatment initiated: ☐☐/☐☐/☐☐☐
Note: If no or unknown skip to Q 32

31.1 Are you still taking TB treatment? Yes ☐ No ☐ Unk ☐ If no, date TB treatment stopped: ☐☐/☐☐/☐☐☐

Note: Ask patients and check medical records for PCP diagnosis and/or treatment

32. Have you ever been diagnosed with PCP before this admission? (check from medical records) Yes ☐ No ☐ Unk ☐
Note: If no or unknown skip to Q 33

32.1 If yes, date last treatment started: ☐☐/☐☐/☐☐☐☐ Date Unk ☐

32.2 If yes, date last treatment stopped: ☐☐/☐☐/☐☐☐☐ Date Unk ☐ Ongoing ☐

32.3 If yes, treatment started with steroid therapy? Yes ☐ No ☐ Unk ☐

33. Has the patient been prescribed and taken antibiotics in the 24 hours before this admission? Yes ☐ No ☐ Unk ☐

Note: If no or unknown skip to Q 34

33.1 If yes, what is the name of the antibiotic? 1. _____ 2. _____
3. _____

AMO Amoxicillin; AMP Ampicillin; AUG Augmentin; CEF Cefuroxime, CIP Ciprofloxacin; CLI Clindamycin; CTX Ceftriaxone; DOX Doxycycline; ERY Erythromycin, PEN Penicillin, TMX/SMX Contrimoxazole, VAN Vancomycin. If other, specify _____

34. Vaccination history. Complete for patients < 5 years, if patient ≥ 5 years skip to Q 35

34.1 Is the person being interviewed the primary caregiver of the child? Yes ☐ No ☐
Note: If no skip to Q 34.3

34.2 If yes, has the child ever been vaccinated? Yes ☐ No ☐ Unk ☐
Note: Excluding the vaccines given at birth

34.3 Was the Road to Health Card seen? Yes ☐ No ☐

34.4 Was a copy of the Road to Health Card made? Yes ☐ No ☐
Note: If no skip to Q 35

34.5 If copy was not made, state reason: Mother refused ☐ Other ☐
(specify) _____

If Road to Health Card seen, please copy the following information from the card:

34.6 What is patients' gestational age: Term ☐ Pre-term ☐ Not recorded on Road to Health Card ☐

If pre-term, record gestational age: _____weeks

34.7 If Road to Health Card seen, please complete the details on the following vaccines for all children < 5 years old

Note: Tick no for vaccines that are not yet due according to the schedule. At 18 months if only the DTP was given tick DTP only and N/A for the combined DTP/HIB, if a combined DTP/HIB was given tick yes under combined and N/A under DTP only

Vaccine	Dose due	Given			Date given
BCG	Birth	Y	N		☐☐/☐☐/☐☐☐☐
DTP + HIB vaccine	Dose 1 (6 weeks)	Y	N		☐☐/☐☐/☐☐☐☐
	Dose 2 (10 weeks)	Y	N		☐☐/☐☐/☐☐☐☐
	Dose 3 (14 weeks)	Y	N		☐☐/☐☐/☐☐☐☐
	Dose 4 (18 months)	Y	N	N/A	☐☐/☐☐/☐☐☐☐
DTP only (tick N/A if DTP+HIB)	Dose 4 (18 months)	Y	N	N/A	☐☐/☐☐/☐☐☐☐
S.pneumoniae conjugate vaccine ($PCV_{7/13}$/Prevenar)	Dose 1 (6 weeks)	Y Batch N°_____ Unk ☐	N		☐☐/☐☐/☐☐☐☐
	Dose 2 (14 weeks)	Y Batch N°_____ Unk ☐	N		☐☐/☐☐/☐☐☐☐
	Dose 3 (9 months)	Y Batch N°_____ Unk ☐	N		☐☐/☐☐/☐☐☐☐

	Catch up	Y Batch N°_____ Unk ☐	N	☐☐/☐☐/☐☐☐☐
Measles	Dose 1 (9 months)	Y	N	☐☐/☐☐/☐☐☐☐
	Dose 2 (18 months)	Y	N	☐☐/☐☐/☐☐☐☐
Hepatitis B	Dose 1 (6 weeks)	Y	N	☐☐/☐☐/☐☐☐☐
	Dose 2 (10 weeks)	Y	N	☐☐/☐☐/☐☐☐☐
	Dose 3 (14 weeks)	Y	N	☐☐/☐☐/☐☐☐☐
Rotavirus	Dose 1 (6 weeks)	Y	N	☐☐/☐☐/☐☐☐☐
	Dose 2 (14 weeks)	Y	N	☐☐/☐☐/☐☐☐☐

Note: Complete for patients ≥ 5 years, if patient < 5 years skip to Q 36

35. Did the patient receive pneumococcal polysaccharide vaccine?

Vaccine	**Dose given**			**Date given**	**Date unknown**
Pneumococcal Vaccine (Pneumovax)	Y	N	UNK	☐☐/☐☐/☐☐☐☐	☐

36. Did the patient receive an influenza vaccine in the past 12 months (For all patients)

Vaccine		**Dose given**			**Date given**	
Influenza vaccine	Dose 1	Y	N	UNK	☐☐/☐☐/☐☐☐☐	**Date unknown** ☐
	Dose 2	Y	N	UNK	☐☐/☐☐/☐☐☐☐	**Date unknown** ☐

QC Performed by: Initials: ☐☐☐ Date: ☐☐/☐☐/☐☐☐☐

Severe Acute Respiratory Illness (SARI) Surveillance

Hospital Results Form (HRF)

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 086 723 3569

SO Initials: ☐☐☐

Date completed: ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

SARI Study ID:

TSAP Study ID:

Note: For Edendale Hospital only if patient co-enrolled in TSAP

Please record these results from the laboratory if they are available.

Note: Only results from this admission except for Q 4, 5 and 8 where the most recent available result should be entered and Q 7 where results before admission must be recorded.

Test			Date of test	Result
1. CRP on admission	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐	_____mg/l
2. ESR on admission	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐	_____mm/Hr
3. Urea on admission	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐	_____mmol/l
4. Documented HIV Antibody Result (ELISA or rapid)	Yes ☐	No ☐	☐☐/☐☐/☐☐☐☐ ***Note: Enter date of most recent result available***	Reactive ☐ Non reactive ☐ ***Note: Enter most recent result available***
5. Documented HIV PCR Result	Yes ☐	No ☐	☐☐/☐☐/☐☐☐☐ ***Note: Enter date of most recent result available***	Positive ☐ Negative ☐ ***Note: Enter most recent result available***
6. Based on all the information available to you, what is the current HIV status of the patient				Positive ☐ Negative ☐ Pending ☐ Unknown ☐
6.1 If current HIV status unknown, why was the patient not tested? Refused consent ☐ Patient died ☐ No guardian ☐ Other ☐ specify_____				
6.2 What was the source of the results? RTHC ☐ Laboratory report ☐ Medical records ☐ Verbal ☐ Other ☐ Specify _____				
6.3 if patient < 5 years, was the child exposed to HIV : N/A ☐ Yes ☐ No ☐ Unk ☐				
7. CD4 count on admission	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐	_____ Absolute CD4 ____._____%
8. CD4 count collected before this admission	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐	_____ Absolute CD4 ____._____%
9. HIV viral load	Done ☐	Not done ☐	☐☐/☐☐/☐☐☐☐ ***Note: Enter date of most recent result available***	_____ HIV RNA copies/ml ____._____ Viral load log ***Note: Enter most recent result available***

10. Was a CXR done on the patient? Yes ☐ No ☐ ***Note :If not done go to Q 11*** 10.1. If X-ray done record X- ray number here: _____	***Note: For Klerksdorp Tshepong Hospital Complex only*** *10.*2 Copy of X-ray downloaded? Yes ☐ No ☐ 10.3 if yes, date X-ray copy downloaded ☐☐/☐☐/☐☐☐☐

11. Bacterial Culture, done **within 48 hours** of admission? Yes ☐ No ☐

Note: If yes, complete the table below, if no skip to Q11

Date of culture	Site			Organism Isolated	If other (99), specify
	Blood	CSF	Pleural fluid		
☐☐/☐☐/☐☐☐☐					
☐☐/☐☐/☐☐☐☐					
☐☐/☐☐/☐☐☐☐					
☐☐/☐☐/☐☐☐☐					

Organism codes:

01 = No growth	**02 = *Streptococcus pneumoniae***	**03 = *Haemophilus influenzae***	**04 = *Klebsiella pneumoniae***
05 = *Staphylococcus aureus / MRSA*	**06 = *Neiserria meningitides***	**07 = *Coagulase negative staphylococcus / Staphylococcus epidermidis***	**08 = *Bacillus Species***
09 = *Corynebacterium species*	**11 = *Cryptococcus neoformans***	**12 = *Escherichia coli***	**13 = *Salmonella species***
14 = *Streptococcus agalactiae / Group B Streptococcus*	**15 = *Acinetobacter baumanii***	**16 = *Pseudomonas aeruginosa***	**17 = *Enterococcus faecalis***
18 = *Streptococcus viridans*	**19 = *Micrococcus species***	**20 = *Salmonella enterica_ Non-Typhodial* (NTS)**	***21 = Salmonella enterica- Typhi***
22 = Salmonella parathyphi	**99 = Other**		

11.1 Blood Specimen and Culture taken by ☐SO ☐ Clinician

11.2. Blood Culture Specimen requested by clinician ☐Yes ☐ No

12. TB testing done during this admission? Yes ☐ No ☐

Date of Test	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐

Specimen*				
AFB's present (Yes/No/Not Applicable)	Y N N/A	Y N N/A	Y N N/A	Y N N/A
Culture Done (Yes/No)	Y N	Y N	Y N	Y N
Culture Results (Positive/Negative/ Contaminated)	POS NEG CONT Date of final results report ☐☐/☐☐/☐☐☐☐	POS NEG CONT Date of final results report ☐☐/☐☐/☐☐☐☐	POS NEG CONT Date of final results report ☐☐/☐☐/☐☐☐☐	POS NEG CONT Date of final results report ☐☐/☐☐/☐☐☐☐
GeneXpert Done	Y N	Y N	Y N	Y N
GeneXpert Results (Positive/ Negative/ Inconclusive)	POS NEG INC	POS NEG INC	POS NEG INC	POS NEG INC

***Specimen codes:**

1 = Sputum 2 = Gastric Washing 3 = Bone Marrow 4 = Pleural Aspirate 5 = Lymph Node 6 = Other (if other, write in full)

Note: Culture results will be reviewed at a later date.

***Do not delay submission of CIF and Result Form while waiting for TB culture results*.**

Note: complete the table below for TSAP (For Edendale Hospital KZN Only):

13. Was a blood count done during this admission? Yes ☐ No ☐

Note: If not done end; if yes, complete table below

WBC ☐☐☐.☐ (1000/µl)	**Platelets** ☐☐☐.☐ (1000/µl) ☐ Not recorded
RBC ☐☐.☐ (10^6/ µl)	**Neutrophils** ☐☐.☐ (%WBC) ☐ Not recorded
Hb ☐☐.☐ (g/dl)	

Hct ☐☐.☐ (%)	**Monocytes** ☐☐.☐ (%WBC) ☐ Not recorded
MCV ☐☐☐.☐ (fl)	**Lympocytes** ☐☐.☐ (%WBC) ☐ Not recorded
MCH ☐☐☐.☐ (pg)	**Eosinophils** ☐☐.☐ (%WBC) ☐ Not recorded
MCHC ☐☐.☐ (g/dl)	**Basophils** ☐☐.☐ (%WBC) ☐ Not recorded
QC perfomed by: **Initials** ☐☐☐	**Date**:☐☐/☐☐/☐☐☐☐

NATIONAL HEALTH LABORATORY SERVICE
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Severe Acute Respiratory Illness (SARI) Surveillance

Final Outcome Form (FOF)

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 086 723 3569

SO Initials: ☐☐☐ SARI Study ID: Date of admission: ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Did any of the following occur during admission?

1. Was TB therapy started?	Yes ☐	No ☐
2. Did the patient receive oxygen?	Yes ☐	No ☐
3. Did the patient receive mechanical ventilation?	Yes ☐	No ☐
4. Did the patient have a cardiac arrest?	Yes ☐	No ☐
5. Was the patient admitted to ICU?	Yes ☐	No ☐
6. Did the patient go into shock (Systolic BP < 90mmHg) or require inotropes?	Yes ☐	No ☐

37. Antibiotics prescribed during this admission: Yes ☐ No ☐ Unk ☐
Note: If yes, complete the table below. If no/unknown, skip to Q 8

	PO	IVI	IMI	Date started (enter date prescribed)	Total number of days
Amoxicillin				☐☐/☐☐/☐☐☐☐	
Augmentin				☐☐/☐☐/☐☐☐☐	
Ceftriaxone (Rocephin)				☐☐/☐☐/☐☐☐☐	
Ciprofloxacin (Ciprobay)				☐☐/☐☐/☐☐☐☐	
Contrimoxazole (Bactrim)				☐☐/☐☐/☐☐☐☐	
Erythromycin				☐☐/☐☐/☐☐☐☐	
Penicillin G				☐☐/☐☐/☐☐☐☐	
Ampiclox				☐☐/☐☐/☐☐☐☐	
Ampicillin				☐☐/☐☐/☐☐☐☐	
Cefotaxime				☐☐/☐☐/☐☐☐☐	

Cefuroxime (Zinnat)				☐☐/☐☐/☐☐☐☐	
Clindamycin				☐☐/☐☐/☐☐☐☐	
Doxycycline				☐☐/☐☐/☐☐☐☐	
Gentamycin				☐☐/☐☐/☐☐☐☐	
Vancomycin				☐☐/☐☐/☐☐☐☐	
Metronidazole				☐☐/☐☐/☐☐☐☐	
Other (Specify):				☐☐/☐☐/☐☐☐☐	

38. Was Oseltamivir (Tamiflu®) prescribed during this admission? Yes ☐ No ☐ Unk ☐

38.1 If yes, date prescribed: ☐☐/☐☐/☐☐☐☐

39. Was *Pneumocystis jirovecii* pneumonia (PCP) treatment prescribed during this admission? Yes ☐ No ☐ Unk ☐
Note: If yes, complete table below, if no or unknown skip to Final Outcome of Patient

	Dose (Specify quantity and unit)	**Oral**	**IMI**	**IVI**	**Frequency**	**Date started (enter date prescribed)**	**Total number of days**
Cotrimoxazole						☐☐/☐☐/☐☐☐☐	
Dapsone						☐☐/☐☐/☐☐☐☐	
Prednisone						☐☐/☐☐/☐☐☐☐	
Hydrocortisone						☐☐/☐☐/☐☐☐☐	
Other (specify) _____						☐☐/☐☐/☐☐☐☐	

Final outcomes of patient (for this admission)

10.1 What was the final outcome (for this admission)?

Discharge ☐ Death ☐ Refused hospital treatment/absconded ☐

Referred to step down ☐ Name of facility: _____

Transferred ☐ Name of facility: _____

10.2 Date of final outcome: ☐☐/☐☐/☐☐☐☐

11.Discharge/final diagnosis or diagnosis on transfer/referral
Neonatal Sepsis ☐ Bronchiolitis ☐ Bronchopneumonia/Pneumonia/Lower Respiratory Tract Infection ☐
Suspected TB ☐ Confirmed TB ☐ Bronchitis ☐ Diarrhoea ☐ Febrile seizures ☐
Meningitis ☐ Sepsis (not neonatal) ☐ Not recorded ☐ Other ☐ (Specify) _____

Outcome follow up *(for all SARI and SRI cases enrolled at Edendale, Klerksdorp and Tshepong Hospitals only)*

12. Date of follow up: ☐☐/☐☐/☐☐☐☐ Not done ☐

12.1 What was the follow up outcome? Death ☐ If died, date of death ☐☐/☐☐/☐☐☐☐ Date Unk ☐

Alive ☐ Unknown (not possible to determine) ☐

QC performed by: Initials: ☐ ☐ ☐ Date: ☐☐/☐☐/☐☐☐☐

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Cohen

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M081042**
PROJECT	Establishment of Sentinel Surveillance for Severe Acute Respiratory Infections (SARI) in South Africa
INVESTIGATORS	Dr C Cohen
DEPARTMENT	School of Public Health
DATE CONSIDERED	08.10.31
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.11.26 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor :

.....

.....

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

.....

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

14 August 2012

Dr Meera Chagan
Department of Paediatrics and Child Health
Nelson R. Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Chagan

PROTOCOL: **Establishment of Sentinel Surveillance for Severe Acute Respiratory Infections (SARI) in South Africa. Dr Cheryl Cohen (Epidemiologist NICD) and Dr Sabir Madhi (Paediatrician). Department of Paediatrics and Child Health. Ref No: BF157/08.**

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved: 22 July 2012
Expiration of Ethical Approval: 21 July 2013

I wish to advise you that your application for Recertification received on 23 July 2012 for the above protocol has been noted and approved by the Biomedical Research Ethics Committee (BREC) at a meeting held on 14 August 2012 for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics

Appendix B: Ethics approvals

The mortality analysis involves analysis of routine data in the public domain and forms part of influenza surveillance at the National Institute for Communicable Diseases. The protocol for these surveillance activities was approved by the University of the Witwatersrand (Wits) Ethics committee on 06 May 2005. Reference R14/49 Schoub.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Schoub

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M060449**
PROJECT	Essential Communicable Disease Surveillance Activities of the National Institute for Communicable Disease (NICD)....
INVESTIGATORS	Prof B Schoub
DEPARTMENT	NICD
DATE CONSIDERED	06.05.05
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 06.05.08 **CHAIRPERSON** .....
pp (Professor PE Cleaton-Jones

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof B Schoub

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementione research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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