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Title: **Epidemiology of influenza and respiratory syncytial virus among individuals presenting with influenza-like illness at two outpatient health facilities in South Africa, 2012 to 2019**

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of MSc Epidemiology in the field of Epidemiology and Biostatistics.

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DECLARATION

I, Yaw Awuku-Larbi, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Science in Epidemiology in the field of Infectious Disease Epidemiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University. _____ (Signature of candidate)

_____day of_____20___in_____

To God and my two dearest nieces

Nana Akua Nyamekye Abrokwah-Larbi

Lois Nana Ama Asantewaa-Larbi

ABSTRACT

Introduction: Influenza and respiratory syncytial virus (RSV) are the main causes of viral-associated acute respiratory illnesses. Respiratory tract infections may cause mild illness warranting outpatient care or severe illness warranting hospitalisation. Although cases with mild illness may not be hospitalised, attending to illness may be costly and affect time off work and productivity. To my knowledge, there are a few data comparing demographic and clinical characteristics of RSV and influenza among outpatients with influenza-like illness (ILI) in South Africa. This study aimed to describe the epidemiology of influenza and respiratory syncytial virus among individuals presenting with ILI at two outpatient health facilities in South Africa. This was done by comparing the seasonality, demographic and clinical characteristics associated with influenza and RSV among outpatients presenting with ILI at Edendale Gateway and Jouberton clinics in South Africa.

Methods: This cross-sectional study examined secondary data from active surveillance for outpatient ILI at two public health clinics in South Africa during 2012-2019. Univariate analysis was conducted to estimate the detection rate of RSV and influenza infections, as well as clinical and demographic characteristics of infected individuals. The average start and duration of influenza and RSV season by age group was estimated using the Moving Epidemic Method (MEM) web application. Logistic regression was employed to investigate risk factors associated with influenza- compared to those of RSV-associated ILI.

Results: RSV and influenza were detected in 5% and 14% of individuals enrolled with ILI from 2012 to 2019, respectively. The RSV season preceded the influenza season, with RSV occurring between January and May and influenza between May and September. Among individuals of all ages with ILI, individuals with laboratory confirmed influenza were more likely to be aged ≥5 years and less likely to be enrolled in summer, autumn or spring, in Jourberton Clinic or infected with HIV than individuals with laboratory confirmed RSV. In the age-stratified analyses among individuals aged <5 years, individuals with laboratory confirmed influenza were less likely to be enrolled in either summer, autumn or spring, or in Jourberton Clinic and more likely to be aged 3-4 years old than individuals with laboratory confirmed RSV. Among individuals aged ≥5 years, individuals with laboratory confirmed influenza were less likely to be aged 25-64 years old, enrolled in either summer, autumn or spring, Jourbeton Clinic, or in 2017 than individuals with laboratory confirmed RSV.

Conclusion: Influenza had a higher detection rate than RSV among individuals of all ages enrolled with ILI. The RSV season fell in autumn each year preceding the winter influenza season, this may be helpful to guide the timing of vaccination programmes and assist clinicians treating patients with respiratory illness. Influenza was more common in individuals aged ≥5 years. In contrast, RSV was more common in young infants, which can be helpful to guide who to target with interventions.

Keywords: influenza, respiratory syncytial virus, influenza-like illness, outpatient, South Africa

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ABBREVIATIONS

AV	Adenovirus
ALRI	Acute Lower Respiratory Infections
BREC	Biomedical Research and Ethics Committee
CIF	Case Investigation Forms
cDNA	complementary Deoxyribonucleic Acid
CRDM	Centre for Respiratory Diseases and Meningitis
EV	Enterovirus
ELISA	Enzyme-Linked Immunosorbent Assay
GOF	Goodness of Fit test
HA	Hemagglutinin
HIV	Human Immunodeficiency Virus
HREC	Human Research and Ethics Committee
HUS	Health Utilisation Survey
ILI	Influenza-like illness
LRTI	Lower Respiratory Tract Infection
hMPV	human Metapneumovirus
MEM	Moving Epidemic Method
MS	Microsoft
NA	Neuraminidase
NICD	National Institute for Communicable Diseases
OR/aOR	Odds Ratio/adjusted Odds Ratio
PIV	Parainfluenza
RNA	ribonucleic acid
RSV	Respiratory Syncytial Virus
rRT-PCR	real-time reverse transcription-polymerase chain reaction
RV	Rhinovirus
SARI	Severe Acute Respiratory Illness
SRI	Severe Respiratory Illness
URTI	Upper Respiratory Tract Infection
WHO	World Health Organisation

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1.0 INTRODUCTION

This introductory chapter begins with 1.1, a brief background on the virology of influenza and RSV. 1.2, describes the epidemiology of influenza- and RSV-associated influenza-like illness (ILI). Within this chapter, the gaps this study aims to fill, and the significance of the study are explained. Finally, 1.3, the overall aim and the specific objectives the study was intended to achieve are presented.

1.1 Background

1.1.1 Global Burden of Influenza and RSV

Influenza and respiratory syncytial virus (RSV) are viral pathogens associated with acute respiratory infections and are related to a substantial disease and mortality burden in all age groups (1,2). In addition, data from Europe suggests that RSV is related to excess morbidity and hospitalization compared to the more endemic influenza viruses (2–4).

Both RSV and influenza are commonly associated with lower respiratory tract infection (LRTI). Examples of LRTI include pneumonia which is associated with mortalilty in all ages, particularly in children and adults aged 65 years and older, and bronchiolitis which is generally limited to children less than 3 years of age (1,5,6). Globally, seasonal influenza is estimated to cause 30.5 to 48.4 million acute lower respiratory tract infection episodes and 291 243 – 645 832 deaths in all ages annually; while RSV is estimated to cause 19.7 – 31.4 million episodes and 94 600–149 400 deaths among young children aged below 5 years annually (1,7).

1.1.2 The burden of Influenza and RSV in Africa

There have been several published studies on burden of RSV and influenza from South Africa (8–11). Although published national estimates of the burden of influenza and RSV using hospital-based surveillance data exists in some other countries (including Madagascar, Kenya and Ghana), data from other parts of Africa are limited (8,10–19). In South Africa, seasonal influenza and RSV were estimated to respectively cause 11800 and 6800 deaths annually in all age groups between 2009 to 2013 using data from different data sources, including surveillance data (16). Influenza and RSV hospitalisation rates have been described in sub-Saharan Africa, including South Africa (10,11,20), Kenya (19), and Madagascar (12). RSV

and influenza usually cause mild diseases that may not require hospitalisation among all age groups in sub-Saharan Africa (19,21). In South Africa, the highest rates of mild influenza-associated illness are reported among individuals aged 5 to 24 years (21). In Kenya, the highest rates of mild RSV-associated illness was reported mainly among children <5 years (19).

1.1.3 Respiratory Syncytial Virus; virology and clinical manifestation

The respiratory syncytial virus (RSV) is a single-stranded RNA virus with only one serotype divided into two groups, "A" and "B". The differences in these groups are attributed to the viral structural membrane protein variation, mainly the attachment protein (22). These two groups co-circulate in the human population, with group A being more prevalent. The reason could be due to a more transient subgroup A-specific immune protection (23). A number of studies have shown varying results on the severity of respiratory illness between infants infected with RSV groups A and B (24,25). RSV spreads from person to person via respiratory droplets, and the incubation period after infection with RSV ranges from 2 to 8 days, with a mean incubation period of 4 to 6 days, depending on host factors such as the age of the patient and whether it is the patient's primary infection with RSV (26).

Almost all humans are infected with RSV in their early years of life, but immunity after infection is neither sustained nor complete. RSV-infected patients present with a broad spectrum of presentation including, asymptomatic infection and clinical illness with symptoms that vary from mild upper respiratory illness (URTI), cough, low-grade fever to severe LRTI in the form of pneumonia or bronchiolitis, which is most commonly observed in young infants (27–30). RSV-infected outpatients particularly present with cough, less commonly fever & nasal congestion, and acute illness, usually lasting 5-10 days. These symptoms may meet the criteria for the WHO case definition for ILI used for influenza surveillance (29,31,32). The World Health Organisation defines this as outpatients presenting with an acute respiratory disease, measured fever of ≥38°C and cough, with an onset in the last ten days (32). In some cases, both RSV and influenza may present without fever, and such cases may be missed by surveillance as they do not meet the WHO case definition for ILI.

1.1.4 Influenza; virology and clinical manifestation

Influenza is an RNA virus of the family Orthomyxoviridae. There are three types of influenza viruses commonly known to infect humans, namely; A, B and C. Influenza A can be further divided into subtypes based on the various combinations of proteins [the hemagglutinin protein (HA) and the neuraminidase (NA)] that occur on the surface of the virus (33). There are 18 different HA subtypes and 11 different NA subtypes (H1-H18 and N1-N11) (34). According to WHO, current subtypes of influenza A virus that routinely circulate are A(H1N1) and A(H3N2) (33). Literature suggests a public health seriousness to influenza A. As far back as 1918, influenza A (H1N1) led to between 50 and 100 million deaths continuing to infect humans in seasonal pandemics (35). The A (H1N1) virus, which now circulates routinely, is the same virus that caused the 2009 pandemic (33). Characteristic changes can occur in the HA and NA glycoproteins that may lead to antigenic shift (abrupt, significant changes associated with epidemics and pandemics) or antigenic drift (minor changes that happen occasionally and associated with localised outbreaks) (36). Antigenic drift or shift may occur due to changes during viral replication, leading to new variations of influenza A virus (37).

Influenza B primarily infects humans and circulates seasonally. There are two influenza B lineages, Yamagata and Victoria, named after the identified areas (33). Influenza C is known to cause mild respiratory illnesses in humans and associated with sporadic cases and minor outbreaks and is not commonly detected through routine diagnostic assays (33).

The influenza virus is most contagious in the first three to four days after symptoms begin. Healthy individuals can, however, infect others before they experience symptoms. Transmission of influenza is mainly by direct contact or through air droplets (29,38). The duration of infectiousness can begin one day before symptoms begin or up to five to seven days after becoming sick (33). Influenza virus may be associated with loss of time in school, work sick days, and discomfort, leading to hospitalisation and even death (39). Influenza infections can range from asymptomatic, mild illness with symptoms of cough, measured fever of ≥38°C, sore throat, nasal congestion, headaches etc., to severe illnesses such as LRTI, central nervous system involvement and/or a significant worsening of underlying medical conditions (38,40).

Viral associated acute respiratory infections caused by influenza and RSV affect the sinuses, throat, airways or lungs.

1.2 Literature Review

Literature was extensively reviewed. The PUBMED, Wiley online library and Google Scholar online database search yielded studies that fall under the following themes: 1.2.1. Mild and severe influenza and RSV illnesses, 1.2.2. risk factors for influenza and RSV associated illnesses, 1.2.3. seasonality of influenza and RSV, and 1.2.4. prevention and interventions for these illnesses.

1.2.1 Mild and severe influenza and RSV illnesses

Several observational epidemiological studies (cross-sectional, case-control and cohort studies) in high and low to middle-income countries have examined the prevalence, incidence, and risk factors for influenza- and RSV-associated ILI among children and adults in hospitalised and outpatient settings.

Influenza and RSV, among other viral-associated acute respiratory tract infections, may cause mild illness requiring outpatient care or severe illness requiring hospitalisation. Though viral respiratory infections are associated with severe disease resulting in hospitalisation and even death, a large number result in relatively mild cases, causing minor respiratory illness before the patient fully recovers (41). Though mild disease cases may not be hospitalised, attending to illness may be costly and affect time off work and productivity. Quantifying both mild and severe viral respiratory infections is necessary to estimate the disease burden to inform public health policies. According to the epidemiological studies conducted in the temperate regions, most respiratory viruses, including influenza and RSV, have seasonal patterns in their outbreaks (2,42). RSV and influenza share common features, including a high mutation rate which may co-occur, leading to recurrent infections and epidemics in winters. Epidemics of mild and severe acute respiratory diseases associated with influenza and RSV are monitored through mostly routine hospital-based surveillance (43). In a Chinese study, using data from a hospital-based surveillance of ILI, influenza A (11.7%) and B (8.2%) were the most commonly detected viruses among individuals with ILI. RSV was detected in 2.3% of outpatients with ILI. By age group, influenza A & B were most commonly detected among individuals with ILI aged 15-59 years, while RSV A & B were most commonly detected among individuals aged 0-4 and ≥ 60 years (44). In a French study that also used surveillance data, influenza was more commonly detected than RSV among individuals with ILI aged >5 years. Among children ≤5 years with ILI, RSV was most commonly detected (45). Although

these two studies used different case definitions for ILI and were conducted at different geographic locations, the findings were similar.

In South Africa, RSV and influenza surveillance are conducted through sentinel surveillance for influenza-like illness (ILI) in an outpatient setting and severe acute respiratory illness in a hospitalised setting using case definitions recommended by the WHO. Surveillance studies have been conducted to monitor trends and seasonality of mainly influenza, RSV and other viral infections [including rhinovirus (RV), adenovirus (AV), enterovirus (EV), human metapneumovirus (hMPV), parainfluenza virus 1, 2, 3 (PIV 1-3)] among patients presenting with mild and severe respiratory illnesses in South Africa (46–48). A study by Pretorius and colleagues estimated the attributable fraction and the detection rate attributable to illness for ten common respiratory viruses (influenza A and B viruses, (PIV 1-3); (RSV); RV, (hMPV), AV, and EV) (49). The study found that influenza, RSV, PIV 2 and hMPV were likely to be associated with illness when they are detected in South African patients with ILI or SARI. A study by Moyes et al., which estimated the burden of RSV in a hospitalised setting in South Africa, suggested that the true burden of RSV-associated respiratory tract infection is not complete without an estimation of the outpatient burden (50). Also, several studies on viral respiratory infections among hospitalised patients have been conducted in South Africa. However, limited information is available on the epidemiology of these in an outpatient setting (10,48,49,51–53).

1.2.2 Risk factors for influenza- and RSV-associated illness

Taylor et al. conducted a study in eight countries, a combination of high and low to middle-income countries (Australia, Latin America and South Asia) among healthy children (6 months to <10 years) with influenza-like illness (ILI). The population sample used in this study was derived from an influenza vaccine trial (NCT01051661) (54). In addition, Taylor et al. conducted active surveillance via scripted telephone contacts after the children had been vaccinated. This study found the prevalence of influenza-associated ILI particularly higher among older children (between 5 to 10 years). However, this was different for RSV-associated ILI, where the prevalence was highest among infants <1 year. Other studies on ILI conducted among children in outpatient settings reported similar findings to what Taylor et al. found in their study(19,49).

Additionally, Souty et al. conducted a study in France that looked at the baseline and clinical characteristics of viral-associated ILI among all ages (45). Similar to the findings of Taylor et al., the results of Souty et al. reported the highest prevalence of influenza-associated ILI amongst older children aged 5-14 years and RSV-associated ILI amongst children <5 years (45).

In Africa, surveillance studies have been conducted in different settings, including HIV-prevalent settings, to estimate the burden and examine the risk factors associated with viral-associated ILI. Emukule et al. 2014 reported the incidence and detection rates of outpatient and inpatient influenza and RSV infections. The study reported RSV was more commonly detected among outpatients aged <5 years than outpatients aged ≥ 5 years with ILI. Similarly, the average annual incidence of medically-attended ILI associated with RSV was significantly higher among children <5 years compared to individuals aged ≥ 5 years. Influenza was more commonly detected among individuals with medically-attended ILI aged ≥ 5 years compared to children <5 years. However, the average annual incidence of medically-attended ILI associated with influenza was significantly higher in children <5 years compared to individuals aged >5 years (19). In a South African study conducted over two years, the mean annual incidence rates for influenza-associated ILI were highest among persons aged 5-24 years (14). Although these studies did not compare influenza- and RSV associated ILI, they suggest that age is a significant risk factor for influenza- and RSV-associated ILI. A study by Hall et al. also found age, specifically younger children aged <5 years, to be a risk factor for RSV infection in an outpatient setting (31).

Other factors for influenza and RSV include long duration of symptoms, race because of socioeconomic disparity, genetic susceptibility, pregnancy and malnutrition in children (20,55).

People living with HIV and infants born to mothers with HIV have an increased risk of RSV- and influenza-related complications (9, 11, 14). South Africa has a disproportionate number of HIV cases- an estimated 7.5 million people living with HIV as of 2019 (56). Several studies of influenza and RSV in both children and adults have assessed the impact of HIV infection on hospitalisation and outpatients independently in South Africa. In a study that examined respiratory viruses role among inpatients and outpatients in a high HIV seroprevalent population, 30% of ILI cases with known HIV serostatus had HIV (49). In an analysis of data from 2011-2016, the study found HIV infection was associated with increased risk of

influenza- (Relative Risk [RR], 2.7; 95% CI, 2.0-3.5) and RSV-associated (RR, 3.8; 95% CI, 3.1-4.8) hospitalisation among children 0-6 months (57). In another study, HIV infection was associated with the increased risk of RSV-associated hospitalisation among adults aged 18-44 years (odds ratio [OR], 26.3; 95% CI, 6.2-112.1) and 45-64 years (OR, 11.4; 95% CI, 2.6-50) (50). Although these studies found HIV infection to be associated with increased risk of hospitalisation and ILI, they did not look at the impact of HIV infection on influenza- and RSV-associated ILI in an outpatient setting.

The impact of viral codetections on respiratory illnesses is debatable. In a study, dual codetections have been linked to more severe illness compared to single viral detections (58). Another study suggests viral codetections may be associated with mild respiratory illnesses representing a commensal situation in which the second virus may have no effect on the predominant infection (41). A study by Goka et al. suggest codetections between RSV, influenza A(H1N1)pdm09, and adenovirus was predominant among <5 years with insignificant increased risk of hospitalisation (59). Other studies suggest decreased risk of severe respiratory illness with rhinovirus and influenza A codetections (60,61).

Individuals with underlying conditions such as cognitive dysfunction, diabetes, cardiovascular, renal, pulmonary, neuromuscular and liver diseases are associated with increased risk of ILI as well as severe RSV- or influenza associated complications that may even lead to death (62–64).

1.2.3 Seasonality of influenza and RSV

Information on influenza and RSV's seasonality is necessary for public health service planning and disease prevention and control strategies, including immunisation strategies. Low temperatures are associated with an increase in RSV and influenza activity, which likely contributes to the fact that influenza and RSV epidemics occur during the winter season in the countries with temperate climates in the southern and northern hemispheres (2,47,65). Studies show that the RSV epidemic precedes the influenza epidemic in South Africa, with the average onset of the RSV season in February, while the influenza season starts in April (2,10,66,67).

1.2.4 Prevention and interventions

With many studies conducted to understand the seasonality and disease burden, interventions have been put in place in preparation for the influenza pandemic and control of epidemics for both RSV and influenza (1). In South Africa, influenza and RSV surveillance systems are in place to describe the epidemiology of influenza- and RSV-associated illness, alert clinicians and facility managers about the start of the season (as the number of consultations and hospital admissions increases). The surveillance systems also monitor changes in circulating strains of influenza and RSV to provide information to inform interventions, for example, groups to be prioritised for influenza vaccination (48,67–69) and strain selection for the Southern Hemisphere influenza vaccine. There is low influenza vaccination coverage in South Africa. Therefore, increasing influenza vaccination coverage among prioritised groups, including health workers and pregnant women, could increase be a useful strategy to increase influenza vaccine coverage in South Africa (70). Studies conducted in South Africa show 43-46% vaccine effectiveness against influenza infection in 2014-2015(71,72). There are no licenced vaccines for RSV at this stage. However, several vaccine candidates are in advanced development stages (73,74). Extensive studies have been conducted to estimate disease burden, understand the aetiology and transmission of influenza and RSV infections among patients with severe respiratory illnesses. However, there is still a need to conduct further studies among outpatients to understand transmission and risk factors associated with influenza- and RSV-associated mild illnesses to reduce severe respiratory disease burden and mortality in South Africa.

1.3 Problem statement

Influenza and RSV infections are known to be among the viral pathogens, including rhinovirus, parainfluenza virus, adenovirus, human metapneumovirus and enterovirus associated with severe respiratory illness (1). However, the majority of viral respiratory infections result in mild respiratory illness before the patient fully recovers (21,41). Though mild illness cases may not result in hospitalisation, attending to illness may be costly and increase time off work, thus reducing work productivity. Several studies have been conducted on influenza- and RSV-associated acute respiratory illnesses among hospitalised patients in South Africa. However, there is limited data on the epidemiology of mild influenza- and RSV-associated illnesses among individuals who do not require hospitalisation in South Africa, i.e.,

outpatients. In addition, to our knowledge, no information on the comparison of RSV and influenza characteristics among outpatients with ILI exists in South Africa (10,48,49,51–53).

1.4 Justification

Much attention has been focused on viral respiratory infections among hospitalised patients, with little focus on less severe respiratory illness, which does not require hospitalisation (10,48,49,51–53). Describing factors associated with common viral respiratory infection causing respiratory illness among outpatients will provide valuable data to allow policymakers informed planning on selecting and setting criteria for routine diagnosis of specific respiratory pathogens to influenza-like illnesses. This will help put in place strategies to prevent mild respiratory illnesses from progressing to severe acute respiratory illness. Because the RSV and influenza seasons' timing may overlap, describing the epidemiology and factors associated with each would help clinical practice.

1.5 Aim

To compare demographic and clinical characteristics associated with influenza and RSV among outpatients presenting with ILI at two selected health facilities in South Africa, 2012 to 2019.

1.6 Research Question

What are the demographic and clinical characteristics associated with influenza and RSV among outpatients presenting with ILI at two selected outpatient health facilities in 2 provinces (Edendale Gateway clinic in Pietermaritzburg, KwaZulu-Natal Province and Jouberton clinic in Klerksdorp, North West Province), in South Africa, 2012 to 2019?

1.7 Objectives

1. To estimate the detection rates of influenza and RSV infections among outpatients presenting with ILI at selected health facilities in South Africa from 2012 to 2019
2. To compare the seasonality of influenza and RSV infections by month and year among outpatients presenting with ILI at selected health facilities in South Africa from 2012-2019.

3. To examine factors associated with influenza as compared to RSV infections among outpatients <5 and ≥5 years presenting with ILI

2.0 METHODS AND MATERIALS

This chapter details the methodology of this study. This includes an overview of the primary study, data collection methods, the design of this study, the study population, laboratory testing, data management, and the statistical analysis conducted to address the study objectives. The chapter concludes with the ethical considerations of the study.

2.1 Overview of the primary study

2.1.1 Research setting and description of the primary study

The primary study aimed to enrol asymptomatic healthy controls and patients with outpatient influenza-like illness (ILI) to describe the burden and aetiology of mild respiratory disease in South Africa, and ultimately describe the full burden of viral-associated respiratory illness. The asymptomatic controls were included to assess the relative contribution of respiratory viruses to ILI and severe respiratory illness (SRI). However, in the current study, asymptomatic controls were not included in the study. The primary study also aimed to describe the risk factors associated with severe disease, allowing policymakers to target vaccinations and other prevention programmes.

The primary study was conducted at two public clinics (Edendale Gateway and Jouberton clinics) by the Centre for Respiratory Diseases and Meningitis (CRDM) at the National Institute for Communicable Diseases (NICD). The two public health clinics are situated in two peri-urban areas, Pietermaritzburg and Klerksdorp which are respectively located within the KwaZulu-Natal and North-West Provinces in South Africa. These clinics were within the catchment area of two public health hospitals (Edendale Hospital and Klerksdorp-Tshepong Hospital Complex, respectively), where surveillance for hospitalised patients with SRI was conducted.

2.1.2 Enrolment procedures for the primary study

The primary study is an active prospective clinic-based surveillance programme. All consecutive eligible patients were enrolled from Monday to Friday between 8 AM and 2 PM throughout the year. In the hours of enrolment, no sampling was done. In this study, outpatients who fit the clinical case definition of ILI were provided with the study information and asked to sign an informed consent (individuals ≥ 18 years or parents/guardians of children <18 years) and assent (children >7 years) forms. Data was collected from consenting participants including demographic details, signs and symptoms of ILI, underlying medical and potential risk factors associated with ILI. This was done through an interview using a structured questionnaire (Appendix 5), which a trained surveillance officer conducted. Respiratory samples, namely, nasopharyngeal aspirates for children aged <5 years and nasopharyngeal and oropharyngeal swabs from persons aged ≥5 years, were collected from enrolled participants for laboratory testing at the NICD.

2.1.3 Laboratory procedures

Respiratory specimens were placed in a universal transport medium, stored at 4-8°C and within three days of collection transported to the NICD. From 2012 to 2016, all specimens were tested for 10 respiratory viruses; influenza A and B, RSV (A and B), PIV 1-3, AV, EV, hMPV, and RV using a real-time multiplex reverse transcription-polymerase chain reaction (rRT-PCR) assay (75). From 2017, samples were only tested for influenza and RSV. Viral nucleic acid material (RNA) was extracted from the samples using an automated RNA extraction system following the manufacturer's instructions. RNA was transcribed to cDNA using the Transcriptor cDNA synthesis kit (Roche Diagnostics). Real-time PCR was then performed using the Light Cycler® 480 Probes Master kit (Roche Diagnostics) was used for detection. From 2016 to 2019, a commercial multiplex rRT-PCR was used (FTD Flu/RSV assay, FastTrack Diagnostics, Sliema, Malta) to test for influenza A and B viruses and, RSV A and B.

HIV status was established from different sources, including patient clinical records when available or verbal HIV positive reports. For consenting ILI cases with unknown HIV status, HIV enzyme-linked immunosorbent assay (ELISA) (or PCR assay for children aged <18 months with positive ELISA or unknown exposure status) was performed.

2.1.4. Data Entry and management

Case Investigation Forms (CIFs) were sent from the two public health clinics to the data management centre at the NICD for data entry. Data for the surveillance study were double data entered into an MS Access database by data entry clerks. Data verification was conducted to see if the two entries corresponded after data had been entered and saved. Routine data checks conducted, generated data queries to clarify any missing data, inconsistencies or invalid data sent to the sites to be resolved. CIFs were stored in the data centre at NICD. Data was stored in password-protected access databases.

2.1.5 Study population of primary study

The study population included all outpatients attending the two public health clinics (Edendale Gateway and Jouberton clinics) who met the ILI case definitions and enrolled into the prospective clinic-based ILI surveillance programme coordinated by the CRDM. To be enrolled in the primary study for ILI, outpatients had to be a resident of the catchment area and present to the outpatient clinic with ILI as defined by WHO (32) that is; acute fever of ≥38 degrees Celsius and/or a self-reported fever within the last ten days AND a cough in the absence of other diagnoses.

2.2 Current study design

This study is a cross-sectional study using secondary data obtained from the primary study described above. We determined the detection rates of RSV and influenza among individuals with ILI, seasonality of RSV and influenza and the risk factors associated with RSV as compared to influenza among individuals with ILI to understand the epidemiology of influenza and RSV in an outpatient setting.

2.2.1 Study population of the current study

The current study looked at all cases that met the ILI case definition, enrolled at the two selected public health clinics from May 2012 to November 2019, and had test results for influenza and RSV. An exclusion criterion in this analysis was a participant presenting with influenza and RSV coinfections.

2.3 Data Collection

This study's original data set and dictionary were received in STATA and Microsoft EXCEL format, respectively, from the gatekeeper at the CRDM, NICD.

2.4. Data Management and statistical analysis methods

2.4.1 Measurement

The following variables were included in this analysis:

2.4.1.1 Outcome Variable

The primary outcome of interest was RSV- or influenza-associated ILI. This outcome was measured as an ILI case that tested positive for either influenza or RSV.

2.4.1.2 Exposure Variables

The exposure variables included age, sex, race, underlying medical conditions, symptom duration ≤3 days, HIV status (for all ages), HIV exposure status (among children), malnutrition (among children), pregnancy, year and public health clinic (PHC). The selection of these variables was based on literature.

2.4.1.3 Source of Bias

Recall bias could play a role as a structured questionnaire was used to collect information, including any underlying illness and symptom duration. As a result, individuals were likely to provide less accurate information as they may have to recall to provide information.

2.4.2 Data management and processing

The data management process included labelling variables and generating new categorical variables from existing variables, using STATA 16.1.

Influenza and RSV variables were initially coded "1" for positive and "0" for negative. A new variable was generated from influenza and RSV variables coded "1" for influenza positives, "0" for RSV positives, and "2" for RSV and influenza codetections. The value "2" was dropped to exclude RSV and influenza codetections in this analysis.

Age was initially a continuous variable from which two categories were created, <5 and ≥5 years, to evaluate potential differences in RSV- and influenza-associated ILI in young and older individuals. In each stratum, age was further categorised into <1 year, 1-2 years, 3-4 years for children <5 years, and 5-14 years, 15-24 years, 25-44 years, 45-64 years, 65 years and above for participants ≥5 years. Sex was regrouped into a binary group, coded "1" for male and "2" for female participants.

HIV status was regrouped into a binary group; coded "1" for HIV infected and "0" for HIV negative.

Race was regrouped into binary group, blacks and non-blacks (Indian, whites and coloured). This regrouping was done due to the small representation in numbers of Indians, whites and coloured in the ILI surveillance study. Symptom duration was regrouped to the following categories; ≤3 days and >3 days. Any underlying medical conditions including (adapted from the questionnaire in Appendix 5); asthma, other chronic lung diseases, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), seizures, liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), and neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions) were aggregated and regrouped into a binary group; yes and no.

RSV or influenza coinfections with any of the eight respiratory viruses were coded "1" for positive and "0" for negative. Data for infections with other respiratory viruses were available from 2012 up to 2016.

Other variables included PHC (Jouberton Clinic vs Edendale Gateway Clinic), years (which had the complete 12 months from 2013 to 2018 except in 2012 where there was no available data until May and 2019 where there was no available data for December) and season (recoded using month i.e. December, January and February for summer; March, April and May for autumn; June, July, August for winter; September, October and November for Spring)

Under the age-stratified analysis among children <5 years, variables included were HIV exposure status (coded as "1" HIV unexposed uninfected, "2" HIV exposed uninfected, "3" HIV infected, and malnutrition as defined by <2 Z scores (-2 standard deviations) of the mean

weight for age in months and gender. This also includes any children recorded as having Kwashiorkor or Marasmus (coded as "1" yes and "0" no).

Under the age-stratified analysis among participants ≥5 years, variables included were pregnancy (coded as "1" yes and "0" no) which was restricted to only females during the analysis.

After extraction, each data table was individually cleaned. Variables were described and browsed through to check for inconsistencies and outliers. Data cleaning included range checks across data and setting extreme values to missing, which were biologically implausible. For example, the variable "age" was compared to the "date of birth" variable to confirm if the "age" recorded was correct. Missing values were identified, coded as (.) and reported in the results section. For participants with missing values for age, they were excluded from the analysis.

2.4.3 Statistical Analysis

All data cleaning and statistical analysis (descriptive, univariate and multivariable) were conducted in STATA version 16.1 (StataCorp Texas, USA), and graphs were generated using Microsoft EXCEL.

2.4.3.1 Descriptive statistics

Background characteristics were analysed descriptively and presented using frequency distribution tables. Continuous variables for example participants' age, were summarised using median and interquartile range, while frequency and percentages were used to show the distribution of categorical variables.

2.4.3.2 Objective 1: determining influenza and RSV detection rates

Detection rate was defined as the number of influenza or RSV positives divided by the number of ILI cases within the exposure group. The cases tested for both pathogens were excluded. The detection rates of influenza and RSV by demographic and clinical characteristics among participants of all ages, <5 and ≥5 years, were compared using Pearson's chi-squared test. A graph showing detection rates of influenza and RSV by age group was plotted.

2.4.3.3 Objective 2: comparing seasonality of influenza and RSV infections

To address the second objective, an epidemiological curve (76), a histogram showing the onset of illness by month and year among RSV and influenza-infected outpatients with ILI from 2012 to 2019, was plotted to describe the seasonal patterns over time.

The weekly trend of influenza and RSV detection rates within the 6-year period (used complete ILI data for 6 consecutive seasons from 2013 to 2018) was applied to describe the seasonality of influenza and RSV. This was done by applying the "Moving Epidemic Method (MEM)" using R version 4.0.4. As initial step, estimating the trends in weekly detection rates of influenza and RSV for each year was done using Excel v-16. A season was from week 1 to 51, as described in past reports of the ILI and pneumonia surveillance in South Africa (67,77). The seasonality and MEM model were extracted from the analysis result of the MEM web application (R version 4.0.4). This includes the average starting and ending season of the epidemics and their 95% confidence intervals. These findings were presented in graphs showing the average starting and ending season of influenza and RSV epidemics.

2.4.3.4 Objective 3: determining factors associated with influenza as compared to RSV infections

To address the third objective, univariate and multivariable logistic regression was used to examine factors associated with influenza as compared to RSV among individuals of all ages, <5 and ≥5 years with ILI. Logistic regression was used in this objective as the outcome variable was binary (which was coded "1" for ILI individuals who tested positive for influenza and "0" for ILI individuals who tested positive for RSV).

In the univariate binary logistic regression, each exposure variable was regressed on the outcome variable (influenza compared to RSV among individuals with ILI) to report the unadjusted odds ratio (OR) and p-values. Following the univariable analysis, explanatory variables with p-values less than 0.15 were individually included in the multivariable model to assess the factors associated with influenza compared to RSV among individuals of all ages, <5 and ≥5 years with ILI. Variables that were considered for inclusion into the model for all ages were age, public health clinic (PHC), season, year, HIV, any underlying medical condition and symptom duration. The model for <5 years included age, public health clinic (PHC), season and HIV. The model for ≥5 years included age, public health clinic, season,

year, HIV and symptom duration. We assessed associations between the characteristics and the outcome variables using adjusted odds ratios (aOR), 95% confidence interval and p-values.

All explanatory variables used in the logistic regression analysis were categorical variables. A reference category was selected for each categorical variable to compare with other levels in the variable. The categorical variable level with the larger number of observations or useful for interpretation purposes was used as the reference category in the logistic regression analyses for categorical variables.

2.5 Ethical Considerations

Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical; M1911159) (Appendix 2) to conduct this secondary data analysis. Permission for data use was obtained from the gatekeepers at the Centre for Respiratory Disease and Meningitis at NICD. Analysis of the data only commenced after the ethics clearance certificate was received. The primary study protocol was approved by the University of the Witwatersrand Human Research Ethics Committee (HREC) and the University of KwaZulu-Natal Human Biomedical Research Ethics Committee (BREC) protocol numbers M120133 (in Appendix 4) and BF080/12, respectively.

3.0 RESULTS

This chapter presents the data analysis results that were performed using the analysis techniques indicated in the method and materials. The descriptive statistics of the sample were summarised using frequency tables and graphs. Age stratified detection rates of influenza- and RSV-associated ILI by clinical and epidemiological characteristics are presented. Graphs demonstrating the comparison of the seasonality of RSV- and influenza-associated ILI are displayed in this section. This chapter concludes with a table showing odds ratios and confidence intervals from the univariate and multivariable binary analysis, which investigates the factors associated with influenza-related ILI compared to RSV-related ILI.

3.1 Overview:

From March 2012 to November 2019, 9410 outpatient cases were enrolled in the ILI surveillance programme at 2 ILI surveillance sites. Of these cases, 1.1% (107/9410) were excluded due to 0.8% (78/9410) cases with missing data on RSV and influenza, 0.2% (15/9410) cases that had influenza and RSV codetections, and 0.1% (14/9410) which had missing data on age. 9303 individuals with ILI were included in the description of characteristics, estimation of influenza and RSV detection rates, and a comparison of the seasonal patterns of RSV and influenza. 1803 of the 9303 ILI cases (19.4%) tested positive for either influenza or RSV. These 1803 positive cases (of either influenza or RSV) were included in the univariate and multivariable logistic regression analysis to determine factors associated with influenza- compared to RSV-associated ILI.

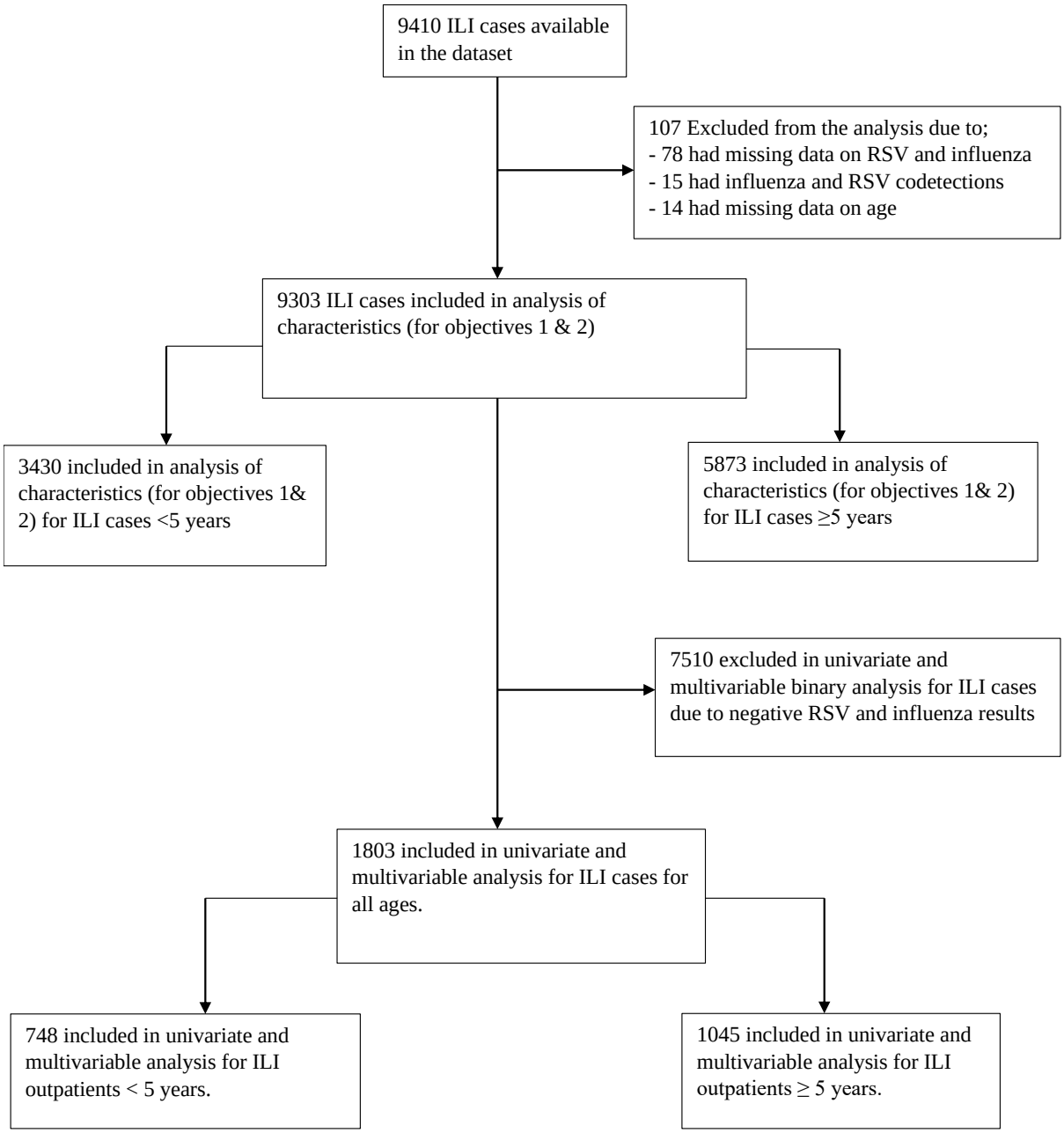

Figure 3.1 Flow chart showing the distribution of ILI cases used in the data analysis by age groups

3.2. Descriptive Statistics

Among the 9303 ILI cases included in this analysis, 60% were female, 99% were black, and most attended Edendale Gateway Clinic (66%). The median age was 13 years (interquartile range (IQR), 2 to 33 years), 63.8% were aged ≥5 years, 36.0% were aged <5 years. The highest enrollment of ILI was recorded in 2016 (1642/9303, 17.7%) (Table 3.1).

Of the 9303 ILI cases, 14% (1304/9303) were positive for influenza, and 5.4% (499/9303) were positive for RSV. Of the 1304 positive influenza cases, most were aged ≥5 years (68.4%), 57.4% were female, 20.8% were HIV positive (6.4% of influenza cases had no data available for HIV), and 11.84% had any underlying medical conditions present. Of the 499 RSV cases, most were aged <5 years (69.3%), 54.31% were female, 11.8 % were HIV positive (5.6% of the RSV cases had no data available for HIV), and 12.4% had any underlying medical conditions present.

Table 3. 1 Demographic and clinical characteristics of all enrolled individuals with ILI and individuals testing RSV and influenza-positive at two public health clinics in South Africa, 2012 to 2019

Characteristics	Influenza	RSV	All ILI patients
	N=1304 (%)	N=499 (%)	N= 9303 (%)
Demographics			
Age group, years			
<5	412 (31.6)	346 (69.3)	3430 (36.9)
≥5	892 (68.4)	153 (30.7)	5873 (63.1)
Race, % Black			
Black	1294 (99.2)	495 (99.2)	9235 (99.3)
Non-black	3 (0.2)	0 (0.0)	16 (0.2)
Missing	7 (0.6)	4 (0.8)	65 (0.5)
Sex, % female			
Female	748 (57.4)	271 (54.3)	5560 (59.8)
Male	550 (42.2)	224 (44.9)	3697 (39.7)
Missing	6 (0.4)	4 (0.8)	46 (0.5)
Time period			
2012	210 (16.1)	48 (9.6)	1004 (10.8)
2013	162 (12.4)	50 (10.0)	1038 (11.2)
2014	209 (16.0)	66 (13.2)	1608 (17.3)
2015	124 (9.5)	76 (15.2)	1186 (12.8)
2016	217 (16.6)	97 (19.4)	1642 (17.8)
2017	207 (15.9)	68 (13.6)	1444 (15.5)
2018	100 (7.7)	49 (9.8)	721 (7.7)
2019	75 (5.8)	45 (9.2)	660 (7.1)
Season			
Summer	6 (0.5)	114 (22.9)	1059 (11.4)
Autumn	180 (13.8)	238 (47.7)	2177 (23.4)
Winter	841 (64.5)	76 (15.2)	3871 (41.6)
Spring	277 (21.2)	71 (14.2)	2196 (23.6)
Public Health Clinic			

Jouberton Clinic	330 (25.3)	195 (39.1)	3192 (34.3)
Edendale Gateway	974 (74.7)	304 (60.9)	6111 (65.7)
Clinical			
Underlying medical conditions present*			
Yes	103 (7.9)	62 (12.4)	870 (9.3)
No	1190 (91.3)	432 (86.6)	8379 (90.1)
Missing	11 (0.8)	5 (1.0)	54 (0.6)
Symptom duration, ≤ 3 days†			
≤ 3 days	973 (74.6)	342 (68.5)	6028 (64.8)
> 3 days	324 (24.9)	147 (29.5)	3188 (34.3)
Missing	7 (0.5)	10 (2.0)	87 (0.9)
HIV, positive			
Positive	271 (20.8)	59 (11.8)	2082 (22.3)
Negative	949 (72.8)	412 (82.6)	6717 (72.1)
Missing	84 (6.4)	28 (5.6)	518 (5.6)
Viral respiratory pathogens‡			
Adenovirus			
Positive	55 (4.2)	23 (4.6)	409 (4.4)
Negative	830 (63.7)	285 (57.1)	5567 (59.8)
Missing	419 (32.1)	191 (38.3)	3327 (35.8)
Enterovirus			
Positive	13 (1.0)	13 (2.6)	152 (1.6)
Negative	872 (66.9)	295 (59.1)	5824 (62.6)
Missing	419 (32.1)	191 (38.3)	3327 (35.8)
Rhinovirus			
Positive	46 (3.6)	53 (10.6)	1242 (13.4)
Negative	839 (64.3)	255 (51.1)	4740 (50.9)
Missing	419 (32.1)	191 (38.3)	3321 (35.7)
Human metapneumovirus			
Positive	11 (0.8)	3 (0.6)	163 (1.7)
Negative	874 (67.0)	305 (61.1)	5813 (62.5)
Missing	419 (32.2)	191 (38.3)	3327 (35.8)
Parainfluenza virus 1			
Positive	5 (0.4)	2 (0.4)	74 (0.8)
Negative	880 (67.5)	306 (61.3)	5907 (63.5)
Missing	419 (32.1)	191 (38.3)	3322 (35.7)
Parainfluenza virus 2			
Positive	1 (0.1)	1 (0.2)	25 (0.3)
Negative	884 (67.8)	307 (61.5)	5956 (64.0)
Missing	419 (32.1)	191 (38.3)	3322 (35.7)
Parainfluenza virus 3			
Positive	4 (0.3)	3 (0.6)	108 (1.2)
Negative	881 (67.6)	305 (61.1)	5873 (63.1)
Missing	419 (32.1)	191 (38.3)	3322 (35.7)

‡Data available up to 2016, missing includes results "not done" as well as missing results †time to symptom presentation at the facility

*Underlying conditions included any of the following: "Asthma, other chronic lung diseases, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), seizures, liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions)"

3.3. Influenza and RSV detection rates

This section presents the detection rates of influenza and RSV by age.

3.3.1. Influenza and RSV detection rates among all ages

Table 3.2 shows the detection rates of RSV and influenza by demographic and clinical characteristics among individuals of all ages enrolled with ILI at two public health clinics in South Africa, 2012 to 2019. There was a significant difference in the detection rates for influenza and RSV by age group, period, and health facility under demographics. The detection rate for influenza was higher among individuals aged ≥5 years compared to among individuals aged <5 years (15.2% vs 12.%, $p<0.001$), in contrast, the detection rate for RSV was higher among individuals aged <5 years compared to among individuals aged ≥5 years (10.1% vs 2.6%, $p<0.001$). Figure 2 shows the detection rates for RSV and influenza by age groups. Detection rates for influenza increase from infancy and peak at the ages of 5-14 years. Above the age of 14 years, detection rate decreases with increasing age, with the lowest detection rate in individuals aged 65 and above. The detection rate for RSV is highest during infancy and then decreases with increasing age.

RSV was significantly more commonly detected among males than in females (6.1% vs 4.9%, $p=0.013$) (Table 3.2). Edendale Gateway had higher influenza detection than in Jouberton Clinic (15.9% vs 10.3, $p<0.001$). Conversely, RSV detection was higher in Jouberton Clinic than in Edendale Gateway (6.0% vs 5.0%, $p=0.024$). The lowest detection rate was observed in 2015 (10.5%) for influenza and 2014 (4.1%) for RSV. The detection rates peaked in 2012 (20.9%) for influenza and in 2018 as well as 2019 for RSV, where the detection rate for RSV was (6.8%) for both years.

Under clinical characteristics, the overall influenza detection rate was significantly higher among participants with symptom duration ≤3 days (16.1%) compared to >3 days (10.2%) [$p<0.001$]. RSV detection rate was significantly different among participants with symptom duration ≤3 days (5.7%) and >3 days (4.6%) [$p=0.011$]. RSV detection rate was significantly higher among individuals not infected with HIV than in HIV infected individuals with ILI (6.1% vs 2.8%, $p<0.001$). There was no significant difference in influenza detection rates among individuals with ILI between those not infected with HIV and those infected with HIV. A higher RSV detection rate was seen among ILI cases with any underlying medical

conditions (7.1%) compared to those who did not present any underlying medical conditions (5.2%) [*p*=0.036].

Table 3. 2 Detection rates of RSV and influenza by demographic and clinical characteristics of all enrolled individuals with ILI and individuals testing RSV and influenza-positive at two public health clinics in South Africa, 2012 to 2019

Characteristics	N (9303)	Influenza detection rate		RSV detection rate	
		N=1304 (%)	*p*-value	N=499 (%)	*p*-value
Demographic characteristics					
Age group, years					
<5	3430	412 (12.0)	<0.001	346 (10.1)	<0.001
≥5	5873	892 (15.2)		153 (2.6)	
Race					
Black	9236	1294 (14.0)	0.649	495 (5.4)	0.610
Non-black	16	3 (18.8)		0 (0.0)	
Missing	51	7 (13.7)		4 (7.8)	
Sex					
Female	5561	748 (13.5)	0.107	271 (4.9)	0.013
Male	3697	550 (14.9)		224 (6.1)	
Missing	45	6 (13.3)		4 (8.9)	
years					
2012	1004	210 (20.9)	<0.001	48 (4.8)	0.025
2013	1038	162 (15.6)		50 (4.8)	
2014	1608	209 (13.0)		66 (4.1)	
2015	1186	124 (10.5)		76 (6.4)	
2016	1642	217 (13.2)		97 (5.9)	
2017	1444	207 (14.3)		68 (4.7)	
2018	721	100 (13.9)		49 (6.8)	
2019	660	75 (11.4)		45 (6.8)	
Season					
Summer	1059	6 (0.6)	<0.001	114 (10.8)	<0.001
Autumn	2177	180 (8.3)		238 (10.9)	
Winter	3871	841 (21.7)		76 (2.0)	
Spring	2196	277 (12.6)		71 (14.2)	
Health Facility					
Jouberton Clinic	3192	330 (10.3)	<0.001	195 (6.0)	0.024
Edendale Gateway	6111	974 (15.9)		304 (5.0)	
Clinical					
Underlying medical conditions present*					
Yes	870	103 (11.8)	0.137	62 (7.1)	0.036
No	8380	1190 (14.2)		432 (5.2)	
Missing	67	11 (16.4)		5 (7.5)	
Symptom duration, ≤ 3 days†					
≤ 3 days	6028	973 (16.1)	<0.001	342 (5.7)	0.011
> 3 days	3189	324 (10.2)		147 (4.6)	

Missing	100	7 (7.0)		10 (10.0)	
HIV					
Positive	6717	271 (13.0)	0.144	59 (2.8)	<0.001
Negative	2082	949 (14.1)		412 (6.1)	
Missing	518	84 (16.2)		28 (5.4)	
Viral respiratory pathogens‡					
Adenovirus					
Positive	409	55 (13.5)	0.008	23 (5.6)	0.456
Negative	5570	830 (14.9)		285 (5.1)	
Missing	3338	419 (12.6)		191 (5.7)	
Enterovirus					
Positive	152	13 (8.6)	<0.001	13 (8.6)	0.085
Negative	5827	872 (15.0)		295 (5.1)	
Missing	3338	419 (12.6)		191 (5.7)	
Rhinovirus					
Positive	1243	46 (3.7)	<0.001	53 (4.3)	0.145
Negative	4742	839 (17.7)		255 (5.4)	
Missing	3332	419 (12.6)		191 (5.7)	
Human metapneumovirus					
Positive	163	11 (6.8)	<0.001	3 (1.8)	0.082
Negative	5816	874 (15.0)		305 (5.2)	
Missing	3338	419 (12.6)		191 (5.7)	
Parainfluenza virus 1					
Positive	74	5 (6.8)	0.002	2 (2.7)	0.313
Negative	5910	880 (14.9)		306 (5.2)	
Missing	3333	419 (12.6)		191 (5.7)	
Parainfluenza virus 2					
Positive	25	1 (4.0)	0.004	1 (4.0)	0.472
Negative	5959	884 (14.8)		307 (5.2)	
Missing	3333	419 (12.6)		191 (5.7)	
Parainfluenza virus 3					
Positive	108	4 (3.7)	<0.001	3 (2.8)	0.265
Negative	5876	881 (15.0)		305 (5.2)	
Missing	3333	419 (12.6)		191 (5.7)	

‡Data available up to 2016, missing includes results "not done" as well as missing results †time to symptom presentation at the facility

* Underlying conditions included any of the following: Asthma, other chronic lung diseases, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), seizures, liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions) or pregnancy

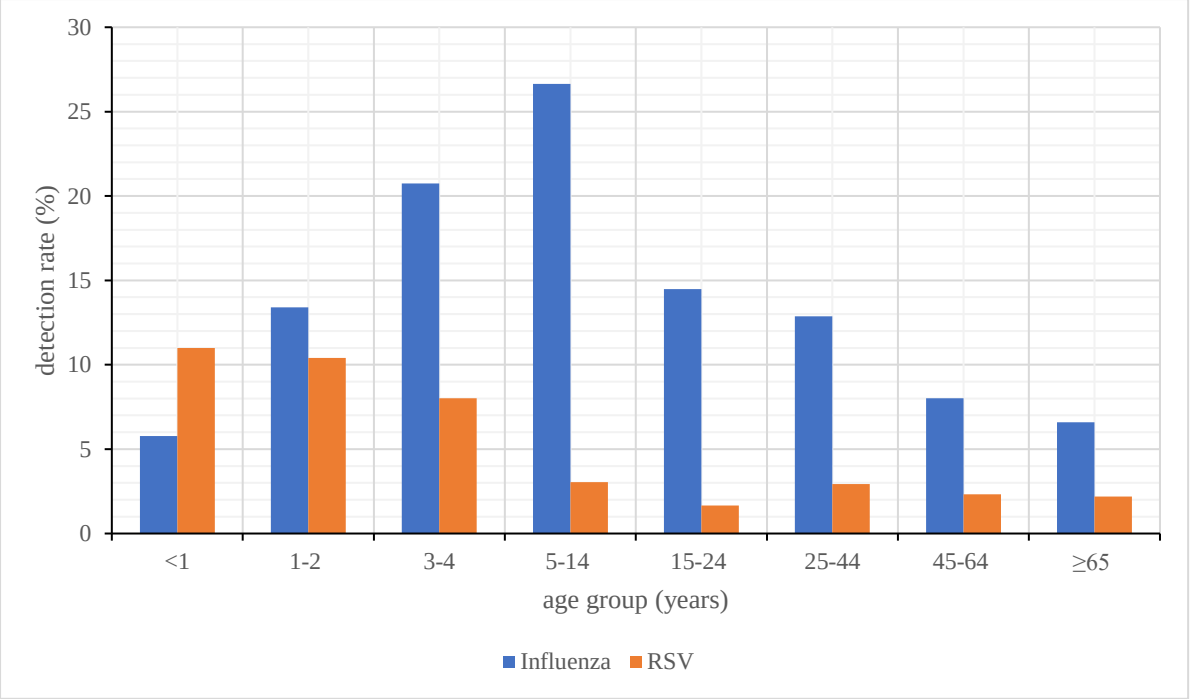

Figure 3.2 Detection rate of influenza and RSV by age group among all enrolled individuals with ILI at two public health clinics in South Africa, 2012 to 2019

3.3.2. Influenza and RSV detection rates among children <5 years

Table 3.3 shows the detection rates of RSV and influenza by demographic and clinical characteristics among individuals aged <5 years enrolled with ILI at two public health clinics in South Africa, 2012 to 2019. Influenza detection increased with age among children <5 years (<1 year: 5.8%, 80/1384; 1-2 years: 13.4%, 169/1260; 3-4 years: 8.0%, 63/786), whereas RSV was more commonly detected among children aged <2 years (<1 year: 11.0%, 152/1384; 1-2 years: 10.4%, 131/1260; 3-4 years: 8.0%, 63/786, p<0.001). Differences in influenza detection rates by race and sex were significant, with non-blacks (37.5%, p=0.027) and males (13.3%, p=0.024) reporting the influenza highest detection rates. Regarding HIV infection status, the highest influenza detection rates were reported among HIV infected children (26.3%), followed by HIV exposed uninfected children (12.6%) (p=0.012). The influenza detection rate was significantly lower among adenovirus (11.7%), enterovirus (10.3%), rhinovirus (4.3%), human metapneumovirus (9.1%), and parainfluenza 1 (2.2%) codetections. RSV detection rate was significantly lower among parainfluenza 1 (2.2%) and parainfluenza 3 (1.7%) codetections. RSV (11% vs 8%, p=0.005) and influenza (13.5% vs 9.3%, p<0.001) were more commonly detected among ILI cases with symptom duration ≤3

days before visiting the public health clinic than in ILI cases with symptom duration >3 days before visiting the public health clinic.

Table 3. 3 Detection rates of RSV and influenza by demographic and clinical characteristics of all enrolled individuals aged <5 years with ILI and individuals testing RSV and influenza-positive at two public health clinics in South Africa, 2012 to 2019

Characteristics	N (3430)	Influenza detection rate		RSV detection rate	
		N=412 (%)	*p*-value	N=346 (%)	*p*-value
Demographic characteristics					
Age group, years					
<1	1384	80 (5.8)		152 (11.0)	
1-2	1260	169 (13.4)	<0.001	131 (10.4)	0.079
3-4	786	163 (20.7)		63 (8.0)	
Race					
Black	3404	407 (12.0)	0.027	344 (10.1)	0.343
Non-black	8	3 (37.5)		0 (0.0)	
Missing	19	2 (6.3)		2 (6.3)	
Sex					
Female	1719	185 (10.8)	0.024	171 (9.9)	0.820
Male	1695	225 (13.3)		173 (10.2)	
Missing	16	2 (6.9)		2 (6.9)	
Clinical					
Underlying medical conditions present*					
Yes	489	52 (10.6)	0.336	55 (11.3)	0.346
No	2920	355 (12.2)		288 (9.9)	
Missing	21	5 (14.7)		3 (8.8)	
Malnutrition					
Yes	279	34 (12.2)	0.848	27 (9.7)	0.861
No	3068	362 (11.8)		307 (10.1)	
Missing	83	16 (19.3)		12 (14.5)	
Symptom duration, ≤ 3 days†					
≤ 3 days	2223	300 (13.5)	<0.001	246 (11.1)	0.005
> 3 days	1182	110 (9.3)		95 (8.0)	
Missing	25	2 (5.3)		5 (13.2)	
HIV					
HIV unexposed uninfected	2080	235 (11.3)		202 (9.7)	
HIV exposed uninfected	1092	138 (12.6)	0.012	117 (10.7)	0.211
HIV infected	38	10 (26.3)		1 (2.6)	
Missing	220	29 (13.2)		26 (11.8)	
Viral respiratory pathogens‡					
Adenovirus					
Positive	240	28 (11.7)	0.411	20 (8.3)	0.228
Negative	1662	226 (13.6)		181 (10.9)	
Missing	1528	158 (10.3)		145 (9.4)	
Enterovirus					
Positive	107	11 (10.3)	0.336	10 (9.4)	0.672
Negative	1795	243 (13.5)		191 (10.6)	
Missing	1528	158 (10.3)		145 (9.4)	
Rhinovirus					

Positive	529	23 (4.3)	<0.001	45 (8.5)	0.07
Negative	1374	231 (16.8)		156 (11.3)	
Missing	1527	158 (10.3)		145 (9.4)	
Human metapneumovirus					
Positive	66	6 (9.1)	0.300	3 (4.6)	0.105
Negative	1839	248 (13.5)		198 (10.8)	
Missing	1528	158 (10.3)		145 (9.5)	
Parainfluenza virus 1					
Positive	45	2 (2.2)	0.065	1 (2.2)	0.026
Negative	1858	253 (13.6)		200 (10.8)	
Missing	1527	158 (10.4)		145 (9.5)	
Parainfluenza virus 2					
Positive	13	0 (0.0)	0.214	0 (0.0)	0.156
Negative	1890	254 (13.4)		201 (10.6)	
Missing	1527	158 (10.4)		145 (9.5)	
Parainfluenza virus 3					
Positive	59	1 (1.7)	0.008	1 (1.7)	0.024
Negative	1844	253 (13.7)		200 (10.8)	
Missing	1527	158 (10.4)		145 (9.5)	

‡Data available up to 2016, missing includes results "not done" as well as missing results †time to symptom presentation at the facility

* Underlying conditions included any of the following: "Asthma, other chronic lung diseases, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), seizures, liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions)"

3.3.3. Influenza and RSV detection rates among participants ≥5 years

Table 3.4 presents the detection rates of RSV and influenza by demographic and clinical characteristics among outpatients ≥5 years with ILI in South Africa, 2012 to 2019. The influenza detection rates significantly varied by age group, symptom duration, HIV infection, rhinovirus, and human metapneumovirus codetections. For example, influenza was more commonly detected among HIV uninfected than HIV infected ILI cases (16.3% vs 12.3%, $p<0.001$). Influenza was more commonly detected among individuals with ILI aged 5-24 years (26.6%, $p<0.001$). Pregnancy and rhinovirus codetection varied significantly by RSV detection. Lower detection rates of both influenza and RSV were observed with rhinovirus and enterovirus codetection.

Table 3. 4 Detection rates of RSV and influenza by demographic and clinical characteristics of all enrolled individuals aged ≥5 years with ILI and individuals testing RSV and influenza-positive at two public health clinics in South Africa, 2012 to 2019

Characteristics	N (5873)	Influenza detection rate		RSV detection rate	
		N=892 (%)	*p*-value	N=153 (%)	*p*-value
Demographic characteristics					
Age group, years					
5-14	1280	341 (26.6)		39 (3.1)	
15-24	1084	157 (14.5)		18 (1.7)	
25-44	2378	306 (12.9)	<0.001	70 (2.9)	0.178
45-64	949	76 (8.0)		22 (2.3)	
≥65	182	12 (6.6)		4 (2.2)	
Race					
Black	5832	887 (15.2)	0.231	151 (2.6)	0.645
Non-black	8	0 (0.0)		0 (0.0)	
Missing	33	5 (15.2)		2 (6.1)	
Sex					
Female	3841	563 (14.7)	0.111	100 (2.6)	0.898
Male	2002	325 (16.2)		51 (2.6)	
Missing	30	4 (13.3)		2 (6.7)	
Clinical					
Underlying medical conditions present*					
Yes	381	51 (13.4)	0.558	7 (1.8)	0.482
No	5459	835 (15.3)		144 (2.6)	
Missing	33	6 (18.2)		2 (6.1)	
Pregnancy					
Yes	28	4 (14.3)	0.857	1 (3.8)	0.749
No	2537	333 (13.1)		66 (2.6)	
Missing	1276	226 (17.7)		33 (2.6)	
Symptom duration, ≤ 3 days†					
≤ 3 days	3805	673 (17.7)	<0.001	96 (2.5)	0.083
> 3 days	2006	214 (10.7)		52 (2.6)	
Missing	62	5 (8.1)		5 (8.1)	
HIV					
Positive	2045	261 (12.8)	<0.001	58 (2.8)	0.356
Negative	3460	563 (16.3)		84 (2.4)	
Missing	368	68 (18.5)		11 (3.0)	
Viral respiratory pathogens‡					
Adenovirus					
Positive	169	27 (16.0)	0.858	3 (1.8)	0.48
Negative	3905	604 (15.5)		104 (2.7)	
Missing	1799	261 (14.5)		46 (2.5)	
Enterovirus					
Positive	45	2 (4.4)	0.039	3 (6.7)	0.088
Negative	4029	629 (15.6)		104 (2.6)	
Missing	1799	261 (14.5)		46 (2.6)	
Rhinovirus					
Positive	713	23 (3.2)	<0.001	8 (1.1)	0.006
Negative	3366	608 (18.1)		99 (2.9)	
Missing	1794	261 (14.6)		46 (2.6)	

Human metapneumovirus					
Positive	97	5 (5.2)		0 (0.0)	0.102
Negative	3977	626 (15.7)	0.004	107 (2.7)	
Missing	1799	261 (14.5)		46 (2.6)	
Parainfluenza virus 1					
Positive	29	4 (13.8)		1 (3.5)	0.780
Negative	4049	627 (15.5)	0.802	106 (2.6)	
Missing	1795	261 (14.5)		46 (2.6)	
Parainfluenza virus 2					
Positive	12	1 (8.3)		1 (8.3)	0.215
Negative	4066	630 (15.5)	0.493	106 (2.6)	
Missing	1795	261 (14.5)		46 (2.6)	
Parainfluenza virus 3					
Positive	49	3 (6.1)	0.069	2 (4.1)	0.521
Negative	4029	628 (15.6)		105 (2.6)	
Missing	1795	261 (14.5)		46 (2.6)	

‡Data available up to 2016, missing includes results "not done" as well as missing results †time to symptom presentation at the facility

* Underlying conditions included any of the following: "Asthma, other chronic lung diseases, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), seizures, liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions)"

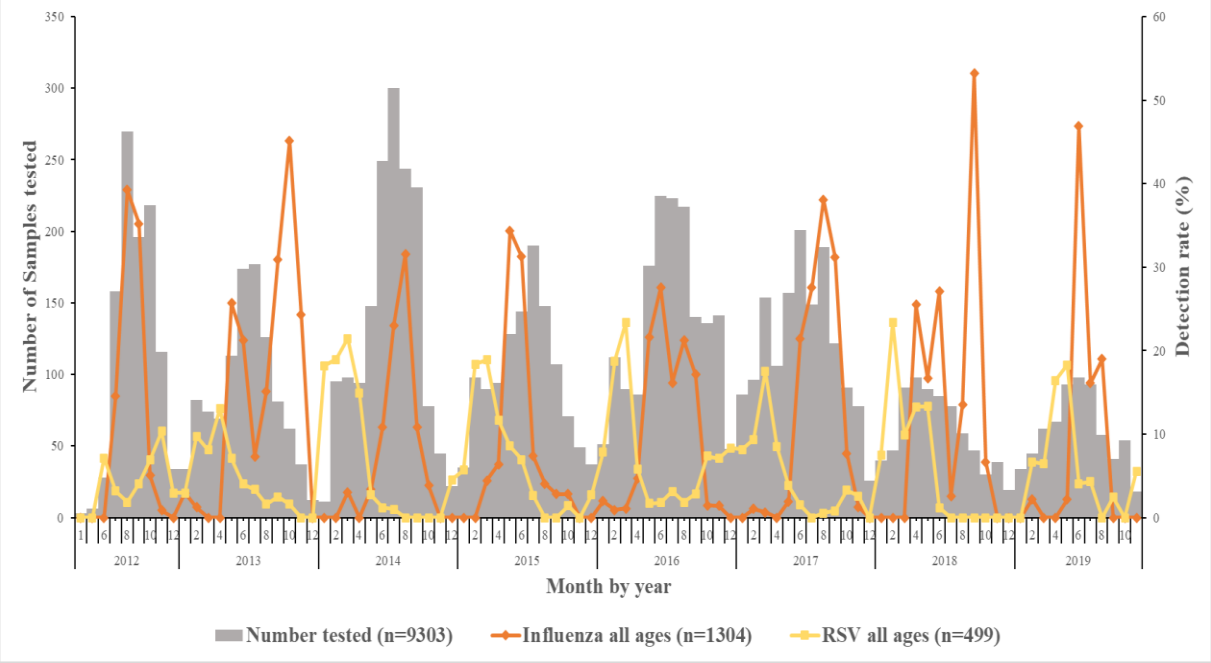

Figure 3.3 Number of samples tested for influenza and RSV and detection rate by month and year, all ages, ILI surveillance at two public health clinics in South Africa, 2012 to 2019

3.4. Seasonality of influenza and RSV by age groups

A seasonal pattern was observed in the occurrence of influenza and RSV from 2012 to 2019 among enrolled individuals with ILI at two public health clinics in South Africa (Figures 3.3). RSV detection was highest in March 2016 (23% out of 90 ILI cases tested) and February 2018 (23% out of 47 ILI cases tested). Influenza detection was highest in September 2018 (53% out of 47 ILI cases tested) (Figure 3.3).

The timing and seasonality were estimated using the moving epidemic method (MEM) using data from 2013 to 2018. The average onset of the influenza epidemic season lies on week 25 (95% CI: 18, 37) towards the end of June among individuals ≥5 years (Figure 3.6) and of all ages (Figure 3.4). This was different for individuals aged <5 years which lied on week 18 (95% CI: 15, 31), early May (Figure 3.5). The average epidemic season for influenza lasted 11 weeks (95% CI: 7.1, 17.6) among individuals of all ages (Figure 3.4). This was higher for individuals aged <5 years which lasted 21 weeks (95% CI: 7.7, 28.9) (Figure 3.5). Among individuals aged ≥5 years, the epidemic lasted an average of 10.5 weeks (95% CI: 7.07, 14.6) (Figure 3.6).

The average onset of the epidemic season for RSV lies on week 2 (95% CI: 1, 4) mid-January for RSV among individuals aged <5 years (Figure 3.5) and of all ages (Figure 3.4). This was different for individuals aged ≥5 years which lied on week 4 (95% CI: 3, 9), end of January (Figure 3.6). The average epidemic season for RSV lasted 19.5 weeks (95% CI: 14.7, 21.6) among individuals of all ages. This was similar among individuals aged <5 years which lasted 20.5 weeks (95% CI: 15.4, 22)

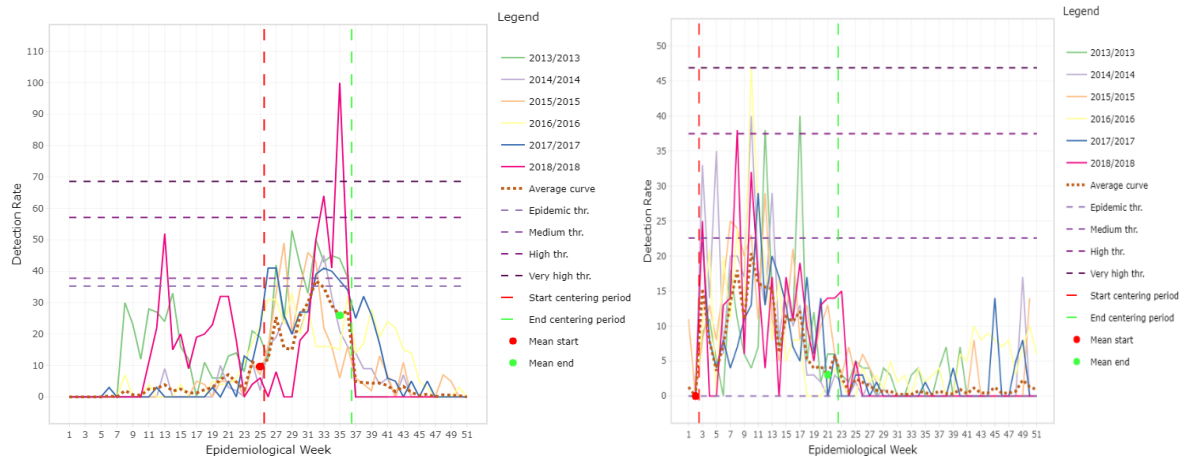

Figure 3.4 Influenza (on the left) and RSV (on the right) detection rates (percentage positive) among individuals of all ages by epidemiological week, ILI surveillance at two public health clinics in South Africa, 2013 to 2018

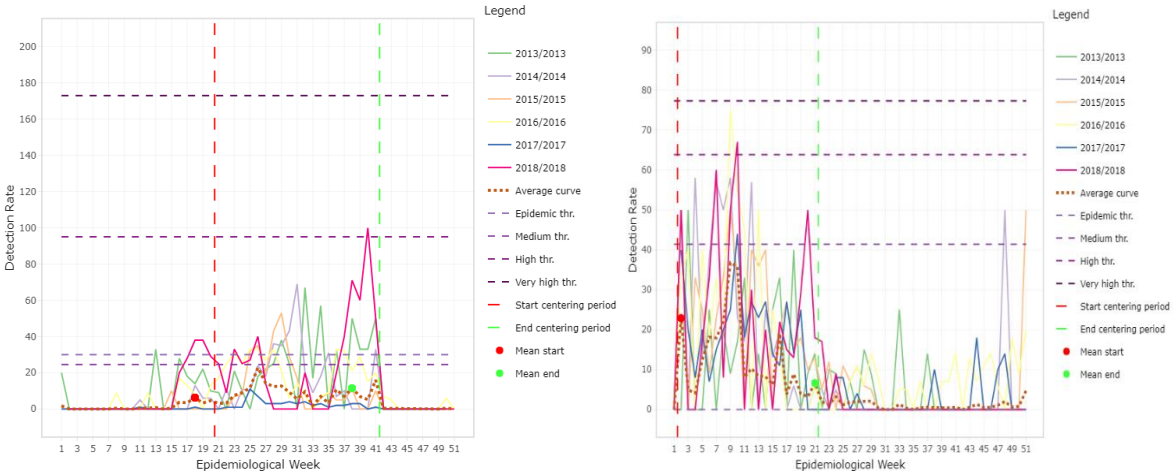

Figure 3.5 Influenza (on the left) and RSV (on the right) detections (percentage positive) among patients aged <5 years by epidemiological week, ILI surveillance at two public health clinics in South Africa, 2013 to 2018

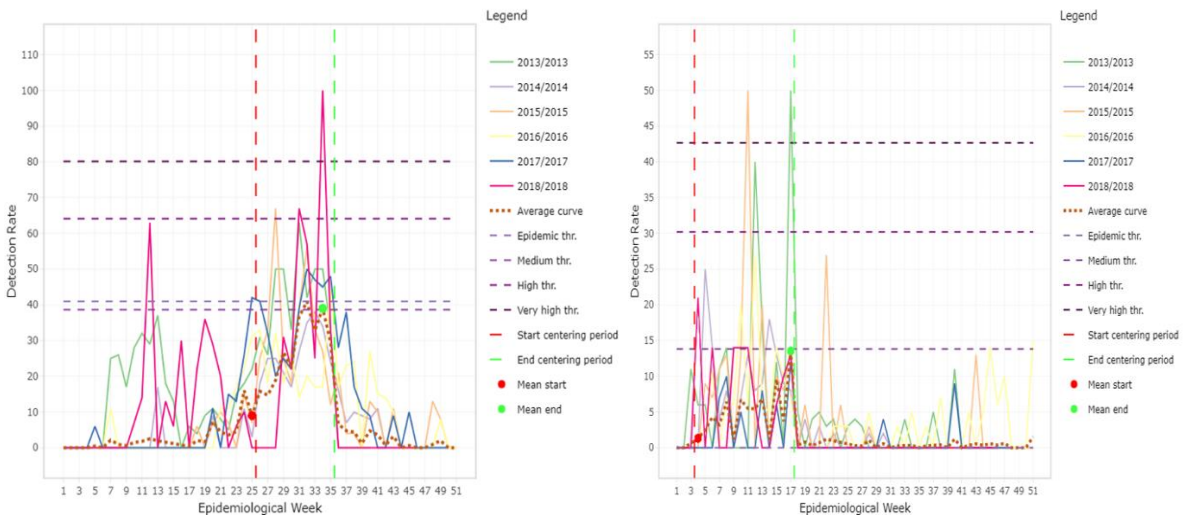

Figure 3.6 Influenza (on the left) and RSV (on the right) detections (percentage positive) among among patients aged ≥5 years by epidemiological week, ILI surveillance at two public health clinics in South Africa, 2013 to 2018

3.5 Factors associated with influenza-associated ILI as compared to RSV-associated ILI

This section presents the final logistic regression model for the factors associated with influenza-associated ILI as compared to RSV-associated ILI. It presents the final models in subsections according to age stratifications.

3.5.1 Factors associated with influenza-associated ILI as compared to RSV-associated ILI among participants of all ages

In the univariate analysis, individuals aged ≥5 years old (OR 4.89, 95% CI 3.91–6.12), enrolled in the year 2012 vs 2016 (OR 1.96, 95% CI 1.32-2.90) and HIV infected (OR 2.02, 95% CI 1.48–2.74) were associated with influenza-associated ILI (Table 3.5). Individuals enrolled at Jourbeton Clinic (OR 0.53, 95% CI 0.42-0.66), with symptom duration of >3 days (OR 1.29, 95% CI 1.02-1.63), with any underlying medical conditions present (OR 0.60, 95% CI 0.43-0.84), summer vs winter (OR 0.005, 95% CI 0.002-0.01), autumn vs winter (OR 0.07, 95% CI 0.05-0.09), and spring vs winter (OR 0.35, 95% CI 0.25-0.5) were associated with RSV-associated ILI.

In the multivariable analysis, age group, season, public health clinic, HIV, symptom duration of >3 days, any underlying medical conditions present and year were kept in the final model for all ages. ILI individuals with laboratory confirmed influenza were 2.72 times more likely

to be aged ≥5 years compared to ILI individuals with laboratory confirmed RSV (aOR 3.72, 95% CI 3.14–5.66). ILI individuals with laboratory confirmed influenza were less likely to be HIV positive (aOR 0.40, 95% CI 0.27-0.51) compared to those with laboratory confirmed RSV. ILI individuals with laboratory confirmed influenza were less likely to be HIV positive (aOR 0.6, 95% CI 0.39-0.93) compared to those with laboratory confirmed RSV (Table 3.5).

Table 3. 5 Factors associated with influenza- as compared to RSV-infected individuals of all ages enrolled with ILI at two clinics in South Africa

Characteristics	All ILI patients positive for influenza or RSV N (%)	Influenza N (%)	RSV N (%)	Unadjusted OR (95%CI)	*p*-value	adjusted OR (95% CI)	*p*-value
Demographics							
Age group, years							
<5	758/1803 (42)	412/1304 (31.6)	346/499 (69.3)	Ref	<0.001	Ref	<0.001
≥5	1304/1803 (58)	892/1304 (68.4)	153/499 (30.7)	4.89 (3.91-6.12)		3.72 (2.66-5.19)	
Sex, % male†	774/1793 (43.2)	550/1298 (42.4)	224/495 (45.25)	0.89 (0.72-1.1)	0.271		
PHC, Jourbeton Clinic	525/1803 (29.1)	330/1304 (25.3)	195/499 (39.1)	0.53 (0.42-0.66)	<0.001	0.40 (0.27-0.51)	<0.001
Season							
Winter	917/1803 (50.9)	841/1304 (64.49)	76/499 (15.2)	Ref	<0.001	Ref	<0.001
Summer	120/1803 (6.7)	6/1304 (0.5)	114/499 (22.9)	0.005 (0.002-0.01)		0.003 (0.001-0.01)	
Autumn	418/1803 (23.2)	180/1304 (13.8)	238/499 (47.7)	0.07 (0.05-0.09)		0.05 (0.04-0.07)	
Spring	348/1803 (19.3)	277/1304 (21.2)	71/499 (14.2)	0.35 (0.25-0.5)		0.40 (0.27-0.61)	
Year							
2012	258/1803 (14.3)	210/1304 (16.1)	48/499 (9.6)	1.96 (1.32-2.90)	<0.001	0.43 (0.25-0.70)	<0.001
2013	212/1803 (11.8)	162/1304 (12.4)	50/499 (10.0)	1.45 (0.97-2.15)		1.36 (0.79-2.40)	
2014	275/1803 (15.3)	209/1304 (16.0)	66/499 (13.2)	1.42 (0.98-2.04)		1.26 (0.73-2.17)	
2015	200/1803 (11.1)	124/1304 (9.5)	76/499 (15.2)	0.73 (0.50-1.06)		1.54 (0.91-2.62)	
2016	314/1803 (17.4)	217/1304 (16.6)	97/499 (19.4)	Ref		Ref	
2017	275/1803 (15.3)	207/1304 (15.9)	68/499 (13.6)	1.36 (0.95-1.96)		1.28 (0.76-2.18)	
2018	149/1803 (8.3)	100/1304 (7.7)	49/499 (9.8)	0.91 (0.60-1.38)		2.79 (1.57-4.92)	
2019	120/1803 (6.7)	75/1304 (62.5)	45/499 (9.0)	0.70 (0.48-1.16)		0.75 (0.39-1.45)	
Clinical							
HIV, positive	330/1702 (19.4)	271/1224 (22.1)	59/478 (12.3)	2.02 (1.48-2.74)	<0.001	0.6 (0.39-0.93)	0.021
Any underlying medical conditions present*	165/1787 (9.2)	103/1293 (8.0)	62/494 (12.6)	0.60 (0.43-0.84)	0.003	0.89 (0.55-1.42)	0.618

Symptom duration, >3 days	471/1786 (26.4)	324/1297 (25.0)	147/489 (30.1)	0.77 (0.62-0.98)	0.030	0.8 (0.57-1.13)	0.211

*Underlying conditions included any of the following: "Asthma, other chronic lung diseases, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), seizures, liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), immunocompromising conditions excluding (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions)"

†not included in the multivariate model because univariate *p*-value≥0.15

3.5.2 Factors associated with influenza-associated ILI as compared to RSV-associated ILI among participants <5 years

In the univariate analysis, children aged <1-year-old vs 1-2 years (OR 0.41, 95% CI 0.27-0.58), enrolled in Jourbeton Clinic (OR 0.73, 95% CI 0.54-0.98), summer vs winter (OR 0.006, 95% CI 0.002-0.02), autumn vs winter (OR 0.09, 95% CI 0.06-0.13) and spring vs winter (OR 0.3, 95% CI 0.21-0.55) were associated with RSV-associated ILI, whiles HIV infection vs HIV unexposed uninfected (OR 8.6, 95% CI 1.09-67.73) and children aged 3-4 years vs 1-2 years (OR 2.01, 95% CI 1.39-2.9) were associated with influenza-associated ILI (Table 3.6).

In the multivariable analysis, age group, public health clinic, season, and HIV were kept in the final model. Among ILI cases, individuals with influenza were less likely to be <1-year-old (aOR 0.39, 95% CI 0.25-0.63) compared to RSV. Among ILI cases, individuals infected with influenza were less likely to occur in summer (aOR 0.003, 95% CI 0.001-0.01), autumn (aOR 0.07, 95% CI 0.04-0.12) or spring (aOR 0.25, 95% CI 0.15-0.44) compared to individuals infected with RSV. Among individuals enrolled with ILI, individuals infected with influenza were more likely to be aged 1-2 years old compared to individuals infected with RSV (aOR 2.37, 95% CI 1.44-3.89) (Table 3.6).

Table 3. 6 Factors associated with influenza-associated ILI as compared to RSV-associated ILI among children <5 years enrolled with ILI at two clinics in South Africa

Characteristics	All ILI patients positive for influenza or RSV N (%)	Influenza-infected N (%)	RSV-infected N (%)	Unadjusted OR (95%CI)	*P*-Value	Adjusted OR (95% CI)	*P*-Value
Demographic characteristics							
Age group, years							
<1	232/758 (30.6)	80/412 (19.4)	152/346 (43.9)	0.41 (0.27-0.58)		0.39 (0.25-0.63)	
1-2	300/758 (39.6)	169/412 (41.0)	131/346 (43.7)	Ref	<0.001	Ref	<0.001
3-4	226/758 (29.8)	163/412 (39.6)	63/346 (18.2)	2.01 (1.39-2.9)		2.37 (1.44-3.89)	
Sex, male[†]	398/754 (52.79)	225/410 (54.88)	173/344 (50.25)	1.2 (0.9-1.6)	0.209		
PHC, Jourbeton Clinic	283/758 (37.3)	140/412 (34.0)	143/346 (41.3)	0.73 (0.54-0.98)	0.037	0.44 (0.29-0.67)	<0.001
Seasons							
Winter	274/758 (36.2)	232/412 (56.3)	42/346 (12.1)	Ref		Ref	
Summer	90/758 (11.9)	3/412 (0.73)	87/346 (25.1)	0.006 (0.002-0.02)		0.003 (0.001-0.01)	<0.001
Autumn	246/758 (32.5)	80/412 (19.4)	166/346 (48.0)	0.09 (0.06-0.13)	<0.001	0.07 (0.04-0.12)	
Spring	148/758 (19.5)	97/412 (23.5)	51/346 (14.7)	0.3 (0.21-0.55)		0.25 (0.15-0.44)	
Year[†]							
2012	75/758 (9.9)	42/412 (10.2)	33/346 (9.5)	1.06 (0.6-1.86)			
2013	70/758 (9.2)	45/412 (10.9)	25/346 (7.2)	1.5 (0.83-2.7)			
2014	108/758 (14.2)	63/412 (15.3)	45/346 (13.0)	1.16 (0.7-1.93)			
2015	105/758 (13.9)	52/412 (12.6)	53/346 (15.3)	0.82 (0.49-1.35)	0.347		
2016	141/758 (18.6)	77/412 (18.7)	64/346 (18.5)	Ref			
2017	118/758 (15.6)	60/412 (14.6)	58/346 (16.8)	0.86 (0.53-1.4)			
2018	84/758 (11.1)	48/412 (11.6)	36/346 (10.4)	1.11 (0.64-1.91)			
2019	57/758 (7.5)	25/412 (6.1)	32/346 (9.3)	0.65 (0.35-1.21)			
Clinical							

HIV, positive							
HIV unexposed uninfected	437/703 (62.2)	235/383 (61.4)	202/320 (63.1)	Ref		Ref	
HIV exposed uninfected	255/703 (36.3)	138/383 (36.0)	117/320 (36.6)	1.01 (0.74-1.38)	0.124	1.13 (0.75-1.72)	0.245
HIV infected	11/703 (1.6)	10/383 (2.6)	1/320 (0.3)	8.6 (1.09-67.73)		11.95 (0.58-247.8)	
Symptom duration, > 3 days†	205/751 (27.3)	110/410 (26.8)	95/341 (27.9)	0.95 (0.69-1.31)	0.752		
Underlying medical conditions, present*†	107/750 (14.3)	52/407 (12.8)	55/343 (16.0)	0.77 (0.51-1.16)	0.205		

*Underlying conditions included any of the following: "Asthma, other chronic lung diseases, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), seizures, liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), immunocompromising conditions excluding (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions)"

†not included in the multivariate model because univariate *p*-value ≥0.15

3.5.3 Factors associated with influenza-associated ILI as compared to RSV-associated ILI among participants ≥5 years

In the univariate analysis, age group (15-24 vs 5-14 years, 25-44 vs 5-14 years, 45-64 vs 5-14 years), season (summer vs winter, autumn vs winter, spring vs winter), public health clinic (Jourbeton Clinic vs Edendale Gateway Clinic), HIV, and symptom duration of >3 days were associated with RSV-associated ILI whilst year (2012 vs 2016, 2017 vs 2016) was associated with influenza-associated ILI (Table 3.7).

In the multivariable analysis, age group, public health clinic, season, year, HIV, and self reported symptom duration >3 days before enrolment with ILI were kept in the final model. Among individuals enrolled with ILI, individuals infected with influenza were less likely to be 25-44 years old (aOR 0.35, 95% CI 0.18-0.65) and 45-64 years old (aOR=0.28, 95% CI: 0.12-0.64) than individuals infected with RSV. Among ILI cases, individuals infected with influenza were less likely to occur in summer (aOR 0.003, 95% CI 0.001-0.01), autumn (aOR 0.04, 95% CI 0.04-0.07) or spring (aOR 0.41, 95% CI 0.21-0.82) compared to individuals infected with RSV. Among ILI cases, individuals infected with influenza were more likely to occur in 2017 (aOR 3.72, 95% CI 1.35-10.26) compared to individuals infected with RSV.

Table 3. 7 Factors associated with influenza-associated ILI as compared to RSV-associated ILI among individuals ≥5 years enrolled with ILI at two clinics in South Africa

Characteristics	All ILI patients positive for influenza or RSV N (%)	Influenza-infected N (%)	RSV-infected N (%)	Unadjusted OR (95%CI)	P-Value	Adjusted OR (95% CI)	P-Value
Demographic characteristics							
Age group, years							
5-14	380/1045 (36.4)	341/892 (38.2)	39/153 (25.5)	Ref		Ref	
15-24	175/1045 (16.8)	157/892 (17.6)	18/153 (11.8)	1.0 (0.55-1.8)		0.91 (0.43-1.92)	
25-44	376/1045 (36.0)	306/892 (34.3)	70/153 (45.8)	0.5 (0.33-0.76)	<0.001	0.35 (0.18-0.65)	0.003
45-64	98/1045 (9.4)	76/982 (8.5)	22/153 (14.4)	0.4 (0.22-0.7)		0.28 (0.12-0.64)	
≥65	16/1045 (1.5)	12/892 (1.4)	4/153 (2.6)	0.34 (0.11-1.12)		0.63 (0.08-5.1)	
Sex, male[†]	376/1039 (36.2)	563/888 (36.6)	100/151 (66.2)	0.88 (0.61-1.27)	0.505		
PHC, Jourbeton Clinic	242/1045 (23.2)	190/892 (21.3)	52/153 (34.0)	0.53 (0.36-0.76)	<0.001	0.29 (0.17-0.5)	<0.001
Seasons							
Winter	643/1045 (61.5)	3/892 (0.3)	27/153 (17.7)	Ref		Ref	
Summer	30/1045 (2.9)	100/892 (11.2)	72/153 (47.1)	0.006 (0.002-0.02)	<0.001	0.003 (0.001-0.01)	<0.001
Autumn	172/1045 (16.5)	609/892 (68.3)	34/153 (22.2)	0.08 (0.05-0.12)		0.04 (0.02-0.07)	
Spring	200/1045 (19.1)	180/892 (20.2)	20/153 (13.1)	0.5 (0.28-0.89)		0.41 (0.21-0.82)	
Year							
2012	183/1045 (17.5)	168/1304 (18.8)	15/153 (9.8)	2.6 (1.38-5.06)		0.75 (0.32-1.76)	
2013	142/1045 (13.6)	117/1304 (13.1)	25/153 (16.3)	1.1 (0.62-1.96)		1.66 (0.74-3.73)	
2014	167/1045 (16.0)	146/1304 (16.4)	21/153 (13.7)	1.64 (0.9-2.97)		1.28 (0.56-2.9)	
2015	95/1045 (9.1)	72/1304 (8.1)	23/153 (15.0)	0.74 (0.4-1.35)	<0.001	1.54 (0.68-3.47)	0.071
2016	173/1045 (16.6)	140/1304 (15.7)	33/153 (21.6)	Ref		Ref	
2017	157/1045 (15.0)	147/1304 (16.5)	10/153 (6.5)	3.47 (1.65-7.29)		3.72 (1.35-10.26)	
2018	65/1045 (6.2)	52/1304 (5.8)	13/153 (8.5)	0.94 (0.46-1.93)		1.93 (0.79-4.7)	
2019	63/1045 (6.0)	50/1304 (5.6)	13/153 (8.5)	0.91 (0.44-1.86)		0.76 (0.28-2.02)	

Clinical							
HIV, positive	319/966 (33.0)	261/824 (31.7)	58/142 (40.85)	0.67 (0.47-0.97)	0.033	0.75 (0.44-1.28)	0.293
Symptom duration, > 3 days	266/1035 (25.70)	214/887 (24.13)	52/148 (35.14)	0.59 (0.41-0.85)	0.005	0.65 (0.38-1.1)	0.111
Underlying medical conditions, present[*†]	58/1037 (5.59)	51/886 (5.76)	7/151 (4.64)	1.26 (0.56-2.82)	0.580		

*Underlying conditions included any of the following: "Asthma, other chronic lung diseases, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), seizures, liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), immunocompromising conditions excluding (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions)"

†not included in the multivariate model because univariate *p*-value≥0.15

4.0 DISCUSSION

This chapter discusses the findings from the results. The chapter discusses the detection rates of influenza and RSV-associated ILI, seasonality of influenza and RSV, and factors associated with influenza as compared to RSV-associated ILI. The chapter concludes with the strengths and limitations of the study.

4.1 Detection rates of influenza and RSV-associated ILI

The study found that the overall detection rate of influenza and RSV-associated ILI was 14% and 5%, respectively. These findings are similar to prior estimates from a South African study that reported influenza and RSV detection rates among individuals with ILI to be 15% and 5%, respectively (49). The ILI case definition may be less sensitive to detecting RSV-associated ILI cases because RSV cases often present without fever (78). In addition, RSV-associated respiratory disease is most common in infants and are presented to hospital for care while in older individuals, illness associated with RSV infection may be asymptomatic or so mild that they do not seek care (46). Overall, detection rates declined with age for RSV-associated ILI ranging from 10.9% in <1 year age group to 1.66% in the 15-24 years age group. Influenza-associated ILI increased from the youngest age group until it peaked in the 5–14 years age group and further declined as one ages. Although this study provides new data on influenza and RSV characteristics in an outpatient setting, the prevalence of viral infections in an outpatient setting is consistent with previous studies. The highest prevalence for influenza-associated ILI among persons aged 5-14 years is comparable to published estimates of 25% among Ghanaians (17) and 24% among French (45) persons within the same age group. Similar to our RSV-associated ILI prevalence of 10.9% among children <5 years, published estimates of RSV-associated ILI prevalence among children range from 8-18% (19,49,54). Although this study did not explore the transmission of influenza and RSV by age group in a community setting, other studies have suggested that children and young adults that intersect appear to drive the spread of influenza and RSV in community settings (79,80). These age groups are potential risk groups for future interventions that will help reduce the spread of influenza and RSV transmission.

Our study found that RSV was detected more in males than in females of all ages, and influenza detected in males than in females for children <5 years. Similar to our findings, a study conducted among children with ILI in 8 countries across Asia, South America and Australia detected RSV in more males (52%) than females (54).

In the unstratified and age-stratified analysis, influenza and RSV were commonly detected among individuals with ILI who reported symptom duration ≤3 days than those who reported symptom duration >3 days. This suggests samples taken at the early stages after symptoms onset are more likely to be detected by pathogens. In a Chinese study, the detection rate of influenza among ILI cases with symptom onset <3 days after samples were taken was 23% (81).

4.2 RSV and influenza seasonality by age groups

This study described the timing and seasonality of influenza and RSV by age groups in an outpatient setting using ILI surveillance data from two public health clinics in South Africa from 2013 to 2018. Intervention strategies for influenza and RSV may need to account for the seasonal nature of the two pathogens as immunity after infection for both pathogens is sustained for a short period (26). Knowledge of seasonal patterns of influenza and RSV will enable targeted interventions strategies for influenza and RSV. In the long run, this will save cost and ensure maximum societal benefit from influenza and RSV interventions.

Over the six-year period, a seasonal pattern was observed for both influenza and RSV. Overall, the RSV season preceded the influenza season, as in other temperate regions in the southern hemisphere (65). In addition, the RSV season has been shown to overlap with the influenza season (82). The circulation of the influenza virus occurred mainly in the winter months of June to August (47,65). In the six years, the mean start for the influenza season epidemic was as early as the last week of April and as late as the second week of September for individuals of all ages and ≥5 years. However, the mean start for the influenza season epidemic was as early as the third week of April and as late as the last week of July for individuals aged <5 years. The onset of the influenza epidemic for children <5 years was within range with previous years in which the season started as early as the third week of April and as late as the last week of July (47). Over the six-year period, the average duration of the influenza season was 10.5 and 11 weeks for individuals aged ≥5 years and of all ages, respectively. The average duration of the influenza season was 21 weeks for children <5 years.

Authors reported that activities of children under five years, such as touching their noses, eyes and mouth, putting things in their mouth, and touching each other during play, might contribute to the ease of influenza transmission (83). Likewise, in a household influenza transmission study, children aged <5 years were at increased risk of developing clinical influenza than adults after coming into contact with an index case (65). These findings may have contributed to the longer duration of the influenza season among children <5 years, as observed in this study.

The RSV season overlapped with the influenza season, occurring in autumn mainly from January to May. The average start of the RSV season over the six-year period was the second week of January for individuals aged <5 years and of all ages. This finding is similar to the start of the 2018 season from the South Africa ILI and pneumonia surveillance report, 2018 (67). However, the average start of the RSV season was delayed for individuals ≥5 years. The overall average start of the season was earlier compared to an Argentinian study in the southern hemisphere, in which the average start of the season was week 7 (65). The difference in timing of seasons between the current study and the Argentinian study may be attributed to different methods used in estimating seasonality and timing.

4.3 Factors associated with influenza compared to RSV-associated ILI

In the final logistic regression model, age was a significant risk factor for influenza and RSV among individuals enrolled with ILI, adjusting for other factors.

Using <5 years as a reference category, individuals infected with influenza were more likely to be aged ≥ 5 years than individuals with RSV for all ages after controlling for other factors. In the stratified model for <5 years, there was increased odds for influenza compared to RSV infections with increasing age using the 1-2 age group as a reference. Individuals with laboratory confirmed influenza were less likely to be aged <1 than individuals laboratory confirmed with RSV. This may be attributed to the high positivity rate for RSV compared to influenza among individuals within this age group. This is consistent with the findings of Hall et al. (30).

In the ≥ 5 years model, the odds for influenza compared to RSV infections reduced with increasing age (i.e for 25-44 and 45-64). Using the age group 5-14 years, individuals infected with influenza were less likely to be aged 25-64 years compared to the RSV infected individuals. This results may be attributed to the high influenza positivity rate among the

reference agegroup. Despite the difference in age categorisation and methods, this finding is consistent with the finding from Bruyndonckx et al., who reported higher odds of RSV than for influenza infection among the elderly aged ≥75 years (43).

In addition to age, season and site were found to be significant risk factors for influenza as compared to RSV infection among individuals with ILI in the multivariable model. In all the three models, individuals with laboratory-confirmed influenza were less likely to be enrolled at Jourbeton Clinic than individuals with laboratory-confirmed RSV. This finding may be associated with difference in relative humidity and temperature levels in the locations of the two PHC's. Humidity promotes aerosol transmission. Although both RSV and influenza are transmitted through aerosols, lower temperatures increase influenza virus survival (84). HIV was significant in the multivariable model for all ages. In the univariate model, individuals infected with influenza were more likely to have HIV than individuals infected with RSV. After controlling for other factors, individuals infected with influenza were less likely to have HIV than individuals with RSV. The reduced effect may have been as a results of other factors confounding the relationship between the outcome and HIV. The findings from the study is consistent with McMorrow et al. (55). Although McMorrow et al., study was conducted in a hospitalised setting. In the multivariate models for <5 years and ≥5 years, HIV was not significant.

4.4 Strengths and Limitations

A major strength of this study is its large sample size across the two sites, which allowed estimation of strict confidence intervals. The outcome, influenza and RSV detections were accurately verified using molecular techniques. The study also provides insight into the timing and seasonality of influenza and RSV among individuals with mild respiratory illnesses aged <5 years and ≥5 years. The study explored factors associated with influenza compared to RSV among outpatients with ILI, which will help develop intervention strategies for mild respiratory illness from progressing to severe acute respiratory illnesses.

Certain limitations of these analyses should be considered. Firstly, any underlying illness and symptom duration were self-reported from the primary study and may have been subjected to a recall bias. Another limitation of this study was missing or incomplete data for some variables of interest, for example, HIV status, which could not be clarified since the analyses of this study used secondary data.

Results from this study were based on an outpatient population from two public health clinics in South Africa, so the results may be biased towards individuals who have access to health care than the general population possibly limiting the generasibility of the findings.

Finally, the study could not estimate the annual rates of influenza and RSV among outpatients with ILI due to incomplete data.

5.0 CONCLUSION AND RECOMMENDATION

5.1 Conclusion

Influenza had a higher detection rate than RSV among individuals of all ages enrolled with ILI. Children <5 years reported the highest RSV detection rate, whiles individuals ≥5 years reported the highest influenza detection rate. Among children <5 years, the RSV detection rate was highest in infants <1-year-old enrolled with ILI. Among individuals ≥5 years, the influenza detection rate was highest in older children 5-14 years old enrolled with ILI. The RSV season was in autumn and the influenza season in winter. The duration for influenza season among children <5 years old with ILI was on average longer than that for individuals ≥ 5 years old. This was also the same for RSV season. Lastly, among all ages, being enrolled in 2018 or being ≥5 years was more common among individuals with laboratory confirmed influenza than RSV. Whilst being enrolled in either summer, autumn or spring, being enrolled in Jourberton Clinic or being infected with HIV was less common among individuals with laboratory confirmed influenza than RSV. In addition, among children <5 years, being 3-4 years old was more common among individuals with laboratory confirmed influenza than RSV. While being enrolled in either summer, autumn or spring, or in Jourberton Clinic was less common among individuals with laboratory confirmed influenza than RSV. Among individuals ≥5 years old, being 25-64 years old, enrolled in either summer, autumn or spring, Jourbeton Clinic, or in 2017 was less common among individuals with laboratory confirmed influenza than with RSV.

5.2 Recommendations

RSV and influenza seasons start as early as January and April in South Africa, respectively. It could be useful for policymakers to consider the seasonality of RSV and influenza when determining the timing of vaccination campaigns. It could also be useful for clinicians to know when the season begins to assist with diagnosis and clinical management in hospitalised patients.

Our study highlights children <5 years old to have a longer seasonal duration for influenza and RSV. It could be useful for health care systems to consider following up on their patients in this age category and creating awareness through community mobilisation and outreach programmes.

Further observational epidemiological research should be conducted on the seasonality of influenza types and subtypes, and RSV groups in an outpatient setting to determine the circulating strains in the season. This will guide inform vaccine selection for the subsequent influenza seasons. Further research should also be conducted to estimate influenza and RSV annual ILI rates needed to estimate influenza and RSV burden.

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7.0 APPENDICES

APPENDIX 1; Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Yaw Awuku-Larbi (Student number: 2244706) am a student registered for the degree of Master of Science in Epidemiology in the academic year 2019.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 29/04/2021

1

APPENDIX 2: Current study clearance certificate
Clearance certificate No: M1911159

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Mr Y Awuku-Larbi and Professor C Cohen

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M1911159

NAME: (Principal Investigator)	Mr Y Awuku-Larbi and Professor C Cohen
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	Epidemiology of influenza and respiratory synctial virus (RSV) among individuals presenting with influenza-like illness (ILI) at two outpatient health facilities in South Africa, 2012 to 2018
DATE CONSIDERED:	2019/11/29
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr S Walaza
APPROVED BY:	Dr N Naran, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/01/02

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore reports and re-certification will be due early in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

APPENDIX 3: Permission to use data for secondary analysis

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Centre for Respiratory Diseases and Meningitis
1 Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6450 Fax: +27 (0)11 882 0596
Reference:

06/11/2019
Yaw Awuku-Larbi
Student Number: 2244706

RE: Permission to use Data

STUDY TITLE: EPIDEMIOLOGY OF INFLUENZA AND RESPIRATORY SYNCYTIAL VIRUS AMONG INDIVIDUALS PRESENTING WITH INFLUENZA-LIKE ILLNESS AT TWO OUTPATIENT HEALTH FACILITIES IN SOUTH AFRICA, 2012 TO 2018

This is to confirm that permission to conduct the above mentioned retrospective study for your M.Sc (Epidemiology) research at the University of the Witwatersrand with existing data collected as part of Influenza-like illness (ILI) surveillance programme is hereby granted. The data should be used for the purposes of meeting requirements for your MSc and should not be shared with others unless cleared with your supervisor/s from National Institute for Communicable Diseases (NICD).

Regards

Dr Sibongile Walaza
Epidemiology Lead
Centre for Respiratory Diseases and Meningitis (CRDM)
National Institute for Communicable Diseases, a division of the National Health Laboratory Service
1 Modderfontein Rd Sandringham,
Johannesburg 2193
Telephone: +27 11 386 6410 Fax:+27 11 882 9979 Mobile: +27 836574741

APPENDIX 4: Ethics approval-Surveillance for Outpatient Influenza-like illness and Asymptomatic Respiratory Virus Colonization in South Africa
Clearance Certificate No: M120133

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Cheryl Cohen

CLEARANCE CERTIFICATE	**M120133**
PROJECT	Surveillance for Outpatient Influenza-like Illness and Asymptomatic Respiratory Virus Colonization in South Africa
INVESTIGATORS	Dr Cheryl Cohen.
DEPARTMENT	School of Public Health
DATE CONSIDERED	27/01/2012
DECISION OF THE COMMITTEE*	

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

DATE **CHAIRPERSON** .....
(Professor PE 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...

APPENDIX 5: ILI surveillance – Case investigation forms

NATIONAL HEALTH LABORATORY SERVICE
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Influenza-Like Illness (ILI) 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: ☐☐☐ ILI/Controls Study ID: ☐☐☐☐☐☐☐☐ completed: ☐☐/☐☐/☐☐☐☐ (DD/MM/YYYY)

Patient seen at: Jouberton Clinic ☐ Edendale Gateway Clinic ☐

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

ILI ☐ Control ☐

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. In home which of the following are used (mark all that apply)? Electric/gas stove ☐ Paraffin stove ☐ Open wood fire or coal fire ☐ Other ☐ Please specify _____ Unknown ☐
7. Does anyone in the home currently smoke? Yes ☐ No ☐
8. What is the interviewee's relationship to the participant? Self ☐ Parent/Caregiver ☐ Other ☐ (Specify) _____
9. Presenting complaint: (Tick all that apply) Sore throat ☐ Runny nose ☐ Headache ☐ Cough ☐ Fever ☐ Myalgia ☐ Other ☐ (Specify) _____
10. Date of onset of symptoms: ☐☐/☐☐/☐☐☐☐

Note: Complete the signs and symptoms at the time of the interview. Some of the signs or symptoms may have resolved by the time you interview the patient.

11. Maximum recorded temperature at time of interview ____.____C° (##.#C°) 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. Patient length (if not recorded, surveillance officer to measure): _____._____cm Percentile (if patient < 5 years) _____ Unk ☐

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

14.2 12.2 Mid upper arm circumference (MUAC) (for patients < 5 years of age only) _____ cm

15. Mental status of the patient (based on AVPU)
Alert ☐ Disorientated ☐ Stuporous ☐ Comatose ☐
Sedated ☐ Unknown ☐
(responds to verbal commands) (responds to painful stimuli)

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

Cough	Y	N	Sore throat	Y	N	Difficulty breathing	Y	N
Headache	Y	N	Rhinorrhoea	Y	N	Myalgia	Y	N
Diarrhoea (>3 loose stool per day)	Y	N	Symptoms presents for ≤3 days	Y	N	Symptoms present for 4-7 days	Y	N
Symptoms present for 7-10 days	Y	N	Wheezing	Y	N	Apnoea	Y	N
Cough >14 days	Y	N	Inspiratory whoop (high pitch gasp for air after bouts of cough)	Y	N	Paroxysmal cough (rapid and numerous bursts of cough)	Y	N
If paroxysmal cough, does patient resume a normal state when not coughing?	Y	N	If paroxysmal cough and child is< 1year,did child turn blue (lips/tongue) during or after bouts of cough	Y	N	Post- tussive vomiting (vomiting after bouts of cough)	Y	N
Gagging with cough	Y	N	Nocturnal cough	Y	N		Y	N

Complete the following questions for children <5 years, if ≥5 years, skip to Q19

17. Does the child attend a day-care center/crèche/school outside the home? Yes ☐ No ☐ Unknown ☐

18. What is the highest level of education that the primary caregiver (parent/person who looks after the child) obtained
No High school ☐ Some high school ☐ Completed matric / grade 12 ☐ completed matric equivalent at technical school ☐

Some college/tertiary education ☐ Tertiary qualification/ degree ☐ Post graduate/professional ☐
Unknown/refused to answer ☐ None of the above ☐

Note: Complete the following questions for patients ≥ 18 years, if patient < 18 years skip to Q 22.

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

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

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

21. Do you currently or have you ever worked in a mine before? Yes ☐ No ☐ Unk ☐
Note: If no or unknown, skip to Q22

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

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

Date Unknown ☐

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

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

22. Do you have any underlying illness or condition at the moment? Yes ☐ No ☐

Note: If no skip to Q 23

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 (verbal report)	Y	N	Obesity / BMI >=30	Y	N	COPD/Emphysema	Y	N
Malignancy/Cancer	Y	N	If yes, specify:			Congenital Heart Disease	Y	N
Currently pregnant	Y	N	N/A	If yes, date of last menstrual period ☐☐/☐☐/☐☐☐☐ Gestational age _____ weeks				
Other	Y	N	If yes, specify:					
Does the patient live in an institution/care facility	Y	N	If yes, name of institution:					

23. Was the patient pregnant within the past 3 months? Yes ☐ No ☐ Unk ☐ N/A ☐

23.1 If yes, date of delivery / pregnancy outcome ☐☐/☐☐/☐☐☐☐ Gestational age at outcome _____ ☐ weeks ☐ months

23.2 If yes outcome Term ☐ premature < 37 weeks ☐ still birth ☐ Spontaneous abortion/miscarriage/ Medical termination ☐

Note: Complete for patients < 5 years, if patient ≥ 5 years skip to Q 25.

24. HIV result during pregnancy (mother of patient): Yes ☐ No ☐ Unk ☐

Note: If no or unknown skip to Q 25

24.1 If yes, what was the result? Positive ☐ Negative ☐ if positive , was mom on ART during pregnancy Yes ☐ No ☐ Ukn ☐

24.2 If yes, date ART started ☐☐/☐☐/☐☐☐☐

24.3 Date of HIV test ☐☐/☐☐/☐☐☐☐

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

24.5 If HIV positive what was the CD4 count during pregnancy _____/mm^3 Date CD4 count taken ☐☐/ ☐☐/☐☐☐☐ Unk ☐

25. Has the patient been tested for HIV prior to this consultation? Yes ☐ No ☐ Unk ☐

Note: If no or unknown skip to Q 26

25.1 If yes, what was the result? Positive ☐ Negative ☐ Unk ☐ Date of test ☐☐/☐☐/☐☐ ☐☐ date Unk ☐

Note: If result unknown skip to Q 26

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

26. If positive, currently on ART? Yes ☐ No ☐ Unknown ☐ If yes, date of initiation of ART: ☐☐/☐☐/☐☐☐☐

Note: If negative skip to Q 27

26.1 Bactrim (contrimoxazole/trimethoprim) prophylaxis taken currently? Yes ☐ No ☐ Unk ☐
Note: If no or unknown skip to Q 27

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

27. Has the patient been tested for HIV during this consultation? Yes ☐ No ☐
Note: if no to Q 27 skip to Q 27.5
NB:ALL PATIENTS WHO DO NOT HAVE A CONFIRMED CURRENT HIV STATUS SHOULD BE OFFERED AN HIV TEST

27.1 If yes, who requested the test? Surveillance officer ☐ Clinic staff ☐

27.2 Which test was done? Rapid Test ☐ PCR ☐ Dry Blood Spot (DBS) ☐ ELISA ☐

27.3 What was the test result? Positive ☐ Negative ☐ Pending ☐ Unknown ☐

Note: Complete for patients < 5 years, if patient ≥ 5 years skip to Q 27.5.

27.4 Based on all the information available to you, what is the current HIV status of the patient Positive ☐ Negative ☐ Pending ☐ Unknown ☐
Note: If current HIV status is positive or pending skip to Q 28

27.5 If current HIV status is negative, what was the source of HIV status? RTHC ☐ Laboratory report ☐ Medical records ☐ Verbal ☐ Other ☐ Specify _____
Note: Please offer an HIV test to all patients >5yrs old with a negative result reported verbally or taken >6 weeks before this consultation.

27.6 If current HIV status unknown, why was the patient not tested at this visit? Refused consent ☐ Other ☐ specify_____

28. Have you ever taken TB prophylaxis? Yes ☐ No ☐ Unk ☐ If yes, date TB prophylaxis initiated: ☐☐/☐☐/☐☐☐☐
Note: If no or unknown skip to Q 29

28.1 Are you still taking TB prophylaxis? Yes ☐ No ☐ Unk ☐ If no, date TB prophylaxis stopped: ☐☐/☐☐/☐☐☐☐
Note: If yes skip to Q 29

29. TB treatment in the last 12 months? Yes ☐ No ☐ Unk ☐ If yes, date TB treatment initiated: ☐☐/☐☐/☐☐☐☐
Note: If no or unknown skip to Q 30

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

30. Has the patient been prescribed and taken antibiotics in the 24 hours before this interview? Yes ☐ No ☐ Unk ☐
Note: If no or unknown skip to Q 31

30.1 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 _____

31. Vaccination history. Complete for patients < 5 years, if patient ≥ 5 years skip to Q 32

31.1 Is the person being interviewed the primary caregiver of the child? Yes ☐ No ☐
Note: If no skip to Q 31.3

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

31.3 Was the Road to Health Card seen? Yes ☐ No ☐ 31.4 Was a copy of the Road to Health Card made? Yes ☐ No ☐

Note: If no skip to Q 33

31.5 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:

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

If pre-term, record gestational age: _____weeks

31.7 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 33

32. Did the patient receive pneumococcal polysaccharide vaccine?

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

33. 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** ☐

Outcome of the clinic visit: Discharged ☐ Referred to hospital ☐ Died ☐ Unknown ☐

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