An evaluation of the incidence and absenteeism rates of health care workers reporting flu-related illnesses at an academic hospital in the Western Cape: a retrospective cohort study

by

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Thesis presented in fulfilment of the requirements for the degree of Master of Medicine (Occupational Medicine) in the Faculty of Medicine and Health Sciences at Stellenbosch University

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December 2017

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ABSTRACT

Introduction

Seasonal Influenza -related illnesses impose a heavy burden on society. Vaccination programmes are the most effective strategy for preventing the illnesses and have been recommended for certain high- risk groups. Healthcare workers involved in the care of these vulnerable patients may be infected clinically or sub-clinically with Influenza. They are therefore urged to accept influenza vaccination as part of the broader control of Influenza policy. This study evaluates the willingness of uptake and the impact that influenza vaccination campaigns might have among healthcare workers in a tertiary health setting.

Objective

To determine the proportion of voluntary vaccine uptake among healthcare workers as well as describing any potential differences between this vaccinated population and their randomly selected unvaccinated controls.

Methods

A retrospective cohort study investigating the incidence of flu and its related illnesses, including its impact on absenteeism rates in the seasonal flu years of 2013 and 2014.

The study setting was Tygerberg Academic Hospital, Parow, Western Cape. All vaccinated employees during the study period were compared to matched unvaccinated controls in a 1:2 ratio.

Employees who got ill during the study period were sourced from the facility's Human Resource database. Illness incidence and absenteeism rates were extracted from this outcome database and analysed to determine trends between study arms as well as between occupational categories.

Results

A total of 4.6% and 2.8% of employees accepted vaccination for the seasonal flu years of the 2013 and 2014 respectively. The study population was 1020 with 340 healthcare workers in the exposed arm. Overall, there were more employees that fell ill compared to those that remained healthy during the study period (700 vs 320). For all instances of Influenza and related illnesses (clinically specified) illnesses, there was no statistically significant difference between the vaccinated and unvaccinated study groups [RR 1.06, 95% CI (0.87- 1.28), p=0.28]. The frequency of illness in the vaccinated was less than that observed in the controls (79 vs 164, z-score=2.04 p-value= 0.041). About 60% of all sick leaves had no clinically specified diagnosis while the incidence of clinically specified illnesses was 32.65% among the vaccinated and 30.88% in the control group. This therefore placed the true incidence rate of influenza-related illnesses between 32,647 to 69,706 /100,000 population per year in the vaccinated and 30,882 to 68,088 /100,000 population per year in the unvaccinated.

Conclusion

There was very low response to calls for influenza vaccination despite unexpected high reports of influenza-related illnesses in our study setting. Among healthcare workers, a higher proportion reported illness incidents and consequently had higher absenteeism rates compared to those that remained healthy during the study duration. These variables did not differ based on vaccination status perhaps due to the low acceptance rate. Healthcare workers are encouraged to partake in the seasonal flu vaccinations to minimise influenza transmission risks to vulnerable patients.

ACKNOWLEDGEMENTS

My appreciation goes to Dr Sydney Carstens for his supervisory role during the conduct of my study. I also acknowledge Dr WAJ Meintjes for his advice and support. I am equally grateful for the contributions of Sisters D Arendse and Y Olkers of the Occupational Health Clinic, Tygerberg Academic Hospital. Sincere appreciations also to Ms Christalien Hüsselmann for her invaluable editing and proofreading.

To God, ALL the glory!

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List of Abbreviations / Meaning of Technical Terms

HCW - Healthcare Worker

HIV - Human Immunodeficiency Virus

TB - Tuberculosis

DOH - Department of Health

OHS - Occupational Health and Safety Act

TIV - Trivalent Inactivated Influenza Vaccines

GP - General Practitioner

ILI - Influenza-like Illness

SARI - Severe Acute Respiratory Illness

Persal number - Personnel and Salary Administration System; it's an integrated public service Human Resources, Personnel and Salary System used at national and provincial levels of the South African government.

Clinicom - Patient Administration System used within selected hospitals in the Western Cape to harmonise clinical records of patients under care.

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

Introduction

Seasonal influenza viruses circulate and cause disease in humans every year. The viruses spread from person-to person through sneezing, coughing, or touching contaminated surfaces. They can cause mild to severe illness and even death, particularly in some high-risk individuals. In temperate climates, disease tends to occur seasonally in the winter months; In South Africa, the influenza season equally occurs in the winter months, typically beginning in the first week of June. However, the onset of the winter season here frequently varies, ranging from the last week in April to the first week of July.[1,2]

The influenza viruses belong to the family *Orthomyxoviridae* and are classified into three types (Influenza A, B and C) according to antigenic differences among their nucleoprotein and matrix proteins.[3] Influenza A viruses circulate naturally in a global avian reservoir; however, some viral strains have crossed the species barrier establishing in pigs, horses and most notably, infecting humans. Influenza A viruses are categorized into subtypes on the basis of characterization of two surface antigens: hemagglutinin and neuraminidase. These are the Influenza A (H1N1) & (H3N2) viruses.[4] The 2009 global influenza pandemic was caused by Influenza A [the H1N1 subtype, hereafter referred to as A (H1N1) pdm09)].[5] The two Influenza A virus subtypes together with Influenza B co-circulate seasonally to cause disease outbreaks and epidemics.[4] Influenza C viruses are rare, infecting dogs, swine and occasionally humans.[6] The Influenza B viruses are separated into two distinct genetic lineages (Yamagata and Victoria), named after the areas where both viruses were first identified.[1] Influenza B viruses almost exclusively infect humans although they present a less pathogenic profile than the Influenza A viruses. Due to their infectivity to humans, relevant strains of influenza A and B viruses are included in seasonal influenza vaccines.[7] Generally, the different Influenza types and subtypes (Influenza A and B respectively) produces illnesses of relatively similar clinical characteristics,[8-10] although differences in severity have been observed.[11-13] Furthermore, in seasons where both viruses co-circulate, the average duration of infection appears to be longer.[14]

Viral respiratory diseases impose a heavy burden on society.[15] This includes an untoward effect on lost work hours as recently reported by the Office of National Statistics, UK, which in its latest analysis report on sickness absenteeism in the Labour market states: "Minor illnesses (such as coughs and colds) were the most common reason for sickness absence in 2016, accounting for approximately 34.0 million days lost (24.8% of the total days lost to sickness)".[16] Within public health facilities in South Africa, approximately 14% of patients hospitalised with lower respiratory tract infection and 25% of patients with influenza-like illness will test positive for influenza on polymerase chain reaction (PCR).[5] In South Africa, the number of persons lost annually to Influenza-associated illnesses has been estimated at between 6 734 and 11 619.[17,18] These estimates portray the huge burden of influenza-associated illnesses experienced by the general population. Caring for this high patient load with an easily transmissible disease agent such as Influenza requires a relatively healthy workforce with a reasonably reduced risk of falling ill themselves.[5,19] Therefore, the goals of any measure aimed at ensuring the protection of health workers should be two-fold; firstly, to reduce the risk of health workers from falling ill and secondly from the employer perspective, minimize the associated absenteeism rates from work arising from the illness itself.

Currently, vaccination programmes for health care workers (HCW) against influenza is considered the most effective strategy for preventing influenza.[20,21] These programmes offer both direct and indirect protection. Direct protection occurs by decreasing the susceptibility of vaccine recipients, hence reducing the probability that they will contract the disease and also by reducing the infectiousness of vaccinated individuals when breakthrough infections occur. Indirect protection takes place by reducing transmission within the population, thereby lowering the transmission rate for both vaccinated and unvaccinated individuals.[22,23] With exposure to members of the general community and even more importantly, to ill patients, the peculiar nature of the occupation of HCWs places them at a higher risk of influenza infection.[24,25] Consequently, recommendations have been made for HCWs together with certain individual groups to be administered with the influenza vaccine before the commencement of the annual influenza season.[5,26] That forms the basis for the undertaking of our study- aimed at assessing the willingness of uptake and the impact that influenza vaccination campaigns might have had among HCWs in our tertiary health setting.

Literature Review

Vaccination is particularly recommended for HCWs who are in direct contact with patients.[27] The same is advised for certain vulnerable groups of patients who are at greater risk of increased morbidity and mortality from Influenza infection. These include pregnant women, HIV-infected individuals, the elderly (persons aged >65 years), those with serious chronic diseases and other immunocompromised persons.[7,26] It therefore becomes crucial that HCWs attending to these individual patient groups are vaccinated to reduce the incidence of influenza among themselves and also prevent disease transmission to these patients.[19,24] Studies have shown significant reduction in nosocomial infections and overall patient mortality when a considerable proportion of HCWs are vaccinated.[28-30] The attack rates of seasonal influenza generally range from 10% to 20% in healthy adults. However, this can exceed 80% in hospital outbreaks and long term care facilities since the virus is a highly contagious viral agent that can cause abrupt onset of respiratory symptoms.[31-33] Furthermore, evidence indicates that infected health care providers could also pass on the virus even when they do not feel ill.[5]

Health care workers who are absent from work because of influenza illness place extra strain on colleagues during the flu season when there is a greater demand for medical treatment.[34] This would inevitably threaten productivity and patient safety.[35] In addition, this disrupts the working environment, reducing staff morale and increasing the costs of public health expenditure.[36,37] In a controlled trial studying the effect of conventional inactivated influenza A vaccine on reducing absenteeism related to respiratory infections among pediatric health care providers; it was found that immunising HCWs significantly reduced total sick leave days by 28% when compared to unvaccinated controls (301 days among cases to 218 days among controls). Furthermore, there was a reduction in the total number of days the HCW self-reported being unable to work when either on or off duty (3.5 days vs. 2.5 days, p = 0.02).[38]

Estimates show that absenteeism costs the South African economy between R12 billion and R19.144 billion per year.[39] In the health care environment, the same challenge remains common and while there are no reliable figures detailing the impact of this phenomenon among the different cadres of hospital employees, considerable work has been done within the nursing profession. Key factors identified in these studies include stress-related illnesses and unfavorable working conditions.[37,40] While these may differ to some degree among the occupational categories, the common central theme is the impact of biological and psychosocial risk factors prevalent in the healthcare settings on workers' performance.

In South Africa, the prevalence of HIV among health workers has been shown to mirror that of the adult population aged 15-49 (15.7% vs 18.9% based on latest estimates).[41-43] It has been shown that HIV infection is the most common underlying risk-factor for influenza-associated lower respiratory tract infection hospitalizations, with another paper placing this risk as high as four to eight times more when compared to HIV-uninfected persons.[42,44] Likewise, considering the relatively high prevalence of tuberculosis in the region, with 2012 estimates of 530,000 (incidence of 860/100 000 for 2013)[46]; current evidence suggests an increased mortality risk among individuals having tuberculosis and influenza co-infections when symptoms persist for at least seven days.[47] At a local level, specifically at the Tygerberg Hospital where the present research is based, recent studies show a mean annual incidence rate of active TB disease for the years 2008–2011 as 397/100 000 population; ranging from 194/100 000 population among medical doctors to 1181/100 000 population among Housekeeping staff members.[48] In addition, the most commonly associated co-morbid illnesses among HCWs in this facility has been shown to be HIV infection and diabetes mellitus.[49]

Seasonal influenza vaccine remains the primary public health tool for preventing influenza although increasing vaccine uptake among the HCW population has been challenging partly because of the persistent misconception among HCW's that influenza is not a serious illness among otherwise healthy working adults.[50-52] In like manner, the rate of vaccine distribution and uptake among the general population has been historically quite low despite the efforts of the National Department of Health, with a 1995 estimate at 12.5/1000 population compared to about 145/1000 population seen in North American countries at that time. The same report documents immunisation rates among HCWs to be less than 30%.[24] No current data exists on current Influenza vaccination rates among HCWs in South Africa. Nonetheless, with a high vaccine efficacy of 70-90% as attested by many studies and with the vaccine's ability to reduce viral transmission to at-risk patient groups, continuous calls for HCWs to be vaccinated has persisted.[20,50,53,54]

The low immunisation rates among HCWs has been explained by various surveys and studies.[51,55,56] These reasons include work inconvenience, the necessity of obtaining written informed consents, concerns about the vaccines effectiveness and side-effects. In addition, the erroneous perception that the vaccine may cause influenza illness itself and the apparent poor understanding of the risks of acquiring and transmitting the infection between healthcare provider and high risks patients also contributes to this situation. Positive predictors of acceptance include previous receipt of the influenza immunisation, older-aged employees and higher socio-economic status. Among HCWs, medical practitioners were more likely to accept vaccination compared to the other health professional groups.[56,57] Perhaps a better understanding of the transmission dynamics of the virus within this occupational sub-group or knowledge of the considerable impact any influenza-illness associated absenteeism could impact on the quality of patient care could account for this increased uptake.

The onus rests on the employer to ensure that the workplace environment is safe for all persons at work, as stipulated in the Occupational Health and Safety Act.[58] For this reason and others explained above- commencing in 2010, the Western Cape Department of Health has prioritised its HCWs as among the vulnerable groups at risk of contracting Influenza. They provide viral flu vaccines which offers protection against at least three strains of influenza vaccines prior to the onset of each winter season when attack rates begin to soar.[59,60] Despite reliable data demonstrating the effectiveness of this preventative measure and the availability of the vaccines at no cost to the vulnerable groups mentioned above- uptake among HCWs, which generally is on an opt-in basis, continues to be low.[5,7,26,61,62]

With due considerations to the issues highlighted above, the need for conducting this study therefore becomes necessary. Between two population groups based on their vaccination status, the **research aims** to evaluate the impact vaccination of HCWs against flu can have on the incidence of all influenza-like illness reports and the absenteeism rates from work linked to these illnesses.

Study Objectives

To determine the proportion of all categories of healthcare workers (nurses, doctors, laboratory personnel, physiotherapists etc.) who accepted the flu vaccination made freely available during the immunisation campaign between 2013 and 2014 and measuring reported incidences of influenza-like symptoms thereafter. Deriving the impact of this measure would be considered in the following contexts:

a) To determine the proportion of health care workers responding to the call for influenza vaccination based on the uptake of flu vaccination at the hospital.

b) To measure the incidence rates of flu-related illness between vaccinated and unvaccinated HCWs groups in the years 2013 and 2014.

c) To describe any differences between the vaccinated and unvaccinated groups of health care workers regarding absenteeism from work for influenza related illnesses.

CHAPTER 2: METHODOLOGY

Design and Setting

A retrospective cohort study with matched controls investigating the incidence of flu and its related illnesses, including the frequency of absenteeism amongst vaccinated and unvaccinated health care workers at Tygerberg Academic Hospital, Parow, during the seasonal flu years of 2013 and 2014.

Tygerberg Academic Hospital is a public hospital situated in the Parow area of the Western Cape Province, South Africa. It is a tertiary teaching hospital in the Tygerberg health sub-district of the Metro Region. The hospital, with almost 1400 beds is the largest hospital in the Western Cape and the second largest in South Africa.[63] It acts as a teaching hospital in conjunction with the University of Stellenbosch's Medical and Health Science Faculty.[64]

The hospital occupies a large geographical premise offering a wide range of specialised clinical services. It employs a huge number of clinical personnel to cope with the enormous public health demands in addition to having a vast supportive network of technical, engineering and allied health services.

The Occupational Health (OH) clinic of the abovementioned hospital serves as an essential platform for improving the health and well-being of the hospital's workers. The clinic attends to incidents related to injuries on duty and other work related health outcomes that staff members of the hospital may suffer from. In addition, the Provincial Department of Health annually provides the clinic with rationed batches of influenza vaccines for onward vaccination of the hospital employees.

Study Population and Sample Size

A HCW for the purpose of this study was any hospital employee involved in the provision of direct or indirect care to patients. The vaccinated group were all HCWs who sourced the seasonal influenza vaccine at the OH clinic of the hospital.

The total number of vaccinated HCWs for the years 2013 and 2014 were obtained from the OH clinic records. This convenience sample was compared to a random sample of unvaccinated HCWs obtained from the institution's employee database, for the same period. Cases were defined from the occurrence of flu-related illnesses among this vaccinated group and their associated controls.

Selection of controls

The hospital's Human Resources (HR) department regularly updates the hospital's electronic employee database. This becomes necessary in view of the turnover that takes place by employees exiting or entering the facility's workforce. Data containing information on all recognized hospital employees employed for the years, 2013 and 2014 were sought from the HR. This electronic database was analysed, and a separate list containing the persal numbers/names of all vaccinated workers for each year was used to extract vaccinated employees from this main database. A stratified random sampling of matched controls was then made from the residual employees on the electronic database. The sampling selection was made in Stata 13.0 software (Stata Corp, College Station, TX, USA) from a Microsoft Office Excel 2016 (Microsoft, Redwoods, WA, USA) list containing all residual (assumed unvaccinated) employees coded by occupational category. When a selected employee was not eligible, either by duration of employment or otherwise, a re-selection was made. Two controls were selected for every vaccinated participant (Figure 1).

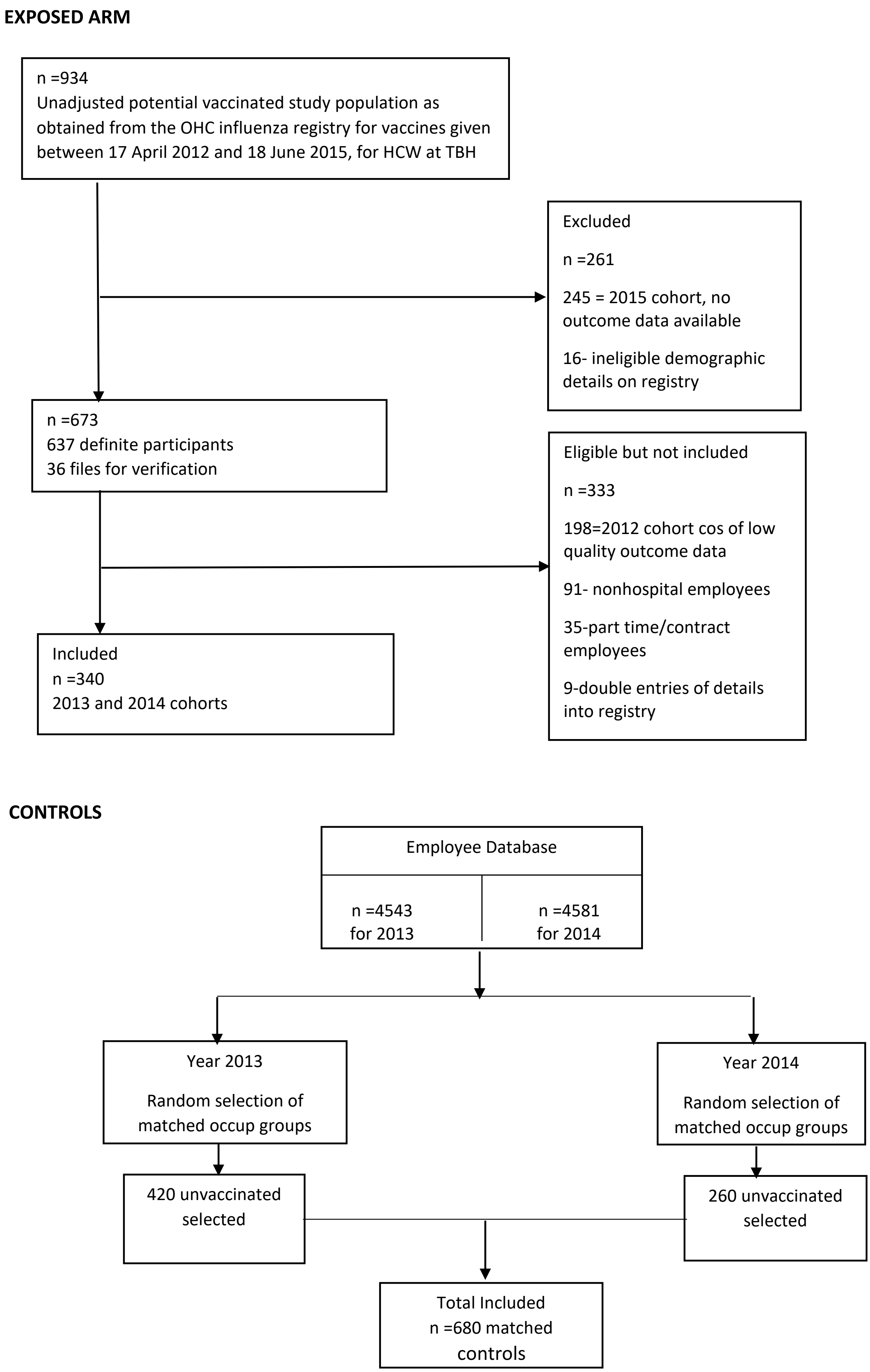

Figure 1: Flow Diagram Illustrating Selection of Study Population

Case Definition

All cases were clinically diagnosed by the study population's General Practitioners (GP). During analysis, cases were defined as those HCWs who presented documented reasons (sick certificates) for being absent from work for 'flu-related' illnesses. To minimise misclassification, a case definition of 'flu-related /Influenza-like illness was made'. This was made with reference to the Healthcare Workers Handbook on Influenza and other reliable sources.[5,65] Two forms of influenza illnesses are recognized: -

- Uncomplicated influenza-or ILI (Influenza-like Illness) presenting as an acute respiratory infection with fever (≥38C°), coryza, generalised symptoms (headache, malaise, myalgia, arthralgia) and sometimes gastrointestinal symptoms, but without any complicated features. Does not require hospital admission, with patients generally treated on an outpatient basis.
- Complicated/severe influenza, frequently referred to as Severe Acute Respiratory Illness (SARI)- usually presents as an acute respiratory infection with lower respiratory and occasionally other systemic manifestations. Often requires hospitalization.

For the purposes of this study, the term 'flu-related illnesses' included both forms of influenza illnesses and cases were defined accordingly. In addition to the clinically specified illnesses, a reasonable proportion of all returned sick notes had no stated diagnosis. In these sick notes, the commonly used terms- 'medical condition' or "non-specified' illnesses were used to define the sick leaves. These too were included in the analysis because a significant percentage of these illnesses could be influenza-related. This sickness outcome data was equally sourced from the HR department of the hospital.

Inclusion Criteria

For inclusion into the study, participants had to meet the following criteria-

- They are hospital employees whose names/ persal numbers are listed in the HR electronic database
- For the vaccinated group, they are HCWs who remained on employment for at least 12 months after receiving the vaccination. Consideration was made for any HCW who received the same vaccination at a peripheral centre and informed the OH clinic.
- For the presumed unvaccinated controls, they must have been in employment from at least the onset of the seasonal flu season for that year until at least a year afterwards.

Exclusion Criteria

The following conditions excluded participants from the study

- Non-permanent employees including contracted employees/employees provided by labour brokers.
- Employees with dual appointment whose main remuneration pay point is not linked to the hospital's.
- Employees on the main electronic database but whose terms of contract are no longer active.

Sample Size

For purposes of this study and due to the free availability and accessibility of the vaccine every week day at the OH clinic prior to the onset of the seasonal flu season, the assumption was that health care personnel whose names or Persal numbers were not recorded in the OH clinic's vaccination log book will be considered unvaccinated for that year. All vaccinated HCWs for the period 2013 and 2014 were included in the sample size. Nevertheless, to test our hypothesis and to ensure our sample was powered enough to detect a possible difference, if any exists, between the vaccinated and unvaccinated populace; we estimated the least required sample size in Stata for comparison of two independent proportions. For an 85% powered sample and with a significance level (alpha error) set at 5%, aiming to detect a 10% difference in proportion between two groups (assuming an illness proportion of 30% among the exposed arm and 40% in the unexposed) while allowing for a 1:2 allocation ratio between groups- we calculated group sizes of 308 in group one and 615 in group two for a total of 923. Hence, to detect any probable difference, our included total sample of 1020 was well powered to achieve this purpose.

Ethical Considerations

Health Research Ethics Committee Clearance

Ethical Clearance was obtained from the Stellenbosch Health Research Ethics Committee (HREC) and the Western Cape Department of Health to conduct the research in Tygerberg

Hospital (reference number S15/10/226). A *waiver of informed consent* was equally granted considering the research only involved the assessment of participants' personal health records. Confidentiality with regards to the handling of these personal health data was continually upheld.

Data Management

Determination of Baseline and Outcome Variables

The scope of Baseline variables was limited because demographic information was sought from an electronic database rather than interviewer or questionnaire-based. Nevertheless, integral variables such as age, gender, race, year of employment, date of vaccination and occupational grouping were derivable from the database.

Certain outcome variables had been earlier defined for assessment in the study protocol. They included; total number of flu-related sick leave reported (duration and episodes), total number of sick incidence, sum of absenteeism days, time to first flu-related illness and sum of total person costs. While information accounting for the first three outcome variables could be extracted from the outcome data gotten from HR, the latter two variables could not be assessed due to missing/complete lack of information available on them.

Since health personnel absent from duties on account of ill-health or any other personal matter are required to submit sick certificates obtained from their GPs detailing the diagnoses of their illnesses; there was a reasonable certainty concerning the completeness of the HCW illness outcome data. A broad definition of flu-related illness was used and they included clinical diagnoses captured as 'flu', 'upper respiratory tract infections',' acute respiratory tract infections' 'acute respiratory illness', acute bronchitis, pneumonia, 'lower respiratory tract infection' 'coryza', 'viraemia' etc. Other extracted related information included the frequency of these claims per year, the duration of each illness event and the occurrence of any other similar ailment affecting study participants.

Control of Confounding

In anticipation of possible confounding factors inherent in any typical observational study, certain variables were considered. The main variable of concern was the differing exposure levels of the various classes of HCWs to the influenza viruses within the healthcare environment. To minimise these differences in exposure levels, the study population was stratified by occupational groupings in a 1:2 ratio i.e. two matched controls for every vaccinated study participant. In addition, the restriction of the study population to only permanent employees and the reliance of a stratified random sampling method to assign controls to each vaccinated populace ensured both study groups were as similar as possible. The gender distribution within the study population was almost identical and this helps to further dispel any confounding concerns. However, to investigate for the possible effect of common variables such as age and race on the susceptibility to a flu-related illness, these latter variables were not matched.

Methods

A data extraction sheet was designed in Microsoft Excel 2016 for obtaining demographic and clinical information. Data from the paper registry of vaccinated employees obtained at the OH clinic were diligently entered into this electronic data extraction sheet. Special validation of entries, logic checks and confirmation of demographic information was done. The latter was achieved by confirming details such as persal numbers, date of births etc. with the hospital Clinicom and the hospital's main employee database. The use of a data dictionary to guide entries was employed at all times.

On receipt of the employee database, an encryption key was inserted to minimise loss of sensitive employee information to unauthorised persons. To ensure further anonymity and security of employee information, column names, initials, identity numbers and any other personal information were deleted from the main files and all further queries and extractions done solely with persal numbers. Duplicate copies of all files were stored in a single backup storage system equally encrypted with a password. All analysis including the generation of a stratified random sample of controls were made with only persal numbers.

Vaccinated participants were analysed and categorised into five main Occupational categories namely; -

- Medical Practitioners- made of medical officers, registrars and medical specialists.
- Nursing Practitioners- comprised of registered professional nurses, operational nursing managers, enrolled/staff nurses and nursing assistants.

- Allied Health practitioners consisting of pharmacists, physiotherapists, occupational therapists, radiographers, medical technologists, social workers, electrocardiogram assistants and clinical technologists
- Administrative personnel- made of medical managers, assistant and deputy nursing managers, HR personnel, administrative clerks, typists and secretaries.
- Others- comprising household aids, messengers, cleaners, artisans, porters and security personnel.

Though the occupational categories listed above is broad, this was done for ease of analysis and for defining each employee based on characteristics peculiar to their occupational group. Having categorised the occupational groupings, appropriate controls were sought in the employees' database to complement each occupational class in a 1:2 ratio as earlier indicated. Adherence to standard operating procedures such as version control through the adoption of appropriate naming conventions for documents and file names were done continually.

Data Analysis and Statistics

No missing data was encountered, rather any missing outcome data was interpreted as the subject remained healthy throughout the 12- month study period (with regards to flu-related illness). About 32% of staff members in the exposure arm had received consecutive vaccination for both years. Notwithstanding, these were analysed without any prejudice because there is unavailable evidence showing vaccination status impacts across two seasons. Overlap between vaccination schedules did not exist since an average interval of 12 months existed between the two flu vaccination campaigns (March to April 2013 and March to May 2014).

Incidence rate was calculated by analysing the number of cases to the study arms they belong (vaccinated or unvaccinated arms). In addition, during analysis of the study population, the contribution of each yearly cohort to summarised statistics such as 'total duration of illness days' was provided. In all instances, differences between variables in the exposed arms and their controls were studied and presented as Relative Risks (RR). Statistical and clinical significance was interpreted for each measure with p-values of 0.05 and 95% Confidence Intervals.

Data was analysed using Stata 13.0 software. Graphical representations such as bar charts, pie charts, box and whisker plots were done in Microsoft Office Excel 2016. During analysis, various measures of interest were calculated relative to that study population's vaccination status.

Prior to analysis, normal distribution was verified by the use of the Shapiro-Wilk test for normality. Continuous variables such as age, number of illness days, number of episodes were presented by standard distribution measures (mean, standard deviation, median, inter-quartile ranges where applicable). Median data were compared using the Wilcoxon rank-sum test. Variable frequencies are presented as numbers and percentages (in brackets). Categorical variables such as gender, duration of employment and age categories were analysed using the chi-square test. The association between influenza immunisation and the categorical variables was tested either by chi-square test or the Fisher's exact test where appropriate.

Associations between demographic variables and vaccination uptake were presented in Odds Ratios and their 95% confidence intervals.

CHAPTER 3: THE RESULTS

Baseline Characteristics of Study Participants

A total of 1020 Healthcare workers were included in the study. 340 (33.3%) of these were vaccinated and matched with two controls each for the seasonal flu seasons of the study years- 2013 and 2014 (Table 1). Of the vaccinated HCWs studied, 210 (61.8%) of them were of the 2013 cohort while the rest, 130 (38.2%) were of the 2014 group. Among the study population, 783 (76.8%) were females, with 259 (76.2%) and 524 (77.1%) representing the 2013 and 2014 cohorts respectively (Table 1). The ethnic profile of the study participants was as follows- Black/African minority 199 (19.5%), Mixed race/Coloured 635 (62.3%), Caucasian 171 (16.8%) and Indian 15 (1.5%) (Figure 1). The distribution of each ethnic group for the vaccinated and unvaccinated participants is shown in Table 1. The study population was stratified into five main Occupational groupings as earlier specified- the Medical Practitioners, Nursing Practitioners, members of the Allied Health, Administrative personnel and Others. Among the occupational categories of the vaccinated, 23 (6.8%) were Medical Practitioners, 129 (37.9%) were Nursing Practitioners, Allied Health professionals were 35 (10.3%), Administrative personnel 66 (19.4%) and "Others" employee groups 87 (25.6%) [Figure 3]. For the study period, the spread of each Occupational category is shown in Table 1. In the study, the Nursing practitioners were the largest occupational grouping - 129 (37.9%) and 261 (38.4%) for the vaccinated and unvaccinated participants respectively, while the Medical Practitioners were the least. Furthermore, 485 (47.6%) of the study population have been employed in the facility for less than 10 years, 151 (14.8%) been employed between 11 to 20 years while 255 (25%) and 129 (12.7%) have their duration of employment as 21 to 30 and greater than 31 years respectively.

Table 1- Baseline Characteristics of Study Participants

Variable	**Vaccinated group**	**Unvaccinated group**	**Total**	**P value**
Total Number (%)	**340 (33.3)**	**680 (66.7)**	**1020**	
Age –Mean (SD)	44.36 (10.37)	42.40 (9.8)	43.06 (1004)	
Median (IQR)	46 (38-52)	43 (35-50)	44 (36-51)	0.003
Gender n (%)				
Male	81 (23.8)	156 (22.9)	237 (23.2)	
Female	259 (76.2)	524 (77.1)	783 (76.8)	0.753
Ethnicity n (%)				
African	68 (20)	131 (19.3)	199 (19.5)	
White	67 (19.7)	104 (15.3)	171 (16.8)	
Mixed	200 (58.8)	435 (64)	635 (62.3)	
Indian	5 (1.5)	10 (1.5)	15 (1.5)	0.301
Vaccination Year n (%)				
2013	210 (61.8)	420 (61.8)	630 (61.8)	
2014	130 (38.2)	260 (38.2)	390 (38.2)	1
Occupational Category n (%)				
Medical Practitioners	23 (6.8)	46 (6.8)	69 (6.8)	
Nursing Practitioners	129 (37.9)	261 (38.4)	390 (38.2)	
Allied Health	35 (10.3)	70 (10.3)	105 (10.3)	
Admin Personnel	66 (19.4)	129 (18.9)	195 (19.1)	1
Others	87 (25.6)	174 (25.6)	261 (25.6)	
Age in Years n (%)				
<30	40 (11.8)	78 (11.5)	118 (11.6)	
30-39	71 (20.9)	180 (26.5)	251 (24.6)	
40-49	111 (32.6)	238 (35)	349 (34.2)	
≥50	118 (34.7)	184 (27)	302 (29.6)	0.052
Duration of employment				
n (%)	150 (44.1)	335 (49.3)	485 (47.6)	
<10	43 (12.6)	108 (15.9)	151 (14.8)	
11-20	97 (28.5)	158 (23.2)	255 (25)	
21-30	50 (14.7)	79 (11.6)	129 (12.7)	0.068
≥31				

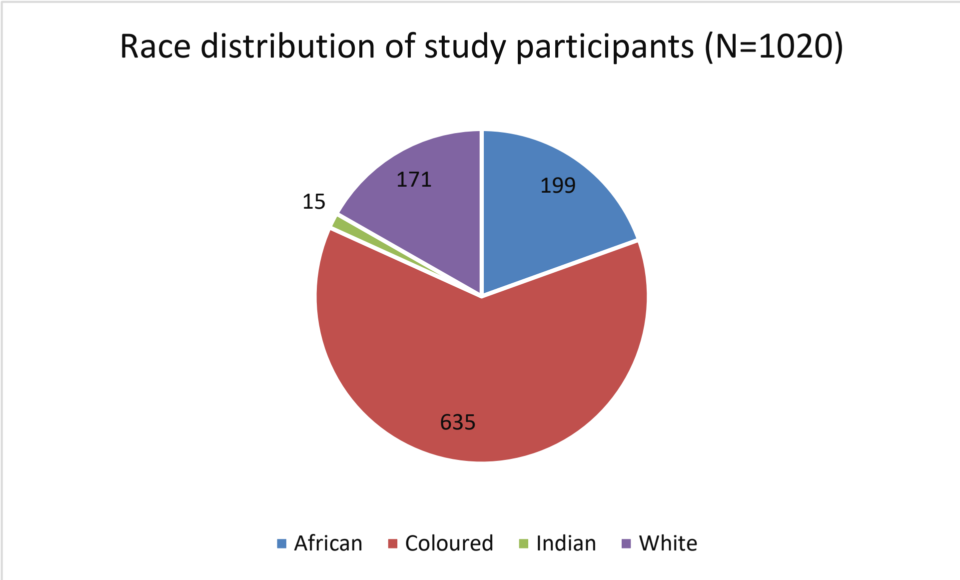

Figure 2- Race distribution

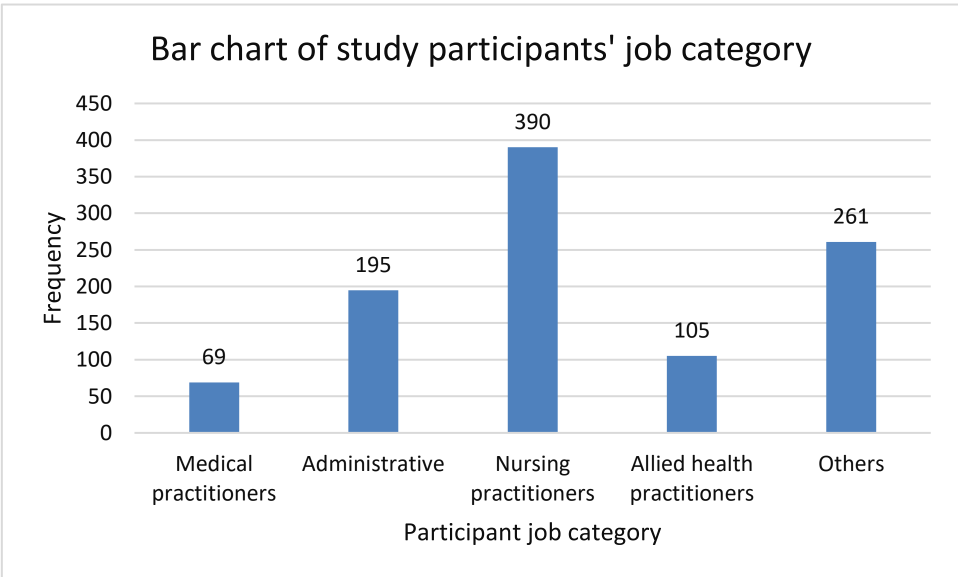

Figure 3- Bar Chart showing participants' Job categories

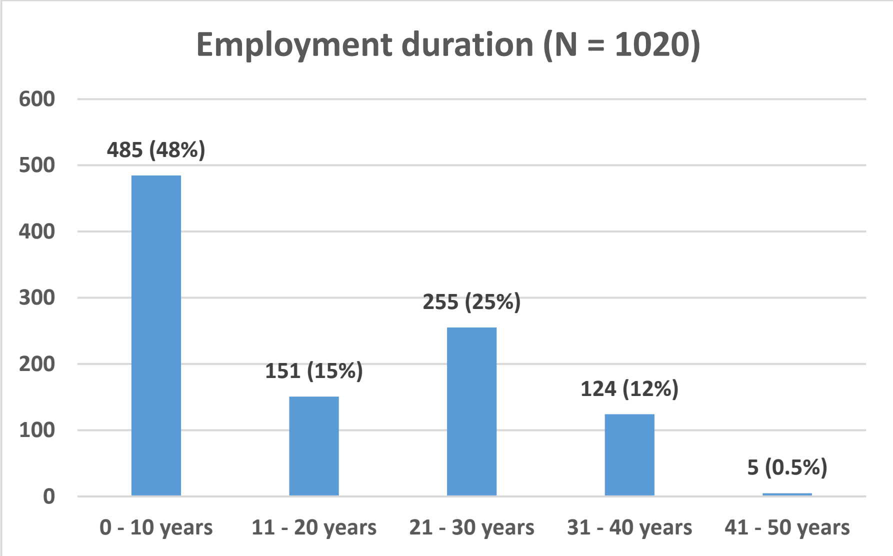

Figure 4- Duration of Employment

Age Distribution

The mean age (Standard Deviation) of the participants was 43.1 years (10.04). The median age (Inter-quartile range) was 44 years (36-51) (Table 1). When classified into age categories by vaccination status; 40 (11.8%) were less than 30 years of age, 71 (20.9%) were aged 30-39, 111 (32.6%) were between 40-49 years and 118 (34.7%) were older than 50 years. These antecedent figures represent the vaccinated HCW group. The histogram (Figure 5) shows the age distribution of the study population, illustrating that the age group with the highest frequencies of 356 (34.9%) were those in the 45 to 50-year age range. The mean age (SD) of the vaccinated employees was 44.36 (10.37) while that of the unvaccinated group was 42.40 years (9.8) and this difference in age was statistically significant (p=0.003) (Figure 6).

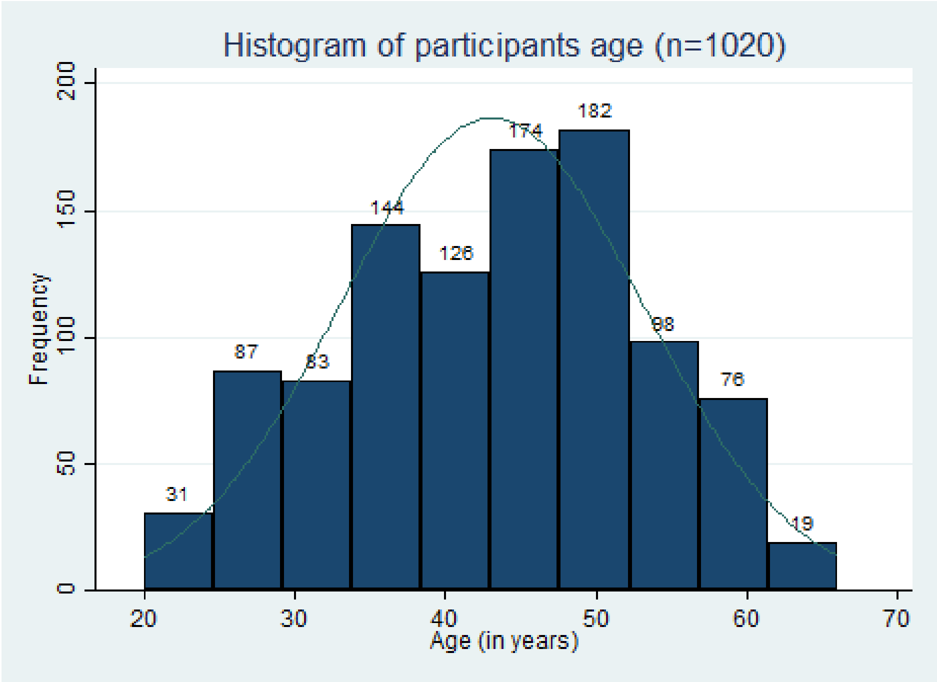

Figure 5- Histogram showing age distribution of study participants

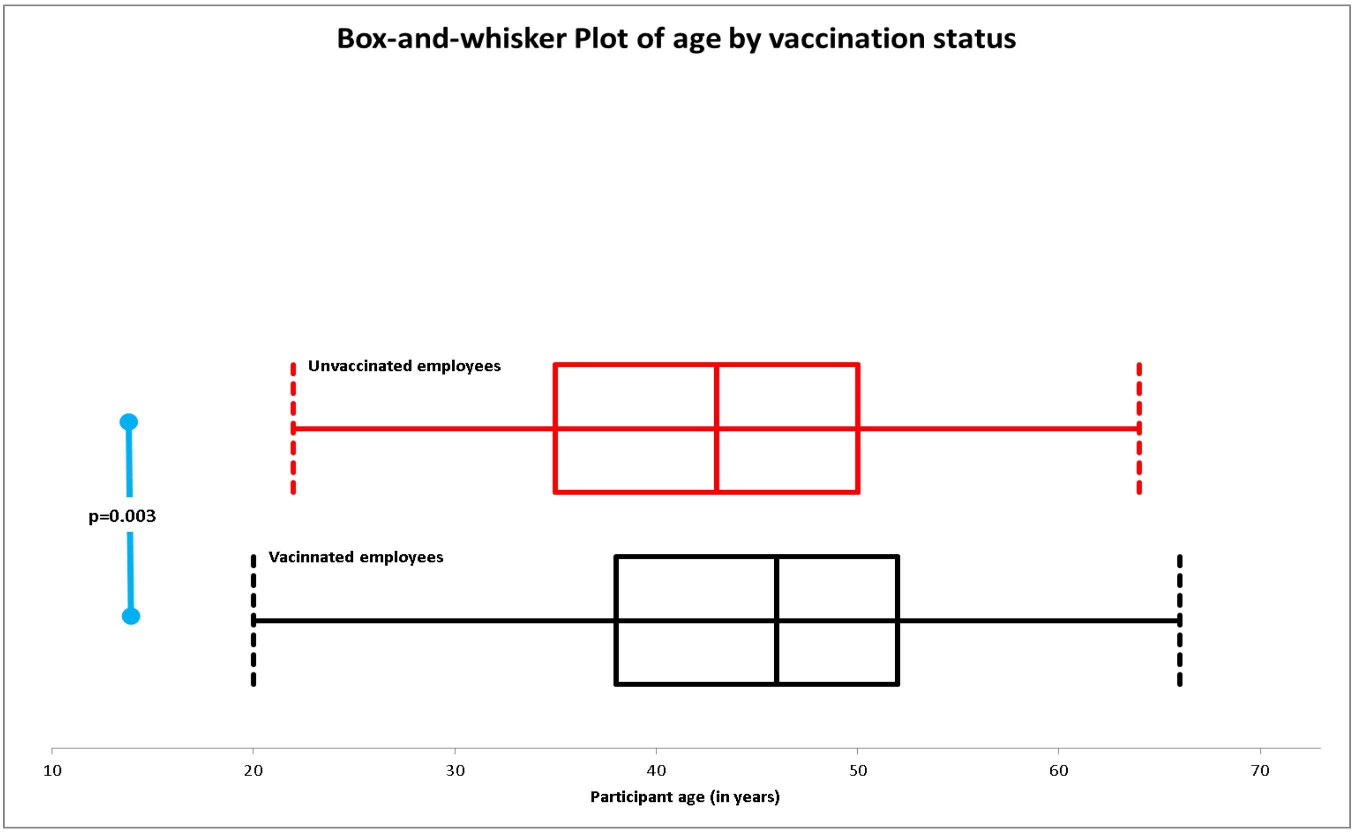

Figure 6: Box and Whisker plot illustrating vaccination status by age

Specified Illnesses- Influenza and Influenza-like illnesses

As indicated on the sick notes, 48 (14.2%) of illnesses in the vaccinated group were diagnosed as 'Influenza/flu' for the combined cohorts. This is proportionately more than the 65 (9.56%) found in the unvaccinated group. This difference was found to be significant [RR 1.48, 95% CI (1.04- 2.09)]. When stratified by cohort year, there were proportionately more influenza cases identified within the vaccinated 2014 cohort compared to the 2013 group [20 (15.38%) vs 28 (13.33%)]. When compared to their matched unvaccinated cohorts, this proportionately higher influenza incidents rate remained, 13.33% vs 8.57% and 15.38% vs 11.15%. Both differences were non-significant as shown in Table 2.

Table 2- Specified Illnesses Influenza/Influenza-like incident rates by vaccination status (clinical diagnosis)

Event	Vaccinated (*N=340*)	Non-vaccinated (*N=680*)	Relative Risk (95% CI)	P-value
Instances Flu Illness N (%)	48 (14.12)	65 (9.56)	1.48 (1.04- 2.09)	0.03
2013 cohort	28 (13.33)	36 (8.57)	1.56 (0.98-2.48)	0.06
2014 cohort	20 (15.38)	29 (11.15)	1.38 (0.81-2.34)	0.24
Instances of Influenza- like illness	79 (23.24)	164 (24.12)	0.96 (0.76- 1.22)	0.76
2013 cohort N (%)	44 (20.95)	91 (21.67)	0.97 (0.70-1.33)	0.84
2014 cohort	35 (26.92)	73 (28.08)	0.96 (0.68-1.35)	0.81
Instances of illnesses (influenza +Influenza-like) N (%)	111 (32.65)	210 (30.88)	1.06 (0.87- 1.28)	0.57

For other associated influenza-like illnesses, there was minimal difference in the instances of incident cases reported between the vaccinated and unvaccinated groups seen in the combined cohorts [79 (23.24% vs 164 (24.12%), RR 0.96, 95% CI 0.76-1.22]. Similar trends were found when groups were analysed by year of vaccination as shown in Table 2 above. These showed slight favourable decreases in illness incidents for the exposed group in comparison to their controls although these differences were statistically insignificant.

Table 3- Distribution of illnesses collated as 'Influenza-like'.

Diagnosis	Vaccinated (*N=340*)	Non-vaccinated (*N=680*)	Relative Risk (95% CI)	P-value (Chi2)
URTI	34 (10)	83 (12.2)	0.82 (0.56-1.19)	0.2973
Pharyngitis	5 (1.47)	20 (2.94)	0.5 (0.19-1.32)	0.1522
Bronchitis	25 (7.35)	38 (5.59)	1.32 (0.81-2.14)	0.270
Rhinitis/Sinusitis	14 (4.12)	37 (5.44)	0.76 (0.41-1.38)	0.361
Coryza	1 (0.29)	3 (0.44)	0.67 (0.07-6.39)	1.000†
Tonsillitis	4 (1.18)	11 (1.62)	0.73 (0.23-2.27)	0.581
Asthma /bronchospasm	6 (1.76)	5 (0.74)	2.4 (0.74-7.81)	0.1335†
Viraemia	5 (1.47)	4 (0.59)	2.5 (0.68-9.25)	0.169†
Tracheitis/Laryngitis	2 (0.59)	8 (1.18)	0.5 (0.11-2.34)	0.510†
Pneumonia	0	2 (0.29)	‡	0.555†
All flu-related illnesses	96 [28.2]	211 [31.03]	0.91 (0.74-1.11)	0.359

‡- Cannot calculate value (0 incidents in non-vaccinated group)

†- Fishers Exact test used

Table 3 above shows the spectrum and frequency of illnesses captured as 'Influenza-like'. As illustrated, under this category, the sum of all events shows less occurrence of illnesses in the vaccinated vs the unvaccinated [96 (28.2%) vs 211 (31.03%) RR 0.91 95% CI (0.74-1.110)]. It also shows that the commonest clinical diagnosis was 'Acute Respiratory Tract/Upper Respiratory Tract illnesses' with proportionate incidences lower in the vaccinated group 34 (10%), in comparison to the unvaccinated group 83 (12.2%). The table further illustrates that the same trend is seen in six other related clinical illnesses when comparing vaccinated vs unvaccinated individuals. They are: Bronchitis (1.47% vs 2.94%), Rhinitis/Sinusitis (4.12% vs 5.44%), Coryza (0.29% vs 0.44%), Tonsillitis (1.18% vs 1.62%), Tracheitis/Laryngitis (0.59% vs 1.18%) and Pneumonia (0% vs 0.29%). However, none of these differences were found to be statistically significant.

Duration of Specified Illness and Frequencies of Occurrence

In determining the number of days spent being ill and the frequencies of their occurrences (analysed per HCW), the Wilcoxon rank sum test was used. Here, no difference in both indicators is observed between the vaccinated and the unvaccinated for specified illnesses except for episodes of influenza-like illnesses. In this instance, the vaccinated group in comparison to their unvaccinated cohorts had a lesser number of events. [79 vs 164, z-score=2.04, p-value= 0.041). This event was statistically significant (Table 4) below.

Table 4- Duration of Illnesses and Number of Events

Event	Vaccinated (no. of events)	Non-vaccinated (no. of events)	z-score	P-value
Duration of Flu illnesses (days)	48	65	z= 0.47	0.638
Flu episodes	48	65	z= 0.18	0.855
Duration of Influenza-like illnesses (days)	79	164	z=0.86	0.388
Influenza-like episodes	79	164	z=2.04	0.041
Duration of Non-Specified illness	208	392	z= -0.33	0.744
Episodes of Non-Specified Illnesses	208	392	z=-0.44	0.659
Total days (All Illnesses)-per HCW	340	658	z=-0.502	0.616

Non-Specified Illnesses

For instances of illnesses not specified on HCW sick certificates; the following were found (Table 5). For the entire study participants, the vaccinated cohort had 208 (61.18%) of events compared to the unvaccinated group with 392 (57.65%) events and with a six percent increased risk of being ill [RR 1.06 95% CI (0.95-1.18)]. This risk was however not statistically significant. Nonetheless, when stratified by cohort year, it is found that the 2013 vaccinated cohort had a statistically significant 14% increased risk of being ill in comparison to their unvaccinated group [RR 1.14, 95% CI (1.02-

1.27)]. When these non-specified illnesses figures are compared to those listed in Table 4, this means 208 of 340 (i.e. 61.18%) of total sick leave events are not declared on returned sick certificates. For the unvaccinated, this figure is 392/658 (59.57%).

Table 5- Non-Specified Illnesses and ALL sick leave instances

Event	Vaccinated (*N=340*)	Non-vaccinated (*N=680*)	Relative Risk (95% CI)	P-value
Non-Specified Illnesses N (%)	208 (61.18)	392 (57.65)	1.06 (0.95- 1.18)	0.28
2013 cohort	151 (71.90)	265 (63.10)	1.14 (1.02- 1.27)	0.03
2014 cohort	57 (43.85)	127 (48.85)	0.90 (0.71- 1.13)	0.35
ALL sick leaves N (%)	237 (69.71)	463 (68.09)	1.02 (0.94- 1.12)	0.60
2013 cohort	164 (78.10)	302 (71.90)	1.09 (0.99- 1.19)	0.10
2014 cohort	73 (56.15)	161 (61.92)	0.91 (0.76- 1.08)	0.27

Combined Sick leaves (all instances)

When the instances of all illnesses are considered, i.e. non-specified and specified illnesses; the vaccinated cohort summarily had a marginal (2%) increased risk of being ill compared to their unvaccinated matched controls [RR 1.02 (95% CI (0.94-1.12)]. This risk was found to be greater between the 2013 matched cohorts (9%) as compared to the 2014 matched cohorts. In this instance, the 2014 cohorts showed a reversal of risks, a reduced 9% risk of being ill between vaccinated vs unvaccinated groups. (Table 5).

Employee Sick Leaves by Occupational Category

In determining sick leaves taken by Occupational groups; by proportion, it was observed that the Medical practitioners had taken the least sick days. In contrast depending on the sick certificate type, the Allied Health employee group and those listed under the 'Others' category utilised the most sick days by proportion as depicted in Table 6 below.

When analysed by sick-leave types; among the nursing group, instances where diagnoses are specified shows a reduced 22% risk of illnesses in vaccinated cohorts compared to their unvaccinated controls [RR 0.78, 95%CI (0.51-1.22)]. This, however, was not statistically significant. In like manner, increased risk of illnesses for specified diagnoses among the vaccinated cohorts compared to their unvaccinated control groups for all other occupational group was equally not significant. Of note, was the unavailability of any incidents seen among the unvaccinated group of medical practitioners.

For non-specified illnesses as reported by each Occupational group, the vaccinated administrative personnel had a statistically non-significant reduced risk of falling ill [RR 0.96, 95% CI (0.74-1.26)]. All other occupational groups appeared to have had marginal increased risks of being ill among their vaccinated cohorts' vs their corresponding unvaccinated cohorts. However, none of these increased risks were statistically significant. Particularly for the nursing category and less so for the other occupational groups, it was observed that there were a consistently higher proportion of leaves taken here compared to those taken for specified illnesses.

Table 6- Distribution of employees presenting with episodes of Sick leave

Job Category	Vaccinated n (%) (*N=340*)	Non-vaccinated n(%) (*N=680*)	Relative Risk (95% CI)	P-value (Chi2)
SPECIFIED ILLNESSES (INFLUENZA/INFLUENZA-LIKE ILLNESSES)				
Administrative personnel	29 (43.94)	51 (39.53)	1.11 (0.79-1.57	0.554
Allied Health	14 (40)	22 (31.43)	1.27 (0.75-2.17)	0.383
Medical practitioners	3 (13.04)	0	‡	0.034†
Nurse practitioners	22 (17.05)	57 (21.84)	0.78 (0.5-1.22)	0.269
Others	43 (49.43)	80 (45.98)	1.08 (0.82-1.4)	0.599
NON- SPECIFIED ILLNESSES				
Administrative personnel	36 (54.55)	73 (56.59)	0.96 (0.74-1.26)	0.786
Allied Health	25 (71.43)	44 (62.86)	1.14 (0.86-1.5)	0.383
Medical practitioners	8 (34.78)	12 (26.09)	1.33 (0.64-2.8)	0.453
Nurse practitioners	86 (66.67)	158 (60.54)	1.1 (0.94-1.29)	0.239
Others	53 (60.92)	105 (60.34)	1.01 (0.82-1.24)	0.929

‡- Cannot calculate value (0 incidents in non-vaccinated group)

†- Fishers Exact test used

All-cause Sick Leave days by Occupational Category

When employees are categorised by illness events as depicted in Table 7, several notable findings are seen. In total, there were more employees that fell ill than those without any instance of illness (700 vs 320). Vaccinated and unvaccinated groups were present within each binary category. Of the vaccinated group, the highest proportion of ill personnel, 77.14% were of the allied health profession, next were the nursing category with 73.64% and the least were the medical practitioners. Among the ill unvaccinated group, the allied health coincidentally recorded the highest proportion of ill employees quite identical to that seen among their vaccinated colleagues, (77.14%). Still within this subset of employees of the ill and unvaccinated, the medical and nursing practitioners had proportionately less personnel that fell ill compared to their vaccinated cohorts (26.09% vs 39.13% and 68.97% vs 73.64% respectively).

Table 7- Distribution of employees presenting with a sick leave day (any cause)

Job Category	With Illness n (%)		Without Illness n (%)		Grand Total
	Vaccinated	Non-Vaccinated	Vaccinated	Non-vaccinated	
Administrative personnel	42 (63.64)	87 (67.44)	24 (36.36)	42 (32.56)	195
Allied Health	27 (77.14)	54 (77.14)	8 (22.86)	16 (22.86)	105
Medical practitioners	9 (39.13)	12 (26.09)	14 (60.87)	34 (73.91)	69
Nurse practitioners	95 (73.64)	180 (68.97)	34 (26.36)	81 (31.03)	390
Others	64 (73.56)	130 (74.71)	23 (26.44)	44 (25.29)	261
Total	237 (69.7)	463 (68.09)	103 (30.29)	217 (31.9)	1020

Average Sick-leave days

Table 8 illustrates the occurrence of sick leave days per occupational category. This was determined by the average of the total sick days per employee per year issued during the study period. Except for the medical practitioners, an estimate of four days per occupational category was observed regardless of vaccination status.

Table 8- Average duration of sick leave (all causes) by employment category

Job Category	Vaccinated Mean (SD)	Non-vaccinated Mean (SD)	p-value
Admin personnel	3.95 (4.63)	3.73 (4.11)	0.728
Allied Health	4.17 (4.14)	4.1 (4.6)	0.938
Medical practitioners	0 [0 - 2]	0 [0 - 0.75]	0.306
Nurse practitioners	4.91 (6.3)	4 (5.2)	0.158
Others	3.94 (3.69)	3.83 (3.9)	0.819

Factors associated with Vaccination

Table 9 describes indicator variables associated with the likelihood of vaccination- among ethnicities, the Caucasian populace had the most odds of being vaccinated [Odds Ratio 1.36, 95% CI (0.97-1.91)]. There was no association of vaccination with gender. It was also seen that those employed for less than 20 years in the hospital were less likely to be vaccinated compared to those employed for a greater duration of time. However, all findings reported above with regards to vaccination factors were statistically non-significant. On the other hand, the 30-39year-old employees were the least likely to get vaccinated while the oldest populace, i.e. employees older than 50 years were the most likely to be vaccinated [OR 0.73, 95% CI (0.53-1.00) vs OR 1.43, 95% CI (1.08-1.90)]. With regards to age, both findings were significant.

Table 9- Factors associated with vaccination

Variable	Vaccinated (*N=340*)	Non-vaccinated (*N=680*)	Odds Ratio (95% CI)	P-value
Ethnicity N (%)				
African	68 (20)	131 (19.3)	1.05 (0.76-1.45)	0.78
White	67 (19.7)	104 (15.3)	1.36 (0.97-1.91)	0.075
Mixed	200 (58.8)	435 (64)	0.8 (0.62-1.05)	0.11
Indian	5 (1.5)	10 (1.5)	1 (0.34-2.95)	1
Gender				
Male	81 (23.8)	156 (22.9)	1.05 (0.77-1.43)	0.753
Female	259 (76.2)	524 (77.1)	0.95 (0.7- 1.29)	0.753
Age Category				
<30	40 (11.8)	78 (11.5)	1.03 (0.69-1.54)	0.890
30-39	71 (20.9)	180 (26.5)	0.73 (0.53-1.00)	0.051
40-49	111 (32.6)	238 (35)	0.90 (0.68-1.19)	0.455
≥50	118 (34.7)	184 (27)	1.43 (1.08-1.90)	0.012
Employment duration				
<10	150	335	0.81 (0.63-1.06)	0.127
11-20	43	108	0.77 (0.53- 1.12)	0.170
21-30	97	158	1.32 (0.98-1.77)	0.067
≥31	50	79	1.31 (0.90-1.92)	0.162

Sensitivity Analysis

Table 10- Sensitivity Analysis (minus the Nursing occupational category)

Variable	Vaccinated (*N=211*)	Non-vaccinated (*N=419*)	Statistic	*P*-value
Combined illness instances *n (%)*	102 (56.87)	170 (40.57)	RR 1.19, 95%CI 0.99-1.43	0.063
Total days spent ill *n (%)*	142 (67.30)	283(67.54)	RR 0.996, 95%CI 0.89-1.12	0.951
Differences in days spent ill	142 events	283 events	*z* test= -1.31	0.191

Table 10 above details the summary observed when the events contributed by the Nursing professional category are deducted. On analysing for instances of all illnesses, there is a 19% increased risk of falling ill in the exposed arm compared to the control group [RR 1.19, 95% CI (0.99-1.43)]. However, when computing for totals days spent being ill by the study population, the increased risk disappears to yield a null difference between study arms [RR 0.996, 95% CI (0.89-1.12)]. In like manner, there appears to be no difference in the actual days spent being ill between both groups although the ranked sum of days of the unvaccinated cohort appears lower than expected (58,725 rather than 60,279). All analysis above shows no statistical difference between the exposed group and their controls. The nursing group was chosen for two main reasons. Firstly, they were the largest professional group in the study population and secondly, as illustrated in Tables 8, on the average duration of illness days per HCW, they spent the most days being ill (4.91 days compared to the second highest of 3.94 days). In summary, a sensitivity analysis without the largest group showed no statistical difference in all illness variables of interest between study arms.

Summary of Results

Proportion of HCW responding to vaccine uptake

Since the exposed arms were comprised of all HCWs who accepted influenza vaccination for the respective years of study, 2013 and 2014; therefore, the total number of vaccinated HCWs in each study period will serve as the numerator while the total employee population size at the beginning of that year will be the denominator. This becomes 210/4543 (for the year 2013) and 130/4581 (for the year 2014)- resulting in 4.6% and 2.8% of HCWs received influenza vaccination in Tygerberg Academic Hospital for the years 2013 and 2014 respectively.

Calculation of Illness Incidence rates

As shown in Table 2, when all clinically specified illnesses are considered, i.e. combining both the Influenza and Influenza-like illnesses; there was a proportionately higher prevalence in the vaccinated group in comparison to the unvaccinated, though this difference was statistically non-significant [111 (32.65%) vaccinated vs 210 (30.88%)] unvaccinated with a Risk Ratio of 1.06 [95% CI (0.87-1.28)]. Likewise, Table 5 depicts the combined sick leave instances the study population experienced during the review period with the exposed group having 237 (69.71%) events and their controls with 463 (68.09%) events. This therefore shows that the true incident rate of influenza-related illnesses as reported by the HCWs lies between 32,647 to 69,706 /100,000 population per year in the vaccinated and 30,882 to 68,088 /100,000 population per year in the unvaccinated.

CHAPTER 4: DISCUSSION

The benefits of vaccinating healthcare workers against Influenza has been well established and generally acknowledged across the medical literature. However, the findings of this study present a different outlay to the expectations set out for vaccinating these professional groups. While, our results in some respect share certain similarities with other studies, it also has some notable differences in outcome with a few others. Also, particularly for clarity purposes, specified illnesses referred to sick certificate submissions bearing definitive influenza-like illness diagnoses while non-specified notes had no stated clinical diagnoses written on them.

The analysis of all instances of sick leaves shows no statistical difference between the vaccinated and their unvaccinated controls, despite a two to six percent increased risk between study arms (favouring the unvaccinated) for specified and non-specified illnesses. In like manner, when the duration of illnesses and the number of episodes (per HCW) are considered, the same conclusion of no difference between groups can be deduced. To support this, two vaccine effectiveness trials on healthcare workers equally arrived at modest conclusions regarding the benefits of vaccination in decreasing illness days and the frequencies of their occurrence.[38,54] Other studies have demonstrated some benefits depending on the outcomes assessed.[66-68] These two summaries present a rather ambivalent picture. Prior to an in-depth discussion of our findings, a closer look at circumstantial factors surrounding our study population is required.

Generally, influenza vaccination coverage is quite low in South Africa.[69] Our study showed a vaccine uptake rate of 4.6% and 2.8% for the 2013 and 2014 seasonal flu seasons respectively. This immunisation coverage appears considerably lower than expected and might have played a role in the ambiguity behind the study findings. However, it should be emphasised though that these low influenza coverages were not entirely due to the unwillingness of HCWs to be vaccinated, but also to the allocated amounts made available to the clinic by the Provincial DOH. Nonetheless, the irony is that, the precedence for the issuance of limited portion of vaccines by the DOH was established from previous seasons when general acceptance by the staff members remained constantly low despite continuous awareness campaigns. Although relating this to our study population, duplicate requests were made from the hospital procurement and OHC for the 2013 flu season, 'erroneously' resulting in an increased delivery of vaccines to the clinic. This subsequently led to the greater number of vaccinations observed that year compared to 2014. In 2016, the National Department of Health undertook a policy decision to procure about 800 000 vaccines for vaccination of high risk individuals at public facilities, with expectations of additional procurement at provincial levels.[70] This figure however appears inadequate to sustain national demands. Invariably, this results in influenza coverage for high risk persons being below optimal levels.

Going further, a low immunisation coverage defies the assumption of protection offered by immunisation. This assumed protection only holds true when the concept of herd-immunity threshold is reached. The 'herd immunity threshold' in simple terms is the herd immunity (i.e. population size) needed to interrupt the transmission of an infectious agent within a population.[71] When this target number of vaccinated persons is reached, the transmission of the agent is blocked in the community, but when this threshold is not attained, the number of infections grows exponentially resulting in the spread of the disease within that population.[72,73] A previously published study which aimed at determining this herd immunity threshold based on a model studying historic influenza outbreaks and epidemics concluded that immunisation coverage of at least 10-30% of vulnerable persons is required to establish herd immunity when the transmission levels are low but with increased transmission rates, coverage as high as 50-60% should be aimed for.[74] Since there are no local reference levels for comparison, a cue could be taken from elsewhere. In the United States, recommendations of an annual vaccination coverage of 80% have been set for targeted groups, including HCWs, while in Europe, the same objective is aimed at achieving 75% coverage. While these proposed targets appear ambitious, it remains the vital step to be reached prior to achieving the goals of HCW vaccination - which is, to reduce viral transmission between HCWs and between HCWs to persons at increased risk of severe influenza illness. Therefore, our finding of less than 5% coverage pales in comparison to these standards.

Another main feature of our study results are the incidence rates of about 30-32 % for all influenza/ influenza-related illnesses among the study population. This is remarkably higher than the annual estimated attack rate of 10-20% among healthy adults frequently quoted in medical literature.[20,30-32] However, our result is not unusual for certain reasons; first, it takes into account the combined incident rates of all clinically diagnosed flu-related illnesses, next, attack rates differ by region and lastly, as earlier indicated, the occupational nature of our study population, being HCWs at a tertiary health center exposed to patients requiring higher levels of care places them at greater risk.[24,25,65]

Currently, few observational studies have provided reliable estimates of incidence of influenza and influenza-like illness among HCWs. A prevalence of 23% was found in a sero-survey done among HCWs, but perhaps due to a high proportion of asymptomatic illness, 59% of them could not recall having an influenza illness and 28% of them, any respiratory illness.[54] In Thailand, a study showed attack rate as high as 24% among unvaccinated HCWs.[31] In addition, an earlier study to determine influenza and rhinovirus attack rates between a vaccinated population of HCWs and their controls found an average of 12% infection rate of influenza but a 37% attack rate by rhinoviruses.[24] For infections by influenza in this same study, this incident rate varied from 5% among HCWs who cared for paediatric patients to 43% among carers of surgical patients. To reiterate, in agreement with the lower incident rates of 10-20% referenced earlier, it should be emphasised that an average incidence rate of 11% and 24% were separately recorded for clinically diagnosed influenza and influenza-related illnesses respectively in our study.

There appears to be an equivocal element to some of our findings. While the diagnosis of influenza appears to be more prevalent among the vaccinated group, that of other influenza-like illnesses was seen more commonly with the unvaccinated arm. For these other respiratory illnesses, the controls had proportionately more episodes than those in the exposed group. It should be recognised that the analysis of the returned sick notes was based on clinical diagnoses made by the respective GPs of the ill HCWs. This is in keeping with current guidelines which stipulates that clinical presentation of certain cardinal symptoms is sufficient for a diagnosis.[21] Although, the use of a combination of cough, headache and fever has been shown to have a positive predictive value of 75% and a negative predictive value of 80% [75]; however, the typical clinical presentation of

Influenza illnesses appears similar to illnesses caused by other viral and non-viral pathogens such as parainfluenza viruses, adenoviruses, respiratory syncytial virus, rhinoviruses, *Chlamydia pneumoniae,* and *Mycoplasma pneumoniae.*[5,45,76]

Influenza vaccines are developed to mainly offer protection against Influenza viruses and therefore have no efficacy when co-infection with other respiratory pathogens occurs.[32] While trying to determine the attributable fraction of commonly encountered respiratory viruses linked to mild or severe illness, a recently concluded surveillance study conducted in South Africa found that rhinoviruses, influenza and adenoviruses causes the most illnesses with notable contributions from respiratory syncytial viruses, human metapneumovirus and enteroviruses.[77] This underlies the fact that many illnesses attributable to influenza might not be caused by the pathogen after all. Therefore, the reliance on clinical presentation alone as common in most GP practices in the diagnosis of influenza illness could result in misclassification of outcomes.[78] When this happens, the differential type of misclassification bias ensues. This differential misclassification of a clinical outcome (i.e. diagnosing a disease when not present or the reverse, not diagnosing a disease when present), consequently leads to errors in clinical management.[79] From the epidemiological perspective, this has an untoward effect of over or underestimation of the true association between an exposure and an outcome.[78,80]

For the combined incidents of influenza-related illnesses, we found a relative risk of 1.06 [95% CI (0.87- 1.28), p=0.57]. This is quite comparable to a systematic review study which reported on the effectiveness of seasonal influenza vaccination among healthcare workers, showing a relative risk of 1.07 [95% CI (0.62- 1.85) p=0.81].[32] Similarly, the review study also found a RR of 1.14 for number of

Influenza-like illness episodes when comparing vaccinated to unvaccinated controls. In addition, on analyzing for the mean difference in days between study groups, the researchers reported a mean difference of minus 0.12 days [95% CI (-0.3 to 0.06) p=0.18] in favour of the unvaccinated population. This also agrees with our study, although we calculated for differences using median days. For all comparisons of illness episodes and their duration, we consistently found little or no significant difference between study arms. In arriving at a similar conclusion, an updated systematic review which included 90 studies, 24 of whom were Randomised Controlled Trials, outlined that 'Influenza vaccines have a very modest effect in reducing influenza symptoms and working days lost in the general population'. This included a substantial 'number needed to vaccinate (NNV)' of 71 [95% CI (64 to 80)] in preventing incidences of confirmed influenza.[15]

Based on the total illness events that occurred during the review period, about 61% of these illness days in the exposed arm and 60% in their associated controls had no stated diagnosis accompanying the returned sick notes. To rephrase, for well over half the times the HCWs had paid sick- leaves, their employer was not aware of the reasons why the employee was away. Although every employee is covered by medical confidentiality priviledges[81]; this may have administrative implications - with regards to record keeping and planning purposes. However, for the purposes of our research, this 'unknown' but sizable diagnostic entities' could have presented a clearer picture of the true association between vaccination and illness days had these clinical diagnoses been declared.

Furthermore, when sick leaves days are defined by occupational categories; it was seen that proportionately, far more employees fell ill than those that remained healthy during the two-year review period (average 68.9% vs 31.1%). Consistent with our previous findings, there were marginal differences between study arms. Additionally, certain trends about examining these absenteeism rates by occupational categories stand out. When analysed in relation to absolute numbers, it appears the nursing professionals contribute to the bulk of ill-health associated sick days suffered by the HCWs (perhaps that should be expected since they form the largest population group). By contrast, when the number of ill HCWs are analysed as a proportion within each of their occupational categories (i.e. 21 doctors became ill out of a total of 69), it is seen that the Allied health professionals were sick the most, with 77% of them being ill at least once. Nevertheless, the exploration of deeper psychological and social aspects of absenteeism within our study population is beyond the scope of this study; a qualitative systematic review of absenteeism among HCWs in low- and middle-income countries opined that three thematic categories of factors contribute to these phenomenon-namely, workplace/content, personal and organizational/cultural factors. Therefore, health system administrators seeking to provide solutions to the absenteeism rates within their workforce could take a cue by modifying these thematic factors appropriately for the overarching purpose of delivering quality and efficient health service.[82]

The two arms of our study population were comparable in all characteristics except for age. Here, there was a two-year difference in mean age with the exposed arm being older. An inference could be drawn on the impact this could have on the general health profile of both groups. Asides, the prevailing endemicity of HIV and TB within our study region,[41,43,46] the likelihood of chronic ailments like hypertension and diabetes mellitus being present is increased especially in our older exposed arm. The fact that about 30% of our study population are 50 years or older further gives credence to this reasoning. It has been well documented that influenza increases the mortality risk of individuals with underlying medical conditions.[70,83] On another note, we found that those of Caucasian ethnicity, employees above 50 years old and those employed for 20 years or longer were more likely to accept vaccination. While we did not explore other predictive factors due to the nature of our study design, however, these findings are in keeping with the results of other investigators in this regard.[57,62,84]

While attempts have been made earlier to address the few disparities of our study findings with those of conventional literature, certain concepts associated with the effectiveness of influenza vaccines should be highlighted. They are the concepts of ‘antigenic drift’ and ‘matching’. The former refers to periodic mutations of the haemagglutinin antigenic material of the Influenza A virus which enables it to evade immune recognition,[20] resulting in seasonal influenza outbreaks while the latter refers to the degree to which seasonal vaccines ‘compare with’ or ‘match’ circulating influenza viral strains.[85] It is generally accepted that matched strains afford the best protection.[7] Conflicting reports between studies have strived to explain the importance of these concepts on the effectiveness of the vaccines. Although, it has been demonstrated to have a crucial bearing on the efficacy of the vaccine among children and the elderly, its impact on effectiveness among healthy adults has not yet been fully established.[85-87] Extrapolating this effect on the effectiveness of the currently available vaccines on our HCWs remains unclear. In recent times, the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) project, a publicly funded network within European Union member states which monitors the effectiveness of vaccines within the region has released some statements concerning this.[88] While commenting on the 2011-2012 influenza season, they declared a low season effectiveness of 43% for the influenza vaccine on high- risk individuals in eight European countries. Later in the same season, private analysts submitted that the effectiveness has further fallen to less than 10%.[89-91]

The distinction between vaccine efficacy and effectiveness should be raised at this point. While the focus most times is on the performance labelled on the vaccines in ideal settings, health administrators should be mindful of the variance that arises under pragmatic conditions. For instance, a vaccine coverage of 20% could result in a 52% vaccine effectiveness (as against 70-90%).[22] Also, this does not take into account the impact of any prevailing medical conditions present in a typical middle-aged group of HCWs. There were no studies found that investigated this matter in our local setting. In view of the issues raised above, this study did not find any appreciable benefits realised so far from the annual seasonal influenza vaccination of HCWs at our study setting. This statement is however not generalisable considering all mitigating factors inherent in the study. Immunisation of HCWs should continue to be encouraged because the effect transcends mere reduction in illnesses incidents or absenteeism days among these invaluable professional group, but also gains accrued from protection of patients under their care.

Finally, according to the Hazardous Biological Agents Regulations (under the OHS Act 1993), the Influenza viruses belong to the Group II category of microbiological agents deemed hazardous to human health. Pathogens that fall under this category are assumed to have the potential to spread to the community and can cause severe human diseases, but to whom effective prophylaxis or treatments are available.[92] As such, regulatory measures, pertaining to risk assessments, exposure monitoring and medical surveillance of biological agents in the work place are applicable.[92,93] For the effective control of Influenza transmission within the healthcare environment; infection prevention and control precautions such as observance of basic hygiene (before and after patients), cough etiquettes and patient isolation measures should be applied when necessary. Moreover, in line with the vision of the national policy on Influenza which aims at reducing influenza-related mortality by two-thirds in 20 years[70]; this might prove to be a crucial part of this journey.

Study Limitations

This study is not without its weaknesses, despite all attempts by the investigators to present a precise reflection of the current status of influenza vaccine effectiveness in our setting. Inherent in study designs of this nature is the risk of selection bias. In our study, the inclusion of all vaccinated HCWs as a convenience sample is evident. Self-selected employees who voluntarily present themselves for vaccination could be aware of underlying medical factors or work at a higher-risk environment within the hospital, thus prompting their acceptance of immunisation. The converse of this could be the "healthy-worker effect' in which HCWs with a healthier enthusiasm towards their health readily accept vaccination. If present, these could have influenced our effect estimates and introduce issues with generalisability of our study findings. As commented earlier, the possibility of Information bias, specifically differential misclassification error is equally recognised. Likely sources of this could be the disparate clinically diagnoses accorded to all influenza-related illnesses. This too could alter the estimates of our results, by under or over-representing the true association.

Our outcome data had been previously collated for administrative purposes and not necessarily for research intents. Therefore, certain pertinent indicators related to determining illness onset and perhaps cost related indices could not be evaluated. Subsequently, the use of Regression models to predict some outcomes could not be done, although this would have been ideal. On another note, it is not uncommon for employees wanting to stay away from duty to claim influenza illness as an apology. This practice is customary especially during the winter seasons. Subsequently, unknown differences between the study groups might have affected the validity of our findings.

Finally, our assumption that all our randomly sampled controls were not vaccinated might be a misrepresentation of the truth. Certain HCWs might have been on some medical schemes offering free vaccinations as part of their care package or purchase the vaccine themselves from retail pharmacies. These assertions on the other hand could not be verified, since our outcome data source was historical and not interviewer/questionnaire-based. However, had we relied on the latter, the additional risk of recall bias might have been introduced.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

Conclusion

Response rate to Influenza vaccination among HCWs within our study centre has been quite low. In contrast, the burden of all influenza-related illnesses was found to be higher than expected. Within our study period, there was a higher proportion of HCWs reporting illness-related absenteeism compared to those that remained healthy. This absenteeism rate did not differ based on vaccination status. Along with the consideration for patient outcomes, renewed calls for a greater participation of Influenza vaccine uptake among our HCWs need to be made.

Recommendations

The natural inclination following overall assessment of our study findings is for health administrators to be dissuaded from promoting influenza vaccination coverage for their employees. However, in view of accumulated evidence to the contrary on this subject matter and with due consideration to several of our study limitations highlighted earlier, we propose calls for more targeted and prospective local studies which could help determine the effectiveness of these campaigns more accurately in our healthcare settings. In the interim, the apparent limited effectiveness of the influenza vaccination could perhaps be attributed to very low coverage among hospital employees. The following measures could be useful in boosting the coverage:

- The hospital administration should consider the mandatory vaccination of all health workers exposed to high-risk patients. These include but not limited to personnel who care for neonatal, geriatric and other immunocompromised patients. The benefits are two-fold as attested by several studies; it helps to reduce staff illnesses, absenteeism rates and invariably the disruption of services in these specialised units. Secondly, patient outcomes are improved because it ensures reduction in patient-HCW transmission and vice-versa.

- The responsibility of vaccine provision to staff members should not be borne by the OHC staff team alone. Health personnel in the Infection Prevention and Control units, Infectious diseases and Internal medicine departments could be involved and delegated to administer the vaccines and thus augment the awareness efforts initiated by the provincial DOH on influenza vaccination for all high-risk persons. This will have the appreciable effect of improving coverage within the academic hospital.
- Improved information and awareness programmes particularly during the winter seasons when attack rates soar should be encouraged. This is currently undertaken by the OHC team but this drive could be further expanded by the hospital PR department and other units mentioned above. In addition, high risk patients under care should be specifically targeted and equally vaccinated to further reduce their vulnerability with regards to morbidity risks acquired through nosocomial transmission. These awareness programmes should be extended to other health supporting service personnel such as the members of emergency medical services (paramedics) and social workers involved in the pre- and post- hospital management of these high-risk persons.
- Targeted education seminars aimed at dispelling erroneous perception of the virus among HCWs should be planned for. HCWs should be duly informed that the vaccines are inactivated (Trivalent Inactivated Influenza Vaccines-TIV) and therefore do not cause illness. They should also be made aware that asymptomatic HCWs can transmit the virus to their colleagues and vulnerable patients even when they appear asymptomatic.

- A suggestion is being made for the revision of returned sick certificates bearing illness associated absenteeism. Such sick certificates should indicate the HCWs' clinical diagnoses. In lieu of medical confidentiality issues, a staff illness database could be exclusively created and restricted access granted only to the OH team and other selected administrative personnel. This will ensure better quantification of the ill-health burden of both acute and chronic diseases among HCWs. This could prove beneficial during moments of ill-health retirement and other policy-making decisions, including an improved assessment of prospective health interventions among staff members in future.

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