ORIGINAL ARTICLE

Assessing influenza vaccination coverage and predictors in persons living with HIV/AIDS in Louisiana, June 2002-June 2013

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Key words

Influenza • Vaccination • HIV

Summary

Background. Despite the burden of disease and increased risk of influenza-associated morbidity and mortality among PLWHA, influenza vaccination has been understudied in this population.

Methods. We built an 11-year cohort of HIV-infected adults from medical records of PLWHA seeking care within the Louisiana State University medical system from June 2002-June 2013. Influenza vaccination uptake among PLWHA was calculated overall and for each medical facility for each influenza season. Linear regression was used to assess influenza vaccination uptake over time, both overall and by facility. Data were restricted to the final influenza season (2012-13) to assess predictors of PLWHA vaccination. Individuals were nested within medical facilities in order

Background

Vaccine preventable diseases represent a significant yet avoidable burden on the United States (US) population. Influenza afflicts 5-20% of the US population in a given year [1]. For most of the population, infection with the influenza virus does not cause severe illness or lead to significant complications. However, for others there are significant sequelae associated with influenza, including hospitalization and death. It is estimated that 200,000 people are hospitalized due to influenza-associated complications and between 3,000 and 49,000 influenzaassociated deaths occur per year in the United States, with the majority of morbidity and mortality experienced by the very young, the very old, and those with comorbid conditions, including persons living with HIV/AIDS (PLWHA) [2, 3].

The PLWHA population is of particular interest in Louisiana, with the metropolitan statistical areas (MSAs) of New Orleans (27.0 cases/100,000 persons) and Baton Rouge (26.9 cases/100,000 persons) ranking 4th and 5th in newly diagnosed HIV infections in the US in 2017 [4]. Nationally, the incidence of HIV infection has decreased in recent years, but there were still approximately 1.1 million people in the US living with HIV at the end of 2017, representing a significant portion of the population [4].

to assess the amount of variability in influenza vaccination rates across medical facilities.

Results. Influenza vaccination uptake among PLWHA increased over the study period (p < 0.01). The overall proportion of PLWHA vaccinated during the 2012-13 influenza season was 33.7%. 37.9% of the variability in the model occurred at the facility-level. **Conclusions.** Although there was an increase in influenza vaccination within the PLWHA cohort over the course of the study, vaccination rates remained low overall. Special efforts must be made to increase vaccination uptake among PLWHA, with particular focus on those within the population who are likely to be at highest risk. The substantial variability at the facility-level indicates that there are unmeasured facility-level factors that contribute significantly to PLWHA vaccination.

PLWHA are at increased risk for influenza-associated morbidity and mortality due to their immunocompromised status [5-11]. The influenza vaccine has been shown to be safe and effective in the prevention of influenza-associated illness and complications [6, 12-18]. As a result, influenza vaccination has been recommended in PLWHA since the early 1990s by the Advisory Committee on Immunization Practices (ACIP) and the United States Public Health Services (USPHS) and current guidelines recommend annual influenza vaccination for all PLWHA, regardless of immune system status [19-21].

Despite these factors, there are few studies that have attempted to quantify influenza vaccination uptake among PLWHA. The first study of influenza vaccination uptake in PLWHA was conducted in the early 1990s and revealed a vaccination rate of approximately 30% in PLWHA [22, 23]. Subsequent studies have shown uptake of influenza vaccination varies between 26.4% and 50.9% in the PLWHA population, with one study showing an influenza vaccination uptake of 55% and 57% in women with HIV/AIDS during the 2006-07 and 2007-08 influenza seasons, respectively [24-28]. Of the US studies that reported vaccination uptake among PLWHA, few describe predictors of influenza vaccination in PLWHA. Within this limited literature, predictors of influenza vaccination.

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Furthermore, those studies that evaluate predictors of influenza vaccination only do so at the individual level. Undoubtedly, there are higher level factors that also influence vaccination rates, including institutional policies and provider practices. The influences of institutional policies and provider practices on influenza vaccination uptake are demonstrable across a diverse body of literature [29-42]. While we cannot directly measure specific policies and practices, we are able to assess the influence of medical facility on vaccination uptake among PLWHA. Medical facilities are likely to vary both in the institutional practices that they implement and the beliefs and practices of the providers that they employ. The absence of analyses accounting for medical facility and other second level factors presents a significant gap in the literature.

The goals of this study are to (1) quantify influenza vaccination uptake among PLWHA, (2) analyze trends in PLWHA vaccination uptake over time, (3) assess the variability of PLWHA vaccination between medical facilities, and (4) determine what factors predict PLWHA vaccination.

Methods

STUDY DESIGN

We assembled an 11-year cohort of HIV-infected adults from electronic medical records of individuals seeking care within the Louisiana State University (LSU) medical system from June 2002 through June of 2013. The LSU medical system included seven medical centers in southern Louisiana, including Bogalusa (Bogalusa Medical Center [BMC]), Baton Rouge (Earl K Long Medical Center [EKL]), Independence (Lallie Kemp Regional Medical Center [LAK]), Houma (L.J. Chabert Medical Center [LJC]), New Orleans (Medical Center New Orleans/Interim LSU Public Hospital [MCL]), Lafayette (University Medical Center [UMC]), and Lake Charles W.O. Regional Medical Center [WOM]). Each of these medical centers provided primary care and specialty HIV care to PLWHA during the study period.

STUDY POPULATION

Patients included in this cohort had an HIV/AIDS ICD-9 diagnosis code (V098 or 042), were aged 18 years or older, and had a minimum of two visits to LSU medical centers during the study period. In yearly analysis, patients were required to be in care, which is defined as having a minimum of two visits during the preceding calendar year. These criteria resulted in a total sample size of 12,001, with a total of 4,586 PLWHA in care during the 2012-13 influenza season.

DATA SOURCE

During the study period, the LSU medical system used three different medical record systems. From 2002-2006, LSU medical centers used paper-based records. In 2006, these records were migrated into the newly developed electronic records system, Clinical Inquiry

(CLIQ). CLIQ was used to maintain medical records until 2012, when LSU medical centers began using the Epic system. All of the medical records in these systems were migrated to the HarmonIQ data warehouse, which was used to form the cohort used in this study.

OUTCOME

The outcome of this study was influenza vaccination status, which was defined as receipt of an influenza vaccine during a given influenza season (October 1st through March 31st). Patients were considered to have received an influenza vaccination if an influenza vaccination was documented in their medical records or was self-reported by the patient and documented by the provider. Prior to 2006, patients were not routinely asked whether they had received influenza vaccination in locations outside of the LSU medical system. From 2006-2012, under the new CLIQ system, providers were expected to either administer an influenza vaccination or to document receipt of an influenza vaccination in another location or refusal of an influenza vaccination. The post-2012 Epic system also allowed providers to document an administered vaccine or report of vaccination in a different setting.

Influenza vaccination status was dichotomized into a yes/no variable for each influenza season. The proportion of PLWHA who received an influenza vaccination was calculated by restricting the sample to PLWHA who were in care during the calendar year and dividing those with a reported vaccination by those without.

INDEPENDENT VARIABLES

LSU medical facility served as a second level unit in which individuals are nested. Select characteristics of included medical facilities are available in Tab I. Medical facility information was obtained from the 2011 LSU Healthcare Services Division (HCSD) Annual Report, which was the final published annual report by the organization (43). Individuals were assigned to a medical facility based on the medical facility where they had the most encounters over the years, apart from 2012-13. For that year, patients were assigned to a medical facility based on the medical facility they had the most encounters from January 2012 through June 2013. Encounters could be inpatient or outpatient visits. A complete list of independent variables can be found in Tab II, and includes demographics, healthcare related variables, cluster of differentiation four (CD4) counts, and conditions at increased risk for influenza-associated morbidity and mortality. Demographics considered for analysis included age, sex, and race. Age was recorded at last visit during the 2012 calendar year and was divided into three categories, aged 18-49 years, aged 50-64 years, and aged 65 years and older, based on age groups the Centers for Disease Control and Prevention (CDC) uses to report influenza surveillance data. Potential responses for sex included male or female. Due to the dominance of Black and White races in Southern Louisiana, race was categorized into racial/ethnic minority (Hispanic ethnicity, Black, and races other than White) and Whites.

Facility Code	Location	Estimated Economic Impact (in Millions)	Full Time Employees	Medical Residents	Licensed Beds	Inpatient Admissions	Inpatient Days	Outpatient Encounters	Emergency Department Encounters
BMC	Bogalusa, LA	\$ 124.52	608	21	98	2,573	10,015	118,946	27,843
EKL	Baton Rouge, LA	\$ 282.25	1,078	191	165	4,884	18,525	194,553	46,720
LAK	Independe- nce, LA	\$ 78.87	405	8	25	1,122	4,273	81,554	27,371
LJC	Houma, LA	\$ 200.60	934	46	156	3,943	15,378	175,403	41,950
MCL	New Orleans, LA	\$ 718.94	2,240	895	390	11,090	56,876	271,664	53,462
UMC	Lafayette, LA	\$ 215.80	916	70	150	4,188	18,417	182,256	44,562
WOM	Lake Charles, LA	\$ 87.72	396	N/A	74	938	3,782	94,598	27,211

Tab. I. Characteristics of medical facilities in the LSU Healthcare Network in Southern Louisiana.

BMC: Bogalusa Medical Center; EKL: Earl K. Long Hospital Center; LAK: Lallie Kemp Regional Medical Center; LJC: L.J. Chabert Medical Center; MCL: Interim LSU Public Hospital; UMC: University Medical Center; WOM: W.O. Regional Medical Center. Medical facility characteristics are based on the LSU Health Annual Report, which was last published in 2011.

A sizable portion of individuals had missing values for race (7.9%). These individuals were included in analysis as "unknown races" and compared against the racial/ ethnic minority and White categories.

Healthcare related variables included insurance status, number of years in care, and number of encounters from January 2012 through June 2013. Insurance status was categorized into three groups: those with insurance (private, Medicare, and Medicaid), those receiving free care (LSU policy per state law designated that those with an income less than 200% of the federal poverty limit are eligible to receive free care at the public hospitals) or grants to cover their HIV management, and those without insurance or who were labeled as uncollectable debt (individuals from whom the medical center did not anticipate recouping money expended for care). Number of years in care was calculated by subtracting the patient's date of HIV/AIDS diagnosis from the date of last visit and dividing the resulting number by 365. The number of encounters an individual had from January 2012 through June 2013 was measured by summing the total number of inpatient and outpatient encounters from any medical facility in the LSU medical system.

The last lab value available for a patient's CD4 count was considered his or her CD4 count for the purposes of analysis. The CD4 counts were categorized based on HIV infection staging (CD4+ T-lymphocyte counts of > 500 cells/ μ L, 200-499 cells/ μ L, and < 200 cells/ μ L). A substantial proportion of the population was missing CD4 counts (18.8%). These patients were grouped into an unknown CD4 category and compared against those without missing CD4 values.

Comorbid conditions considered to be high risk for influenza-associated morbidity and mortality included chronic conditions such as diabetes status (type 1 and type 2), kidney disease (chronic kidney disease, nephritic syndrome, renal transplantation, hemodialysis, end stage renal disease), heart disease (heart failure, hypertensive heart disease, pulmonary heart disease, heart valve disorders, arrhythmias, congenital heart defects, stroke), liver disease (cirrhosis, jaundice, viral hepatitis, hemochromatosis, Reye's syndrome, Wilson's disease), chronic lung disease (bronchitis, chronic bronchitis, emphysema, COPD, asthma, bronchiectasis), and all cancers. If a patient was diagnosed with any of these conditions, it was assumed from that point on that they were afflicted with the condition. If a patient had a diagnosis code for any of these conditions, they were considered to have at least one comorbid condition.

STATISTICAL ANALYSIS

PLWHA influenza vaccination uptake was calculated for each influenza season during the study period. Trends in influenza vaccination uptake were assessed using linear regression models, with vaccination uptake set as the dependent variable and influenza season as the independent variable. Regressions were performed for each medical facility, enabling a comparison in vaccination uptake between medical facilities. P-values of these models were used to assess the significance of these trends over time.

Data were restricted to the most recent available influenza season to assess the variability of influenza vaccination uptake among PLWHA between medical facilities and determine what factors predict PLWHA vaccination. Additionally, patients had to be in care to be considered for analysis. This resulted in a sample size of 4,586 for analysis.

In order to account for the differences in influenza vaccination status between medical facilities, a multilevel model with patients nested within medical facility was constructed. The multilevel models used in this study were random-intercept, which allowed the assessment of variability between facilities. A series of multilevel models, with each predictor variable individually, medical facility (2nd level variable), and vaccination status were used to generate unadjusted

ORs. To obtain adjusted ORs, vaccination status was regressed on all potential predictors in a full multilevel model. Medical facility was set as the second level unit of analysis. A crude intraclass correlation coefficient (ICC) was obtained from the full model. Predictors were eliminated from the model based on a threshold p-value of 0.05. When all the remaining predictors had p-values less than or equal to 0.05, adjusted ORs and an intraclass correlation coefficient (ICC) were obtained.

Inclusion of unknown values as additional comparison groups of a categorical variable can potentially bias the results of the analysis (44). In order to assess whether bias was present and the magnitude of the potential bias, a sensitivity analysis restricted to individuals with complete records was conducted. Removing those with missing values reduced the analytic sample size from 4519 to 3391 individuals. To obtain adjusted measures for the sensitivity analysis, vaccination status was regressed on all potential predictors in a full multilevel model. Predictors were eliminated from the model based on a threshold p-value of 0.05. When all the remaining predictors had p-values less than or equal to 0.05, adjusted ORs and an ICC were obtained.

All analyses were performed using SAS 9.4. This study was approved by the LSUHSC IRB (IRB#10178).

Results

Table I describes the characteristics of medical facilities included in this analysis. Although none of these data were included as predictors in the multilevel model and their statistical impact was not evaluated, they provide important context and relevant descriptions of included facilities. Estimated economic impact ranged from \$78.87 million in LAK to \$718.94 million in MCL. All other facility-related factors, such as number of full time employees (range: 396-2,240), number of medical residents (range: 0-895), number of licensed beds (range: 25-390), number of inpatient admissions (range: 938-11,090) and inpatient days (range: 3,782-56,876), number of outpatient encounters (range: 81,554-271,664), and emergency department encounters (27,211-53,462), correlated to the estimated economic impact of the medical facility. Facilities in urban areas, such as EKL in Baton Rouge (\$282.25 million) and MCL in New Orleans (\$718.94 million) had the highest economic impacts.

From a qualitative perspective, economic impact and all other corresponding factors did not appear to correlate to increased influenza vaccination uptake within facilities. For instance, MCL, the facility that serves the largest population, has the largest economic impact, the largest number of full time employees and medical residents, and so on, had an influenza vaccination uptake of just 10.6% among PLWHA during the 2012-13 influenza season. The two most successful facilities, LJC (PLWHA vaccination uptake: 74.7%) and WOM (PLWHA vaccination uptake: 58.8%) had the second and fourth lowest economic impacts of the facilities included in this study.



Figure 1 shows influenza vaccination uptake among PLWHA from the 2002-03 through the 2012-13 influenza seasons. Results are presented for overall influenza vaccination uptake and vaccination uptake by medical facility. With the exception of BMC (7.4% increase in influenza vaccination uptake), influenza vaccination uptake among PLWHA increased significantly from baseline over the study period within all medical facilities (EKL, 11,650.0% increase; LAK, 343.2% increase; LJC, 97.6% increase: MCL. 68.2% increase: UMC. 25.650.0% increase; WOM, 129.6% increase. Overall, PLWHA influenza vaccination uptake increased over the study period (471.2% increase), with a substantial increase in the 2006-07 and 2007-08 influenza seasons, stable rates until the 2011-12 influenza season, and substantial decrease in the 2012-13 influenza season. The decrease between the 2011-12 and 2012-13 influenza seasons was fueled primarily by a 76.3% decrease in influenza vaccination in MCL, the largest medical center in the LSU healthcare network. The proportion of PLWHA receiving influenza vaccination in LSU medical facilities followed the same general trend as the overall proportion of PLWHA, except for the 2012-13 influenza season. While the overall proportion of PLWHA receiving influenza vaccination decreased from the 2011-12 to the 2012-13 influenza seasons, EKL, LJC, and WOM all experienced increases of between 6.3-15.0% in PLWHA influenza vaccination uptake.

Table II shows the overall distribution of vaccination status, demographics, healthcare related variables, CD4 counts, and comorbid conditions at increased risk for influenza-associated morbidity and mortality as well as the relationship between the independent variables and vaccination status. The proportion of PLWHA who received an influenza vaccination during the 2012-13 influenza season was 33.7%. The majority of PLWHA were served by medical facilities in two major-metropolitan areas (Baton Rouge, LA and New Orleans, LA), MCL (40.0%), and EKL (29.4%). The majority of the population sample was aged 18-49 years (56.3%),

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	Overall	Vaccinated	Unvaccinated	
Study Variables	(n = 4586)	(n = 1547)	(n = 3039)	p-value*
	n (%)	n (%)	n (%)	
Outcome				
Vaccination				
Vaccinated	1547 (33.7)	N/A	N/A	N/A
Unvaccinated	3039 (66.3)			
2 nd Level Variable				
Medical Facility				
MCL	1834 (40.0)	195 (10.6)	1639 (89.4)	
BMC	139 (3.0)	8 (5.8)	131 (94.2)	
EKL	1345 (29.4)	632 (47.0)	713 (53.0)	- 0.01
LAK	230 (5.0)	106 (46.1)	124 (53.9)	< 0.01
LJC	277 (6.1)	207 (74.7)	70 (25.3)	
UMC	624 (13.6)	322 (51.6)	302 (48.4)	
WOM	131 (2.9)	77 (58.8)	54 (41.2)	
Predictors				
Insurance Status				
Uncollectable Debt/Uninsured	1390 (30.7)	247 (17.8)	1143 (82.2)	0.04
Free Care/Grant	1092 (24.1)	463 (42.4)	629 (57.6)	< 0.01
Insured	2042 (45.1)	824 (40.4)	1218 (59.7)	
Sex				
Female	2004 (43.7)	659 (32.9)	1345 (67.1)	0.28
Male	2582 (56.3)	888 (34.4)	1694 (65.6)	
Age				
Aged 18-49 Years	2581 (56.3)	832 (32.2)	1749 (67.8)	0.05
Aged 50-64 Years	1748 (38.1)	623 (35.6)	1125 (64.36)	0.05
Ages 65 Years and Older	257 (5.6)	92 (35.8)	165 (64.2)	
Race				
Non-White	3236 (70.6)	1098 (33.9)	2138 (66.1)	0.04
White	986 (21.5)	387 (39.3)	599 (60.8)	< 0.01
Unknown	363 (7.9)	62 (17.1)	301 (82.9)	
Comorbid Conditions				
No	1759 (38.4)	523 (29.7)	1236 (70.3)	< 0.01
Yes	2827 (61.6)	1024 (36.2)	1803 (63.8)	
CD4				
< 200	736 (16.1)	216 (29.4)	520 (70.65)	
200-499	1540 (33.6)	534 (34.7)	1006 (65.3)	< 0.01
500+	1449 (31.6)	583 (40.2)	866 (59.8)	
Unknown	861 (18.8)	214 (24.9)	647 (75.2	
Study Variables		Mean (SD)		p-value
Years in Care	6.33 (4.02)	6.58 (3.90)	6.21 (4.08)	0.05
Encounters from January 2012-June 2013	15.01 (12.38)	16.52 (11.37)	14.24 (12.79)	< 0.01

Tab. II. Characteristics of in care PLWHA in Southern Louisiana 2012-13, by vaccination status (n = 4586).

n: population; N/A: not applicable; BMC: Bogalusa Medical Center; EKL: Earl K. Long Hospital Center; LAK: Lallie Kemp Regional Medical Center; LJC: L.J. Chabert Medical Center; MCL: Interim LSU Public Hospital; UMC: University Medical Center; WOM: W.O. Regional Medical Center. * Chi-squared tests used to calculate p-value for categorical variables and t-test used to calculate p-value for continuous variables.

male (56.3%), racial and ethnic minority (70.6%), insured (45.1%) or received free care or had care that was covered by a grant (24.1%), had at least one comorbid condition (61.6%), and had CD4 counts above 200 (65.2%). The mean number of years in care was 6.33 years (SD =4.02) and the mean number of encounters from January 2012 through June 2013 was 15.01 (SD = 12.38). All potential predictors, including demographics, healthcare related variables, CD4 count, and conditions at increased risk for influenza-associated morbidity and mortality, with the exception of sex, demonstrated an unadjusted relationship with vaccination status ($p \le 0.05$).

Table III shows the unadjusted and adjusted ICCs, the unadjusted relationship between each of the predictors

and vaccination status in a multilevel model, and adjusted relationship between significant predictors and vaccination status in a multilevel model. The unadjusted model had an ICC of 0.377, indicating that 37.7% of the total variability in influenza vaccination uptake was between medical facilities. Even after accounting for significant individual-level predictors of vaccination status and compositional differences in these predictors across medical facilities, the ICC remained high, at 0.379. This result indicates that 37.9% of the total variability in influenza vaccination uptake was between medical facilities.

Insurance status, sex, CD4 count, and number of encounters from January 2012 through June 2013

Predictors	Unadjusted* OR (95% CI)	Adjusted** OR (95% CI)	Adjusted Sensitivity Analysis*** OR (95% CI)	
<i>Insurance Status</i> Uncollectable Debt/Uninsured Free Care/Grant Insured	Reference 1.46 (1.18-1.80) 1.54 (1.27-1.86)	Reference 1.24 (0.99-1.54) 1.34 (1.11-1.64)	Reference 1.20 (0.92-1.55) 1.42 (1.13-1.78)	
<i>Sex</i> Female Male	Reference 1.23 (1.07-1.42)	Reference 1.21 (1.04-1.40)	Reference 1. 29 (1.09-1.52)	
Age Aged 18-49 Years Aged 50-64 Years Aged 65 Years and Older	Reference 1.18 (1.02-1.37) 1.01 (0.75-1.36)	N/A	N/A	
Race Racial and Ethnic Minority White Unknown	Reference 1.11 (0.93-1.33) 0.80 (0.58-1.11)	N/A	N/A	
Comorbid Conditions No Yes	Reference 1.26 (1.09-1.46)	N/A	N/A	
CD4 < 200 200-499 500+ Unknown	Reference 1.35 (1.09-1.67) 1.61 (1.30-1.99) 0.60 (0.47-0.77)	Reference 1.41 (1.13-1.75) 1.70 (1.37-2.11) 0.66 (0.51-0.85)	Reference 1.42 (1.13-1.78) 1.66 (1.32-2.08) Excluded	
Years in Care [#]	1.05 (1.03-1.06)	N/A	N/A	
Number of Encounters from January 2012- June 2013 [#]	1.03 (1.02-1.04)	1.03 (1.02-1.04)	1.03 (1.02-1.04)	
ICC	0.377*	0.379**	0.395***	

Tab. III. Unadjusted and adjusted relationships between predictive variables and vaccination status among in care PLWHA in Southern Louisiana, 2012-13 (n = 4519).

n: population; N/A: not applicable; OR: odds ratio; CI: confidence interval; ICC: intraclass correlation coefficient. Bolded values are significant at $p \le 0.05$. # ORs calculated as one unit offsets from the mean. * Model includes all potential predictors. ** Model includes insurance status, sex, CD4 count, and number of encounters from January 2012-June 2013. *** Model uses only complete cases (n = 3391) and includes insurance status, sex, CD4 count, and number of encounters from January 2012-June 2013.

remained significant predictors of vaccination status in the final model. Those who were insured (OR = 1.34, 95% CI [1.11, 1.64]) and who had free care or care covered by a grant (OR = 1.24, 95% CI [0.99, 1.54]) were more likely to receive an influenza vaccination than those who were uninsured. Males (OR = 1.21, [1.04, 1.40]) were more likely than females to receive an influenza vaccination. Those with CD4 counts higher than 200 were more likely to receive influenza vaccination (OR₂₀₀₋₄₉₉ = 1.41, 95% CI [1.13, 1.75]; $OR_{500+} = 1.70, 95\%$ CI [1.37, 2.11]), while those with unknown CD4 counts were less likely to receive an influenza vaccination (OR_{Unknown} = 0.66, 95% CI [0.51, 0.85]). Additionally, those with greater numbers of encounters from January 2012-June 2013 were more likely to receive an influenza vaccination (OR = 1.03, 95% CI [1.02, 1.04]).

The results of the sensitivity analysis are presented in Table III. The adjusted model in the sensitivity analysis contained the same predictors as the adjusted model in the primary analysis. The ORs describing the relationship between the predictors and the outcome did not differ substantially between the two models. The ICC in the sensitivity analysis (0.395) was slightly higher than the ICC in the primary analysis (0.379).

Discussion

Despite the safety and effectiveness of the influenza vaccine in PLWHA, the increased risk of influenzaassociated morbidity and mortality in PLWHA, and the recommendation that PLWHA receive the influenza vaccine, influenza vaccination uptake among PLWHA was low across both facilities and influenza season. Annual influenza vaccination uptake among PLWHA seeking care within the LSU healthcare network (4.1-46.0%) was drastically lower than the recommended vaccination goal of 90% for those with high risk conditions [45]. However, the overall proportions of PLWHA receiving an influenza vaccination from 2007-08 through 2012-13 (25.8-46.0%) in the cohort were similar to those quantified in previous literature [24-28]. The increase in influenza vaccination uptake beginning in 2006-07 and extending through the end of the study period was likely attributable to Healthcare Effectiveness Programs implemented by HCSD. In 2006, HCSD built and implemented CLIQ, a hybrid system that combined medical guidelines, patient medical records, and clinical decision support tools to provide providers with realtime information on the patient. Multiple guidelines were built into the system, reminding providers to address

certain healthcare needs, including vaccination. HCSD also began implementing competitions among clinical leads and their teams within LSU medical facilities in an effort to improve quality metrics. Those that excelled in the Healthcare Effectiveness programs or showed drastic improvement in a particular area received awards from HCSD.

The 76.3% drop in influenza vaccination in MCL from the 2011-12 to 2012-13 influenza season is a particularly interesting result. Through data validation, we have ensured that this was not a data tracking error and that the drop in vaccination uptake is a true result. One possible explanation for the drop in vaccination proportions is the switch to the Epic healthcare records system. The Epic system contained many more areas of focus than the CLIQ system. It is possible that other portions of the HCSD Healthcare Effectiveness Program were prioritized over influenza vaccination, leading to lower vaccination proportions overall and specifically in MCL.

The adjusted, multilevel model showed that those with insurance or free care or care covered by a grant, those of male sex, those of CD4 counts higher than 200, and those with more encounters from January 2012 through June 2013 are more likely to receive the influenza vaccine. The limited research on the predictors of influenza vaccination in PLWHA provides an inconsistent profile of those who receive influenza vaccinations. Across studies, number of visits is predictive of influenza vaccination [24, 25, 27, 28]. Insurance status, increased CD4 count, and male sex have all been identified in one or more studies as significant predictors of influenza vaccination [24, 25, 27, 28]. Predictors found significant in other studies, including age and race, were found to be non-significant among PLWHA in the LSU healthcare system [24, 25, 28].

Insurance status, sex, CD4 count, and number of encounters logically correlate with higher vaccination rates. An increased number of visits indicates that a patient is more engaged in care, potentially has additional risk factors that would indicate influenza vaccination, and has an increased opportunity to receive a provider recommendation, which has been shown to be predictive of influenza vaccination across studies [38, 39, 41, 42]. Those who are insured or receive free care or care covered by a grant are more likely to have access to medical care, visit the medical facility with regularity, receive a provider recommendation, and receive an influenza vaccine as a result. Men were more likely than women to receive a vaccination in our sample. This may be due to unmeasured confounders such as income, education, employment, and other socio-economic or demographic factors that typically correlate with gender. Those with higher CD4 counts were more likely to receive an influenza vaccination, despite the fact that those with lower CD4 or unknown counts are more likely to experience influenza-associated morbidity and mortality [8, 46, 47]. Lower or unknown CD4 counts potentially indicate increased non-adherence to HIVrelated care and preventive care in general, which would include influenza vaccination.

The multilevel model indicated that there was a large amount of unexplained variance (37.9%) in vaccination uptake across medical facilities. The large proportion of unexplained variance at the facility-level suggests that there are unmeasured factors at the facility-level that are contributing to the overall difference in vaccination rates among PLWHA. The qualitative characteristics of the medical facilities do not seem to offer any clear patterns that would contribute to the different influenza vaccination uptake between facilities. As such, it is likely that differing institutional policies and provider beliefs and practices between the facilities either promote or inhibit influenza vaccination uptake. Although we cannot measure these institutional policies and provider practices and beliefs, we can make inferences based on what we know about the programs. All of the hospitals in the LSU health system were managed by HCSD and used the same EHR. This would indicate that tactics such as standing orders, electronic alerts, quality improvement programs, and others would be the same between the hospitals. However, there is no way to tell if each of the programs initiated by HCSD were implemented and prioritized to the same degree. Also, there are efforts that could have been undertaken by each of the hospitals, such as making efforts to reduce out-of-pocket costs to patients, sending patient reminders, piloting incentive programs within the PLWHA population, and providing assessment and feedback to providers. Additionally, there are factors that likely varied with respect to providers, such as knowing how to bill for vaccinations, lack of time with patients, prioritization of other health conditions over the influenza vaccine, and not consistently recommending the influenza vaccine. In any case, the amount of variation occurring at the facilitylevel is substantial, indicating that understanding what is occurring at these higher levels is absolutely essential to understanding differences in influenza vaccination uptake among PLWHA.

The adjusted sensitivity analysis did not reveal any substantial differences from the primary analysis. This suggests that inclusion of the "unknown" categories in the race/ethnicity and CD4 count variables did not bias the adjusted measures produced by the adjusted multilevel model. Therefore, we elected to keep the "unknown" categories in order to maintain a larger sample size.

LIMITATIONS

This study is subject to several limitations. Outcome assessment was based on patient medical records. Although these medical records allowed providers to indicate whether a patient had received a vaccination in a location outside of the medical facility, there is no guarantee that providers consistently input this information, and the degree of this inconsistency cannot be quantified. This would result in individuals being misclassified as unvaccinated, which would artificially suppress the proportion of individuals who received influenza vaccination. These effects are minimized because the LSU medical facilities were the source of

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primary care for most patients and the patients included in this study were classified as in care. The combination of these factors reduces the likelihood that patients would receive influenza vaccination in settings other than LSU medical facilities. In any case, the estimates in this paper provide a conservative estimate of the overall influenza vaccination rates in the HIV population.

The use of medical records limited the number of potential predictive variables included in the multilevel model. Notably, certain demographic and socioeconomic variables, such as income, education, and employment, among others, were not recorded in the medical records but have been shown to influence influenza vaccination among non-PLWHA adults [40, 48-52]. Furthermore, reasons why influenza vaccination was not received were not recorded or captured in the medical records. Negative attitudes and beliefs and structural barriers influence an individual's choice to receive an influenza vaccination but were unable to be assessed given the data source [50, 53, 54].

There were clear differences in the proportion of PLWHA who received influenza vaccination by medical facility. These differences are likely due to unmeasured institutional policies and provider beliefs and practices. Due to the limitations of the data, the unmeasured factors could not be identified and their influence could not be quantified.

The demographic composition of the cohort used in this study was primarily racial/ethnic minority, with the large majority of racial and ethnic minorities being Black. These demographics, combined with the use of medical records, may indicate that this cohort is not generalizable to the rest of the United States, particularly of White Hispanics and those who are not in care.

STRENGTHS

This study uses a large cohort of HIV-infected individuals (n = 12,001) to assess influenza vaccination uptake among PLWHA over time, to assess predictors of influenza vaccination, and to assess facility-level variability in influenza vaccination. The results of this study provide the most up-to-date analysis of the predictors and influenza vaccination uptake in the PLWHA population and was the first study to assess the influence of medical facility on influenza vaccination among PLWHA.

Conclusions

Despite the recommendation that PLWHA should universally receive the influenza vaccine, the proportion of PLWHA who received the vaccine remained low over the course of this 11-year period. Moreover, those PLWHA who were not receiving the influenza vaccine, including those with low or unknown CD4 counts, those who are uninsured, and those with fewer numbers of encounters are those who are more likely to be at risk of influenza-associated morbidity and mortality. Special efforts must be made to increase influenza vaccination

rates in the PLWHA population, particularly among those who are at highest risk. There was also clear variation by medical facility in this study, even though all facilities were managed by the same entity. This indicates a need for universal standards for PLWHA influenza vaccination across medical facilities and a method to evaluate these standards must be developed. There is significant room for further research on these topics, particularly as it relates to the barriers and facilitators of influenza vaccination in PLWHA. Medical records cannot be used to ascertain the reasons why individuals are not being vaccinated, whether it be negative attitudes and beliefs regarding the influenza vaccine, structural barriers to vaccination, or other reasons. The high variability at the facility-level indicates that institutional policies and provider beliefs and practices influences individual PLWHA influenza vaccine uptake. Future research should be dedicated to identifying these higher level factors. Identifying barriers to influenza vaccination is the key to increasing overall influenza vaccination rates within the PLWHA population.

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Conflict of interest statement

None of the authors report any conflict of interest.

Authors' contributions

PM conceptualized, designed, and implemented this study. He supervised the establishment of the PLWHA cohort, performed all data analyses, and authored the manuscript. AR aided in study design and provided feedback on the analyses and manuscript. SB advised on the multilevel analyses conducted in this manuscript. JC assisted in establishing the cohort of PLWHA seeking care at LSU hospitals. EP and SSB aided in study design and provided feedback on the analyses and manuscript.

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