Influenza Vaccination Uptake in Pediatric Patients with Cancer and Sickle Cell Disease

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Abstract

Background: Influenza causes greater morbidity in pediatric patients with cancer or sickle cell disease (SCD). Limited data exists on influenza vaccination uptake for these populations in a low-vaccination state. Outpatient interventions improve vaccine uptake but isolated inpatient interventions remain unstudied. Procedure: We reviewed influenza vaccination of pediatric patients with cancer or SCD treated at Children's Healthcare of Atlanta (CHOA) during three influenza seasons. An opt-out inpatient admission order set was implemented prior to the 2019-2020 influenza season. Vaccination status of patients that were admitted during an influenza season was compared pre- and post-intervention via Chi-squared analysis and multivariate logistic regression. Results: 1548 and 2549 patients with cancer and SCD (respectively) were eligible. The oncology (60%-62%) and SCD cohorts (61%-65%) had similar-to-higher vaccination uptake to the US (58-64%, p=0.01-0.79) and higher uptake compared to Georgia (51%-56%, p<0.01). There was no significant improvement in uptake after implementation of the inpatient intervention for admitted patients with cancer (40% vs 56%, p=0.05-0.88) or SCD (44% vs 56%, p=0.01). Multivariate logistic regression also found no significant increase in vaccine uptake (Hematologic Malignancy: 0.8 [0.73-0.98], Solid Tumor: 0.9 [0.80-1.90], CNS Tumor: 0.9 [0.71-1.14], SCD: 0.9 [0.85-0.99]). Conclusion: Pediatric patients with cancer and SCD have similar-to-greater influenza vaccination uptake compared to Georgia and the United States. An intervention focused on vaccinating hospitalized patients did not significantly improve the proportion of cancer or SCD patients who received influenza vaccine in each season. Future studies are needed to identify alternative approaches to improving vaccine uptake in these cohorts.

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Abbreviations:

SCD	Sickle Cell Disease
ACIP	Advisory Community on Immunization Practices
CNS	Central Nervous System
IIV	Inactivated Influenza Vaccine
CHOA	Childrens Healthcare of Atlanta
CDC	Center for Disease Control and Prevention
HSCT	Hematopoietic Stem Cell Transplant
GRITS	Georgia Registry of Immunization Transactions and Services
EHR	Electronic Health Record
REDCap	Research Electronic Data Capture

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Abstract

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Procedure: We reviewed influenza vaccination of pediatric patients with cancer or SCD treated at Children's Healthcare of Atlanta (CHOA) during three influenza seasons. An opt-out inpatient admission order set was implemented prior to the 2019-2020 influenza season. Vaccination status of patients that were admitted during an influenza season was compared pre- and post-intervention via Chi-squared analysis and multivariate logistic regression.

Results: 1548 and 2549 patients with cancer and SCD (respectively) were eligible. The oncology (60%-62%) and SCD cohorts (61%-65%) had similar-to-higher vaccination uptake to the US (58-64%,p =0.01-0.79) and higher uptake compared to Georgia (51%-56%,p <0.01). There was no significant improvement in uptake after implementation of the inpatient intervention for admitted patients with cancer (40% vs 56%, p =0.05-0.88) or SCD (44% vs 56%, p=0.01). Multivariate logistic regression also found no significant increase in vaccine uptake (Hematologic Malignancy: 0.8 [0.73-0.98], Solid Tumor: 0.9 [0.80-1.90], CNS Tumor: 0.9 [0.71-1.14], SCD: 0.9 [0.85-0.99]).

Conclusion: Pediatric patients with cancer and SCD have similar-to-greater influenza vaccination uptake compared to Georgia and the United States. An intervention focused on vaccinating hospitalized patients did not significantly improve the proportion of cancer or SCD patients who received influenza vaccine in each season. Future studies are needed to identify alternative approaches to improving vaccine uptake in these cohorts.

Introduction

Pediatric cancer affects 15 000 new patients less than 20 years of age every year, while sickle cell disease (SCD) affects approximately 100 000 Americans and occurs in 1 out of every 365 Black or African-American births.[1,2] Morbidity from seasonal influenza is significantly higher for pediatric patients with cancer and

sickle cell disease compared to the general pediatric population in the United States. Children with SCD are hospitalized for influenza at 56 times the rate of children without SCD, though disease severity and length of hospitalization tend to be similar.[3] Among pediatric patients with cancer that contract influenza, 30-70% of patients require hospitalization and 10-20% require intensive care; this was found to be more common with the 2008-2009 pandemic H1N1 strain.[4–6] Importantly, delays in chemotherapy caused by viral infections like influenza affect up to a third of all pediatric cancer patients, increasing the risk of treatment failure.[7]

The Advisory Committee on Immunization Practices (ACIP) recommends annual inactivated influenza vaccination (IIV) for all immunocompromised individuals.[8] Historically, IIV uptake has been poor in both SCD and pediatric cancer populations, ranging from 20-60% in SCD, 40-50% in solid and central nervous system (CNS) tumors, and 60-70% in hematologic malignancies.[9–13] Quality improvement studies have shown the efficacy of outpatient interventions.[12–16] In prior work, we demonstrated that opt-out clinical decision support (CDS) promoting influenza vaccine increased the chances that eligible children would receive influenza vaccine prior to hospital discharge in the general population.[17] However, it remains unknown whether such an intervention improves total IIV vaccine coverage in oncology and SCD populations.

This study aimed to compare influenza vaccination rates in pediatric patients with oncologic diagnoses or SCD to that of the general pediatric population in the United States and in the state of Georgia, a historically low uptake state for influenza vaccination (ranked fifth lowest state in influenza vaccination uptake nationally during the 2019-2020 influenza season).[18] We hypothesized that influenza vaccine uptake among pediatric patients with cancer and SCD are higher than both the state and national general pediatric populations. We also explored contributing patient factors to influenza vaccine uptake in these two patient populations to inform future interventions. Lastly, we examined the efficacy of an inpatient opt-out CDS intervention for improving influenza vaccination uptake among patients admitted during an influenza season. We hypothesized that pediatric patients with cancer or sickle cell disease admitted at least once during an influenza season and exposed to the order set would have higher IIV uptake than those admitted patients that were not exposed to the intervention.

Methods

Participants

Our study sample consisted of pediatric patients with cancer and SCD treated at the Aflac Cancer and Blood Disorders Center at Children's Healthcare of Atlanta (CHOA), a large pediatric hematology-oncology program in the southeastern United States. Across a three-hospital system, CHOA sees approximately 450-500 new oncology diagnoses a year and cares for approximately 1900 children and adolescents with SCD annually. All study participants were active patients aged six months to 20.99 years at the beginning of at least one of three recent influenza seasons (September 1 to April 30; 2017-2018, 2018-2019, 2019-2020). Influenza season date ranges are based on influenza season data from the Centers of Disease Control and Prevention (CDC) and the first availability of influenza vaccines at CHOA.[19] Patient eligibility was unique to each influenza season and a patient could be eligible for more than one season based on their age and/or off-therapy date.

Active pediatric oncology patients were categorized as children undergoing active, cancer-targeted treatment ("on therapy") or who had completed treatment ("off therapy") less than six months prior to the study date range described above. For example, a patient eligible for the 2019-2020 influenza season cohort would either be on therapy during the season or have an off-therapy date on or after March 1, 2019 (six months prior to the start of the season). Active sickle cell patients were defined as patients with a documented SCD genotype who had at least one health maintenance visit annually during the calendar year of the start of the influenza season (i.e., January-December 2017 for the 2017-2018 season). Patients with sickle cell trait were excluded. Patients that underwent hematopoietic stem cell transplant (HSCT) during an influenza season could still be eligible for that season; if the HSCT concluded their active anti-neoplastic therapy, the patient's transplant date was considered their off-therapy date. Patients that lived or were treated outside of the state of Georgia at any point during an influenza season were excluded because vaccination status was

ascertained from the Georgia Registry of Immunization Transactions and Services (GRITS) for this study.

To analyze the effect of the inpatient admission order set, we utilized the subset of the eligible cohort above that had been admitted at least once during an influenza season. Like the general cohort above, the inpatient cohort was unique for each influenza season. Admitted patients were identified through admission billing codes of "Inpatient", "Observation", or "Surgery Admit – IP" for greater than 24 hours.

Intervention

For the 2019-2020 influenza season, a quality improvement group at CHOA implemented a system-wide opt-out influenza vaccination order set within every inpatient admission order set for both general pediatrics and subspecialty services to improve vaccination rates, described elsewhere.[17] Briefly, the CDS system checked to see if the patient was in the appropriate age group, whether they had already received an influenza vaccine that season, and checked for any history of anaphylaxis to influenza vaccination. If the patient was deemed eligible by these criteria, the algorithm placed pre-selected orders for the influenza vaccine and nursing instructions to administer the vaccine prior to discharge. The admitting provider had the option to deselect the orders if clinically indicated, and the patient or parent had the option to refuse the vaccine at the time of discharge.[20] These orders were incorporated into Oncology and SCD admission order sets on October 3, 2019, and October 23, 2019, respectively, 4-8 weeks after influenza vaccinations became available. There were no other novel concurrent interventions for improving influenza vaccine uptake implemented during the study period. CHOA had previously implemented non-interruptive opt-in reminders in the electronic health record (EHR) for influenza vaccine at all outpatient clinic encounters using the same eligibility criteria.

Data Abstraction and Management

Patient demographic data, disease-specific data, and vaccination status were abstracted from the EHR (Epic Systems, Verona, WI) and from clinical databases of all patients with cancer and SCD that are maintained internally within CHOA. The Cancer Registry of CHOA reports detailed demographic and cancer-related information on all patients with pathology or imaging-confirmed pediatric cancer to the Georgia Cancer Registry (GCR), a statewide population-based cancer registry that is part of the National Cancer Institute's SEER Program. Additionally, any history of relapsed, progressive, or refractory disease was abstracted from the CHOA Cancer Registry. Off-therapy dates for study eligibility were updated through October 2020. Off-therapy dates were set as the last day of chemotherapy or radiation, or the day of definitive surgical resection, whichever occurred later. Patients who were off-therapy prior to January 1, 2017, who died due to their primary disease, who transferred to another institution prior to the end of therapy, who were lost to follow up, or whose end of therapy date was otherwise not available (i.e., completed therapy at another institution prior to coming to CHOA) were deemed ineligible. Patients with solid or CNS tumors who did not undergo definitive resection or receive chemotherapy treatment were excluded.

For the SCD cohort we utilized the Sickle Cell Disease Clinical Database of CHOA, a comprehensive, prospective database housed in REDCap tasked with capturing utilization data from all patients with a laboratory-confirmed diagnosis of SCD with [?]1 healthcare encounter at CHOA from 2010 onward. Data capture includes laboratory-verified SCD genotype, SCD treatment history (specifically hydroxyurea, chronic transfusions, and HSCT), and dates and diagnoses of all healthcare utilization at CHOA. Any history of pneumococcal vaccine polyvalent 23 administration (as a marker of vaccine acceptance), splenectomy, hydroxyurea use, acute chest syndrome, and chronic transfusion were also abstracted from the Sickle Cell Database.

Age at the start of each season, race, ethnicity, sex, history of influenza vaccination in prior influenza seasons, IIV administration during the target influenza season, prior pneumococcal vaccination, number of admissions per season, and history of stem cell transplant were auto-abstracted from the EHR for all patients. Vaccine data were drawn from the GRITS database, a statewide registry of all immunizations given in the state of Georgia since 1996. Medical providers and any other persons licensed to administer vaccines in the state of Georgia are mandated to submit documentation of all immunizations within 30 days of administration.[21] Through a partnership between GRITS and CHOA, every new CHOA encounter (inpatient or outpatient) for

a patient queries the GRITS database and pulls the updated immunization record into the EHR. Exposure to the inpatient CDS intervention was abstracted automatically as described elsewhere.[17]

Twenty patient charts for each were randomly chosen for manual abstraction to verify the validity of data obtained from auto-abstraction. Overall influenza vaccination uptake for the general pediatric population of the United States and the state of Georgia were acquired from the CDC's Influenza Seasons Vaccination Coverage Trend Report, which provides national and state-specific data on influenza vaccination uptake since 2010.[18]

Statistical Analysis

The unit of analysis was the proportion of patients per season that received the IIV (patient-season). Age was calculated for September 1 of the eligible seasons. Sex was recorded as binary (boy/girl). Race and Ethnicity were combined into groups of Asian, Hispanic/Latino, Non-Hispanic White/Caucasian, Non-Hispanic Black/African American, and Other (American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, Multiple Races, Unknown, or Refused to Answer). SCD genotype categories were hemoglobin HbSS, HbSC, HbS/β^+thalassemia, HbS/β^0 thalassemia, and Other.

Statistical analysis was performed through R version 4.1.0.[22] Chi-squared analysis was performed to compare the proportion of influenza vaccination uptake among the pediatric oncology subgroups (hematologic malignancies, non-CNS solid tumors, primary CNS tumors) and patients with SCD with uptake in the general pediatric population for Georgia and the United States. Multivariate logistic regression was performed to explore potential contributing factors to differences in IIV uptake between disease groups. For the inpatient cohort, Chi-squared analysis was performed to determine differences in IIV uptake between admitted patients eligible and exposed to the intervention and those eligible but not exposed to the intervention (i.e., only admitted prior to the intervention's start date, including historical controls from the first two influenza seasons). Multivariate logistic regression modeling was performed to determine which covariates mentioned above may contribute to IIV uptake; this was repeated using hospital admission as the unit of analysis.

Results

Overall, 1548 pediatric patients with cancer were eligible for at least one season (range 812-1323 patients per season). Of those oncology patients, 654 (42.2%) had hematologic malignancies, 473 (30.6%) had non-CNS solid tumors, and 421 (27.2%) had primary CNS tumors that met criteria for being on-therapy or within six months of their off therapy dating during at least one influenza season. At least one influenza vaccination for any previous influenza season was documented for 80-88% of oncology patients. There were 2539 pediatric patients with SCD that were eligible for the study. At least one influenza vaccination for any previous influenza season was documented for 76-94% of patients with SCD, and 66-92% had a history of prior pneumococcal vaccination (if eligible) (**Table 1**).

Influenza Vaccine Uptake Compared to the United States and Georgia

IIV uptake for the general pediatric population of the United States ranged between 58-64% over the three influenza seasons, compared to 51-56% for the state of Georgia. Pediatric oncology patients overall had influenza vaccination uptake 60-62%, differing by disease subtype. Influenza vaccination uptake for pediatric patients with SCD ranged between 61-65% (**Figure 1**).

In comparison to Georgia's pediatric population, patients with hematologic malignancies had significantly higher IIV uptake (67-75%,p <0.01). Patients with solid and CNS tumors had similar uptake to the state population (Solid tumor 47-52%, p =0.15-0.26; CNS tumor 52-58%, p =0.38-0.80). Compared to the national pediatric population, patients with hematologic malignancies had similar-to-higher IIV uptake (67-75%, p =0.01-0.15), while patients with solid and CNS tumors had similar-to-lower uptake (Solid tumor 47-52%, p <0.01; CNS tumor 52-58%,p =0.04-0.10). Patients with SCD had significantly higher uptake than both state (61-64%, p <0.01) and national (61-64% , p =0.01-0.02) populations, even among the national population of Non-Hispanic African American children (61-64% vs 55%-60%,p <0.01) (**Table 2**).[18]

Correlates to Influenza Vaccine Uptake

Patients with hematologic malignancies had significantly higher IIV uptake compared to patients with solid and CNS tumors combined (OR 1.09 [1.06-1.13], p <0.01). Younger age (OR per year 0.996 [0.994-0.999], p <0.01), prior IIV vaccination (OR 1.94 [1.85-2.03], p <0.01), greater number of admissions per season (OR per admission 1.007 [1.001-1.014],p =0.04), absence of relapsed or refractory disease (OR 0.95 [0.92-0.99], p =0.01), and chemotherapy given during the season (OR 1.07 [1.03-1.11], p <0.01) were significantly associated with increased IIV uptake, while race, sex, history of hematopoietic stem cell transplant (HSCT) were not. There was no significant difference in IIV uptake between patients with cancer and SCD (OR 1.01 [0.99-1.03], p =0.54).

Influenza Vaccine Uptake After the Opt-Out Admission Order Set

From the initial cohort, 1143 oncology patient-seasons (592 with hematologic malignancy, 331 with non-CNS solid tumors, and 220 with primary CNS tumors) and 2135 sickle cell patient-seasons were eligible for the inpatient cohort. Eligible patients per season ranged from 354-423 for oncology and 686-734 for SCD. Among the three influenza seasons, 17%, 19%, and 27% of admitted patients with cancer received their IIV while inpatient, respectively. For SCD, 8%, 7%, and 27% of admitted patients received their IIV while inpatient, respectively. During the 2019-2020 season, 46% of admitted patients with cancer and 52% of admitted patients with SCD were eligible for the admission order set. At the time of implementation, 48% of patients with cancer and 56% of patients with SCD had already received the IIV (**Figure 2**). Due to the stepwise implementation of the order set, 63% (121/193) of order set-eligible oncology encounters were exposed to the order set; 40% (48/121) of exposed oncology encounters received the IIV that season compared to 60% (43/72) for the unexposed. Similarly, 64% (197/307) of order set-eligible admitted patients with SCD were exposed; 44% (87/197) of exposed patients with SCD received the IIV that season compared to 78% (86/110) for the unexposed patients. The inpatient cohort saw no difference in uptake comparing before and after the order set implementation for patients with hematologic malignancies (56% vs 44%, p =0.07), solid tumors (59% vs 38%, p =0.05), and CNS tumors (47% vs 41%, p =0.88) but decreased uptake for patients with SCD (56% vs 44%, p<0.01).

In multivariate analysis, there was no significant difference in vaccine uptake after order set implementation for patients with solid tumors (p =0.38) or CNS tumors (p =0.37) but decreased uptake for patients with hematologic malignancies (p =0.03) and SCD (p =0.02) (**Table 3**). A history of prior influenza vaccination was strongly associated with greater IIV uptake for all subgroups (p <0.01). Except for patients with hematologic malignancies, a greater number of admissions during the influenza season was strongly associated with greater IIV uptake for all subgroups. Older patients with SCD were also more likely to have higher IIV uptake.

Adjusting the unit of analysis to hospital admission for those unvaccinated at the time of admission, we found a significant difference in IIV uptake between patients exposed to the order set and those not exposed to the order set for both the inpatient oncology (22% vs 18%,p <0.01) and SCD (24% vs 13%, p <0.01) cohorts. Mixed effects multivariate logistic regression also found a significant increase in IIV for oncology (OR 2.0 [1.14-3.45]) and SCD (OR 4.3 [2.66-7.03]); fewer complex chronic medical conditions correlated with increased IIV uptake in the oncology cohort (**Table 4**).

Discussion

Immunization against influenza is an important preventative health measure for all individuals, with potential benefit for vulnerable populations with chronic illness; yet nationwide, vaccine acceptance remains sub-optimal. We found that patients with cancer had similar rates of vaccination to the general pediatric national population but higher rates of vaccination than their healthy peers in a low vaccination state. Conversely, patients with SCD had significantly higher rates of influenza vaccination than the state and nation, which remained true when compared to the United States' general population of Black or African-American children.[18] Our findings are similar to the IIV uptake rates found in other states' pediatric cohorts with cancer or SCD, suggesting similar uptake among these pediatric populations across states with different

degrees of IIV uptake.[9–13]

Prior studies have shown significant improvement in influenza uptake among pediatric patients with cancer through outpatient interventions such as provider reminders, clinic flow changes, and telephone and mail recall systems. The greatest improvements were seen in interventions that targeted the outpatient clinic, though the effect tended to diminish later in the influenza season.[12–16]Similarly, outpatient interventions in provider and patient education, electronic medical record enhancement, patient registries, and reminder/recall systems have shown to improve vaccine uptake among patients with SCD.[23] Our study sought to optimize opportunities for increasing IIV uptake through planned and unplanned inpatient encounters. The probability of influenza vaccination prior to discharge increased in the oncology cohort (aOR 1.98 [1.14-3.45]) although less than the general pediatrics cohort (aOR 3.25 [2.94-3.59]).[17] The impact during hospitalization was even greater among SCD patients (aOR 4.33 [2.66-7.03]). Nonetheless, the proportions of *patients per season* receiving the vaccine did not significantly change with the intervention for either cohort, regardless of the number of admissions that each patient had.

Reasons underlying our results include the staggered study design of the order set intervention and the prevalence of outpatient influenza vaccination. **Figure 2** shows that about half of all patients with cancer and SCD that were eligible for the inpatient cohort and the intervention received their IIV prior to the start of the intervention. A portion of those patients could have received their IIV during an admission prior to receiving it in the outpatient setting; however, those patients would likely be willing to receive their IIV early regardless of the location, so the inpatient intervention would not have added much to the existing outpatient systems. One prior study included an inpatient order set concurrently with other outpatient and education interventions to boost IIV uptake among pediatric patients with cancer, but due to the nature of concurrent interventions, the authors were unable to assess the specific utility of the inpatient intervention. They speculated that the effect was minor, as only 10% of their vaccines were administered on an inpatient basis.[12]Our study found that 17-27% and 8-27% of vaccinated patients in the admitted oncology and SCD cohorts received their IIV while inpatient, respectively, with marked increase of inpatient vaccination for both inpatient cohorts during the 2019-2020 influenza season. Additionally, IIV uptake fell for our full eligible (inpatient and outpatient) oncology and SCD cohorts (particularly among patients with hematologic malignancies) while national and state uptake improved or remained stable, questioning the representativeness of the 2019-2020 season for our two cohorts.

Our study has limitations. The retrospective nature of the study limited our ability to control for confounding bias when assessing the efficacy of the inpatient intervention. Eligible patients who underwent HSCT may have been ineligible for vaccination if their transplant date occurred during the influenza season. Eligible patients born in September or October of their eligible influenza season would be much less likely to receive an influenza vaccination. Finally, the COVID-19 pandemic starting in the early months of 2020 could have affected IIV uptake during the second half of the 2019-2020 influenza season, though the effect was likely small as 88-92% of influenza immunizations were given prior to December 31 for each influenza season.

By determining the effect of an inpatient intervention, we sought to further define strategies for enhancing vaccine uptake among immunocompromised populations and better capitalize on vaccination opportunities in patients' existing healthcare encounters. Our results suggest that pediatric patients with cancer or SCD living in a low-vaccination state tend to follow national rather than local uptake trends. Our inpatient admission order-set intervention was ineffective at improving IIV uptake in these populations followed at our institution, though the rise of inpatient vaccinations and fall of overall vaccine uptake in 2019-2020 suggests that inpatient interventions may still be a viable strategy for increasing influenza vaccine uptake. The intervention continues to go through iterative changes with each influenza season, so a follow up study focusing on subsequent influenza seasons will help assess the full effect of the intervention. As our study confirmed that 30-50% of pediatric patients with cancer or SCD remain unvaccinated against influenza, additional qualitative or mixed-methods studies could explore additional barriers to influenza vaccine uptake, while follow up intervention studies could explore methods of increasing influenza vaccination among the patients' families as well. Greater optimization of seasonal vaccine uptake like influenza will improve

infectious outcomes among immunocompromised pediatric patients with cancer and SCD.

Conflict of Interest

Dr. Evan Orenstein is a co-founder and equity holder in Phrase Health, a clinical decision support analytics company.

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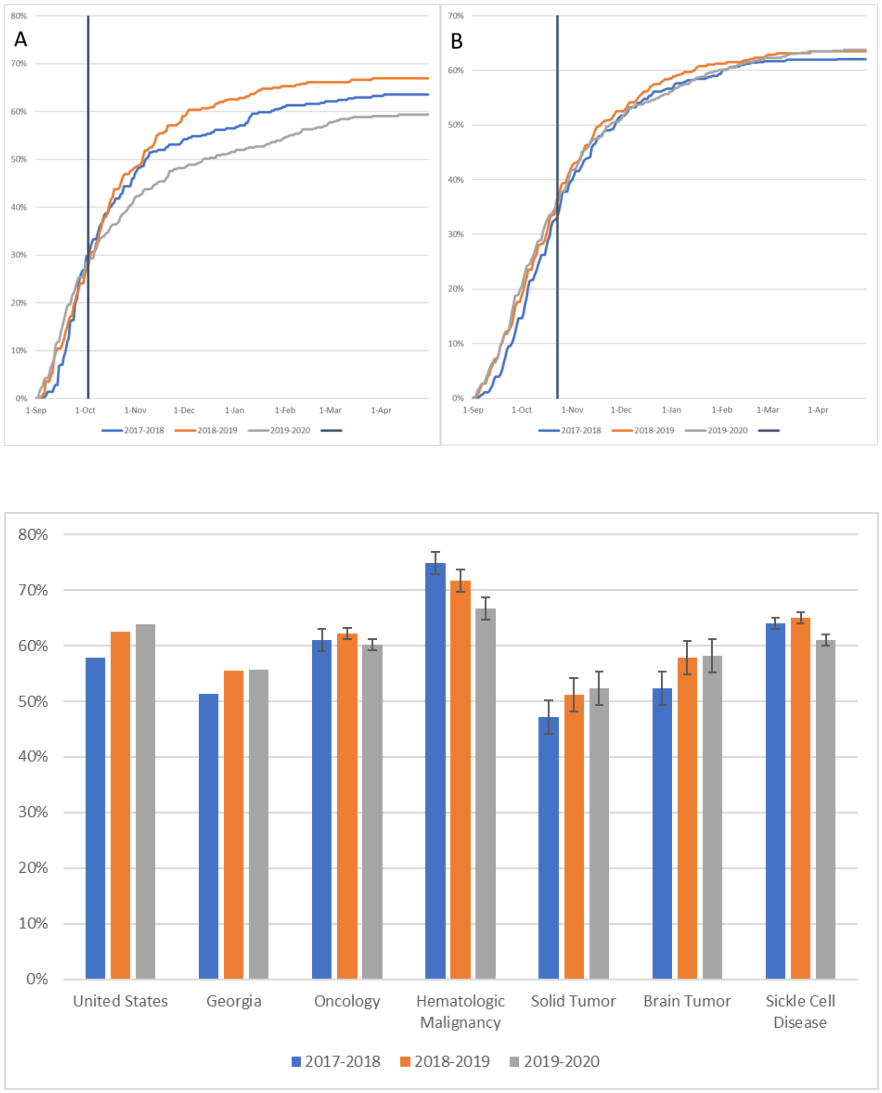

FIGURE 1: Influenza vaccine uptake among patients with cancer and sickle cell disease treated at CHOA compared to state and national general pediatric populations over three influenza seasons.

FIGURE 2 : Influenza vaccine uptake among inpatient oncology (A) and sickle cell disease (B) cohorts. The vertical line represents the date of order set implementation in 2019-2020 season.