Influenza Vaccination Coverage Among Adult Survivors of Pediatric Cancer

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Background: A large proportion of long-term survivors of childhood cancer have treatment-related adverse cardiac and pulmonary late-effects, with related mortality. Consequently, this population of approximately 379,000 individuals in the U.S. is at high risk of complications from influenza infections.

Purpose: To estimate influenza vaccination coverage overall and among subgroups of adult survivors of pediatric cancer aged 18–64 years and to compare coverage with the general adult U.S. population.

Methods: Data from the 2009 Behavioral Risk Factor Surveillance System were analyzed in 2013 using binomial regression to estimate influenza vaccination coverage differences (CDs) and corresponding 95% confidence limits (CLs) between adult survivors of pediatric cancer and the general U.S. population. Analyses were stratified by demographic characteristics and adjusted for design effects, non-coverage, and non-response.

Results: Influenza vaccination coverage was 37% for adult pediatric cancer survivors overall and 31% for the general adult U.S. population (CD=6.3%, 95% CL=0.04%, 13%). Dramatically lower coverage was observed for non-Hispanic black survivors (6%) than for non-Hispanic blacks in the general U.S. population (26%; CD=−18%, 95% CL=−25%, −11%).

Conclusions: Although influenza vaccination coverage was modestly higher among adult survivors of pediatric cancer than the general U.S. population, coverage was less than desirable for a population with a high prevalence of cardiopulmonary conditions and early mortality, and far lower than the Healthy People 2010 goal of 60% or Healthy People 2020 goal of 80% for the general population.
(Am J Prev Med 2014;46(6):552–558) © 2014 American Journal of Preventive Medicine

Introduction

Influenza is an acute respiratory illness with deleterious health and economic impacts.[1,2] Although generally resolved without progressive sequelae among healthy individuals, influenza-related complications such as pneumonia, pulmonary disease, or exacerbation of pre-existing cardiovascular conditions are more common among high-risk populations.[1,2] These populations include immunocompromised individuals, children

aged <5 years, adults aged >65 years, pregnant women, and individuals with chronic illnesses such as cardiovascular, pulmonary, metabolic, or neurologic diseases.[3] Consequently, annual vaccination is recommended for all individuals aged >6 months but especially important for high-risk populations.[4]

Given advancements in treatment and supportive care, an estimated 379,000 individuals of all ages who were diagnosed with cancer as a child or adolescent (ages 0–19 years) were alive in the U.S. as of January 1, 2010.[5] Chronic conditions that affect a variety of organ systems are common for long-term (>5 years) pediatric cancer survivors,[6,7] many of which may be undiagnosed.[7] For example, 65% of pediatric cancer survivors exposed to pulmonotoxic cancer therapy had abnormal pulmonary function >10 years after diagnosis, with 36% undiagnosed until comprehensive clinical screening.[7] Furthermore, 56% of survivors exposed to cardiotoxic therapies had cardiac abnormalities >10 years after diagnosis,

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with 47% undiagnosed until comprehensive clinical screening.[7] The deleterious effects of cancer treatment on survivors of childhood cancer are also illustrated by the substantially increased standardized mortality ratio (SMR) from cardiac (SMR=7.0, 95% CL=5.9, 8.2) and pulmonary (SMR=8.8, 95% CL=6.8, 11.2) conditions.[8] Organizations that formulate influenza vaccination guidelines have not recognized pediatric cancer survivors as a high-risk group for whom influenza vaccination should be emphasized.[3] Nevertheless, given the emerging evidence regarding pediatric cancer survivors' burden of chronic diseases that confer a high risk of influenza-related complications, survivors may deserve explicit recognition as a high-risk group.

Several studies have addressed influenza vaccination coverage among pediatric cancer patients on active therapy or immediately following completion of therapy[9–11]; vaccination coverage ranged between 47% and 87% in these studies. In contrast, little is known about influenza vaccination coverage among long-term pediatric cancer survivors. Therefore, the aim of this study was to estimate influenza vaccination coverage among long-term survivors of pediatric cancer and compare coverage between survivors and the general U.S. population.

Methods

Data Source

Data from the 2009 Behavioral Risk Factor Surveillance System (BRFSS)[12] were used to identify a cohort of pediatric cancer survivors and a comparison cohort of the general U.S. population. The BRFSS targets non-institutionalized individuals aged ≥18 years to measure behavioral risk factors related to morbidity and mortality. A probability-based sample of adults (one per household) was recruited to complete computer-assisted telephone interviews. All responses are based on self-reports. The BRFSS includes a core module of questions administered in all states with options for each state to include additional modules.

Study Population

Data from all 2009 BRFSS respondents were used to identify a cohort of ≥5-year adult survivors of pediatric cancer using questions related to previous cancer diagnosis (*Have you EVER been told by a doctor, nurse, or other health professional that you had cancer?*) and age at cancer diagnosis (*At what age were you told that you had cancer?* For respondents who reported more than one diagnosis, *At what age was your first diagnosis of cancer?*). Survival time was computed as the difference between age at the time of the survey and age at cancer diagnosis. Individuals who reported being diagnosed with cancer between age 1 and 20 years and survived ≥5 years after diagnosis were eligible for analysis as part of the survivor cohort. Individuals who reported a primary diagnosis of *other skin cancer* were excluded based on the assumption that this response likely referred to a non-melanoma skin cancer. In addition, the population was restricted to pediatric cancer

survivors aged 18–64 years at the time of survey given sparse data for older age groups and lack of survey information for those aged <18 years. The same data source (all 2009 BRFSS respondents) was used to identify a comparison cohort without a history of pediatric cancer that represented the general U.S. population. All respondents aged 18–64 years were eligible for analysis as part of the comparison cohort, including those with prevalent conditions.

Variables

The outcome of interest was influenza vaccine uptake, defined as receipt of the inactivated virus vaccine by injection (*A flu shot is an influenza vaccine injected into your arm. During the past 12 months, have you had a flu shot?*) or live attenuated virus vaccine by nasal spray (*During the past 12 months, have you had a flu vaccine that was sprayed in your nose? The flu vaccine sprayed in the nose is also called FluMist™*). The questions about influenza vaccination thus encompassed a vaccination period between January 2008 and December 2009 depending on which month the 2009 survey was completed. Given that vaccines for the H1N1 pandemic were also available in 2009 and the BRFSS data do not differentiate between this vaccine and the seasonal vaccine, vaccine uptake could have referred to either the seasonal or pandemic vaccine. Nevertheless, the proportion of responses referring to the pandemic vaccine is likely small because the guidelines for the 2009 H1N1 pandemic vaccine were not issued until August 2009 when vaccine supplies were available only in limited quantities.[13]

Outcome information was linked with sociodemographic information ascertained through the survey. Specifically, race/ethnicity was defined using the BRFSS-derived self-reported measure that identified non-Hispanic white, non-Hispanic black, Hispanic, other, and non-Hispanic multiracial groups. The other and non-Hispanic multiracial categories were collapsed into one category of "other" given sparse data. Educational attainment was measured as high school or less, some college, and college degree or higher. Household income was measured as <$25,000, $25,000–$49,999, $50,000–$74,999, and ≥$75,000. Insurance status was dichotomized based on the answer to the question *Do you have any kind of health care coverage, including health insurance, prepaid plans such as HMOs, or government plans such as Medicare?*

Data Analysis

Data were analyzed in 2013 using binomial regression with an identity link to estimate influenza vaccination coverage differences (CDs; equivalent to prevalence difference) and corresponding 95% CLs[14] between pediatric cancer survivors and the general U.S. population adjusted for age, gender, and race/ethnicity. The identity link in binomial regression computes estimates on an absolute scale (e.g., CDs) in contrast to the use of a log link, which computes estimates on a relative scale (e.g., coverage ratios).[14] An absolute measure was selected for between-group comparisons in this analysis because it may be more meaningful than relative measures for measuring and prioritizing inequalities for public health action.[15] The models incorporated design effects and population weights to adjust for non-coverage and non-response in the BRFSS and enhance generalizability to the target population.[16] Stata, version 12 (StataCorp, College Station TX) was used for all analyses.

Given that the "exposure" in our analysis is pediatric cancer, measured variables such as current household income and insurance

status are intermediates in the causal path to influenza vaccination. For example, an effect of current household income on past diagnosis of pediatric cancer is temporally impossible, but pediatric cancer could influence current household income given that survivors are less likely to have higher-paying occupations.[17] Similarly, an effect of current insurance on past diagnosis of pediatric cancer is temporally impossible, but prior to the recently instituted Affordable Care Act (the period consistent with our analysis), a diagnosis of pediatric cancer resulted in lower rates of and difficulty obtaining insurance coverage as an adult.[18] Adjustment for intermediates (i.e., overadjustment) is known to bias estimates of the total effect[19–21] and thus was avoided in this analysis.

Results

The survivor population comprised 1,065 eligible long-term survivors of pediatric cancer, of whom 1,025 (96%) had sufficient exposure and outcome data for analysis. The general U.S. population comprised 292,629 eligible BRFSS respondents, of whom 285,481 (98%) had sufficient data for analysis (Figure 1).

Table 1 summarizes characteristics of the evaluable study population, where the absolute numbers in each stratum are unweighted, but the percentages incorporate design effects and population weighting. Briefly, pediatric cancer survivors and the general U.S. population were primarily women (70% and 50%, respectively) but differed in age distribution (survivors: mean=42 years, SD=12; general U.S. population: mean=47 years, SD=12). The predominant racial/ethnic group for pediatric cancer survivors and the general U.S. population was non-Hispanic white (77% and 66%, respectively). A larger proportion of survivors had household income <$25,000 compared with the general U.S. population (39% and 24%, respectively), but health insurance coverage was comparable between the groups (survivors: 81%; general U.S. population: 82%).

Table 2 summarizes the overall and stratum-specific (i.e., age, gender, race/ethnicity, education, household income, and insurance coverage) influenza vaccination CDs between 5-year survivors of pediatric cancer and the general U.S. population after adjustment for design effects and population weights. Overall, influenza vaccination coverage was modestly higher among survivors (37%) compared with the general U.S. population (31%; CD=6.3%, 95% CL=0.04%, 13%). Pediatric cancer survivors had higher influenza vaccine coverage compared with the general U.S. population within all age groups, with the largest difference among individuals aged 18–24 years (CD=20%, 95% CL=−2.7%, 42%). Point estimates for influenza vaccination coverage were higher for male and female survivors compared with men and women in the general U.S. population, respectively (men: CD=10%, 95% CL=−3.2%, 24%; women: CD=4.4%, 95% CL=−2.4%, 11%). Non-Hispanic black survivors had the lowest influenza vaccination coverage of any racial/ethnic subgroup (6.4%) and had a large deficit in coverage when compared with non-Hispanic blacks in the general U.S. population (CD=−18%, 95% CL=−25%, −11%). In contrast, Hispanic survivors had the highest influenza vaccination coverage of any racial/ethnic subgroup, which resulted in a large CD compared with Hispanics in the general U.S. population (CD=30%, 95% CL=1.4%, 59%). Influenza vaccination coverage was higher for pediatric cancer survivors within subgroups of educational attainment, with the largest difference observed for survivors with some college education compared with the general U.S. population with some college education (CD=13%, 95% CL=3.2%, 23%). Similarly, influenza vaccination coverage was higher for pediatric cancer survivors within subgroups of household income, particularly within that of household income between $50,000 and $74,999 (CD=17%, 95% CL=2.8%, 30%). Uninsured pediatric cancer survivors had modestly lower vaccination coverage than uninsured individuals in the general U.S. population (CD=−1.8%, 95% CL=−11%, 7.6%).
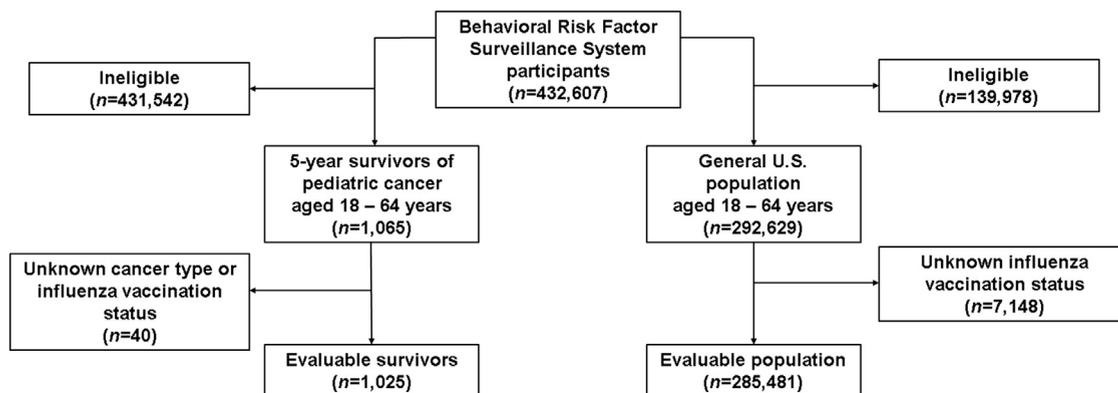

Figure 1. Selection of 5-year survivors of pediatric cancer and representatives of the general U.S. population from the 2009 Behavioral Risk Factor Surveillance System survey participants

Discussion

The findings of this study suggest that despite being a population at high risk of influenza-related complications, overall and subgroup-specific influenza vaccination coverage among ≥5-year survivors of pediatric cancer is only modestly higher than or comparable to the general U.S. population. The exception is remarkably lower vaccination coverage among non-Hispanic black survivors compared with those in the general U.S. population. Nonetheless, influenza vaccination coverage is uniformly suboptimal among pediatric cancer survivors and the general U.S. population when considering past and future Healthy People goals (60% for 2010[22] and 80% for 2020[23]).

A search of the current published literature did not identify prior studies that estimated influenza vaccination coverage specifically among long-term survivors of pediatric cancer, but several studies reported coverage estimates among survivors of adult cancers.[24–28] For example, a 2009 study of survivors of adult cancers in the U.S. reported 58% coverage.[29] In contrast with influenza vaccination coverage of pediatric cancer survivors observed in the current study using data from the same year, the estimate for survivors of adult cancers was close to the Healthy People 2010 goal of 60%[22] but considerably below the future Healthy People 2020 goal of 80% for the general population.[23] Unlike the present analysis, the study among survivors of adult cancers included individuals aged >65 years who generally have higher vaccination coverage than younger adults.[30] Furthermore, older age among cancer survivors appears to be uniquely associated with influenza vaccine coverage.[31]

To provide additional context for our findings, the reported estimates of influenza vaccination coverage for other high-risk groups are higher than those observed for pediatric cancer survivors in this study. An estimated 53% of individuals in any high-risk group were vaccinated between 2007 and 2011.[32] Despite considerable variation (e.g., 70% vaccination coverage for patients with renal disease and 46% coverage for individuals with asthma) and with the exception of pregnant women (36% vaccination coverage), the reported estimates of influenza vaccine coverage are uniformly higher for all high-risk groups compared to pediatric cancer survivors in this study.[32] Nevertheless, these reported estimates were aggregated over several years, and most high-risk subgroups included individuals aged >65 years, which may contribute to differences in vaccination coverage estimates between survivors and other high-risk populations.

The burden of influenza-related complications for pediatric cancer survivors is unknown for our study period, which included the 2009 H1N1 pandemic season. Nevertheless, low vaccination coverage accentuates

Table 1. Characteristics of pediatric cancer survivors and general U.S. population, 2009 Behavioral Risk Factor Surveillance System,[a] n (%)

Characteristic	Pediatric cancer survivors (n=1,025)	General U.S. population (n=285,481)
Age (years)		
18–24	54 (14)	12,729 (14)
25–34	245 (40)	36,264 (22)
35–44	282 (23)	58,460 (24)
45–54	252 (14)	84,796 (23)
55–64	192 (8.7)	93,232 (18)
Gender		
Women	808 (70)	174,055 (50)
Men	217 (30)	111,426 (50)
Race/ethnicity[b]		
Non-Hispanic white	817 (77)	217,229 (66)
Non-Hispanic black	59 (7.5)	25,068 (11)
Hispanic	47 (8.0)	23,085 (16)
Other	99 (6.8)	17,903 (7.2)
Education[c]		
High school or less	387 (36)	98,833 (37)
Some college	320 (30)	79,866 (27)
College degree or higher	318 (35)	106,461 (36)
Household income[d]		
<$25,000	367 (39)	61,033 (24)
$25,000–$49,999	210 (20)	64,961 (23)
$50,000–$74,999	152 (17)	47,158 (17)
≥$75,000	217 (25)	84,675 (36)
Insurance coverage[e]		
Insured	857 (81)	243,587 (82)
Uninsured	168 (19)	41,894 (18)

Note: Some percentages do not total to 100% due to rounding.
[a]The absolute numbers (*n*) are unweighted, but percentages incorporate design effects and population weights
[b]*n*=3 missing for pediatric cancer survivors, *n*=2,196 missing for general U.S. population
[c]*n*=321 missing for general U.S. population
[d]*n*=88 missing for pediatric cancer survivors, *n*=27,654 missing for general U.S. population
[e]*n*=3 missing for pediatric cancer survivors, *n*=640 missing for general U.S. population

vulnerability on a population-level to influenza-related complications with virulent strains of pandemic or seasonal influenza.[33] This vulnerability may be more

Table 2. Overall and stratum-specific influenza vaccine coverage differences and 95% confidence limits

	Coverage %[a]		Coverage difference (% [95% CL])
	Pediatric cancer survivors	General U.S. population	
Overall[b]	37	31	6.3 (0.04, 13)
Age (years)			
18–24	42	23	20 (−2.7, 42)
25–34	32	25	5.2 (−5.5, 16)
35–44	33	28	2.9 (−6.4, 12)
45–54	41	34	5.1 (−4.2, 14)
55–64	53	48	3.5 (−8.8, 16)
Gender[c]			
Men	36	29	10 (−3.2, 24)
Women	37	34	4.4 (−2.4, 11)
Race/ethnicity[d]			
Non-Hispanic white	39	34	7.3 (0.34, 14)
Non-Hispanic black	6.4	26	−18 (−25, −11)
Hispanic	53	23	30 (1.4, 59)
Other	26	32	−4.7 (−17, 8.1)
Education[b]			
High school or less	30	26	4.5 (−4.7, 14)
Some college	44	30	13 (3.2, 23)
College degree or higher	38	38	4.2 (−8.5, 17)
Household income[b]			
<$25,000	27	25	4.2 (−6.4, 15)
$25,000–$49,999	37	28	8.8 (−4.5, 22)
$50,000–$74,999	49	33	17 (2.8, 30)
≥$75,000	45	38	8.9 (−5.4, 23)
Insurance coverage[b]			
Insured	42	35	8.5 (1.6, 15)
Uninsured	14	16	−1.8 (−11, 7.6)

[a]Coverage estimated after accounting for design effects and population weights
[b]Adjusted for age (continuous variable), sex, and race/ethnicity
[c]Adjusted for age (continuous variable) and race/ethnicity
[d]Adjusted for age (continuous variable) and sex
CL, confidence limits

vaccination coverage for non-Hispanic black survivors in our study, studies of adult survivors have reported similar racial/ethnic disparities in influenza vaccine coverage.[34,35]

Several issues warrant attention when interpreting these findings. After accounting for design effects and sample weights, nearly 70% of our pediatric cancer survivor population were women. A partial explanation for this skewed gender distribution is differences in late mortality between genders for survivors. Although men have a 13% higher relative incidence of pediatric cancer, women comprise a larger proportion (6% more women than men) of pediatric cancer survivors aged between 20 and 59 years.[36] Clearly, this modest difference does not fully account for the gender distribution observed in our study population. Selection bias is a potential explanation for this discrepancy, which may occur despite analytic adjustment for non-coverage and non-response,[37] and adjustment for gender in comparisons with

pronounced for non-Hispanic black survivors because of the remarkably low vaccination coverage observed for this group in our study compared with other racial/ethnic subgroups who have higher vaccination coverage. Although sparse data precluded precise estimation of

the general U.S. population. If so, the estimates for overall or subgroup-specific CDs may be upward- or downward-biased depending on whether non-participant male pediatric cancer survivors had lower or higher influenza vaccination coverage, respectively.

Unfortunately, relevant data are unavailable to further explore the impact of this potential selection bias.

Another consideration is that the data for influenza vaccine uptake were based on self-reports, which raises the possibility of misclassification of true vaccination status. Although self-reported influenza vaccination status has 95% sensitivity and 95% specificity compared to medical records as the reference standard,[38] differences in accuracy of self-reports between pediatric cancer survivors and the general U.S. population could result in estimates that are sensitive to misclassification. For example, some pediatric cancer survivors exhibit memory deficits[39] that may negatively affect the ability to accurately recall influenza vaccination status. Consequently, the modest difference in vaccine coverage compared with the general U.S. population observed in our study could be larger than observed if the accurate vaccination status were known. Unfortunately, the accuracy of self-reported influenza vaccination among pediatric cancer survivors and the general population in this study is unknown.

In summary, influenza vaccine coverage in 2009 was modestly higher among adult survivors of pediatric cancer than in the general U.S. population. Nonetheless, the 37% overall vaccination coverage rate was less than desirable for a population at high risk of cardiopulmonary complications and early mortality. The reasons for low uptake of the influenza vaccine among long-term survivors of pediatric cancer are not well defined. The primary reasons for low uptake may be similar to those of the general population (e.g., barriers to vaccine access and concerns about effectiveness and safety[33]), but the magnitude of these reasons may differ, and survivors may have unique reasons for low uptake. For example, pediatric cancer survivors often have problematic transitions of care out of the pediatric cancer setting and into community health care.[40] Community healthcare providers are not always aware of the unique health concerns of survivors,[40] which could result in inadequate preventive measures such as influenza vaccination. Future studies should focus on approaches for improving uptake among survivors of pediatric cancer, particularly non-Hispanic black survivors.

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