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Evaluation of Mass Influenza Immunization Clinics in Puerto Rico during the 2013-14 Influenza Season

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An abstract of
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Abstract

Evaluation of Mass Influenza Immunization Clinics in Puerto Rico during the 2013-14 Influenza Season

By Anirudh Rao

Background: During the seasonal influenza epidemic of 2013-2014, the Puerto Rico Department of Health held mass vaccination clinics across the island in response to increased influenza activity. To provide information that can be used to tailor future mass vaccination campaigns, this study examined factors associated with influenza vaccination at these mass vaccination clinics versus vaccinations provided at other facilities, as well as vaccinations given during mass vaccination clinics early in the season compared to those given later in the season.

Methods: Data were obtained from the Puerto Rico Immunization Registry (PRIR) for the 2013-2014 influenza season. Log-binomial regression analysis was conducted to determine whether age, sex, race and insurance status were associated with vaccination at early mass clinics among all age groups, including adults, compared to vaccination at later mass clinics. Log-binomial regression was also used to determine whether these same factors were associated with vaccination at mass clinics compared to non-mass vaccination clinics, among children 6 months to 18 years of age.

Results: The PRIR reported 267,273 influenza vaccinations provided in Puerto Rico during the 2013-2014 influenza season. After adjusting for all other factors, vaccinations that were less likely to be given at early mass vaccination clinics than at late mass vaccination clinics were those given to persons of Other Race (aPR 0.86, relative to Whites). Vaccinations given to Black children in the PRIR were more likely to be received at mass vaccination clinics than at non-mass vaccination sites (aPR 1.78, relative to White children). In addition, vaccinations that were less likely to be received at mass vaccination clinics than at non-mass vaccination sites were those given to children 6 months-4 years (aPR 0.35, relative to 13-18 year olds) and those given to children under Medicaid, or to children without insurance (aPR 0.52 and aPR 0.55, respectively, relative to privately insured children).

Conclusions: : There were sociodemographic differences in vaccinations given at early mass vaccination clinics compared to those given at late mass vaccination clinics. Factors were also associated with vaccinations given to Puerto Rican children at mass vaccination clinics compared to those vaccinations given at other venues. The Puerto Rico Department of Health can use these findings to modify their influenza vaccination strategies during future epidemics, through directing vaccine stocks to providers who vaccinate children. Additionally, the results of this study demonstrate the utility of Immunization Information System (IIS) data in evidence-based evaluation of immunization programs and activities.

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Background/Literature Review

Epidemiology of Influenza

Influenza is a respiratory illness that can cause severe morbidity and mortality. The causative agents for influenza are influenza viruses belonging to the *Orthomyxoviridae* family of RNA viruses. These viruses are divided into three types: Influenza A virus, Influenza B virus, and Influenza C virus. Virus type C has seven single-stranded RNA segments, and only one major surface glycoprotein, hemagglutinin-esterase fusion (HEF) (1). In type A and B viruses, eight segments of single-stranded RNA code for 11 proteins, including two surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA). These two proteins play roles in both the development of disease, and immune protection from infection (2). These surface glycoproteins can also be used to further divide influenza A viruses, into 18 H subtypes and 11 N subtypes (3). Of these type A subtypes, three types of hemagglutinin (H1, H2, H3), and two types of neuraminidase (N1 and N2) play or have played roles in sustained human-to-human transmission of influenza. Strains of influenza A are named based on combination of these subtypes, along with host of origin (if animal), geographic site of first classification of the specific virus, strain number from identifying laboratory, and year of identification. For example, A/California/7/2004(H3N2) or A/Perth/16/2009(H3N2) specify two different influenza A H3N2 viruses from human origin while A/swine/Taiwan/1/1970 (H3N2) specifies an influenza A H3N2 virus from swine origin (4). Virus types A, B, and C can circulate among humans, pigs and other mammals, and birds, with the primary reservoir of many influenza A subtypes shown to be aquatic birds (5, 6). Influenza A viruses can cause moderate to severe disease in humans (7). Influenza B infection in humans, caused by two lineages (B/Victoria and B/Yamagata), may be

less severe compared to type A infection (2, 5, 7, 8). Influenza C can also cause infection in humans, however, the disease is generally mild (2).

In humans, influenza occurs in either epidemic or pandemic forms. Epidemics of influenza are generally seen as seasonal outbreaks, and result from new variant strains with point mutations in the antigenic sites in the HA and NA glycoprotein (antigenic drift). Both influenza A and B types have been associated with epidemics (2). In the Northern Hemisphere, the influenza season typically extends from October to May, with a majority of cases occurring December through February (9, 10). In the Southern Hemisphere, the flu season usually coincides with the Southern winter (May through September). Seasonality in tropical regions can vary, with a year-round presence and seasonal increases in incidence during rainy seasons (9). Island nations in the American tropics, such as Cuba and the Dominican Republic, see year-round influenza presence, with increases in cases between May and September (11). Puerto Rico, also located in the American tropics, experiences year-round influenza presence. However, unlike nearby Cuba and Dominican Republic, Puerto Rico sees one or two peaks in confirmed cases in a given season (12, 13). For example, during the 2013-2014 season, Puerto Rico reported two peaks in cases, which corresponded a fall peak between August and December (start of 2013-2014 season) and a late winter-early spring peak starting in January that continued through May, before declining through August (end of 2013-2014 season) (13). This suggests the epidemiology of influenza in Puerto Rico might be a cross between Northern and tropical climate influenza seasons.

In contrast to seasonal influenza, pandemics of influenza are the result of major genetic changes that lead to a new subtype of influenza A virus (antigenic shift), either through reassortment of genetic sequences in human and animal influenza strains, or direct transmission

of an animal strain to humans (2). This creates a new virus subtype, to which there is little to no prior immunity. With most or all of the population susceptible to this new subtype, pandemic influenza A viruses can spread rapidly across the globe and can cause substantial morbidity and mortality in all age groups. The influenza pandemic of 1918-1919 caused an estimated 20 to 50 million deaths globally in the first 12 months, at the time making it the deadliest pandemic since the Black Death of the 14th century (2).

Usually a self-limiting disease, influenza infection in humans is characterized by fever, dry cough, headache, myalgia, fatigue, and sore throat that last between three and seven days (5). Although influenza infections generally resolve without major problems, some patients may experience serious complications such as primary influenza viral pneumonia and secondary bacterial pneumonia. Typically, the populations most at risk for complications are children younger than two years of age; adults 65 years of age or older; pregnant women; and individuals with high-risk medical conditions. These medical conditions include: asthma and other chronic pulmonary disorders; cardiovascular disorders (except hypertension); neurological or neurodevelopmental conditions such as cerebral palsy, stroke, epilepsy; hematologic disorders such as sickle cell disease; renal, hepatic, or metabolic disorders (including diabetes mellitus); and immunosuppression (caused by medications, or HIV) (14). Death is reported in less than 1 per 1,000 cases, with the majority occurring among adults 65 years of age or older (5, 7). Transmitted through contact with respiratory secretions, influenza has an incubation period in humans between one and four days. Infected hosts are capable of transmitting the virus from before the onset of clinical disease up to the fourth or fifth day of clinical illness in adults (5).

Treatment of most influenza cases generally involves relieving symptoms until the disease resolves. However, antiviral drugs can be used to decrease the severity of influenza

disease if taken within two days of symptom onset. Currently, three neuraminidase inhibitors (oseltamivir, peramivir, and zanamivir) are approved for treatment of uncomplicated influenza A or B infection (5, 7, 15). While antivirals are a potential method of treatment and prophylaxis, influenza vaccination remains the most efficient method for prevention (16).

Influenza Vaccine

Influenza virus type A was isolated in 1933, and research on a vaccine started soon after the virus was shown to grow in chicken embryos. An early human trial using a bivalent vaccine containing virus types A and B during the 1943-1944 influenza season showed that an inactivated whole virus vaccine was approximately 70% effective in reducing clinically assessed influenza disease (2). Influenza vaccines work by inducing production of antibodies against the major surface glycoproteins HA and NA. In individuals who have previously been exposed to influenza or previously been vaccinated for influenza (primed), the primary response to influenza vaccination is the development of anti-HA IgG. In previously unexposed or unvaccinated children (unprimed), systemic IgM antibodies might be more evident (17). In healthy, primed individuals, serum antibody levels peak between two and four weeks after vaccination. In unprimed children, and the elderly, antibody levels in the serum may not peak until after four weeks (17). Children in the US between six months and nine years of age require two doses of vaccine initially, given four weeks apart, to induce appropriate antibody response (7, 16). Once two doses have been received, those children need only one dose annually.

Current influenza vaccine types available in the United States are: inactivated influenza vaccine (IIV), live attenuated influenza vaccine (LAIV), recombinant influenza vaccine (RIV), and cell-culture-based inactivated influenza vaccine (ccIIV), all of which induce antibodies

primarily against the HA protein (7). Inactivated vaccines are effective in preventing disease in approximately 60% of healthy individuals younger than 65 years, depending on how similar the vaccine strain is to the circulating strain in a given season (7). Efficacy of influenza also varies by age, and by health conditions. In adults ≥65 years, vaccine efficacy is approximately 30-40%, although the vaccine can be effective in preventing hospitalization and death (7). In immunocompromised individuals with conditions such as HIV, influenza vaccination may be less effective compared to healthy individuals (18).

In the past, only trivalent influenza vaccines were available, which protect against two influenza A viruses (H1N1 and H3N2), and one influenza B virus representing one of the two major lineages of influenza B virus (Victoria or Yamagata). Quadrivalent vaccines, which include the second type B virus lineage along with the three viruses in the trivalent vaccine, are also now available. The selection of strains to be included in trivalent and quadrivalent vaccines is based on annual reviews of global influenza surveillance data. Historically, inactivated vaccines were cultured in embryonated hen's eggs, however the production process requires millions of eggs annually (2). Egg supply can be a problem if there is a major epizootic outbreak of avian influenza killing poultry. Further, the egg-based production method has limited surge capacity to respond to the need to rapidly develop vaccines when pandemic influenza viruses have been detected circulating in the population. While newer production methods for inactivated vaccines such as cell-cultured vaccines and recombinant DNA vaccines are available, the majority of inactivated virus influenza vaccines manufactured are egg-based vaccines (2). Newer production techniques would have the advantage of faster start-up of vaccine production in the event of a pandemic.

Vaccines using cold-adapted live attenuated influenza viruses (LAIVs) have been shown to have similar effectiveness to inactivated virus vaccines in populations for whom LAIV is licensed. FluMist is an intranasal LAIV that has been approved for individuals between 2 and 49 years of age in the US. However, the nasal spray vaccine is not approved for use in children under 2 years of age, adults 50 years of age and older, pregnant women, or the immunocompromised.

Influenza Vaccine Recommendations and Trends in Influenza Vaccination

Due to antigenic drift of the circulating influenza viruses, it is necessary to receive an influenza vaccination every year as it is likely that at least one of the strains in the vaccine has changed (7). Further, immunity induced by influenza vaccines decreases over time without revaccination. Studies in young adults have found that efficacy against H1N1 and H3N2 illness decreased in the second year following influenza vaccination (19). Prior to the 2009 pandemic, target groups for protection through influenza vaccination were: children 6 months-18 years of age; adults older than 50 years of age; pregnant women (or women who will be pregnant during influenza season); and adults and children with high-risk conditions (20). In addition, influenza vaccination was recommended for persons who live with or care for individuals at high-risk for complications: health care providers; household contacts (including children) and caregivers of children less than 5 and/or adults older than 50 years of age; and household contacts (including children) and caregivers of persons with high-risk conditions (21). Following the 2009 pandemic, the CDC's Advisory Committee on Immunization Practices (ACIP) updated their annual influenza vaccination recommendation for future seasons to include all people over six months of age (2). The reason for this expansion was that by 2009, annual influenza vaccination

had been recommended for approximately 85% of the US population, and the only group not under the recommendation were non-pregnant adults 18-49 years of age without high-risk conditions. If vaccine supplies are limited, the focus should be to vaccinate children between 6 and 59 months of age, adults older than 50 of age, individuals with high-risk conditions, pregnant women (or those who will become pregnant during influenza season), and health care providers (22).

Although the CDC recommends annual influenza vaccination for all individuals older than 6 months of age, influenza vaccination rates in the U.S. tend to be low: approximately 40% in adults and 60% in children (23). Vaccination rates in individuals 18-49 years of age and 50-64 years of age are usually lower than in adults 65 years of age and older. During the 2013-2014 influenza season, vaccination rates in the U.S. among adults 65 years of age and older were approximately 65%, compared to 32% in adults 18-49 years of age and 45% in adults 50-64 years of age (23). In children, vaccination coverage is highest among children 6-23 months of age and coverage in children decreases with age, with adolescents having lower vaccination rates than young children. During the 2013-2014 season, influenza vaccination coverage (defined here as receiving at least one dose of influenza vaccine since July 1, 2013) in the United States was approximately 74% in children 6 months-4 years of age, and approximately 68% in children 2-4 years of age. In comparison, vaccination coverage for children 5-12 years of age was 61%, and in adolescents 13-17 years of age was 46% for the same season (23).

Influenza vaccination rates in Puerto Rico are lower than vaccination rates in the US, for all age groups. A 2013 study by Arriola et al. found mid-season vaccination rates from July 1, 2013 to November 25, 2013 among Puerto Rican adults 18-49 years of age were 11%, as compared to 28% and 27% among adults 50-64 and ≥65 years of age, respectively (24). Monthly

cumulative influenza vaccination coverage estimates for Puerto Rico calculated using NIS-Flu and BRFSS data found that during the 2013-2014 influenza season, only 22% of 18-49 year olds had received an influenza vaccination, compared to 26% and 45% in adults 50-64 and ≥65 years, respectively. At the same time, 48% of children 6 months-23 months, 38% of children 2-4 years, 32% of children 5-12 years, and 30% of adolescents 13-17 years were estimated to have received at least one dose of influenza vaccine during the 2013-2014 influenza season (25).

In addition to age, demographic characteristics such as sex, race, and insurance status are also associated with receipt of vaccination. Vaccination rates do not vary greatly between males and females among children 6 months-17 years (23). However, in adults, vaccination rates vary slightly between males and females. During the 2013-14 influenza season, vaccination coverage in the U.S. was 36% in females 18-49 years of age, compared to 29% in males of the same age group (23). Among adults 50-64 years, vaccination coverage among females was 48%, compared to 43% in males. The differences in coverage between males and females in the 18-49 year group, as well as in the 50-64 year group, were statistically significant ($p<0.05$) (23). There was no statistically significant difference between vaccination rates in females, compared to males, in the ≥65 age group (23).

A study by Williams et al. using National Health Interview Survey (NHIS) data found that influenza vaccination coverage in the U.S. for the 2013-2014 season among adults 19 years of age or older was higher among White adults (46.7%), than among Black adults (36.5%), Hispanic adults (33.2%), or adults reporting other race (38.6%) (26). These vaccination rates are similar to vaccination rates for adults, by race, provided by NIS-Flu and BRFSS data (23). During the 2013-2014 season, influenza vaccination coverage among children 6 months to 17 years differed by race. In children, Whites had lower coverage, which is opposite of disparities

seen in adults (23). Previous studies have also shown that influenza vaccination coverage in the United States is higher among individuals with private health insurance, compared to individuals with public health insurance, or individuals without insurance (27).

Influenza and Mass Vaccination

Mass vaccination programs involve the delivery of vaccine to a large number of people in a short time period, at one or more locations. These have been historically used as part of public health campaigns in response to emerging epidemics, such as meningitis and influenza outbreaks; to deliver vaccines to displaced populations, such as measles vaccines in refugee camps; as part of disease eradication campaigns, such as smallpox and polio; or to increase vaccination coverage (28). Although ACIP recommends that healthcare providers offer influenza vaccination as soon as they become available, if possible before October, individuals may not visit health providers before (or during) an influenza season. Therefore, influenza vaccine is well suited for delivery by mass vaccination programs. These campaigns are often held outside of clinical settings, such as in pharmacies, workplaces, schools, religious institutions, etc. During the 2009 H1N1 pandemic, mass vaccination clinics were used by health officials around the world in order to rapidly make vaccine more accessible to large numbers of persons for whom vaccine was recommended. In a study comparing costs of two mass vaccination campaigns for delivery of H1N1 vaccinations in New York City during 2009, investigators found that school based campaigns, as well as wider mass vaccination clinics were cost effective strategies to increase influenza vaccination rates for both children and adults (29). A study conducted in Taiwan following the 2009 pandemic found that even though the vaccination coverage rate in Taiwan was only approximately 22%, mass influenza vaccination helped to prevent a substantial

proportion of potential influenza cases (30). Puerto Rico has held mass clinics in the past, in response to epidemics and pandemics, and the Office of Public Health Preparedness holds at least one every year (31).

2013-2014 Influenza Season and Response in Puerto Rico

The 2013-2014 influenza season in the United States was the first season since the 2009 pH1N1 pandemic in which pH1N1 influenza A viruses predominated. During the 2013-2014 season, 90.3% of influenza A viruses identified by the World Health Organization and National Respiratory and Enteric Virus Surveillance System collaborating laboratories in the United States were pH1N1, compared to 4% during the previous season (32). Adults 50-64 years of age experienced increased rates of hospitalization during the 2013-14 season (38.7 per 100,000), when compared to the previous seasons during which A(H3N2) was predominant (29.4 per 100,000 in 2012-13) (32, 33). This was likely due to several factors, including lack of cross-protective immunity to pH1N1, which would have occurred with previous infection with antigenically related viruses, as well as lower vaccination coverage among adults 18-64 years of age, in comparison to children or adults older than 65 years of age (34).

In Puerto Rico, influenza is a reportable disease, and influenza surveillance consists of: 1) a virologic surveillance system using influenza rapid diagnostic tests; 2) a telephone survey syndromic surveillance system, that tracks outpatient influenza-like illness (ILI); and 3) a mortality surveillance system, which tracks influenza-associated pediatric mortality (35, 36). Between June 1st and October 17th, 2013, Puerto Rico reported 16 influenza-associated deaths; 0-2 deaths are typically reported every season. Puerto Rico also reported an increase in influenza-like illness activity in mid-August 2013 that was almost three times greater than at the same time

during 2012. Initially on September 25, 2013, Puerto Rico's Department of Health announced six mass vaccination clinics to occur between October 3 and December 7, 2013. On October 14th, 2013, the Department of Health declared an epidemic of influenza and the mass vaccination clinic program originally planned for 6 clinics from October to December of 2013 was expanded to 14 mass clinics to occur between October and December of 2013 (Figure 1) (37).

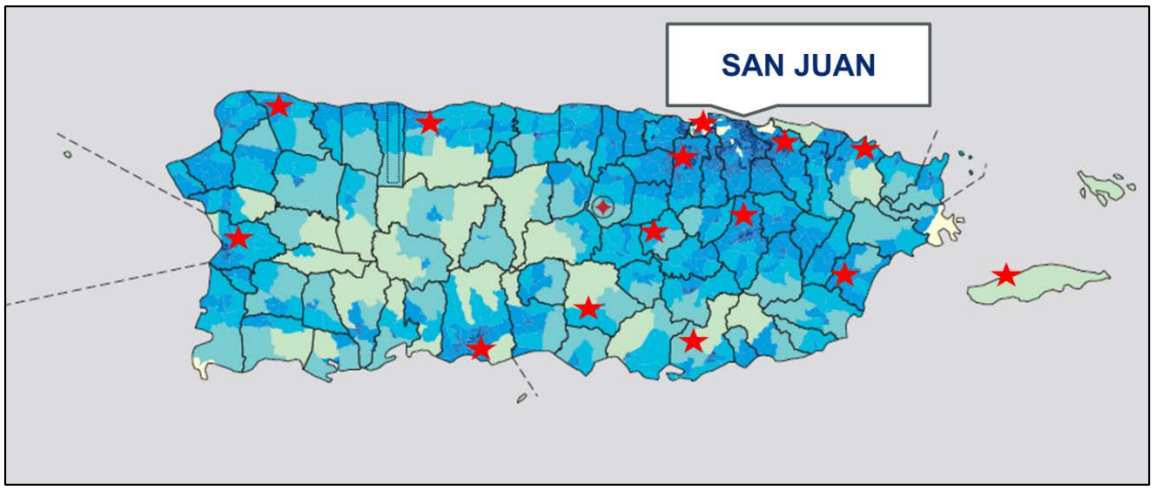


Figure courtesy of Dr. Sofia Arriola

Figure 1: The population density map above shows the location of the 14 mass vaccination clinics held between October 2013 and December 2013. Dark blue indicates regions with high population density. Light blue indicates regions of low population density. The red stars indicate the location of mass vaccination clinics.

These mass vaccination clinics were daylong events held in large community centers, such as convention centers and indoor sports arenas. Clients who attended these clinics were registered and following vaccination, all registration and influenza vaccination information was entered into Puerto Rico's Immunization Registry by clinic staff or by health department staff in the months following the mass vaccination campaign.

The Puerto Rico Immunization Registry (PRIR) is a confidential, lifetime, population-based Internet database application that is used by clinicians and health providers to record and track immunizations administered and dates of immunization for children and adults in Puerto Rico. The goal of the PRIR is to provide a resource for health care providers, as well as individual citizens, to monitor and access their immunization records. Immunization registries such as the PRIR are also known as Immunization Information Systems (IIS), which are confidential, population-based, computerized databases that record all immunization doses entered by participating providers to persons residing within a given geopolitical area. IIS serve two main purposes: first, at the point of clinical care, an IIS can provide a consolidated immunization history for use by a vaccination provider; and second, at the population level, they provide aggregate data on vaccinations for surveillance and program operations (38). Although an IIS generally covers an entire state, territory or island nation, some US cities, such as New York City, Chicago, the District of Columbia, Houston, Philadelphia, and San Antonio report their immunization data separately (39). Core data elements include client information such as: patient name, contact information, social security number, demographic characteristics (sex, race, and ethnicity), and client status (includes active, inactive, and deceased). With regard to client status, active and inactive can be determined at the provider level, and at the geographic jurisdiction level. At the provider level, an individual is considered active if he or she has received an immunization from a provider, or has been identified as a patient of or by a provider. The individual would be inactive at the provider level if he or she were documented to have moved, or been lost to follow-up. At the geographic distribution level, an individual is designated as active if there is documentation of whether he or she resides within the geographic jurisdiction. An individual is considered inactive if there is documentation that he or she no

longer resides in the geographic jurisdiction (40). The core data elements also include vaccine information such as: vaccine type, vaccination date, vaccine manufacturer, and vaccine lot number (41). In addition to tracking immunization records, IIS registries have also been used to evaluate vaccination coverage, and to inform public health decisions such as: vaccine forecasting, vaccine inventory and accountability, and vaccination reminder recall (42, 43). In influenza pandemic situations, the IIS can be used by public health officials to notify individuals to get their first dose, as well as be used to send reminders for a second dose of vaccine.

Mandatory entry of immunization records varies from state to state. Some states, such as Michigan, require immunization information to be reported to the IIS for all persons 19 years of age and younger. Other IIS, such as New York City , require reporting of immunization information for persons aged 0-18 years; reporting immunizations for patients 19 years of age and older is voluntary and requires written consent from the patient (44). In Puerto Rico, before 2009, only providers who received federally funded vaccine were required to report doses administered. Starting in July 2009, an administrative order was created such that all providers, including public and private, who administer publically purchased vaccines are required to enter all data from these vaccines into the PRIR, regardless of the age of the vaccinee (45). There is currently no requirement to report administration of privately purchased vaccine. Childhood or adolescent participation in an IIS is defined as having two or more recommended vaccinations for children <6 years of age or 11-17 years of age, respectively, entered into the IIS (46). Adult participation is defined as having one or more recommended vaccinations for adults older than 19 years of age entered into the IIS. Participation is calculated by dividing the number of individuals meeting vaccine and age criteria by the Census estimated population for that age group (46). National 2013 participation rates for children 6 years of age or younger was 90%,

while participation rates for adolescents 11-17 years of age, and adults 19+ years of age were 64% and 32%, respectively (47). In comparison, in 2013, Puerto Rico reported 100% of children <6 years of age participating in the PRIR, 84% participation among adolescents 11-17 years of age, and 26% participation among adults 19 years of age and older (48).

Manuscript

Abstract

Background: During the seasonal influenza epidemic of 2013-2014, the Puerto Rico Department of Health held mass vaccination clinics across the island in response to increased influenza activity. To provide information that can be used to tailor future mass vaccination campaigns, this study examined factors associated with influenza vaccination at these mass vaccination clinics versus vaccinations provided at other facilities, as well as vaccinations given during mass vaccination clinics early in the season compared to those given later in the season.

Methods: Data were obtained from the Puerto Rico Immunization Registry (PRIR) for the 2013-2014 influenza season. Log-binomial regression analysis was conducted to determine whether age, sex, race and insurance status were associated with vaccination at early mass clinics among all age groups, including adults, compared to vaccination at later mass clinics. Log-binomial regression was also used to determine whether these same factors were associated with vaccination at mass clinics compared to non-mass vaccination clinics, among children 6 months to 18 years of age.

Results: The PRIR reported 267,273 influenza vaccinations provided in Puerto Rico during the 2013-2014 influenza season. After adjusting for all other factors, vaccinations that were less likely to be given at early mass vaccination clinics than at late mass vaccination clinics were those given to persons of Other Race (aPR 0.86, relative to Whites). Vaccinations given to Black children in the PRIR were more likely to be received at mass vaccination clinics than at non-mass vaccination sites (aPR 1.78, relative to White children). In addition, vaccinations that were less likely to be received at mass vaccination clinics than at non-mass vaccination sites were those given to children 6 months-4 years (aPR 0.35, relative to 13-18 year olds) and those given to children under Medicaid, or to children without insurance (aPR 0.52 and aPR 0.55, respectively, relative to privately insured children).

Conclusions: : There were sociodemographic differences in vaccinations given at early mass vaccination clinics compared to those given at late mass vaccination clinics. Factors were also associated with vaccinations given to Puerto Rican children at mass vaccination clinics compared to those vaccinations given at other venues. The Puerto Rico Department of Health can use these findings to modify their influenza vaccination strategies during future epidemics, through directing vaccine stocks to providers who vaccinate children. Additionally, the results of this study demonstrate the utility of Immunization Information System (IIS) data in evidence-based evaluation of immunization programs and activities.

Introduction

Influenza is a public health concern, with epidemics capable of causing high morbidity and mortality worldwide (2, 7). Vaccination against influenza is the most effective method of preventing influenza infection, and the Advisory Committee on Immunization Practices (ACIP) recommends that all persons 6 months of age and older receive an influenza vaccination annually (49).

Puerto Rico experienced a moderately severe 2013-2014 influenza season with an increased number of influenza-associated deaths, compared to previous years (24). By October 14, 2013, Puerto Rico had reported 16 influenza-related deaths when 0-2 deaths are typically reported annually, and there were 29 deaths between June 1, 2013 and May 31, 2014 (24, 50). Puerto Rico has previously used mass vaccination clinics during influenza pandemics and epidemics to provide free vaccinations to persons seeking vaccination at the clinics. During the 2013-14 influenza season health authorities from the Puerto Rico Department of Health initially announced six mass vaccination clinics to be held across the island, between October and December of 2013. In response to the increase in influenza activity, the Puerto Rico Department of Health increased the number of planned mass influenza vaccination clinics to fourteen to occur during the same time period (24, 37, 51).

Factors associated with receipt of influenza vaccination in Puerto Rico, such as provider recommendation and barriers to vaccination access, have previously been studied. In a survey conducted in 2013, barriers to access such as lack of time to get vaccinated, lack of vaccine availability, and lack of knowledge as to where to seek vaccination were all provided as primary reasons for not getting vaccinated against influenza (24). However, given the use of mass influenza vaccination clinics in Puerto Rico, it is notable that factors associated with receipt of

influenza vaccination during influenza mass vaccination clinics have not been well studied. It is not clear whether persons who receive influenza vaccinations during an outbreak through the routine delivery system are different from persons who receive vaccinations during mass clinics. Further, it is not known whether individuals who receive influenza vaccination at mass clinics are different based on date of the mass vaccination clinic (e.g., earlier versus later clinics). To address these issues, we investigated whether factors such as age, sex, race, and insurance status were associated with persons obtaining vaccination during early mass vaccination clinics in October and early-November compared to characteristics among persons vaccinated through mass vaccination clinics later in the season. We also investigated characteristics associated with receipt of influenza vaccination at mass vaccination clinics compared to other vaccination facilities among children 6 months to 18 years of age during the 2013-2014 influenza season.

Methods

Data Source

Influenza immunization records were accessed from the Puerto Rico Immunization Registry (PRIR). The PRIR is a lifespan immunization information system (IIS) that is used to record and track immunization data in Puerto Rico. The PRIR is a confidential, population-based computerized database that allows health care providers to enter vaccination data of clients receiving a vaccination. Vaccinations received at all mass vaccination clinics conducted by the Puerto Rico Department of Health are also entered. The Centers for Disease Control and Prevention defines childhood or adolescent participation in an IIS as having two or more recommended vaccinations for children <6 years of age or 11-17 years of age, respectively, entered into the IIS (42). Adult participation is defined as having one or more recommended

vaccinations for adults older than 19 years of age entered into the IIS. Participation is calculated by dividing the number of individuals meeting vaccination and age criteria by the Census estimated population for that age group (42). In 2013, Puerto Rico reported PRIR participation proportions of 100% for children <6 years of age, 84% among adolescents 11-17 years of age, and 26% among adults 19 years of age and older (48).

We focused our analysis to records reported in the registry between July 1, 2013 and June 30, 2014. Vaccinations were excluded if they were given to individuals younger than 6 months of age or if the vaccinations recorded were unavailable for the 2013-14 season (such as monovalent H1N1 influenza vaccine) (Figure 2, Appendix). For individuals with multiple vaccinations reported on the same day, we utilized one record for this vaccination through individual- and date-level deduplication. Multiple vaccinations for an individual, when recorded as administered on different days, within the 2013-14 season were included, in order to account for all vaccinations reported to the PRIR. For eligible vaccinations (n=267,273), the following data elements were extracted: client's unique ID, date of birth, race, sex, insurance status recorded at time of vaccination, vaccination date, and provider PIN. Ethnicity was available for analysis; however, 99% of the records were for patients that were Hispanic or Latino and therefore the variable was dropped from analysis.

Vaccinations provided at mass vaccination clinics were determined by provider PIN and vaccination date. Influenza vaccination at an early mass clinic was defined as receipt of vaccination at a mass clinic between October 1 and November 6, 2013. November 11 was chosen as the cut-point, as the number of vaccinations per clinic were highest during clinics held October 1 and November 6, and dropped after November 6 (Figure 3). Influenza vaccination at a late mass clinic was defined as receipt of vaccination at mass clinics occurring between

November 12, 2013 and December 31, 2013, or April 1, 2014 and June 31 of 2014. No mass clinics were held between January and April of 2014.

Age at vaccination was calculated from date of birth and date of the first vaccination in the 2013-14 season, and was categorized into the following age groups: 6-months to 4 years, 5-12 years, 13-17 years, 18-49 years, 50-64 years, and ≥65 years. This categorization was chosen for comparability with other influenza vaccine uptake estimates, and follows categorization for previously recommended groups for influenza vaccination (23). Health insurance at time of vaccination was categorized as: private insured (regardless of whether the insurance provider covered influenza vaccination), Medicaid, uninsured, and unknown insurance type or status. Race was categorized as: Native American/Alaska Native; Asian, Native Hawaiian or Pacific Islander; Black; White; and Other Race.

Mass Clinic Date	Number Vaccinated
3-Oct-13	5,137
5-Oct-13	9,726
19-Oct-13	10,024
22-Oct-13	8,069
24-Oct-13	5,314
30-Oct-13	6,229
2-Nov-13	6,400
6-Nov-13	4,630
12-Nov-13	2,485
16-Nov-13	2,754
21-Nov-13	3,020
22-Nov-13	232
3-Dec-13	1,476
5-Dec-13	523
Total vaccinated at original 14	66,019

Figure 3: List of the 14 mass vaccination clinics held in 2013, and the number of patients vaccinated at each clinic. The division between November 6, 2013 and November 12, 2013 indicates the clinics between early mass clinics and late mass clinics. Clinics held after December 5 are not listed, as they were organized after the initial expansion to 14 clinics.

Data Analysis

Demographic characteristics, and insurance status of persons receiving vaccination at early mass vaccination clinics were compared to persons receiving vaccination at late mass vaccination clinics for all age groups using frequencies and proportions. Although all influenza vaccinations were entered into the PRIR if they were received at a mass clinic, we know not all vaccinations given at non-mass vaccination sites were entered into the PRIR. In 2013, Puerto Rico reported 100% of children <6 years old participating in the PRIR, 84% participation among adolescents 11-17 years, and 26% participation among adults 19 years and older (48). Therefore, the analysis comparing vaccination at mass vaccination clinics to non-mass vaccination sites was restricted to vaccinations given to children under 18 years of age, as children and adolescents have more complete participation in the PRIR. Chi-square tests of independence were carried out for both analyses in order to examine relationships across all levels of individual variables. Chi-square goodness of fit tests were carried out for both analyses in order to test observed proportions for equality within each level of an individual variable. All differences were assessed to be significant at the $\alpha=0.05$ level.

Dependent variables in this analysis were: 1) vaccinations given at early mass vaccination clinics among all ages including adults (vs vaccinations given at late mass vaccination clinics and 2) vaccinations given at mass clinics among children (vs vaccinations given at non-mass vaccination sites among children). Independent variables included in both analyses were: sex (male, female [referent]); age group (6-level variable: 6 month-4 years, 5-12 years, 13-17 years, 18-49 years, 50-64 years, 65+ years [referent]); health insurance status (4-level variable: private insurance [referent], Medicaid, not insured, unknown); and race (5-level variable: American Indian/Alaska Native; Asian, Native Hawaiian or Other Pacific Islander; Black or African-

American; Other Race; or White [referent]). Bivariate analyses were conducted using log-binomial regression models to investigate associations between the dependent variables and each independent variable. Adjusted associations between each dependent variable and the independent variables were investigated using multivariable log-binomial regression models. Unadjusted and adjusted prevalence ratios were reported, along with 95% confidence intervals.

This project was determined to be "research not involving human subjects", and did not require further IRB review. All analyses were performed using SAS v9.4 (The SAS Institute, Cary, North Carolina)

Results

Overall Study Demographics

The total number of influenza vaccinations reported to be administered in the PRIR between July 1, 2013 and June 30, 2014 and meeting our inclusion criteria was 267,273 (Table 1). A majority of vaccinations were given to persons of Other Race (66%), compared to 15% given to Whites. Vaccinations given to adults over 18 years of age represented 68% of influenza vaccinations during the 2013-14 season. Vaccinations given to children 6 months-4 years of age and 5 years-17 years of age represented approximately 10% and 23% of influenza vaccinations for the 2013-14 season, respectively. With regard to health insurance, 220,357 (82%) vaccinations were given to persons who were reported at the time of vaccination to have some type of insurance. Of these individuals, 135,378 (61% of the insured group) were covered under Medicaid. Chi square tests of independence were significant for age group, race, and insurance type for both comparisons, early mass vaccination clinics vs late mass vaccination clinics, as

well as all mass vaccination clinics vs non-mass vaccination clinics ($p<0.0001$). In addition, the Chi-square test of independence for sex was significant for the comparison of vaccinations given at early mass vaccination clinics vs late mass vaccination clinics ($p<0.005$), though it was not significant for the comparison between vaccinations given at mass vaccination clinics vs non-mass sites ($p>0.05$).

Early Mass Vaccination Clinics vs Late Mass Vaccination Clinics, all ages

During the 2013-2014 season, a total of 70,834 vaccinations were provided at mass vaccination clinics. Of these vaccinations, 55,676 (79%) were given at early mass vaccination clinics between October and November of 2013, while 15,158 vaccinations (21%) were given at late mass vaccination clinics (Table 2). Among vaccinations provided at early mass vaccination clinics, the majority (34,007 or 61%) were given to persons of Other Race, followed by 10,329 (19%) vaccinations given to Whites. Comparatively, among the 15,158 vaccinations provided at late mass vaccination clinics, 12,028 (79%) were given to people of Other Race, while 1,637 (11%) were given to Whites (χ^2 $p<0.001$). In early mass vaccination clinics, 47,710 vaccinations (86%) were given to persons with either private insurance or Medicaid. This was similar in late mass vaccination clinics, individuals with insurance constituted approximately 85% of vaccination recipients at late mass vaccination clinics.

After adjusting for all other factors, vaccinations given to individuals of Other Race were less likely to be received at early mass vaccination clinics than at late mass vaccination clinics, compared to vaccinations given to individuals of White race (aPR 0.86 [0.85, 0.87]) (Table 2). Vaccinations given to children 6 months-4 years (aPR 1.08, [1.06, 1.10]), to children 5-12 years

(aPR 1.06, [1.05, 1.08]), and to children 13-18 years (aPR 1.05, [1.04, 1.07]), were all more likely to be received at early mass vaccination clinics than at late mass vaccination clinics, compared to adults 65 years and older. Vaccinations given to persons on Medicaid (aPR 0.97, [0.96, 0.98]) and to persons with unknown insurance type (aPR 0.95, [0.93, 0.96]) were less likely to be received at early mass vaccination clinics than at late mass vaccination clinics, compared to vaccinations given to persons with insurance.

Total Mass Vaccination Clinics vs Non-Mass Vaccination Sites, children

The total number of influenza vaccinations given to children 6 months to 18 years of age during the 2013-2014 season and reported to the PRIR, was 94,078. Of these vaccinations, 16,960 (18%) were received at mass vaccination clinics, and 77,118 (82%) vaccinations given to children were received at a non-mass vaccination clinic (Table 3). Among vaccinations given to children, those given to children 6 months-4 years of age were less likely to be received at a mass vaccination clinic (7.5%) than at a non-mass vaccination site (92.5%) (χ^2 p-value <0.001). Vaccinations given to children ages 5-12 years were also less likely to be received at a mass vaccination clinic (21%) than at a non-mass vaccination site (79%). Vaccinations given to adolescents 13-18 years of age were less likely to be received at a mass vaccination clinic (23%) than a non-mass vaccination clinic site (77%). Of the 16,138 vaccinated children with health insurance (non-Medicaid), 5,312 (33%) received influenza vaccination at mass vaccination clinics while 11,470 (67%) received influenza vaccine through other providers. All differences were significant (χ^2 p-value <0.001).

Adjusting for all other factors, vaccinations given to children 6 months-4 years of age were less likely to be received at a mass vaccination clinic than at a non-mass vaccination site, compared to children 13-18 years (aPR 0.35, 95% CI [0.34, 0.37]) (Table 3). Vaccinations given to children between 5-12 years of age were also less likely to be received at mass vaccination clinics than at non-mass vaccination sites, compared to children 13-18 years of age (aPR 0.93 [0.90, 0.96]). Similarly, vaccinations given to uninsured children (aPR 0.55, [0.51, 0.59]), to children covered under Medicaid (aPR 0.52 [0.51, 0.54]), and to children with unknown insurance status (aPR 0.55, [0.52, 0.57]) were all less likely to be received at mass vaccination clinics than at non-mass vaccination sites, compared to vaccinations given to insured children, adjusting for all other factors. Vaccinations given to Black children were more likely to be received at mass vaccination clinics than at non-mass vaccination sites, compared to vaccinations given to White children, adjusting for all other factors (aPR 1.78, [1.60, 1.97]). Finally, vaccinations given to American Indian/Alaska Native children (aPR 0.71, [0.57, 0.87]) were less likely to be received at mass vaccination sites than at non-mass vaccination sites, compared to vaccinations given to White children.

Vaccinations given to male children, to children belonging to the 5-12 year age group, and to children belonging to the Asian, Native Hawaiian or Other Pacific Islander race group were no more likely to be received at mass vaccination clinics than at non-mass vaccination sites, compared to their respective referent groups (Vaccinations given to females, to children 13-18 years, and to White children).

Table 1: Demographic characteristics by influenza vaccination site for vaccinations registered in Puerto Rico Immunization Information Registry

Total n=(267, 273)	Total Mass Vaccination (n= 70,834)		Early Mass Vaccination[a] (n= 55,676)		Late Mass Vaccination[b] (n=15,158)		Non-Mass Vaccination (n= 196,439)		χ^2 tests of independence Total Mass vs Non-Mass χ^2 p-value	Early Mass vs Late Mass χ^2 p-value
	Median	**[Min, Max]**	**Median**	**[Min, Max]**	**Median**	**[Min, Max]**	**Median**	**[Min, Max]**		
Age	43	[1, 85]	43	[1, 84]	45	[1, 85]	28	[1, 85]		
Sex	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**		
Female (n=150,597)	40,043	26.6	31,641	21.0	8,402	5.6	110,554	73.4	0.2469	0.002
Male (n=116,676)	30,791	26.4	24,035	20.6	6,756	5.8	85,885	73.6		
Race	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**		
American Indian or Alaska Native (n=1,039)	341	32.8	301	29.0	40	3.8	698	67.2	<0.0001	< 0.0001
Asian, Native Hawaiian, or Other Pacific Islander (n=158)	75	47.5	63	39.9	12	7.6	83	52.5		
Black or African-American (n=1,917)	966	50.4	828	43.2	138	7.2	951	49.6		
White (n=39,257)	11,966	30.5	10,329	26.3	1,637	4.2	27,291	69.5		
Other Race (n=177,521)	46,035	25.9	34,007	19.2	12,028	6.8	131,486	74.1		
Missing	11,451		10,148		1,303		35,930			
Age Group	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**		
6 months-4 years (n=26,428)	**1,990**	**7.5**	**1,633**	**6.2**	**357**	**1.4**	**24,438**	**92.5**	< 0.0001	< 0.0001
6-23 months (n=5,969)	186	3.1	158	2.6	28	0.5	5,783	96.9		
2-4 years (n=20,459)	1,804	8.8	1,475	7.2	329	1.6	18,655	91.2		
5-17 years (n=62,588)	**13,975**	**22.3**	**11,294**	**18.0**	**2,681**	**4.3**	**48,613**	**77.7**		
5-12 years (n=39,068)	8,309	21.3	6,752	17.3	1,557	4.0	30,759	78.7		
13-17 years (n=23,520)	5,666	24.1	4,542	19.3	1,124	4.8	17,854	75.9		
≥18 years (n=178,257)	**54,869**	**30.8**	**42,749**	**24.0**	**12,120**	**6.8**	**123,388**	**69.2**		
18-49 years (n=90,027)	25,334	28.1	19,769	22.0	5,565	6.2	64,693	71.9		
50-64 years (n=50,187)	17,020	33.9	13,202	26.3	3,818	7.6	33,167	66.1		
≥65 years (n=38,043)	12,515	32.9	9,778	25.7	2,737	7.2	25,528	67.1		
Insurance Type	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**		
Insured (n=84,979)										
Insured, Vaccine Covered (n=58,660)	23,816	40.6	18,830	32.1	4,986	8.5	34,844	59.4	< 0.0001	< 0.0001
Insured, Vaccine Not Covered (n=7,407)	2,334	31.5	1,911	25.8	423	5.7	5,073	68.5		
Native American / Alaska Native (n=13)	8	61.5	8	61.5	0	0.0	5	38.5		
Insured, Vaccine Eligibility Unknown (n=18,899)	5,569	29.5	4,618	24.4	951	5.0	13,330	70.5		
Medicaid (n=135,378)	28,878	21.3	22,343	16.5	6,535	4.8	106,500	78.7		
No Insurance (n=14,234)	3,656	25.7	2,956	20.8	700	4.9	10,578	74.3		
Insurance Unknown (n=32,682)	6,573	20.1	5,010	15.3	1,563	4.8	26,109	79.9		

[a] Defined as mass vaccination clinics occurring between October 1, 2013 and November 11, 2013

[b] Defined as mass vaccination clinics occurring between November 12, 2013 and December 31, 2013, and April 1, 2014 and June 30th, 2014

Table 2: Bivariate and multivariate predictors of vaccination at early mass vaccination clinics, Puerto Rico IIS, October 1, 2013 - November 11, 2013

					Comparing Early vs Late			
	Early Mass Vaccination[a]		Late Mass Vaccination[b]		**Bivariate analysis**		**Multivariate Analysis adjusted**	
Total n=70,834	(n= 55,676)		(n=15,158)		**Prevalence Ratio**		**Prevalence Ratio**	
Sex	**No.**	**%**	**No.**	**%**	**PR**	**95% CI[e]**	**aPR**	**95% CI[e]**
Female (n=39,869)	31,641	79.0	8,402	21.0		**referent**		
Male (n=30,628)	24,035	78.1	6,756	21.9	0.99	(0.98, 1.00)	0.99	(0.98,1.00)
Race	**No.**	**%**	**No.**	**%**	**PR**	**95% CI**	**aPR**	**95% CI**
American Indian or Alaska Native (n=341)	301	88.3	40	11.7	1.02	(0.98, 1.06)	1.02	(0.98, 1.06)
Asian, Native Hawaiian or Other Pacific Islander (n=75)	63	84.0	12	16.0	0.97	(0.88, 1.07)	0.97	(0.88, 1.07)
Black or African-American (n=965)	828	85.7	138	14.3	0.99	(0.97, 1.02)	0.99	(0.97, 1.02)
Other Race (n=45,762)	34,007	73.9	12,028	26.1	0.86	(0.85, 0.86)	0.86	(0.85, 0.87)
White (11,918)	10,329	86.3	1,637	13.7		**referent**		
Age Group	**No.**	**%**	**No.**	**%**	**PR**	**95% CI**	**aPR**	**95% CI**
6 months-4 years (n=1,938)	1,633	82.1	357	17.9	1.05	(1.03, 1.07)	1.08	(1.06, 1.10)
5-12 years (n=8,247)	6,752	81.3	1,557	18.7	1.04	(1.03, 1.05)	1.06	(1.05, 1.08)
13-17 years (n=5,652)	4,542	80.2	1,124	19.8	1.03	(1.01, 1.04)	1.05	(1.04, 1.07)
18-49 years (n=25,240)	19,769	78.0	5,565	22.0	1.00	(0.99, 1.01)	1.01	(1.00, 1.02)
50-64 years (n=16,952)	13,202	77.6	3,818	22.4	0.99	(0.98, 1.01)	1.00	(0.99, 1.01)
≥65 years (n=12,468)	9,778	78.1	2,737	21.9		**referent**		
Insurance Type	**No.**	**%**	**No.**	**%**	**PR**	**95% CI**	**aPR**	**95% CI**
Insured [d] (n=31,629)	25,367	80.0	6,360	20.0		**referent**		
Medicaid (n=28,692)	22,343	77.4	6,535	22.6	0.97	(0.96, 0.98)	0.97	(0.96, 0.98)
Not Insured (n=3,640)	2,956	80.9	700	19.1	1.01	(1.00, 1.03)	1.02	(1.01, 1.04)
Unknown (n=6,536)	5,010	76.2	1,563	23.8	0.95	(0.94, 0.97)	0.95	(0.93, 0.96)

[a] Defined as mass vaccination clinics occurring between October 1, 2013 and November 11, 2013

[b] Defined as mass vaccination clinics occurring between November 12, 2013 and December 31, 2013, and April 1, 2014 and June 30, 2014

[d] Defined as: Insured (Vaccine covered); Insured (Vaccine not covered); Insured (Vaccine elegibility unknown); Native American/Alaska Native

[e] 95% Confidence Intervals may not appear to contain the estimated value, due to rounding

Table 3: Bivariate and multivariate predictors of vaccination at mass vaccination clinics among children 6 months-18 years registerd in Puerto Rico IIS

	Mass Vaccination		Non-Mass Vaccination		Comparing Mass Vaccination Clinics vs Non-Mass Sites: Bivariate analysis Prevalence Ratio		Multivariate Analysis adjusted Prevalence Ratio	
Total n=94,078	(n= 16,960)		(n= 77,118)					
Sex	**No.**	**%**	**No.**	**%**	**PR**	**95% CI**	**aPR**	**95% CI**
Female (n=46,525)	8,416	18.1	38,109	81.9	**referent**			
Male (n=47,553)	8,544	18.0	39,009	82.0	0.99	(0.97, 1.02)	0.99	(0.97, 1.02)
Race	**No.**	**%**	**No.**	**%**	**PR**	**95% CI**	**aPR**	**95% CI**
American Indian or Alaska Native (n=584)	72	12.3	512	87.7	0.68	(0.55, 0.85)	0.71	(0.57, 0.87)
Asian, Native Hawaiian or Other Pacific Islander (n=60)	12	20.0	48	80.0	1.11	(0.67, 1.84)	1.07	(0.65, 1.75)
Black or African-American (n=565)	197	34.9	368	65.1	1.93	(1.72, 2.17)	1.78	(1.60, 1.97)
Other Race (n=68,583)	12,671	18.5	55,912	81.5	1.02	(0.99, 1.06)	1.01	(0.98, 1.05)
White (n=15,120)	2,728	18.0	12,392	82.0	**referent**			
Age Group	**No.**	**%**	**No.**	**%**	**PR**	**95% CI**	**aPR**	**95% CI**
6 months-4 years (n=26,428)	1,990	7.5	24,438	92.5	0.32	(0.36, 0.40)	0.35	(0.34, 0.37)
5-12 years (n=39,068)	8,309	21.3	30,759	78.7	0.91	(0.92, 0.97)	0.93	(0.90, 0.96)
13-18 years (n=28,582)	6,661	23.3	21,921	76.7	**referent**			
Insurance Type	**No.**	**%**	**No.**	**%**	**PR**	**95% CI**	**aPR**	**95% CI**
Insured [a] (n=16,138)	5,312	31.7	11,470	68.3	**referent**			
Medicaid (n=53,300)	8,652	15.0	49,030	85.0	0.47	(0.48, 0.51)	0.52	(0.51, 0.54)
Not Insured (n=4,139)	753	17.3	3,605	82.7	0.55	(0.52, 0.59)	0.55	(0.51, 0.59)
Unknown (n=14,061)	2,243	14.7	13,013	85.3	0.46	(0.46, 0.50)	0.55	(0.52, 0.57)

[a] Defined as: Insured (Vaccine covered); Insured (Vaccine not covered); Insured (Vaccine elegibility unknown); Native American/Alaska Native

Discussion

To our knowledge, this is the first study to look at factors associated with receipt of vaccination at mass vaccination clinics. After adjusting for all other factors, vaccinations that were more likely to be given at late mass vaccination clinics than at early mass vaccination clinics were those given to persons of Other Race (relative to White), and those given to persons receiving Medicaid benefits or to persons with unknown insurance type (relative to privately insured). Vaccinations given to children <18 years of age were more likely to be received at early mass vaccination clinics than late mass vaccination clinics, compared to adults older than 65 years. However, with regard to insurance status, while associations were statistically significant, the strength of association was low and thus these may not be considered strong predictors. In addition, we were able to find that vaccinations that were less likely to be received at mass vaccination clinics than at non-mass vaccination sites were those given to children 6 months-4 years (relative to 13-18 year olds), and those given to children under Medicaid, or to children without insurance (relative to privately insured children). Further, among children <18 years who received an influenza vaccination during the 2013-2014 season, Black children were more likely to receive influenza vaccination at mass vaccination clinics than at non-mass vaccination sites, compared to White children. These associations remained significant in multivariate regression analysis after adjustment for other factors.

With regard to the association seen with Other Race and receipt of vaccination at early mass vaccination clinics, it is not clear why vaccinations for this group were more likely to have been provided at late mass vaccination clinic than at early mass vaccination clinics, compared to White individuals. Although disparities in influenza vaccination by race and disparities in knowledge, attitudes and practices (KAP) regarding influenza vaccination by race have been

described, the association between race and timing of influenza vaccination is unknown. Previous studies have shown that Whites were more likely to believe in the efficacy of influenza vaccine, compared to Blacks and Hispanics (52). It is possible that White individuals registered in the PRIR as having received influenza vaccine during the 2013-14 season went to earlier mass clinics due to differing KAP than individuals of Other Race. It should also be noted that there is no clear categorization for "Other Race" in the PRIR. In order to develop interventions to target this population, it is necessary to investigate the categorization of "Other Race" in the PRIR.

In our study, vaccinations given to younger children were more likely to be received in other venues than at mass clinics, compared to vaccinations given to older children. This matches existing literature, which has found that children are more likely to receive their vaccines at doctor's offices, or health centers, compared to venues such as health departments, pharmacies, schools, or non-medical places. A study by Santibanez et al using National Immunization Survey-Flu data from the 2013-14 influenza seasons in the United States found that approximately 77% of children between 6 and 23 months, and 72% of children between 2 and 4 years received their influenza vaccination at a doctor's office. In comparison, 64% of children 5-12 years of age and 58% of children 13-17 years of age received their vaccination at a doctor's office (53). These findings suggest that during epidemics or pandemics, Puerto Rico should ensure that vaccines are distributed to doctor's offices that vaccinate children. Further, the PRIR should be utilized during future pandemic planning in order to ensure evidence-based vaccine allocation, based on vaccination trends and past distribution. Otherwise, if vaccine stocks are distributed primarily to mass vaccination sites, and children do not utilize these clinics, this important group may be missed during a vaccination campaign.

In addition to age, we found that among children who received a vaccine during the 2013-14 season, children of certain races were more likely to be vaccinated at mass vaccination clinics than at other providers, compared to children of other Races. Black children who were vaccinated were more likely to receive their vaccine at a mass vaccination clinic than at a non-mass vaccination site, compared to White children. This is consistent with existing evidence for the 2013-14 season in the United States that shows that of children who were vaccinated, more White children were vaccinated at doctor's offices (74%) than were Black children (67%) (53). Although the number of Black children in the PRIR was small, this finding suggests that certain populations in Puerto Rico might seek vaccinations at health department facilities, such as mass vaccination clinics, rather than at other providers. As stated earlier, disparities in knowledge, attitudes and practices towards influenza vaccination exist between race among adults, including differences in attitudes towards vaccination and preventive care, tendency to seek and accept vaccination, and differences in concerns about vaccination (54). Increased health communication campaigns by the Puerto Rico Department of Health could improve influenza vaccination seeking behaviors in racial minority groups. Otherwise, these populations might be missed during future influenza seasons, if mass clinics are not as available as during the 2013-14 season.

Interestingly, vaccinations provided to children who were uninsured, whose insurance status was unknown, or who were covered under Medicaid, were less likely to be given at mass vaccination clinics than non-mass vaccination sites, compared to vaccinated children who had insurance. It is possible that the uninsured or those on Medicaid visited other low-cost or free vaccination centers that were not part of the mass vaccination clinic plan. For example, the Vaccines for Children (VFC) program is a federally funded program that allows children of families who cannot pay for vaccines, to be vaccinated at VFC enrolled health care providers

(55). This includes children younger than 19 years of age, children who are uninsured, underinsured, are enrolled in Medicaid, or are American Indian/Alaska Natives. All publically provided vaccinations (such as through VFC) are required to be entered into the PRIR. Therefore, individuals vaccinated through these facilities would have been entered into the registry, and are thus more likely to be counted than other non-mass vaccination site patients. However, as VFC providers were not part of the mass vaccination clinics that Puerto Rico held during 2013-14, these individuals would have been classified as "non-mass vaccination clinic" clients in our analysis. This could account for the association seen with children 6 months to 4 years of age being less likely to receive vaccine at mass vaccination clinics, than at non-mass vaccination sites. In addition, since vaccinations given to insured children were more likely to be provided at mass vaccination clinics than at non-mass vaccination sites, Puerto Rico could use PRIR data to identify insured persons who received vaccinations at mass vaccination clinics. The Department of Health could then bill insurers in order to recoup some costs of mass vaccination campaigns.

There were a number of limitations that affected our analysis. First, while we were able to analyze data on vaccinations given to individuals whose data were entered into the PRIR, we were not able to consider individuals who did not receive influenza vaccination during the 2013-2014 season. Therefore, although our study is largely representative of the vaccinations given to children, and of vaccinations given to persons of all ages at mass vaccination clinics in Puerto Rico during 2013-2014, our analysis and interpretations must be limited to influenza vaccinations that were entered into the PRIR. In addition, although we were able to account for all vaccinations reported to the PRIR for the 2013-14 season by allowing multiple vaccinations per person for the season, we were not able to tell if multiple vaccinations received were data

entry errors. However, the number of individuals with multiple vaccinations in our analysis is small (3% of all vaccinations evaluated), and are unlikely to affect our estimates. In addition, not all influenza vaccinations may have been entered into the registry. This is especially true for vaccinations given to adolescents and adults outside of mass vaccination clinics, for whom 2013 PRIR coverage rates were approximately 84% and 26%, respectively (48). While PRIR entry was 100% for children and adolescents who received vaccinations at mass vaccination clinics, it is possible that adolescents who received vaccines at non-mass vaccination sites were left out of our analysis if they received a vaccination from a provider who is not entering data into PRIR. If this were true, it could weaken the association between age and receipt of vaccination at mass vaccination clinics, meaning older children may not be more likely to visit mass vaccination clinics than non-mass vaccination sites, compared to younger children.

We did not receive data on individuals with high-risk conditions, and were unable to assess vaccination coverage, or vaccination location for this important group. Individuals with high-risk conditions, such as cardiovascular disease, pulmonary disease, and diabetes are at elevated risk for developing serious complications such as pneumonia (5). During influenza outbreaks, it is important that individuals with high risk conditions are vaccinated early, and mass vaccination clinics can be a way to target these special populations. Previous studies have shown that adults with chronic conditions such as cardiovascular disease, pulmonary disease, diabetes, and cancer, were more likely to access influenza vaccination in medical settings (doctor's office, clinics/health centers, hospitals, and health departments) than at nonmedical settings (workplace, stores, senior/recreation/community centers, schools or other places) (56). However, as we were not able to directly assess these individuals in our study, we are unable say whether vaccinations given to persons with high-risk conditions were received at mass vaccination clinics, or if the

association between any of our other predictors might have changed had we been able to adjust for vaccinations given to persons with high-risk medical conditions. Finally, mass vaccination clinics in 2013-14 occurred within an outbreak situation when there was increased media attention and potentially increased demand for influenza vaccine. As such, the results of this study may not be generalizable to seasonal vaccination when there is not increased influenza activity.

Although there were a number of limitations, the results of this evaluation can still provide information to inform future mass vaccination clinics in Puerto Rico. Through analysis of the Puerto Rico Immunization Registry, we were able to identify sociodemographic differences in Puerto Rican children who received an influenza vaccination at mass vaccination clinics compared to those who received an influenza vaccination in other venues. Additionally, the results of this study demonstrate the utility of IIS data in evidence-based evaluation of immunization programs and activities. The Puerto Rico Department of Health should utilize the PRIR to identify patterns in influenza vaccination by age and other demographic factors to assist in planning, appropriate vaccine distribution, and to target under-vaccinated populations in preparation for future influenza epidemics or pandemics.

Public Health Implications and Future Directions

Despite limitations, the results of this study still have implications for public health practice. First, these findings provide information that can be used to inform future mass vaccination clinics in Puerto Rico. For example, in this study, we found that among children who received influenza vaccination in 2013-2014, those without insurance, or those on Medicaid were actually less likely to receive vaccination at the early mass vaccination clinics, than at non-mass vaccination sites, when compared to those children with insurance. In addition, younger children who received vaccines were more likely to be vaccinated at non-mass vaccination sites than at mass vaccination clinics, compared to adolescents 13-18 years of age. In the future, Puerto Rico can use this information to ensure that during future influenza vaccination efforts, vaccines are distributed to providers who are vaccinating uninsured children or children covered under Medicaid, rather than directing vaccine stocks primarily to mass vaccination clinics.

This analysis also shows the usefulness of Puerto Rico's Immunization Registry data as part of program evaluation. Although there were limitations due to the variables available, and the population represented in the data was not the entire population of Puerto Rico, the data obtained through the PRIR provided information regarding influenza vaccination seeking during an epidemic when mass vaccination clinics are conducted in the territory. As the PRIR expands, it will be important to not only capture more data from different providers, but also to ensure completeness of data/data quality. More complete data with regard to ZIP code, etc. can help Puerto Rico better tailor their immunization strategies in the future. For example, we were unable to analyze whether client location was associated with vaccination at mass vaccination clinics, as ZIP code data was missing for a majority of clients. If data regarding ZIP code or region were more complete, Puerto Rico's Department of Health could carry out an analysis similar to the

one in this study in order to identify regions of the island that have low influenza vaccination coverage (i.e., have vaccinations in the PRIR but did not have an influenza vaccination entered). They could then target these locations for future mass clinics, or education and outreach programs. Further, the PRIR could be used to study vaccine demand by provider over time, and this information could be used to better distribute vaccine stocks.

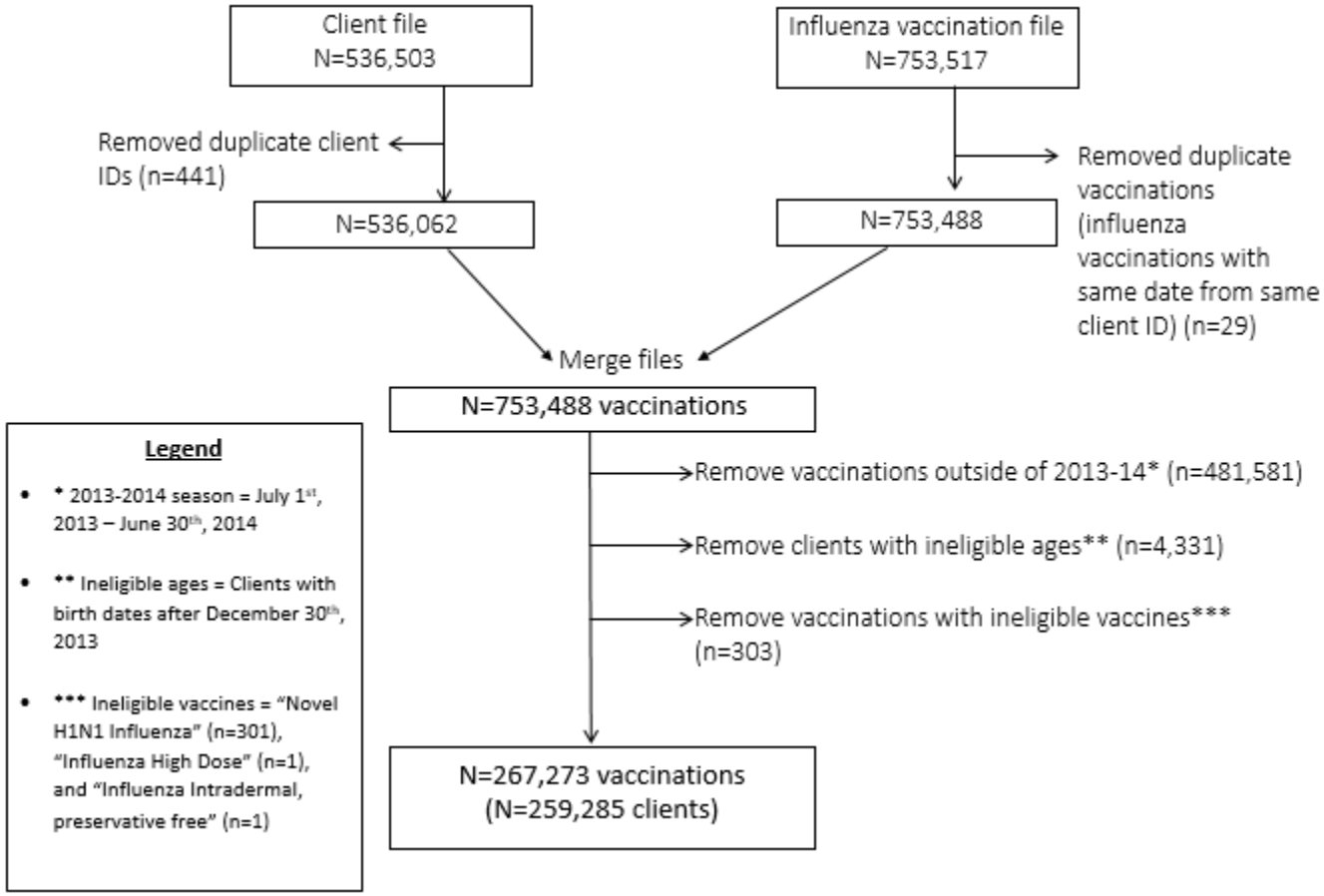
There are several directions for future research. First, it would be vital to address the issue of multiple vaccinations within a season. Future studies should investigate whether multiple vaccinations entered into the PRIR are valid doses (e.g., given to children 6 months – 8 years of age and/or given 28 days apart, according to ACIP recommendations). The Puerto Rico Department of Health can utilize the IIS to identify providers not following recommendations, or those having multiple data entry errors (e.g. those with many duplicate entries for individuals older than 9 years of age). This would not only be helpful to Puerto Rico as a potential data quality step, but could also show the benefits of using an IIS to inform vaccination decisions at the patient and provider levels.

It would also be important to investigate vaccination coverage during 2014-2015 and 2015-2016 seasons, in order to evaluate whether receipt of vaccination at mass vaccination clinics during 2013-2014 increased influenza vaccination coverage in subsequent seasons. Previous research has shown that a major predictor of influenza vaccination in a given season is previous influenza vaccination (57). Further, it would be important to assess whether persons receiving influenza vaccination at mass vaccination clinics during 2013-14 continued to receive influenza vaccinations in subsequent seasons and if so, where they received the vaccination. The costs associated with holding mass vaccination clinics might pay off in the end, if Puerto Ricans continue to revaccinate after their initial visit to a mass clinic, due to decreased influenza

infection and medical costs associated with influenza-related hospitalizations. Another question that should be addressed is whether it would be possible to use proxy data from the PRIR, such as client's county of residence, as a means to collect some data on geographic characteristics of vaccinees in the absence of the more optimal data on ZIP code. Due to a majority of ZIP code data being missing, it was not possible to control for location in this analysis. However, location could play a major role in the association between a predictor and receipt of vaccination at a mass clinic. By using proxy data, it might be possible to at least partly adjust for location. This analysis also points to generic problems with entry of data such as ZIP code, which should stimulate efforts to assure such information is entered in the registry

Appendix

Figure 2: Flow Diagram of Data Merging and Cleaning



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