Neighborhood Contribution to Childhood Influenza Vaccination and Mortality

by

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PREFACE

Influenza illness is a major public health concern. Because of the transmissibility of seasonal influenza virus, illness can spread through populations quickly. Once an individual is infected with influenza virus, it can cause severe disease leading to hospitalization and death. Efforts to respond to the problems posed by influenza have resulted in surveillance activities to identify the magnitude of influenza's burden and characterize its epidemiology. To curtail the burden of influenza, research efforts have focused on the development of safe and effective vaccines and those vaccines have become the cornerstone of prevention. When vaccines are not well-matched to the circulating virus, are unavailable, or have not been used by the public, antiviral medications that have been developed can treat influenza infection and reduce complications in the absence of antiviral resistance of the influenza virus and if applied appropriately.

Despite the advent of influenza vaccines nearly 75 years ago, disparities still exist in the receipt of prevention and treatment measures and in the risk of adverse health outcomes experienced by individuals such as hospitalization and death. Characteristics of the influenza virus itself have been identified and have been shown to account for a part of the disparity in adverse health outcomes (e.g., the H3N2 subtype causes more severe disease than the H1N1 subtype). Individual characteristics have also been identified to account for part of the disparity in the receipt of prevention and treatment measures (e.g., perceptions about influenza vaccine effectiveness and care-seeking behavior) and risk of adverse disease outcomes (e.g., access to medical care).

Viral and individual factors do not fully explain disparities in prevention, treatment, and adverse health outcomes and it is therefore necessary to consider novel determinants of influenza disparities. Neighborhood factors, such as poverty and education, have helped explain disparities in other infectious diseases affecting adults and children. The purpose of this dissertation is to extend the investigation of neighborhood factors to influenza to understand their contribution to influenza vaccination and mortality in the pediatric population.

In the introductory chapter, first, I will summarize the epidemiology of the influenza virus and the current medical and public health response. Second, I will address the individual factors associated with the prevention, treatment, and adverse health outcomes of influenza. Finally, I will discuss the current knowledge of how neighborhood factors can help explain the disparity remaining in the receipt of prevention and treatment measures and the risk of adverse health outcomes after accounting for individual risk factors. After providing a background on what is known about influenza and neighborhood factors, the following chapters will address the contribution of neighborhood factors to explain disparities in pediatric influenza vaccination and mortality in the United States.

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Introduction

The burden of influenza disease is higher than all other vaccine preventable infections due to annual epidemics leading to infection, disease, hospitalization, and death.[1] Annually, influenza is responsible for 3 to 5 million cases of severe illness and 500,000 deaths worldwide and the Centers for Disease Control and Prevention (CDC) estimates 200,000 hospitalizations and an average of 23,607 deaths in the United States.[2-3] The economic burden in the U.S. from influenza in 2003 was $10.4 billion in direct medical costs and $16.3 billion from projected lost earnings due to illness and loss of life, which places the combined annual estimated economic burden at $87.1 billion.[4] These data were projected from the estimated 610,660 life-years lost, 3.1 million hospital days, and 31.4 million outpatient visits associated with influenza.

Viral factors

Influenza virus is a member of the orthomyxovirus family and three types have been identified in nature: A, B, and C. Influenza A virus was first isolated in 1933 and is most closely associated with seasonal epidemics and severe disease. Influenza B virus was identified in 1936 and causes milder epidemics. Influenza C virus is rarely documented as a cause of human illness due to its mild symptoms and because infection usually occurs in small, localized outbreaks. Influenza A is characterized by two surface antigens, hemagglutinin (H) and neuraminidase (N),

which form the viral subtypes. Seventeen different H antigens and ten N antigens have currently been identified.[5] Only three of the hemagglutinin antigens typically cause widespread disease in humans: H1, H2, and H3. Three additional antigens, H5, H7, and H9, have more recently been identified with human infection and cause sporadic or localized illness.[6]

Influenza can present in pandemics, epidemics, localized outbreaks, or as sporadic cases.[7] Epidemics occur annually with attack rates of 10% to 30% in the general community to more than 50% in closed populations such as institutional settings.[7] Influenza subtype A, and to a lesser extent subtype B, account for most of influenza's annual morbidity and mortality. Influenza has a distinct pattern of epidemic transmission occurring between December and March resulting in an estimated 200,000 influenza-related hospitalizations and an average of 23,607 deaths (range 3,349 to 48,614).[4] Over the past three decades, influenza has predominately peaked during February (47% of seasons).[4] The epidemic curve of influenza often peaks within 3 weeks after initial introduction of influenza into a community and ends by approximately 8 weeks.[6]

The United States is a large, geographically diverse area, a fact that complicates the study of seasonality using the timing of influenza epidemics. Studies of the timing of the annual epidemic curves have shown the epidemic peak to vary by an average of 4 weeks across all states with a distinct west to east movement.[8-10] No delay of influenza's peak activity has been witnessed between urban and rural areas, but the age of individuals and movement patterns of populations can influence, by days or weeks, influenza's transmission and peak activity.[11-13]

The seasonality of influenza viruses partly results from changes in hemagglutinin and neuraminidase antigens called antigenic drift and antigenic shift. Antigenic drift results when

minor mutations occur to the gene segments of the influenza virus that result in a change of surface antigens expressed by the virus. Protection derived from exposure to influenza viruses in prior seasons is limited or decreased, which contributes to epidemic transmission. In antigenic shift, a large change occurs to the gene segments of the influenza virus, resulting from exchange of an entire gene segment or other recombination. Antigenic shift may involve mixing of non-human influenza viruses, such as those from birds or pigs, and is responsible for worldwide pandemics like the swine-origin 2009 (H1N1) pandemic.[3]

Seasonality relies on rapid transmission of influenza through the community. Influenza viruses are spread via respiratory droplets generated when an infected person coughs, sneezes, or talks. The virus can also be spread through direct and indirect contact with respiratory secretions of an ill individual. Influenza virus attaches to respiratory epithelial cells in the trachea and bronchi using the hemagglutinin antigen on the surface of the virus. Neuraminidase antigen is required for release of the virus from epithelial cells. In an exposure that results in infection, the incubation period is short, 1 to 4 days. There is the potential for influenza to spread up to 1 day prior to symptom onset through 3 to 5 days after onset in adults and 7 to 10 days or more in children.[14] Signs and symptoms of influenza infection may include fever, non-productive cough, sore throat, myalgia, malaise, headache, rhinitis, and prostration. Rarely are gastrointestinal symptoms observed in adults, but in children vomiting, abdominal pain, diarrhea, and nausea more commonly occur.[6]

Without complication, influenza resolves 3 to 7 days after symptom onset. The most frequent complication of influenza infection is pneumonia. Primary viral pneumonia is a life-threatening but uncommon complication. Secondary bacterial pneumonia occurs more frequently and may manifest up to 2 weeks after the influenza infection.[6] Co-infection with other viral or

bacterial pathogens complicates influenza infection and recovery.[15-18] Other complications include acute respiratory distress syndrome, croup, encephalitis, sinusitis or otitis media, and exacerbation of medical conditions such as cardiac disease, including myocarditis, or pulmonary disease, including chronic bronchitis.[19] Reye syndrome is a rare complication, usually only seen in children taking aspirin following influenza B infection, resulting in coma.[6]

In the most severe cases, influenza or its complications can lead to death. Over 90% of influenza deaths are among those 65 years of age or older, but the potential for influenza to cause severe morbidity and mortality in children has been established.[3,20-21] Pediatric influenza mortality gained prominence in September 2003 after release of a Morbidity and Mortality Weekly Report highlighting a Michigan cluster of 14 severe cases, 4 of whom died, during the 2002-2003 influenza season.[22] CDC requested voluntary reporting of acute encephalopathy-associated infections in children on December 12th, 2003, and expanded voluntary reporting to all influenza-associated pediatric deaths on January 2, 2004.[23-24] Reporting during the 2003-2004 influenza season showed 153 pediatric influenza deaths and spurred the approval of influenza-associated pediatric mortality as a nationally notifiable condition in June 2004 by the Council of State and Territorial Epidemiologists.[25] Formally, influenza-associated pediatric mortality was implemented as a nationally notifiable condition on October 2004 and since then, approximately 100 pediatric influenza deaths have been reported annually.[18,26]

Medical and Public Health Response

It has been said that medicine practices public health one patient at a time. It is that alliance of disciplines that infuses the response to influenza. Because influenza infection does not impart lifelong immunity, individuals are at risk for repeated infections and only a few

interventions are available. The first intervention to decrease the risk of infection was the influenza vaccine, developed in 1943.[6] Since that time, influenza vaccination has become the cornerstone of influenza prevention. Another influenza prevention strategy is use of non-pharmaceutical interventions. Non-pharmaceutical interventions include self-sequestration of ill individuals to their home and social distancing measures, such as school closure or working from home, that are designed to decrease the societal impacts of influenza.[27] Treatment options for influenza infection and its complications include antibiotics and antivirals. Antiviral medications were first developed in 1987 to treat the most severe cases of influenza illness and antibiotics, first manufactured in the 1940's, have been used when bacterial infection complicates influenza infection and recovery.[28]

Currently, two types of influenza vaccine exist: trivalent inactivated vaccines and live-attenuated influenza vaccine. Both vaccines contain the same influenza virus components but differ in several respects.[29] First, administration of trivalent inactivated vaccine is done by needle injection into the muscle or under the skin whereas live-attenuated influenza vaccine is sprayed intranasally.[30] Second, the recommendations for use of live-attenuated influenza vaccine are slightly more restrictive, excluding the very young and older adults, than for the trivalent inactivated vaccine.[30] Finally, neither of the two vaccines are 100% efficacious and they differ based on the age of the vaccine recipient and the recipient's ability to mount an immune response to the vaccine.[30-31] For both vaccines, timing of administration is important in order to allow at least two weeks for antibody protection against influenza virus. Current recommendations state vaccine should be given as soon as supplies are available to avoid missed opportunities for vaccination although concerns have been raised about the waning of influenza vaccine efficacy in persons receiving early vaccination.[30,32-34] Vaccine issues including the need for annual

immunization and personal and neighborhood perceptions about vaccine efficacy are among the factors that impact an individual's decision to receive influenza vaccine.[35] Studies investigating neighborhood factors that influence the decision to receive influenza vaccination are scarce and fewer still address the factors influencing the decision to receive influenza vaccination in a pediatric population.[35-36]

Recommendations from the Centers for Disease Control on the use of influenza vaccine are overseen by the Advisory Committee on Immunization Practices which issues yearly recommendations for the "Prevention and Control of Influenza with Vaccines". Vaccine recommendations are also issued by the American Academy of Pediatrics and the American Academy of Family Physicians with attempts by all organizations to harmonize the recommendations. In the past decade, influenza vaccine recommendations have undergone dramatic changes first beginning in 2004 with the addition of children 6-23 months. Since then, changes in the Advisory Committee on Immunization Practices recommendations have occurred in 2006 with the addition of children 24-59 months and persons with certain high-risk medical conditions, in 2008 with the addition of children 5 through 17 years, and in 2010 with the recommendation of universal vaccination for all children and adults.[37-39] The emergence of the pandemic influenza A (H1N1) virus in 2009 created additional challenges for vaccine manufacturers, public health practitioners, medical practitioners, and the general public. In addition to the seasonal influenza vaccine, a monovalent pandemic influenza A (H1N1) vaccine was also recommended by the Advisory Committee on Immunization Practices for vaccination.[40] Pandemic influenza A (H1N1) vaccine production was conducted simultaneously with seasonal influenza vaccine production. Public health practitioners and medical practitioners needed to inform the public and patients about the need for two vaccines. In order to receive both vaccines,

the public needed to be motivated to find where vaccine was offered and often needed to wait in line to receive vaccination.[41]

Besides the prevention of influenza using vaccine, treatment options are available for those who become ill with influenza. Two classes of antiviral medications are Food and Drug Administration (FDA) approved for use against influenza: the adamantanes and the neuraminidase inhibitors. Antiviral medications may be used in two ways: chemoprophylaxis or treatment.[42] Chemoprophylaxis is the use of an antiviral to prevent illness following an exposure to a person with influenza infection. Treatment is the use of an antiviral to limit the duration of illness and/or decrease the severity of illness. Treatment is reliant on a physician's clinical judgment regarding a patient's underlying conditions, disease severity, and time since symptom onset. Despite the existence of two antivirals, since 2006 only neuraminidase inhibitors have been recommended for use due to resistance of the circulating influenza virus against the adamantanes class.[42-44]

A key activity in the public health response to influenza is surveillance. Influenza surveillance is essential to understanding and monitoring the epidemiology of influenza within populations and across time. Influenza viruses are constantly and rapidly changing, making the need for flexible and redundant means of collecting data for surveillance key to informing public health decision-making and informing medical practice. In the United States, influenza surveillance is conducted by the Centers for Disease Control and consists of 5 components from 8 data sources:[25]

- Viral surveillance: Comprised of 85 U.S.-based World Health Organization (WHO) collaborating laboratories and 60 National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories across the nation. Participating laboratories submit reports on the number and results of specimens tested.

- Outpatient illness surveillance: Visits to more than 2,700 healthcare providers in all 50 states for influenza-like illness are collected by participating providers as part of the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet).
- Mortality surveillance: Influenza-associated deaths are reported through two systems. The 122 Cities Mortality Reporting System receives the number of death certificates processed and the number listing pneumonia or influenza as the underlying or contributing cause of death from vital statistics offices. Influenza-associated Pediatric Mortality Surveillance System receives notice of any pediatric influenza death in a child meeting the clinical case definition as part of case-based nationally notifiable disease surveillance.
- Hospitalization surveillance: Laboratory-confirmed, influenza-associated hospitalizations are reported from the Influenza Hospitalization Network (FluSurv-NET). This surveillance is designed to be closely representative of the U.S. child and adult population by covering 80 counties in 10 states funded as part of the Emerging Infections Program.
- Geographic spread: State health departments report the extent of geographic spread within their public health jurisdiction. Activity levels, in increasing order, are categorized as no activity, sporadic, local, regional, and widespread.

Individual factors

An individual's exposure to the influenza virus and receipt of preventive and treatment measures does not wholly determine his/her health outcome. Given a new subtype of influenza, all people are generally susceptible to infection. However, household studies of influenza transmission show children under 5 years of age followed by children 5 to 18 years of age have higher attack rates than adults.[45-49] Higher attack rates have also been shown for persons with underlying medical conditions including respiratory disease, neurological disease, and immune impairment.[47]

A vast body of literature has described the individual risk factors associated with the outcomes of illness, hospitalization, and death.[50-55] Individuals at highest risk for influenza infection and/or complication include: children aged 6 months to 4 years; adults aged 50 years or older; individuals with chronic medical conditions including pulmonary disorders,

cardiovascular disorders, and neurological disorders; the immune impaired; women who are or will become pregnant during the influenza season; American Indians/Alaskan Natives; and the morbidly obese, defined as a body mass index of 40 or more (for children, defined as greater than the 95th percentile for height and weight); children on long-term aspiring therapy; nursing home residents; and healthcare professionals.[30] This list of conditions, developed by the Advisory Committee on Immunization Practices, have shown to increase the risk of infection through several different pathways.[29-30] For young children, a naïve immune system decreases the ability to mount an immune response to influenza virus. Similarly, older adults have decreased immune system function from the aging process, termed immunosenescence.[56] Chronic medical conditions of pulmonary, cardiovascular, or neurologic origins likely impair normal respiratory functioning and decrease respiratory secretion clearance.[53] The racial disparity of increased medical complications for American Indians/Alaskan Natives may result from an increased proportion of chronic medical conditions.[55] No simple explanation for the increased risk seen in morbidly obese individuals has been identified, but increased intensive care stays, prolonged ventilation, and more death have been reported.[54]

In general, the increased risk of adverse health outcomes manifests in the following ways. Age-specific hospitalization rates show a J-shape with children aged less than 1 year at higher risk of hospitalization than older adults over 65 years of age.[3] Mortality rates on the other hand appear to increase with age.[25] For children and adults of any age, having one or more high-risk conditions dramatically increases the risk of infection, hospitalization, and death.[3,15,19,47,57-60]

Many studies have observed an association with the race or ethnicity of a person and adverse health outcomes. Most often these race/ethnic disparities are reported with Blacks and Hispanics having more hospitalizations and deaths across all ages.[61-64] The reasons underlying

the observed race/ethnic increases in influenza-related hospitalizations and deaths are still being identified, but the neighborhood where a person resided has been shown to account for some of the disparity.[61] Another reason considered to explain the race/ethnic disparity is the proportion of chronic medical conditions of the race/ethnic groups, but no studies could be found addressing this hypothesis.[55]

Neighborhood factors

What is a neighborhood characteristic? In order to define neighborhood characteristics, a clear definition of the neighborhood must be established. In early research on chronic disease and mental health, neighborhoods were defined by readily available measures such as the U.S. Census Bureau. This is a crude yet effective way of organizing individuals that shared a loosely-defined geographic area or neighborhood.[65] The census characteristics of a neighborhood such as poverty, crowding, and education, were then analyzed to find the factors associated with adverse health outcomes. The strength of neighborhood associations and health can be affected by the choice of spatial scales such as zip code, census tract, or block group that define a neighborhood.[66] The census-defined neighborhood factors are proxies by which at-risk neighborhoods can be identified but they lack the ability to show the causative mechanism.[65] A move toward direct measurement of the neighborhood is now under way with the emphasis on identifying specifics causative factors that lead to adverse health outcomes. However, most of the infectious disease research incorporating neighborhood factors still relies on census-derived measures.

Influenza research does not differ from other infectious disease research in the use of census-derived measures. Much of the influenza research that incorporates neighborhood factors

is focused on hospitalization and has yielded the finding that hospitalization rates differ by several neighborhood factors including the percentage of residents living below the federal poverty line, median household income, and material deprivation. [58,61,63-64,67-68] For example, hospitalization rates for children and adults living in low income neighborhoods are 2 to 7 times greater than the rates for those living in middle or high income neighborhoods.[58,61,63,67-68] While there have been studies of pediatric influenza mortality, the focus has been on elaborating the clinical characteristics or highlighting the increased risk of mortality with chronic medical conditions or other individual-level factors.[15-16,60] Only one study, conducted by Thompson et al., could be found that examined the neighborhood factors associated with mortality and included children, although the focus was on both children and adults and was limited to describing only 35 deaths.[61] Thompson et al. included the neighborhood factors median income and urbanicity, but was only able to measure median income at the county level and urbanicity at the zip code level.[61] A major limitation of their study was the geographic scale of the neighborhood variables, which were at the county and zip code level. Zip code scale or larger may fail to detect gradients as opposed to measures at the geographic scale of the census tract because they are larger areas by design and contain less homogenous populations than census tracts.[66]

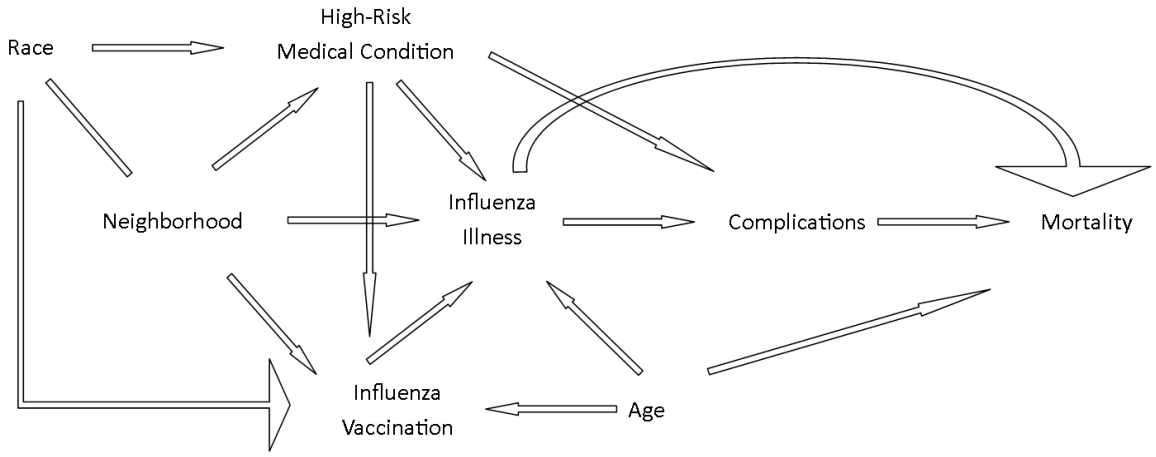
Research using public health surveillance data has also begun to use linkages with the U.S. Census Bureau in order to include neighborhood factors in analyses. The intent of including neighborhood factors in studies using surveillance data is to expand the ability to monitor changes in trends within and across neighborhoods and to identify at-risk neighborhoods for expanded surveillance, public health interventions, and to inform policy change. The focus of this dissertation is to use public health immunization information system and surveillance data

linked to the 2000 Decennial Census to identify neighborhoods factors associated with influenza vaccination and influenza pediatric mortality.

Hypotheses

The three analyses put forth in the following chapters are informed by the understanding of the neighborhood on pediatric influenza vaccination and mortality as described in Figure 1.1.

Figure 1.1. Conceptual Diagram for Neighborhood and Pediatric Influenza Vaccination and Mortality



In the first analysis, it is hypothesized that the type of vaccine provider will impact the receipt of influenza vaccination in children and that the association will be influenced by neighborhood factors. The hypothesis being tested in the second analysis is that neighborhood factors will play a role in determining a child's risk of influenza mortality and that neighborhood characteristics will help explain the observed race/ethnic disparity in influenza mortality. The third analysis hypothesizes that neighborhood factors modify the timing of influenza illness onset and influence the interval from illness onset to death. Finally, the conclusion includes a summary of the major findings, the public health implications of these findings, and outlines plans for future research.

References

1. Poland GA. Valuing influenza vaccine: medical, economic, and social benefits. Clin Infect Dis. 2009;48(3):299-301.

2. Carrat F, Flahault A. Influenza vaccine: the challenge of antigenic drift. Vaccine. 2007;25(39-40):6852-6862.

3. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. In: Atkinson W WS, Hamborsky J, McIntyre L., ed. 11th Ed. Washington DC: Public Health Foundation; 2009.

4. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine. 2007;25(27):5086-5096.

5. Centers for Disease Control and Prevention. Seasonal Influenza: Types of Influenza Viruses. 2012; http://www.cdc.gov/flu/about/viruses/types.htm. Accessed February 25th, 2013.

6. Steinhoff MC. Epidemiology and Prevention of Influenza. In: Nelson KE, Masters Williams CF, ed. Infectious Disease Epidemiology: theory and practice. 2nd Ed. Sudberry, MA: Jones and Bartlett Publishers; 2007:577-600.

7. Influenza. In: Chin J, ed. Control of Communicable Diseases Manual. 17th ed. Washington DC: American Public Health Association; 2000:270-276.

8. Wenger JB, Naumova EN. Seasonal synchronization of influenza in the United States older adult population. PloS One. 2010;5(4):e10187.

9. Schanzer DL, Langley JM, Dummer T, Aziz S. The geographic synchrony of seasonal influenza: a waves across Canada and the United States. PloS One. 2011;6(6):e21471.

10. Schanzer DL, Langley JM, Dummer T, Viboud C, Tam TW. A composite epidemic curve for seasonal influenza in Canada with an international comparison. Influenza Other Respi Viruses. 2010;4(5):295-306.

11. Schanzer D, Vachon J, Pelletier L. Age-specific differences in influenza A epidemic curves: do children drive the spread of influenza epidemics? Am J Epidemiol. 2011;174(1):109-117.

12. Olson DR, Heffernan RT, Paladini M, Konty K, Weiss D, Mostashari F. Monitoring the impact of influenza by age: emergency department fever and respiratory complaint surveillance in New York City. PLoS Med. 2007;4(8):e247.

13. Viboud C, Bjornstad ON, Smith DL, Simonsen L, Miller MA, Grenfell BT. Synchrony, waves, and spatial hierarchies in the spread of influenza. Science. 2006;312(5772):447-451.

14. Centers for Disease Control and Prevention. Seasonal Influenza: Clinical Signs and Symptoms of Influenza. 2013; http://www.cdc.gov/flu/professionals/acip/clinical.htm. Accessed February 25th, 2013.

15. Randolph AG, Vaughn F, Sullivan R, et al. Critically ill children during the 2009-2010 influenza pandemic in the United States. Pediatrics. 2011;128(6):e1450-1458.

16. Williams DJ, Hall M, Brogan TV, et al. Influenza coinfection and outcomes in children with complicated pneumonia. Arch Pediatr Adolesc Med. 2011;165(6):506-512.

17. Coffin SE, Zaoutis TE, Rosenquist AB, et al. Incidence, complications, and risk factors for prolonged stay in children hospitalized with community-acquired influenza. Pediatrics. 2007;119(4):740-748.

18. Finelli L, Fiore A, Dhara R, et al. Influenza-associated pediatric mortality in the United States: increase of Staphylococcus aureus coinfection. Pediatrics. 2008;122(4):805-811.

19. Lee EH, Wu C, Lee EU, et al. Fatalities associated with the 2009 H1N1 influenza A virus in New York city. Clin Infect Dis. 2010;50(11):1498-1504.

20. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med. 2000;342(4):232-239.

21. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003;289(2):179-186.

22. Centers for Disease Control and Prevention. Severe morbidity and mortality associated with influenza in children and young adults--Michigan, 2003. MMWR Morb Mortal Wkly Rep. 2003;52(35):837-840.

23. Centers for Disease Control and Prevention. Request for information about acute encephalopathy associated with influenza virus infection in children. MMWR Morb Mortal Wkly Rep. 2003;52(49):1197-1220.

24. Centers for Disease Control and Prevention. CDC request for reports of influenza-associated deaths among children. MMWR Morb Mortal Wkly Rep. 2003;52(51 & 52):1245-1276.

25. Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. J Infect Dis. 2006;194 Suppl 2:S82-91.

26. Centers for Disease Control and Prevention. Seasonal Influenza: FluView Interactive. 2013; http://www.cdc.gov/flu/weekly/fluviewinteractive.htm. Accessed February 25th, 2013.

27. Centers for Disease Control and Prevention. Interim pre-pandemic planning guidance: community strategy for pandemic influenza mitigation in the United States - early, targeted, layered use of nonpharmaceutical interventions. 2007:1-109.

28. Food and Drug Administration. Drugs @ FDA: FDA approved drug products. 2013; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed February 25th, 2013.

29. Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)--

United States, 2012-13 influenza season. MMWR Morb Mortal Wkly Rep. 2012;61(32):613-618.

30. Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Morb Mortal Wkly Rep. 2010;59(RR-8):1-62.

31. Ambrose CS, Levin MJ, Belshe RB. The relative efficacy of trivalent live attenuated and inactivated influenza vaccines in children and adults. Influenza Other Respi Viruses. 2011;5(2):67-75.

32. Kissling E, Valenciano M, Team IMC-CS. Early estimates of seasonal influenza vaccine effectiveness in Europe among target groups for vaccination: results from the I-MOVE multicentre case-control study, 2011/12. Euro Surveill. 2012;17(15).

33. Jimenez-Jorge S, de Mateo S, Pozo F, et al. Early estimates of the effectiveness of the 2011/12 influenza vaccine in the population targeted for vaccination in Spain, 25 December 2011 to 19 February 2012. Euro surveill. 2012;17(12).

34. Valenciano M, Ciancio B, team IMs. I-MOVE: a European network to measure the effectiveness of influenza vaccines. Euro surveill. 2012;17(39).

35. Kumar, S, Quinn, SC, Kim, KH, Musa, D, Hilyard, KM, Freimuth, VS. The social ecological model as a framework for determinants of 2009 H1N1 influenza vaccination uptake in the United States. Health Educ Behav. 2012;39:229-243.

36. Zimmerman, RK, Nowalk, MP, Raymund, M, et al. Tailored interventions to increase influenza vaccination in neighborhood health centers serving the disadvantaged. Am J Public Health. 2003;93:1699-1705.

37. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2004;53(RR-6):1-40.

38. Centers for Disease Control and Prevention. Prevention and Control of Influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morbid Mortal Wkly Rep. 2006;55(RR-10):1-42.

39. Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. MMWR Morbid Mortal Wkly Rep. 2008;57(RR-7):1-60.

40. Centers for Disease Control and Prevention. Use of influenza A (H1N1) 2009 monovalent vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Morbid Mortal Wkly Rep. 2009;58(RR-10):1-8.

41. Fletcher L, Khan H. H1N1 Vaccine Shortages Create Panic, Worry. 2009. http://abcnews.go.com/GMA/OnCall/swine-flu-h1n1-flu-vaccine-shortage-panic/story?id=8915650. Accessed February 25th, 2013.

42. Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza – recommendations of the Advisory Committee on Immunization Practices. MMWR Morbid Mortal Wkly Rep. 2011;60(RR-1):1-28.

43. Centers for Disease Control and Prevention. High levels of adamantane resistance among influenza a (H3N2) viruses and interim guidelines for use of antiviral agents – United States, 2005-06 influenza season. MMWR MorbMortal Wkly Rep. 2006;55(2):44-46.

44. Food and Drug Administration. Drug Safety and Availability: Influenza (Flu) antiviral drugs and related information. 2013; http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm100228.htm. Accessed February 25th, 2013.

45. Monto AS, Kioumehr F. The Tecumseh Study of Respiratory Illness. IX. Occurence of influenza in the community, 1966--1971. Am J Epidemiol. 1975;102(6):553-563.

46. Glezen WP, Couch RB. Interpandemic influenza in the Houston area, 1974-76. N Engl J Med. 1978;298(11):587-592.

47. Carcione D, Giele CM, Goggin LS, et al. Secondary attack rate of pandemic influenza A(H1N1) 2009 in Western Australian households, 29 May-7 August 2009. Euro surveill. 2011;16(3).

48. France AM, Jackson M, Schrag S, et al. Household transmission of 2009 influenza A (H1N1) virus after a school-based outbreak in New York City, April-May 2009. J Infect Dis. 2010;201(7):984-992.

49. Cauchemez S, Donnelly CA, Reed C, et al. Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. N Engl J Med. 2009;361(27):2619-2627.

50. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA. 2004;292(11):1333-1340.

51. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. N Engl J Med. 2006;355(1):31-40.

52. Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003-2004. N Engl J Med. 2005;353(24):2559-2567.

53. Keren R, Zaoutis TE, Bridges CB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. JAMA. 2005;294(17):2188-2194.

54. Morgan OW, Bramley A, Fowlkes A, et al. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. PloS One. 2010;5(3):e9694.

55. Centers for Disease Control and Prevention. Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/Alaska Natives - 12 states, 2009. MMWR Morb Mortal Wkly Rep. 2009;58(48):1341-1344.

56. Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of ageing. J Pathol. 2007;211(2):144-156.

57. Skarbinski J, Jain S, Bramley A, et al. Hospitalized patients with 2009 pandemic influenza A (H1N1) virus infection in the United States--September-October 2009. Clin Infect Dis. 2011;52 Suppl 1:S50-59.

58. Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infections on persons with chronic underlying conditions. JAMA. 2000;283(4):499-505.

59. Louie JK, Schechter R, Honarmand S, et al. Severe pediatric influenza in California, 2003-2005: implications for immunization recommendations. Pediatrics. 2006;117(4):e610-618.

60. Louie JK, Acosta M, Winter K, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA. 2009;302(17):1896-1902.

61. Thompson DL, Jungk J, Hancock E, et al. Risk factors for 2009 pandemic influenza A (H1N1)-related hospitalization and death among racial/ethnic groups in New Mexico. Am J Public Health. 2011;101(9):1776-1784.

62. Dee DL, Bensyl DM, Gindler J, et al. Racial and ethnic disparities in hospitalizations and deaths associated with 2009 pandemic Influenza A (H1N1) virus infections in the United States. Ann Epidemiol. 2011;21(8):623-630.

63. Levy NS, Nguyen TQ, Westheimer E, Layton M. Disparities in the severity of influenza illness: a descriptive study of hospitalized and nonhospitalized novel H1N1 influenza-positive patients in New York City: 2009-2010 influenza season. J Public Health Manag Pract. 2013;19(1):16-24.

64. Yousey-Hindes KM, Hadler JL. Neighborhood socioeconomic status and influenza hospitalizations among children: New Haven County, Connecticut, 2003-2010. Am J Public Health. 2011;101(9):1785-1789.

65. Diez Roux AV, Mair C. Neighborhoods and health. Ann N Y Acad Sci. 2010;1186:125-145.

66. Krieger N, Waterman PD, Chen JT, Soobader MJ, Subramanian SV. Monitoring socioeconomic inequalities in sexually transmitted infections, tuberculosis, and violence: geocoding and choice of area-based socioeconomic measures--the public health disparities geocoding project (US). Public Health Rep. 2003;118(3):240-260.

67. Balter S, Gupta LS, Lim S, Fu J, Perlman SE, New York City HNFIT. Pandemic (H1N1) 2009 surveillance for severe illness and response, New York, New York, USA, April-July 2009. Emerg Infect Dis. 2010;16(8):1259-1264.

68. Lowcock EC, Rosella LC, Foisy J, McGeer A, Crowcroft N. The social determinants of health and pandemic H1N1 2009 influenza severity. Am J Public Health. 2012;102(8):e51-58.

CHAPTER II

Influenza Vaccination of Michigan Children by Provider Type and Residence, 2010-2011

INTRODUCTION

Influenza vaccination is the cornerstone of public health strategies to prevent significant morbidity and mortality among children in the United States.[1] Private and public providers are at the forefront in offering preventive services including influenza vaccinations. Differences in childhood vaccination rates by provider type exist, making provider type an important risk factor. [2-8] These differences have likely been exacerbated by the changing influenza vaccine recommendations in recent years including the expansion of age group recommendations made by the Advisory Committee on Immunization Practices (ACIP) and the addition of the influenza A (H1N1) monovalent vaccine during the 2009-2010 season to protect against the H1N1 pandemic virus.[9-12]

Studies have shown higher influenza vaccination rates in children age 6-23 months if the child had more well-child visits, had a provider visit during the influenza season, or received vaccine from a private versus a public provider.[2-3] Higher rates in up-to-date status of routine immunizations for children in private compared to public providers have been documented elsewhere[4-7], although one study showing private providers with higher up-to-date vaccination rates for patients at 12 months of age revealed no private-public provider difference at 24 months of age.[5] This difference in private versus public providers has also been shown to vary by geography. In a multi-state study of four communities with federally designated health

professional shortage areas, half of the communities reported no disparity but the other half reported a disparity in up-to-date status of routine pediatric immunizations with public providers having slightly higher rates than private providers for children 12 to 35 months.[8]

The community in which a child lives likely plays a role in receiving routine childhood vaccinations and influenza vaccination. Communities with higher median family income, higher percentage of residents living above the poverty line, and higher percentage of non-Hispanic White children under 5 years of age have demonstrated higher vaccination rates.[13-14] However, no studies to date have specifically examined if these community characteristics help explain the association between provider type and receipt of influenza vaccine.

In this study, data from the Michigan Care Improvement Registry (MCIR) was analyzed to assess whether provider type is associated with childhood influenza vaccination and identify if the private-public provider association is influenced by county factors in Michigan during the 2010-2011 influenza season.

METHODS

We used influenza vaccinations reported to MCIR on all Michigan residents aged 6 months through 17 years during the 2010-2011 influenza season; the season was defined as August 2, 2010 through June 30, 2011. This period denoted the first date influenza vaccine was available in Michigan and the last date before the vaccine expired. The study eligibility criteria included children ages 6 months through 17 years, in-state residence according to the MCIR, and presence of any provider-verified immunization record in the MCIR. Children with no immunization-provider assigned as a point of contact, typically reflective of children born in

Michigan and included in the birth cohort upload to MCIR but living elsewhere, were considered ineligible.

Data on influenza vaccination were derived from the MCIR, a web-based immunization information system in operation in Michigan since 1998, although it contains immunization records prior to that year. Healthcare providers, health departments, school health centers, pharmacies, and other immunization providers can electronically input vaccinations given to people of any age into the MCIR. Under Michigan's public health code, immunization providers are required to report school exclusionary vaccinations to the MCIR if the individual was born after December 31, 1993, and is younger than 20 years of age; influenza vaccine is not required for school entry. Immunization providers may electively report influenza and other vaccines not required for school entry or vaccinations given to adults. The MCIR is continually populated with the electronic birth certificates of all children born in Michigan after December 31, 1993. Reporting of mother's race from electronic birth certificates began January 1, 2005. Other methods of reporting into the MCIR include direct data entry via the web application and data transfer from electronic medical records.

The child's demographic record included date of birth, mother's race, county of residence, and medical home. Each vaccination record included the influenza vaccine provider, vaccine funding source, date of vaccine administration, and type of vaccine administered. Age was calculated at the beginning of the study period, August 2, 2010. Children were grouped into 4 age-groups: 6-23 months, 24-59 months, 5-12 years, and 13-17 years. Mother's race was categorized as White, Black, American Indian, Chinese, Filipino, other Asian or Pacific Islander, other non-White, and other. The medical home is a model of healthcare delivery whereby a physician or other medical professional provides comprehensive and continuous medical care to

patients. The medical home was identified as the last immunization provider to administer a dose of a vaccine, excluding the Hepatitis B birth dose or seasonal or H1N1 influenza vaccine doses. Assignment of the medical home provider occurred on August 2, 2010. The provider type of the medical home was designated as either public or private for this analysis. A public immunization provider designation was assigned for local health departments, Federally Qualified Health Centers, Rural Health Centers, Indian Health Service clinics or tribal clinics, community/migrant health centers, and Women Infants and Children clinics. A private immunization provider designation was assigned for non-governmental providers, faculty medical practices, health maintenance organizations, and private hospitals. To identify whether the assigned medical home provider matched the current season's influenza vaccine provider in a child's vaccination record, concordant pairs were assessed by a simple frequency table. A child's influenza immunization provider was also their medical home provider in 71% of cases. The medical home provider, as opposed to the provider administering the influenza immunization, was used for all analyses because of the focus of this analysis on the provider likely to have the most influence on a child's receipt of a vaccine. The medical home model of providing continuous medical care to a child, including vaccinations, fit this purpose.

Children with any immunization administered in the previous 12 months, i.e., between August 1, 2009 and August 1, 2010, were considered to have a recent provider visit. A child's vaccine funding source was based on the funding source for the last dose of vaccine received by the child prior to August 2, 2010, and excluded hepatitis B birth dose and previous influenza doses. The child's vaccine funding sources were categorized as Vaccines for Children (VFC) program vaccines, private/self insurance, and other. VFC is a federal program providing free vaccines to protect eligible children against sixteen different diseases, including influenza, as

recommended by the ACIP. To be eligible to receive VFC vaccines, children must be less than 19 years of age and be Medicaid-eligible, uninsured, American Indian/Alaskan Native, or underinsured.

The community factors analyzed in the study used Michigan county-level data from the 2010 Census that was linked to the child's county of residence. County-level variables included the percent unemployed, median household income, percentage of families living below the federal poverty line in the past 12 months, percentage of Black residents, and percent of families with a female head of household with children under 18 years old. The percentage of Black residents in a county was used as a proxy measure for racial composition as Blacks constitute the largest minority presence in Michigan's population at 14%.

The outcome of interest for children was "vaccinated" versus "unvaccinated" for influenza during the 2010-2011 season. A child was defined as vaccinated if he/she received the recommended number of influenza vaccine doses for their age and vaccination history, based on ACIP recommendations.[1] The ACIP recommendations were more complex than in past years due to the use of an H1N1 influenza vaccine and a seasonal influenza vaccine during the previous season, which necessitated an algorithm in the 2010-2011 season for determining the number of doses a child needed to fulfill the recommendation and be considered "vaccinated". Children without an influenza vaccine in the MCIR or receipt of only one dose when two doses were recommended based on the algorithm, were considered unvaccinated. Using the more stringent definition of "vaccinated" and excluding children with only one out of the two recommended doses, the investigators expected the measure of association to be underestimated. Receipt of influenza vaccine was designated without regard to the manufacturer or mechanism of action (e.g. inactivated versus live-attenuated).

Data Analysis

Univariate and bivariate statistics were calculated to describe the study population. To evaluate the relationship between immunization provider and influenza vaccination, odds ratios and 95% confidence intervals (CIs) were estimated using marginal logistic regression models using the Genmod procedure in SAS, version 9.2. Marginal models accounted for clustering of risk factors by county units, resulting in counties being more homogeneous in the likelihood of a child being vaccinated. In the multivariable analysis, covariates were included in the final model if they were considered confounders either *a priori* or if the change in estimate criteria on the odds ratio scale was greater than ten percent and statistically significant when a single confounder was added to the unadjusted model. The marginal logistic regression models were used to control for clustering of children within counties, but in order to compare the influenza vaccination rates between counties, a generalized linear mixed model with a random intercept for county was used. Geographic patterns of the deviation in the state mean influenza vaccination rate for each county were examined by organizing the counties into five groups or quintiles for mapping. This study was exempted from patient consent by the Michigan Department of Community Health IRB (#937-PHAEPI) and the University of Michigan IRB (HUM00047622).

RESULTS

A total of 2,373,826 children aged 6 months through 17 years from the MCIR were eligible for inclusion in the study. Of these, 394,881 (17%) were vaccinated against influenza. Based on age, coverage was highest in 6-23 month-olds and decreased with increasing age from 27% in 6-23 month-olds, 18% in 24-59 month-olds, 15% in 5-12 year-olds, to 13% among 13-17 year-olds (Table 2.1). The distribution of MCIR-documented influenza dose administrations,

aggregated by week, is shown in Figure 2.1. First-dose administrations peaked during the week ending October 23rd, 2010 with 52,701 doses administered and second-dose administrations peaked six weeks later during week ending December 4th, 2010, with 5,228 doses administered.

Among the 394,881 children vaccinated for influenza, 81% (n=318,571) had a private provider designated as the medical home and 19% (n=76,310) had a public provider. The influenza coverage rate for all children served by a private provider was only slightly higher (18%) than the rate for those served by a public provider (13%). (Table 2.1) Children with a provider visit in the past 12 months had higher coverage (27%) compared to no visits (8%). Children with a vaccine funding source of private/self funding (22%) also had higher influenza vaccination rates than children whose vaccine funding sources was VFC-eligible (16%). Information on mother's race was missing for all children >5 years of age since the data were only available in the MCIR starting in 2005. For this reason, race was not included in the primary analysis. However, in an analysis of children aged 6-59 months, the children of White mothers showed higher vaccination coverage than the children of Black mothers, 24% versus 11%, respectively.

Using logistic regression, public providers had a 34% lower odds of vaccinating children against influenza compared to private providers (OR=0.66, 95% CI [0.57, 0.76]) (Model 1; Table 2.2). The association was attenuated (OR=0.88, 95% CI [0.78, 0.99]) when controlling for child's age, provider visit in the past 12 months, vaccine funding source, and county variables including median household income, percentage of families living below the poverty line in the past 12 months, and percentage of Black residents (Model 2; Table 2.2). Since family medicine and pediatric clinics comprised 99% of the private immunization providers, a comparison was conducted between these provider types. Pediatric clinics had a 36% greater odds of vaccinating

children aged 6 months to 17 years compared to family medicine clinics after adjusting for the covariates in Model 2 (data not shown).

The relationship between immunization provider and child's age was assessed by looking at the public-private provider association within age groups, 6-23 months, 24-59 months, 5-12 years, and 13-17 years. While the odds of vaccination varied by age in the adjusted model (Model 2; Table 2.2), only 5-12 year-olds showed a statistically significant decrease in the odds of vaccination for public versus private providers. (Model 3; Table 2.2) Nonetheless, the odds ratios were quite similar across all age groups.

To better understand the role of mother's race in this analysis, a separate analysis of children aged 6-59 months was conducted. Because race is associated with provider type, after adding race to the model, the medical home provider was no longer a significant predictor of influenza vaccination (OR=0.98 for public vs. private, 95% CI [0.82, 1.18]). Children with mothers of Black race had a 45% lower odds of being vaccinated and children with Chinese mothers had a 53% greater odds of being vaccinated compared to children with mothers of White race, after controlling for the covariates in Model 2. (data not shown)

County factors were examined in addition to individual and immunization provider characteristics to assess for any association with influenza vaccination rates. While statistically significant, only small differences between vaccinated and unvaccinated children were observed for the county variables. In fact, the percentage of Black residents variable differed the most of all county variables for vaccinated (13%) and unvaccinated children (16%). (Table 2.1) However, in adjusted models, the percentage of Black versus White residents was only

associated with a 9% lower receipt of influenza vaccination while a 28% lower receipt of influenza vaccination existed for those living below versus above the poverty line (Table 2.2).

An examination of the remaining variation in influenza vaccination rates, by county, was modeled while controlling for a child's age, medical home provider, recent provider visit, a child's vaccine funding source, and the county variables, median household income, percentage of families living below the poverty line, and percentage of Black residents. A generalized linear mixed model showed significant county-to-county variation ($p<0.0001$) indicating the potential for unmeasured factors at the individual and county level. Clusters of counties in Michigan's Southeast region had influenza vaccination rates below the state mean while clusters in the Southwest and Northwest regions had higher rates. (Figure 2.2)

CONCLUSIONS

Michigan children with a public provider designated as their medical home, as opposed to a private provider, had a significantly lower chance of being vaccinated against influenza during the 2010-2011 influenza season. Regardless of the provider type, children with a provider visit in the past 12 months were much more likely to be vaccinated against influenza. The odds of influenza vaccination decreased if the child was VFC-eligible. Evidence has shown that having recent contact with a healthcare professional has been associated with greater likelihood of vaccination[2,15-16] and may also be indicative of more continuity in the relationship between a child and his/her medical home. Children participating in the VFC program, as opposed to those with private insurance, were more likely to miss influenza vaccination opportunities.[17] Several studies have attributed lower socioeconomic status and fewer interactions with a healthcare provider as reasons why children miss out on influenza and routine childhood vaccinations. [2,18-21]

A greater percentage of the children receiving care at health departments have been noted to be VFC-eligible[22], which could help explain the lower influenza vaccination rates of public providers in our study. Like our study, previous research has documented the public-private provider disparity in the success with which they provide influenza and other routine childhood vaccinations. Santibanez et al found higher influenza vaccination rates for private compared to public providers for children 6-23 months during the 2002-2003 and 2003-2004 influenza seasons, using National Immunization Survey (NIS) data.[3] Groom et al observed slightly higher rates in private versus public providers for up-to-date vaccination status for children 19-35 months using 2004 NIS data.[4]

Differences in influenza vaccination coverage by age were observed in the descriptive data and adjusted model, which could partly be explained by the time elapsed since expansion of influenza vaccine recommendations between 2004 and 2008 to include 6-23 month-olds, 24-59 month-olds, 5-12 year-olds, and finally 13-17 year-olds. Influenza vaccination rates were low for all age groups. While the previous two years of influenza vaccination data in Michigan showed increasing coverage rates for all children, our data reflect decreases in all but children aged 13-17 year-olds.[23] However, the final model showed significantly decreased odds of vaccination with 5-12 year-olds only, when comparing public and private providers. This finding may be due to a decreased sense of perceived risk of influenza at this age on the part of the parents, combined with a reduced number of opportunities for vaccination.[24-25]

The percentage of families living below the poverty line in the child's county of residence was an important factor in explaining influenza vaccination. Although non-significant, a ten percent increase in the percent of families living below the poverty line decreased the odds of vaccination by 28%, which is a moderately large effect size. Inclusion of county factors in the

models helped explain the association between provider type and influenza vaccination, but likely also resulted in residual confounding. This is due to the county variables being imperfect proxies for underlying factors such as access to healthcare services, attitudes and beliefs on the healthcare system and vaccination, or adequacy of medical care.[24,26]

Despite the inclusion of county variables in the statistical models, significant variations between counties remained. These variations appear to be geographically correlated as several counties have similarly high or low influenza vaccination rates compared to the state mean. Residual confounding from the county variables and unmeasured county factors were also possible factors leading to county variation. Unmeasured confounders include the local health department oversight within and across counties, the existence of large clinics with coverage areas across counties, or the voluntary reporting of influenza doses administered by providers to the MCIR could have influenced the county-specific vaccination rates since no reporting requirement for influenza vaccine was instituted until August 2012.

Limitations

Our study was subject to several limitations. First, MCIR data were used to determine vaccination status and therefore we had to rely on the voluntary reporting of influenza vaccinations by immunization providers. If a child had no record of vaccination or if a child was incompletely vaccinated, the child was considered unvaccinated. This likely overestimated the number of unvaccinated children. The complexity of the algorithm to determine which children needed two doses of vaccine in the 2010-2011 season also contributed to the number of unvaccinated children because of the immunization provider's understanding of the recommendations and reliance on incomplete parental vaccination histories. In Michigan,

influenza vaccines are not required to be reported to the MCIR with the exception of VFC providers who are required to enter influenza doses as part of Michigan's implementation of the VFC program. The misclassification of influenza vaccinations would likely manifest as higher vaccination rates for public providers since VFC enrollment is more common in this group. Despite this, public providers had lower influenza vaccination rates. The medical home provider was identified from the MCIR and denotes the last provider to administer a vaccine. This likely represents continuous medical care between a child and physician similar to the American Academy of Pediatrics definition, a relationship shown to result in more up-to-date routine childhood immunizations that our study was unable to discern.[15,27] The variable, provider visit in the previous 12 months, was used as a proxy for continuous medical care. A final limitation was the inability to include unmeasured confounders. At the individual level, no data exist to incorporate stressors such as single-parent households and flexibility in time off from work, parental education, vaccination attitudes and beliefs, and our analysis of mother's race was limited to children aged <5 years. For the immunization providers, we lacked information on provider location, patient volume, and the use of expanded vaccination strategies, which are factors that have been associated with influenza vaccination rates in children.[2] Unmeasured county factors included immunization provider concentration, penetration of vaccine messaging, and other socioeconomic factors.[28]

In conclusion, provider type influences whether a child is vaccinated against influenza in Michigan and children with public providers are less likely to receive influenza vaccine compared to private providers. County factors help describe, but not diminish the public-private provider disparity. Specifically, factors such as the density of poverty and area-based measure of income partly account for the effect of vaccination receipt regardless of provider type. The

current findings underscore the need for more effective strategies to improve vaccination rates for all Michigan children and the need to advance our understanding of how communities affect individuals and providers.

Figure 2.1. Influenza Vaccinations by Week, MCIR, 2010-11 Season

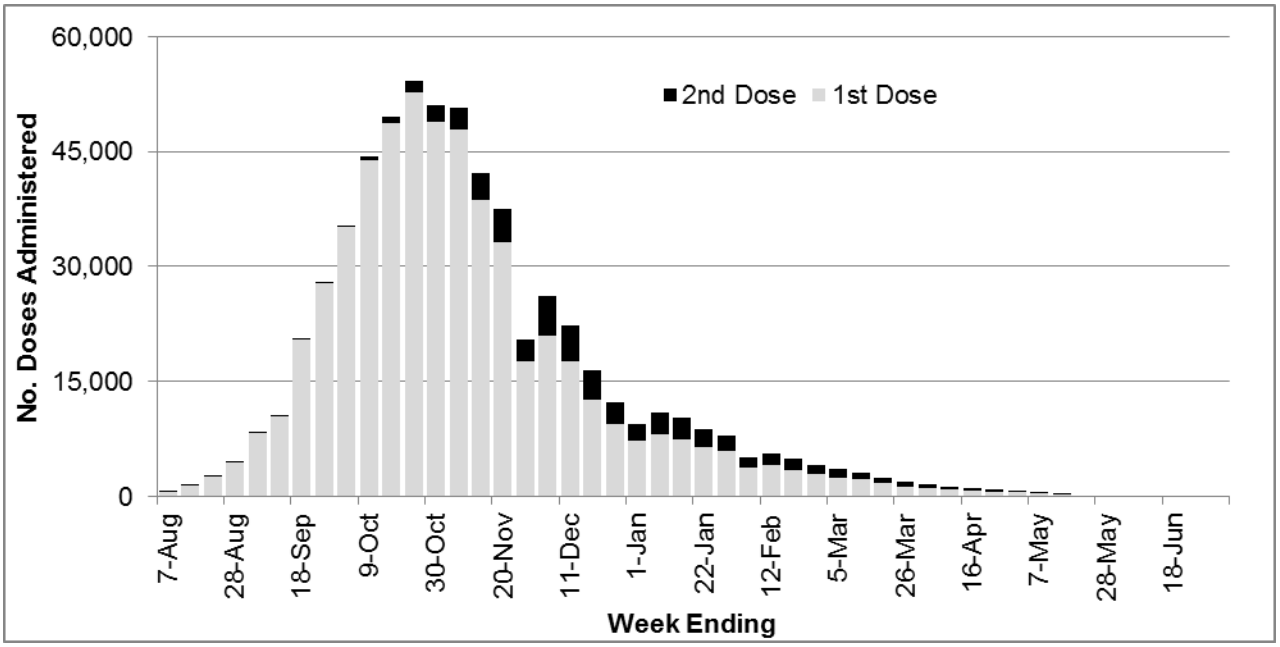


Figure 2.2. Counties above and below the Michigan mean influenza vaccination rate for children age 6 months through 17 years, 2010-2011

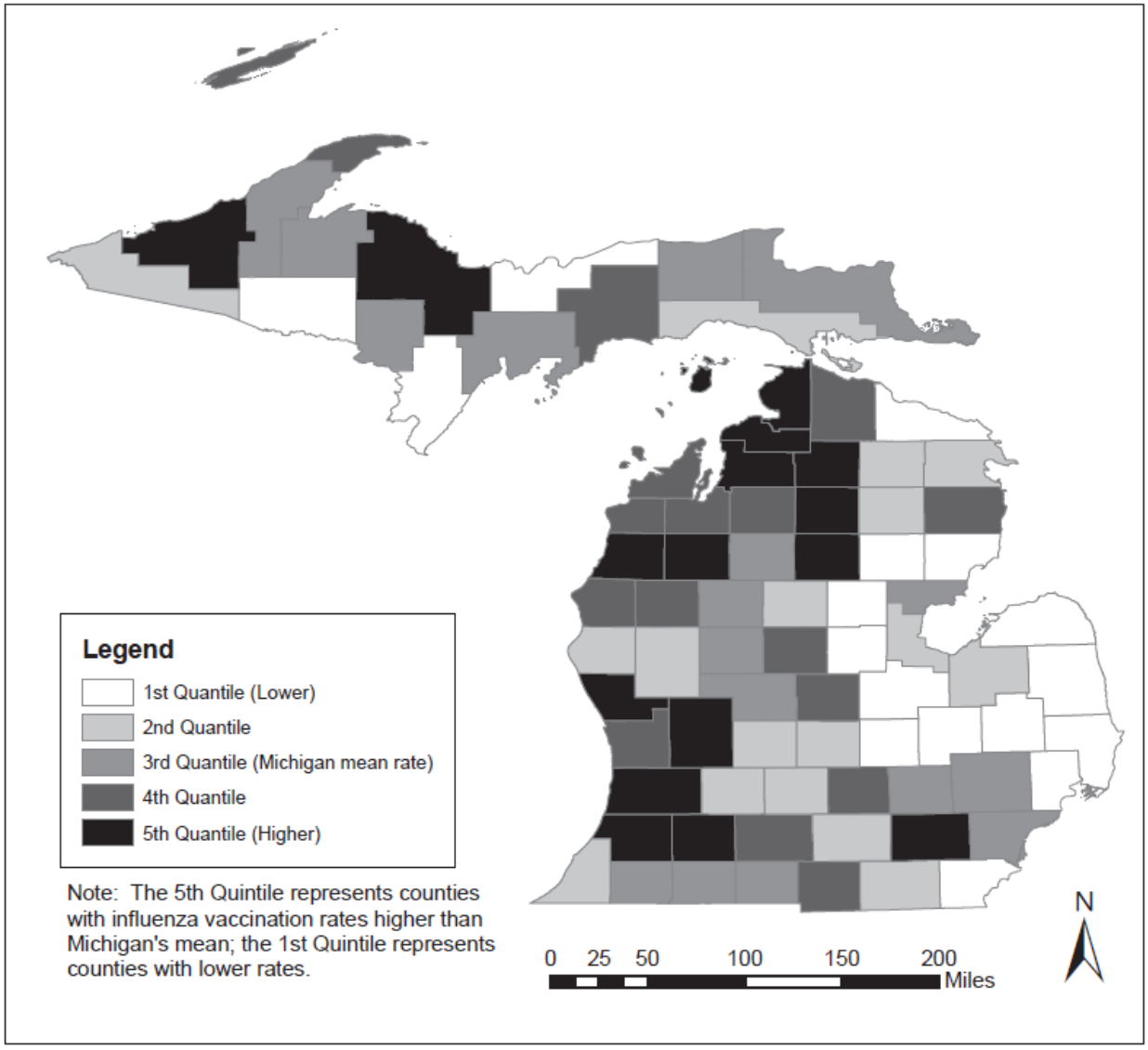


Table 2.1. Characteristics of Michigan Children Influenza Vaccination, 2010-2011 Seasons

Variable		Vaccinated (%)[a]	Unvaccinated (%)	Chi-square p-value	N
Medical home provider	Public	76,310 (13)	527,836 (87)	<0.0001	2,373,826
	Private	318,571 (18)	1,451,109 (82)		
Mother's race[b]	White	92,046 (24)	296,890 (76)	<0.0001	515,934
	Black	10,555 (11)	84,120 (89)		
	American Indian	652 (23)	2,129 (77)		
	Chinese	3,039 (36)	5,397 (64)		
	Filipino	1,756 (24)	5,477 (76)		
	Other Asian or Pacific Islander	1,662 (25)	4,983 (75)		
	Other non-White	1,065 (20)	4,270 (80)		
	Unknown	367 (19)	1,526 (81)		
Age group	6-23M	49,967 (27)	132,354 (73)	<0.0001	2,564,665
	24-59M	70,100 (18)	327,502 (82)		
	5-12Y	183,799 (15)	1,003,056 (85)		
	13-17Y	101,365 (13)	696,512 (87)		
Provider visit in past 12 months	Yes	288,098 (27)	772,753 (73)	<0.0001	2,389,934
	No	109,251 (8)	1,219,832 (92)		
Vaccine funding source	VFC	154,394 (16)	824,614 (84)	<0.0001	1,859,173
	Private/self	192,517 (22)	666,211 (78)		
	Other	4,742 (22)	16,695 (78)		
County variable		**Mean (SD)**	**Mean (SD)**	**Chi-square p-value**	**N**
Pct. Unemployed		11.1 (2.9)	11.9 (3.0)	<0.0001	2,564,665
Median household income		$50,018 (9,097)	$49,016 (8,966)	<0.0001	2,564,665
Pct. families below poverty line		10.3 (3.8)	11.0 (4.0)	<0.0001	2,564,665
Pct. Black race		13.0 (12.7)	15.6 (14.2)	<0.0001	2,564,665
Pct. Female head of household		7.2 (1.9)	7.6 (2.1)	<0.0001	2,564,665

Pct., percent

[a] Vaccinated according to ACIP recommendations[15]

[b] Data represents children aged 6-59 months; first available from birth certificate in 2005

Table 2.2. Predictors of Pediatric Influenza Vaccination, 2010-2011 Season

Variable		Model 1: Unadjusted OR N=2,373,826	95% CI	Model 2: Adjusted OR[a] N=1,850,969	95% CI	Model 3: Interaction OR[b] N=1,850,969	95% CI
Medical home provider	Public	0.66	(0.57, 0.76)	0.88	(0.78, 0.99)	-	-
	Private	Reference		Reference			
Age group	6-23M			1.23	(1.13, 1.34)	-	-
	24-59M			0.85	(0.78, 0.93)	-	-
	5-12Y			1.05	(1.01, 1.08)	-	-
	13-17Y			Reference			
Provider visit in past 12 month	Yes			3.38	(3.13, 3.66)	3.38	(3.12, 3.66)
	No			Reference		Reference	
Vaccine funding source	VFC			0.72	(0.68, 0.77)	0.72	(0.68, 0.77)
	Private/self			Reference		Reference	
	Other			0.94	(0.64, 1.38)	0.94	(0.88, 1.38)
Median household income[c]				0.94	(0.78, 1.14)	0.94	(0.78, 1.14)
Pct. families below poverty line[d]				0.72	(0.34, 1.51)	0.72	(0.34, 1.51)
Pct. Black race[d]				0.91	(0.82, 1.03)	0.91	(0.82, 1.03)
Interaction term (p-value=0.13)							
Public vs Private		-		-			
6-23M						0.89	(0.73, 1.09)
24-59M						0.88	(0.75, 1.02)
5-12Y						0.87	(0.77, 0.97)
13-17Y						0.91	(0.82, 1.00)

[a] Adjusted for categorical age, provider visit in the past 12 months, vaccine funding source, median household income, percentage of families living below the poverty line, and percentage of county residents of Black race

[b] Adjusted for provider visit in past 12 months, vaccine funding source, median household income, percentage of families living below the poverty line and percentage of county residents of Black race

[c] A one unit increase is equivalent to a $10,000 change in median household income

[d] A one unit increase is equivalent to a 10% change

References

1. Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep 2010;59(RR-8):1-62.

2. Poehling, KA, Fairbrother, G, Zhu, Y, Donauer, S, Ambrose, S, Edwards, Kathryn, et al. Practice and child characteristics associated with influenza vaccine uptake in young children. Pediatrics 2010;126(4):665-673.

3. Santibanez, TA, Santoli, JM, Bridges, CB, Euler, GL. Influenza vaccination coverage of children aged 6 to 23 months: the 2002-2003 and 2003-2004 influenza seasons. Pediatrics 2006;118(3):1167-1175.

4. Groom, H, Kolasa, M, Wooten, K, Ching, P, Shefer, A. Childhood immunization coverage by provider type. J Public Health ManagPract 2007;13(6):584-589.

5. Morrow, AL, Rosenthal, J, Lakkis, HD, Bowers, JC, Butterfoss, FD, Crews, RC, et al. A population-based study of access to immunization among urban Virginia children served by public, private, and military health care systems. Pediatrics 1998;101(2):1-10.

6. Mennito, S,Darden, P. Impact of practice policies on pediatric immunization rates. J Pediatr 2010;156(4):618-622.

7. Zhao, Z, Luman, E. Progress toward eliminating disparities in vaccination coverage among US children, 2000-2008. Am J Prev Med 2010;38(2):127-137.

8. Rosenthal, J, Rodewald, L, McCauley, M, Berman, S, Irigoyen, M, Sawyer, M, et al. Immunization coverage levels among 19- to 35-month-old children in 4 diverse, medically underserved areas of the United States. Pediatrics 2004;113(4):e296-302.

9. Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2004;53(RR-6):1-40.

10. Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2006;55(RR-10):1-42.

11. Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. MMWR Recomm Rep 2008;57(RR-7):1-60.

12. Centers for Disease Control and Prevention. Use of influenza A (H1N1) 2009 monovalent vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009;58(RR-10):1-8.

13. Lifson, AR, Roddy, M, Ehresmann, KR. The association of poverty and low immunization rates in ZIP code areas: a retrospective survey of Minnesota kindergartners. Minn Med 2000;83(8):51-55.

14. Centers for Disease Control and Prevention. County-level trends in vaccination coverage among children aged 19-35 months – United States, 1995-2008. MMWR Surveill Summ 2011;60(SS-4):1-86.

15. Allred, NJ, Wooten, KG, Kong, Y. The association of health insurance and continuous primary care in the medical home on vaccination coverage for 19- to 35-month-old children. Pediatrics 2007;119(Suppl 1):S4-11.

16. Uwemedimo, OT, Findley, SE, Andres, R, Irigoyen, M, Stockwell, MS. Determinants of influenza vaccination among young children in an inner-city community. J Community Health 2012;37:663-672.

17. Daley, MF, Beaty, BL, Barrow, J, Pearson, K, Crane, LA, Berman, S, et al. Missed opportunities for influenza vaccination in children with chronic medical conditions. Arch Pediatr Adolesc Med 2005;159:986-991.

18. Fairbrother, G, Friedman, S, DuMont, KA, Lobach, KS. Markers for primary care: missed opportunities to immunize and screen for lead and tuberculosis by private physicians serving large numbers of inner-city Medicaid-eligible children. Pediatrics 1996;9(6):785-790.

19. Allred, NJ, Poehling, KA, Szilagyi, PG, Zhang, F, Edwards, KM, Staat, MA, et al. The impact of missed opportunities on seasonal influenza vaccination coverage for healthy young children. J Pub Health Manag Pract 2011;17(6):560-564.

20. Bardenheier, BH, Yusuf, HR, Rosenthal, J, Santoli, JM, Shefer, AM, Rickert, DL, et al. Factors associated with underimmunization at 3 months of age in four medical underserved areas. Public Health Rep 2004;119:479-485.

21. Luman, ET, McCauley, M, Stokley, S, Chu, SY, Pickering, LK. Timeliness of childhood immunizations. Pediatrics 2002;110(5):935-939.

22. Santoli, JM, Barker, LE, Lyons, BH, Gandhi, NB, Phillips, C, Rodewald, LE. Health department clinics as pediatric immunization providers: a national survey. Am J Prev Med 2001;20(4):266-271.

23. Centers for Disease Control and Prevention. Seasonal influenza vaccination coverage among children aged 6 months--18 years --- Eight immunization information system sentinel sites, United States, 2009-10 influenza season. MMWR 2010;59(39):1266-1269.

24. Nowalk, MP, Zimmerman, RK, Lin, CJ, Ko, FS, Raymund, M, Hoberman, A, et al. Parental perspectives on influenza immunization of children aged 6 to 23 months. Am J Prev Med 2005;29(3):210-214.

25. Centers for Disease Control and Prevention. National Center for Immunization and Respiratory Diseases (NCIRD). Available at http://www.cdc.gov/ncird Accessed September 17, 2012.

26. Bhat-Schelbert, K, Lin, CJ, Matambanadzo, A, Hannibal, K, Nowalk, MP, Zimmerman, RK. Barriers to and facilitators of child influenza vaccine – perspectives from parents, teens, marketing and healthcare professionals. Vaccine 2012;30:2448-2452.

27. American Academy of Pediatrics. National Center for Medical Home Implementation. Available at http://www.medicalhomeinfo.org Accessed September 17, 2012.

28. Fu, LY, Cowan, N, McLaren, R, Engstrom, R, Teach, SJ. Spatial accessibility to providers and vaccination compliance among children with medicaid. Pediatrics 2009;124(6):1579-1586.

CHAPTER III

Influenza Mortality Rates in Children and the Role of Neighborhood Characteristics

INTRODUCTION

Influenza is a major cause of morbidity and mortality among children in the United States. Pediatric influenza mortality became a notifiable condition in the United States in October 2004 following initial reports of severe influenza and death in children and 153 pediatric deaths voluntarily reported to the Centers for Disease Control and Prevention (CDC) during the 2003-2004 season.[1-2] Influenza and its complications have been responsible for an average of 100 pediatric deaths annually since reporting was formalized in October 2004.[3] This figure includes a four-fold increase in pediatric deaths observed during the 2009 influenza A (H1N1) pandemic compared to the preceding five year average.[4-5] Overall, an estimated 26,500 hospitalizations occur among children (<18 years of age) from influenza annually.[6-7]

Individual-level risk factors, such as younger age, children with chronic neurological, pulmonary, cardiovascular, or immunosuppressive conditions, and co-infection with *Staphylococcus aureus*, increase the risk of influenza morbidity and mortality.[8] The burden of influenza is not equal for all children. Black, Asian/Pacific Islander, American Indian/Alaskan Native, and Hispanic children face a disproportionate burden of influenza morbidity and mortality. Influenza hospitalization rates of Black, Asian, and Hispanic children are 2.3 to 3.6 times higher than those of White children.[9-13] During the 2009 H1N1 pandemic, Black, Asian, American Indian, and Hispanic children accounted for a higher percentage of the mortality

compared to the percentage of the U.S. population they comprise.[9,14] The reasons for the observed disparity by race and ethnicity are not clear. The prevalence of chronic medical conditions or the access to medical care has been proposed as potential explanations.[14] Chronic medical conditions potentially account for part of the observed disparity in influenza mortality by race and ethnicity.[9,14] Fully 53% to 68% of pediatric influenza deaths occurred among children with at least one high-risk medical condition.[2,5]

Individual-level factors, such as age and presence of a chronic medical condition, only partly explain pediatric influenza mortality, suggesting that other factors either at the individual or possibly ecological level may help explain disparities in pediatric mortality.[2] Neighborhood-level characteristics, at the census tract level, such as the percentage of residents living below the federal poverty level, the educational attainment of people over 25 years of age, the percentage of crowded households, and the median household income, have been associated with respiratory morbidity in children and adults for diseases such as tuberculosis, pneumococcal disease, and respiratory syncytial virus.[14-18] Several studies also examined the contribution of neighborhood factors to the racial and ethnic disparity in respiratory disease morbidity of children and adults and found the disparity was attenuated when adjusting for neighborhood factors.[15-16] Very few studies have examined neighborhood-level characteristics as potential risk factors for pediatric influenza morbidity and mortality specifically, and fewer still explore the race/ethnic disparity.[10,19-23] Because tuberculosis, pneumococcal disease, respiratory syncytial virus, and influenza share the same mode of transmission, via aerosolization of droplet nuclei that persist in the air and larger droplets that fall out of the air three to six feet away from an infected individual, and because these infectious diseases may have similar risk factors, it is important to look at the neighborhood factors associated with influenza morbidity and mortality.

We hypothesized that the neighborhood in which a child resides plays a role in determining their risk of influenza mortality and that individual-level racial and ethnic disparities in influenza would be partly explained by those neighborhood characteristics. To address this question, state surveillance data from influenza-associated pediatric mortality cases was linked to U.S. Census Bureau data via the census tract. Stratifying by age, we assessed the extent to which neighborhood composition, socioeconomic status, access to medical care, and living conditions, account for the observed relationship between a child's individual racial and ethnic identity, and his/her influenza mortality rate.

METHODS

We conducted a population-based retrospective cohort study of children <18 years of age to determine mortality rates due to influenza. Cases were extracted from public health surveillance data on influenza-associated pediatric mortality, a nationally-notifiable condition, from October 2004 through April 2011. Case data were linked to census data in order to calculate age-specific and race/ethnicity-specific rates of influenza mortality. Census data at the tract level served as proxy for neighborhoods which allowed for the assessment of several neighborhood characteristics presumed to be associated with pediatric influenza mortality.

Data Sources. Twenty-three states with high cumulative incidence, comprising 80% of all deaths, were identified at the end of the 2010-2011 influenza season. We contacted the State Epidemiologist in those 23 states to request their state's influenza-associated pediatric mortality case data and of these, 18 State Epidemiologists (78%) agreed to participate. Three additional states with low case counts were approached to be more broadly representative of the United States population based on geography and incidence. Participating states included Arizona, California, Iowa, Illinois, Michigan, Minnesota, New Mexico, New York (including the New

York City Health Department), North Carolina, Ohio, Oklahoma, Pennsylvania, South Carolina, South Dakota, Tennessee, Virginia, Washington, and Wisconsin. (Figure 3.1) Wisconsin was included for the crude mortality rates only as no case address information was available for geocoding. Case geocoding was conducted by states with the exception of New Mexico which was done by the investigators.

The cases from the 18 participating states accounted for 57% of the 795 cases of influenza-associated pediatric mortality reported to the Centers for Disease Control and Prevention from the 2004-2005 to the 2010-2011 influenza season. Inclusion criteria were defined as a child <18 years of age residing in a participating state who died from influenza or its complications with laboratory evidence of influenza virus infection with no recovery to baseline, according to the Centers for Disease Control/Council for State and Territorial Epidemiologist influenza-associated pediatric case definition, and reported to a state health department between October 2004 and April 2011.[24]

The 2000 Decennial Census at the tract level was used for age and race/ethnic-specific population counts (population at risk) as was the level of aggregation for the neighborhood-level characteristics. The census tract is defined as a county subdivision "…between 2,500 and 8,000 persons and, when first delineated, are designed to be homogeneous with respect to population characteristics, economic status, and living conditions."[25] Census data included age and race/ethnic-specific population counts for calculation of crude mortality rates and the mortality ratios. Race and ethnicity were asked in two questions and thus are not mutually exclusive. The number of pediatric influenza deaths was aggregated to the census tract level into four categories for race and age: White or Black race aged <5 years and White or Black race aged 5-17 years. Cases were also aggregated into four categories for ethnicity and age: Hispanic/Latino or Non-

Hispanic White aged <5 years and Hispanic/Latino or Non-Hispanic White age 5-17 years. The outcome was the count of pediatric influenza deaths in each category.

Census tract data included the following variables: overcrowding, which was defined by the U.S. Department of Housing and Urban Development as greater than 1.01 people per room; severe overcrowding, as greater than 1.51 people per room; the percentage of individuals living in an urban area; and average household size. Census tract socio-demographic characteristics included median household income in 1999 dollars, the percentage of households living below the federal poverty line, the percentage of individuals aged 25 years or older with a high school degree or with a college degree, the percentage of unemployed individuals aged 16 or older, and the percentage of persons of White or Black race. The percentage of households living below the federal poverty line was defined in the 2000 Census as annual income less than $17,050 for a family of four.

The Health Resources and Services Administration (HRSA) Area Resources File (ARF) contains over 6,000 county variables on "health facilities, health professions, measures of resource scarcity, health status, economic activity, health training programs, and socioeconomic and environmental characteristics."[26] Six variables at the county level were included from the ARF: the number of hospitals; the number of primary care physicians (includes doctors of medicine [M.D.] and osteopathy [D.O.] in four specialty areas of general or family practice, general internal medicine, pediatrics, and obstetrics and gynecology); the percentage of children under 19 years of age without health insurance; designation of the whole, a part, or none of the county as a Health Professional Shortage Area (HPSA); population density, defined as the population per land area square mile; and the housing density, defined as the houses per land area square mile.

The study was designated as not regulated by the University of Michigan Institutional Review Board (IRB) due to the use of data on deceased individuals [HUM00034214]. Reliance on the IRB determination and, as necessary, additional state IRB approval was received prior to analysis.

Statistical Analysis. The outcome was death of a child from influenza. Descriptive statistics were calculated for neighborhood characteristics, the main predictor. Correlation of neighborhood characteristics was examined using Pearson correlation coefficients. In constructing the adjusted Poisson models, only one of a set of highly correlated variables were used. Crude mortality rates were calculated by dividing the number of influenza deaths by the age and race/ethnic-specific person-years. These rates are expressed per million person-years. Our analysis is precluded from examining differences across race and ethnicity based on the manner in which race and ethnicity were asked in the census. Crude mortality rates were also calculated for sex.

Poisson regression models with an offset for person-time were used to calculate the independent relationship of each neighborhood factor to the rate of influenza mortality in children. All variables were then entered into a single model. Deletion of neighborhood variables not associated with the rate of pediatric influenza mortality was continued until only the significantly associated neighborhood factors remained. The significance level used for this process was alpha=0.10. The individual-level race/ethnicity variable was modeled for the observed relationship to the rate of pediatric influenza mortality. The neighborhood factors significantly associated with pediatric influenza mortality were then added to the model to explain the observed race/ethnic disparity with pediatric influenza mortality. Findings were reported as mortality ratios and 95% confidence interval. The offset was population at risk in a

census tract for the seven year period (person-years). Akaike's Information Criteria (AIC) values and likelihood ratio tests were used during model development.

Model Diagnostics. The Pearson chi-square statistic, a goodness of fit measure, was obtained from the Poisson models and evaluated for over-dispersion (>1.0). A graph of the observed proportions in the data along with the Poisson and negative binomial probabilities for a count variable were assessed to verify our choice in the count model. Based on the findings shown in Figure 3.2, use of either the Poisson or negative binomial regression models were appropriate and Poisson models were chosen. Standardized Pearson residuals were plotted to examine the relationship to the predicted values. Based on the findings shown in Figure 3.3, a slight floor effect is seen when deaths equal zero, otherwise there is no pattern to indicate a lack of model fit. SAS 9.2 and STATA 12 were used in the analysis.

RESULTS

Population. A total of 455 pediatric influenza deaths were reported to public health in participating states during the study period, October 2004 through April 2011. Seventy-nine percent of cases (N=360) were geocoded successfully to the census tract in order to examine factors within the neighborhood of residence; 95 cases (21%) were excluded from analysis due to missing census tracts. In relation to the United States population, the sample was similarly proportioned with children <18 years of age comprising 28.6% for both the sample and nationally; percent White race was 73.8% in the sample and 75.1% nationally, percent Black race was 11.4% in the sample and 12.3% nationally, and the percent Hispanic/Latino was 13.2% in the sample and 12.5% nationally.

Neighborhood-level Factors. Neighborhood characteristics at the census tract and county levels are shown in Table 3.1. Census tracts had mean values of 80% of residents living in urban areas, 72% of residents indicated as White and 13% of residents indicated as Black. Mean unemployment in neighborhoods was 4% and an average of 24% of persons graduated from college. Within counties, 8% of children <19 years of age had no health insurance. The mean number of hospitals and primary care physicians per 100,000 population was 4.5 and 6.0, respectively. Using Poisson regression, mortality ratios (MR) were calculated for neighborhood characteristics and presented in Table 3.2. Pediatric influenza mortality was associated with more urbanized neighborhoods, neighborhoods characterized by fewer persons with a college education, and with a greater percentage of children <19 years of age lacking insurance.

Correlations were determined for census tract and county variables. Median household income was moderately correlated with the percentage of households living below the federal poverty line (-0.667) and the percentage of persons with a high school degree (0.596) or college degree (0.694). Negative correlations were noted between the percentage of persons with a high school degree and crowding (-0.684) or severe crowding (-0.578). Income and education were correlated with neighborhood racial composition; the percentage of households living below the federal poverty line (-0.591) and percentage of persons with a high school education (0.569) were correlated with the percentage of White residents.

Individual-level Factors. Most pediatric influenza deaths were in Whites (59%), followed by Blacks (19%), Asians (5%), American Indians (3%), or other/unknown race (14%). Cases tended to be male (56%) and the majority were aged 5-17 years (53%) as opposed to <5 years of age (47%); in both cases a noticeable but not large difference. Ethnically, more non-

Hispanic White children (33%) died of influenza than Hispanic/Latinos (26%); the remainder consisted of 14% Non-Hispanic Black, 8% other Non-Hispanic, and 19% lacked ethnicity data.

The observed crude mortality rates for White and Black children aged <5 years were 2.4 and 4.7 deaths per million person-years, respectively. (Table 3.3) Mortality rates for children aged 5-17 years were lower with 1.2 and 1.6 deaths per million person-years for Whites and Blacks, respectively. By ethnicity, Hispanic/Latino children <5 years of age had a higher mortality rate, 4.1 deaths per million person-years, than did 5-17 year olds with 1.6 deaths per million person-years. Hispanic/Latino children had higher rates than Non-Hispanic White children for both the <5 year and 5-17 year age groups. Only a slightly higher mortality rate for males compared to females, 1.8 deaths versus 1.5 deaths per million person-years, was observed so sex-specific rates were not analyzed further.

Using Poisson regression, unadjusted mortality ratios comparing Blacks to Whites showed a 66% greater rate of death for children <5 years of age (MR=1.66, 95% CL (1.11, 2.48)) and a 15% greater rate for children 5-17 years of age (MR=1.15, 95% CL (0.71, 1.86)). (Table 3.4) Comparing Hispanic/Latinos to Non-Hispanic Whites, children <5 years of age had a 176% greater rate of death (MR=2.76, 95% CL (1.77, 4.31)) and children 5-17 years had a 64% greater rate of death (MR=1.64, 95% CL (1.08, 2.49)).

Disparity Analysis. To examine if neighborhood factors explain the observed race/ethnic disparity in pediatric influenza mortality, neighborhood factors were added to the unadjusted mortality ratios from Table 3.4. The neighborhood factors included were those found to be predictive of pediatric influenza mortality from the final model in Table 3.2 and included the

percentage of persons with a college degree, percentage of persons living in an urban area and the percentage of children under 19 years of age without insurance.

The Poisson regression model addressing the observed race/ethnic disparity showed that after adjusting for neighborhood characteristics, the Black-White disparity in influenza mortality was attenuated for children <5 years of age (MR=1.53, 95% CL (1.02, 2.31)). For children 5-17 years of age, the unadjusted model was non-significant but the mortality ratio decreased slightly after adjustment for neighborhood factors. For Hispanic/Latinos, inclusion of neighborhood factors was also shown to decrease the mortality ratios for both children aged <5 years (MR=2.27, 95% CL (1.46, 3.53)) and 5-17 years (MR=1.35, 95% CL (0.88, 2.05)).

CONCLUSIONS

In this first study to examine the role of neighborhood characteristics as risk factors for pediatric influenza mortality, we found that higher pediatric mortality rates were observed for both census tract-level and county-level measures. Census tracts with fewer rather than more college-educated residents as well as census tracts that were more urban had elevated rates of pediatric influenza mortality. The less likely a child was to be covered by insurance in a county, the more deaths were reported to occur. In addition to the contribution of neighborhood factors in explaining pediatric influenza mortality, neighborhood factors were added to models showing that race and ethnicity were associated with pediatric influenza mortality. The neighborhood factors, educational attainment, urbanicity, and insurance status, partly accounted for the observed racial and ethnic disparities in mortality.

The neighborhood factors, educational attainment, urbanicity, and insurance status, have not been examined as extensively as other neighborhood factors in earlier research of influenza

morbidity and mortality. The majority of studies looking at the association between neighborhood and influenza morbidity and mortality have focused on one or two factors including the percentage of persons living below the poverty level and median household income.[10,23] The percentage of persons living below the federal poverty level and median household income were less informative in explaining the pediatric influenza mortality rate than percentage of residents with a college degree, percentage of residents living in an urban area, and percentage of children <19 years of age without health insurance. We proffer that these neighborhood factors measure economic deprivation, medical care access, and social contact.

The percentage of residents with a college degree is a measure of educational attainment that has been used to describe a neighborhood's economic deprivation.[27] Neighborhoods with fewer degree holders are likely to have lower incomes and more unemployment than neighborhoods with more degree holders because of the occupational opportunities and earning potential that come with more education.[28] Education has also been linked to health literacy and adoption of healthy behaviors by individuals, such as influenza vaccination, because of the knowledge and life skills education imparts.[29] The benefits provided by more education may extend beyond an individual and exert influence on the individual's neighborhood. For example, the influence of neighborhood educational attainment of a high school degree was found to be associated with pediatric influenza hospitalization in a study of children and adults.[20]

The percentage of children <19 years of age without health insurance was a county-level neighborhood factor to measure access to medical care. The percentage of children without health insurance was considered because uninsured compared to insured children are 8 times more likely not to have a usual source of healthcare, more likely to go without medical or other healthcare, and less likely to have seen a physician in the past year.[30-31] The lack of health

insurance impacts both the use of preventive services, such as influenza vaccination, as well as timely medical care.[32-33] Decreased influenza vaccine use would theoretically increase the risk of influenza infection and, thus, death from influenza. It can also be hypothesized that delays in care-seeking would disproportionately and negatively impact children with chronic medical conditions if a higher percentage of the influenza infections in these children lead to severe infection requiring hospitalization and death. The ideal of health insurance for all Americans has been at the forefront of the Affordable Care Act. A goal has been to increase health insurance coverage through expansions in public insurance, such as Medicaid and Medicare, and require coverage for immunizations against vaccine preventable diseases, including influenza vaccination, which has the potential to decrease pediatric influenza mortality.[34-35] Another goal of the Affordable Care Act, through creation of the Institute for Comparative and Clinical Effectiveness Research, is to study methods of expanding delivery of healthcare services to at-risk populations as well as monitoring the effect of current and expanded healthcare delivery options to provide feedback on health and healthcare disparities.[34] Our study findings of neighborhood factors that help explain race/ethnic disparities in pediatric influenza mortality can help inform future Affordable Care Act research by identifying at-risk neighborhoods that may benefit from expanded healthcare delivery to reduce observed race/ethnic disparities. The Affordable Care Act also aims to expand programs to recruit primary care professionals and expand community health centers.[34] Findings from our study show these activities are likely to have limited effects on the health of Americans in relation to pediatric influenza as the number of hospitals, number of primary care physicians, and county designation as a health provider shortage area were not associated with pediatric influenza mortality.

The percentage of persons living in an urban area is hypothesized to represent the likelihood of social contact within the neighborhood, differing from the contact that occurs within a household, and is a necessary component for the community transmission of influenza. One study showed areas that are primarily urban compared to rural increased the odds of influenza mortality among children and adults, but was not statistically significant.[23] Our study differs from this earlier work in two important ways. Our study includes more than 350 deaths compared to just 35 deaths in Thompson et al, giving us more power to detect an association. Also, the urban/rural definitions were defined at the zip code level, a much larger spatial scale, rather than at the census tract. Census tract has been shown to be a better choice than zip code for areas-based measures in identifying associations in health research.[36] These two factors may explain why our findings of a direct association between increasing urbanicity and influenza mortality rates did not match the Thompson et al. study.

Our approach to examining neighborhood factors differed from other studies. All potential neighborhood factors were included in our initial model with backward elimination of factors not significantly associated with pediatric influenza mortality. Most studies to date have instead focused on a limited set of neighborhood factors, primarily the percentage of persons living below the poverty level and median household income.[10,19-23]

Neighborhood factors helped explain the racial and ethnic disparity in pediatric influenza mortality for Black and Hispanic children. Greater reductions, based on percent change in the mortality ratios, were seen comparing Hispanics to Non-Hispanic Whites (18%) than comparing Blacks to Whites (8%) after the neighborhood factors were added. These findings are similar to two studies of influenza hospitalization that found rates differed by race and ethnicity but inclusion of neighborhood factors helped explain the racial and ethnic disparity.[10,23] Our findings

indicate that neighborhood factors, such as educational attainment, urbanicity, and insurance status, could reasonably be used to monitor and evaluate disparities in pediatric influenza mortality in addition to race and ethnicity. A change to routinely using neighborhood factors for monitoring respiratory disease disparities has been proposed for invasive pneumococcal disease.[17] The advantages of using neighborhood risk factors are three-fold. First, neighborhood factors represent modifiable risk factors that can be used as targets for programs and interventions. Second, routinely collected surveillance data already includes address information from which census data can be used to derive neighborhood characteristics. Third, the stability of disease surveillance data over time provides a steady source of data from which to evaluate changes in disparities over time.

Limitations

Our data comprise a sample of all pediatric influenza deaths in the U.S. and may not be externally generalizable to the entire U.S. population. The race proportions of the sample are comparable to the U.S. population with the exception of the Black population. The Black population comprises a slightly greater percentage in our sample than nationally (13.2% versus 12.5%) which would potentially over-estimate the effect of Black race. Our findings are in line with studies that were published using single or multiple years of pediatric influenza mortality data.[2,5,37-39] Reporting bias may also have influenced our results. If being Black or Hispanic/Latino were associated with under-reporting of pediatric influenza mortality, the crude mortality estimates and mortality ratios would be under-estimated and the disparity with non-Hispanic Whites would be greater.

There are at least two unmeasured factors in our analysis that limited the assessment of the neighborhood on the race/ethnic disparity in pediatric influenza mortality. First, there are

likely other neighborhood characteristics not included in the analysis. Influenza vaccination status at the individual and neighborhood levels is an important factor in determining risk of infection and death.[40] Vaccination directly protects the individual, but can indirectly protect against influenza infection with a high enough rate of vaccination.[41-42] Second, the presence and distribution of high-risk medical conditions, including neurologic disorders and chronic pulmonary disease, in our population not only increases the risk for severe infection and death but complicates the assessment of race/ethnic disparities in those populations.[4-5,9,11,21] While analysis of high-risk medical conditions was not possible because the population distribution of those risk factors is not available, 42% of our pediatric mortality cases had >=1 chronic medical condition.

A number of pediatric influenza deaths were missing data on the census tract of residence (N=74, 16%) or race (N=34, 7%) or both (N=12, 3%). It is unclear the extent the missing data may have biased our results as it is unlikely the data are missing completely at random. If deaths in poorer neighborhoods were less likely to be geocoded, the findings would be biased toward the null to show no effect of neighborhood factors. Census tract as a proxy for the child's neighborhood has the potential for mis-estimation of the true construct of the neighborhood. While concerning, many studies have successfully used census tracts as a good and reliable area-based measure of the socioeconomic environment for analysis of inequalities.[16,36,43-46] The 2000 Census was used to proxy neighborhoods as opposed to using American Community Survey estimates or interpolations between the 2000 and 2010 Census. This gives a slight disconnect in the age groups giving rise to the cases. Since the population counts are denominators for the mortality rates and form the offset for the mortality ratios, small population shifts over time

could influence our results. The 2000 Census was used because it had a large number of variables available at the census tract level at the time of our analysis.

Strengths

This is the first study we know of to examine the neighborhood factors that influence rates of influenza mortality in children and the first to address the race/ethnic disparity in pediatric influenza mortality. Our approach of conducting a population-based retrospective cohort study using existing public health surveillance data using a uniform case definition that is linked to U.S. Census Bureau data is a further strength as the framework has been shown effective in evaluating neighborhood factors for infectious and chronic diseases in addition to examining racial and ethnic health disparities.[16,36,43-46]

Neighborhood characteristics, including urbanicity, percentage of residents with a college degree, and percentage of children without health insurance, were predictive of influenza deaths in children. These neighborhood factors increased pediatric influenza mortality rates and partly explained the observed racial and ethnic disparity in pediatric influenza mortality. By using neighborhood factors to explain pediatric influenza mortality rather than race and ethnicity, we provide modifiable risk factors that can be used to decrease morbidity and mortality. The percentage of children without health insurance is a modifiable neighborhood factor that significantly impacted the risk for pediatric influenza mortality, a finding that should help inform healthcare reform discussions about the importance of children's insurance coverage. Further research linking public health surveillance data with census data is warranted to monitor changes in neighborhoods and disparities over time.

Figure 3.1. Geographic distribution of states participating in the pediatric influenza mortality analysis (N=18)

Figure 3.2. Probability distribution for pediatric influenza deaths implied by the Poisson and negative binomial models against actual deaths (aggregated to the county)

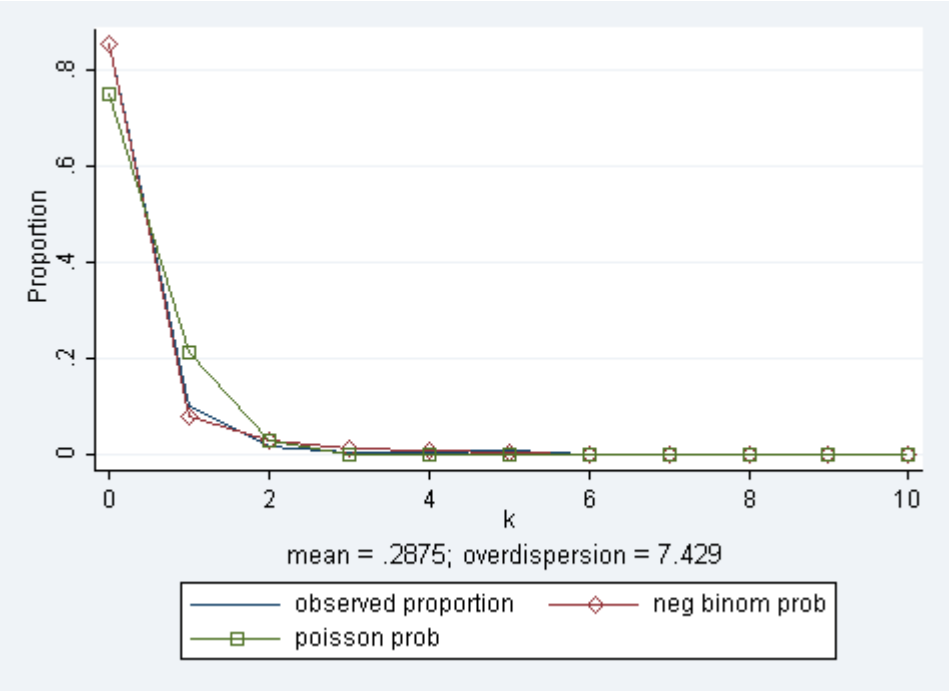


Figure 3.3. Plot of standardized deviance residuals against predicted pediatric influenza mortality rates (condensed to the state)

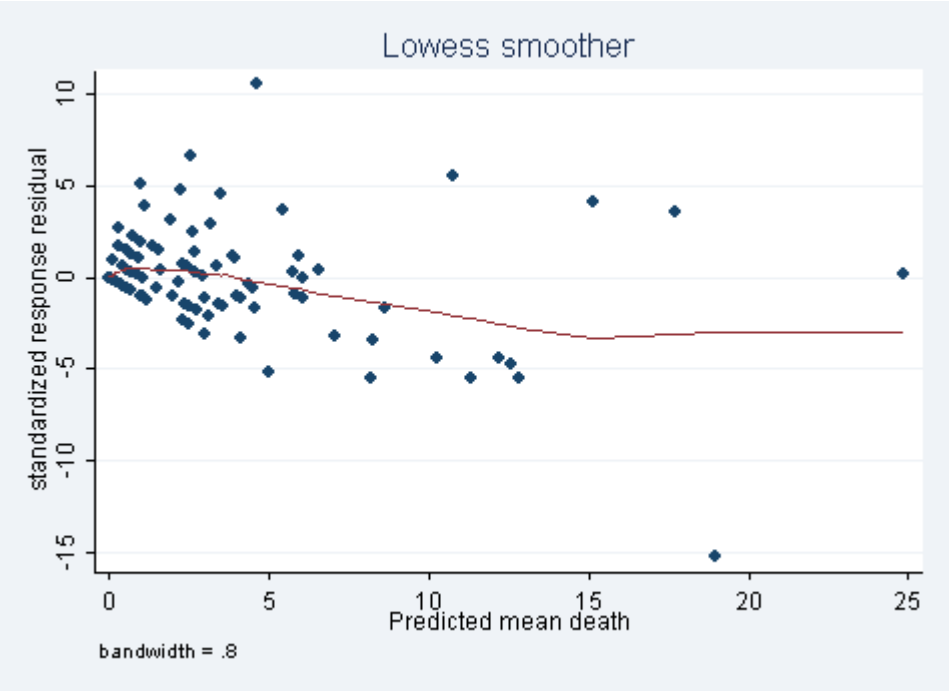


Table 3.1. Census tract- and county-level characteristics of states in the pediatric influenza mortality analysis

		N	Mean	SD	Range
Census Tract	Pct. Urban	36,264	80.3	35.8	0-100
	Pct. White	36,264	72.1	27.5	0-100
	Pct. Black	36,264	12.8	22.9	0-100
	Average HH Size	36,522	2.65	0.54	0-7
	Median HH Income	36,522	45,001	21,331	0-200,001
	HH Below Poverty	36,188	12.9	11.1	0-100
	Pct. HS Graduate	36,259	78.9	14.6	0-100
	Pct. College Grad.	36,259	23.6	17.4	0-100
	Pct. Unemployed	36,264	4.0	3.4	0-100
	Pct. Overcrowding	36,191	7.3	11.0	0-100
	Pct. Severe Overcrowding	36,191	1.6	4.3	0-100
County	HPSA	1,323			
	--0=None of County		0=330	24.9%	
	--1=Whole County		1=596	45.1%	
	--2=Part of County		2=397	30.0%	
	# Hospitals per 100,000 population	1,324	4.50	2.80	0-74
	# Primary Care Physicians per 100,000 population	1,324	60.4	53.6	0-461
	Pct. children <19 without health insurance	1,324	8.49	7.50	0-224
	Population Density (log base 2)	1,321	6.03	5.85	0-16
	Household Density (log base 2)	1,304	4.93	4.74	0-15

Pct. =percent
HH =household

Table 3.2. Pediatric influenza mortality ratios for census tract- and county-level characteristics (N=35,952)

	Bivariate		Final	
Neighborhood Characteristic	Mortality Ratio	95% CI	Mortality Ratio	95% CI
Pct. Urban	1.03	(1.00, 1.06)	1.04	(1.00, 1.07)
Pct. College Grad.				
<15%	1.45	(1.03, 2.04)	1.44	(1.01, 2.04)
15 to 25%	1.06	(0.72, 1.56)	1.08	(0.73, 1.59)
26 to 40%	1.34	(0.91, 1.98)	1.34	(0.91, 1.98)
41 to 100%	REF		REF	
Pct. Black				
<5%	REF			
5 to 15%	1.16	(0.88, 1.54)		
16 to 100%	1.30	(1.01, 1.67)		
Pct. Unemployed				
<1.9%	REF			
1.9 to 2.7%	1.03	(0.73, 1.46)		
2.8 to 3.7%	0.73	(0.60, 1.24)		
3.8 to 5.5%	1.35	(0.98, 1.86)		
5.6 to 100%	1.19	(0.78, 1.52)		
Average HH Size	0.94	(0.77, 1.15)		
Median HH Income	0.94	(0.89, 0.99)		
HH Below Poverty	1.08	(0.98, 1.18)		
Pct. HS Graduate	0.95	(0.89, 1.02)		
Pct. Overcrowding	1.02	(0.94, 1.11)		
Pct. Severe Overcrowding	1.05	(0.86, 1.29)		
# Hospitals per 100,000 population				
<1.0	REF			
1 to 2.0	1.09	(0.81, 1.45)		
2.1 to 3.0	1.54	(1.08, 2.20)		
3.1 to 6.0	1.82	(1.27, 2.62)		
6.1 to 74.3	1.94	(1.11, 3.41)		
Pct. children <19 without health insurance	1.06	(1.03, 1.09)	1.06	(1.03, 1.09)
HPSA				
None of County	REF			
Whole	1.11	(0.81, 1.52)		
Part	1.11	(0.79, 1.56)		
# Primary Care Physicians per 100,000 population	1.00	(1.00, 1.00)		
Population Density (log base 2)	0.97	(0.93, 1.01)		
Household Density (log base 2)	0.97	(0.93, 1.01)		

Pct. =percent
HH =household

Table 3.3. Crude pediatric influenza mortality rates by age and race/ethnicity

Race and Age[a]	No. of Deaths (N=455)	No. in population	Mortality Rate (million person-years)
Age <5 years			
White	110	6,511,996	2.413
Black	44	1,332,467	4.717
Age 5-17 years			
White	160	18,804,117	1.216
Black	43	3,932,901	1.562
Ethnicity and Age[b]			
Age <5 years			
Hispanic/Latino	62	2,140,924	4.137
Non-Hispanic White	57	5,663,776	1.438
Age 5-17 years			
Hispanic/Latino	55	5,051,047	1.556
Non-Hispanic White	94	16,811,561	0.799

[a] Ninety-nine pediatric influenza deaths were as follows: 22 Asian, 12 Native American, 4 Native Hawaiian, and 60 children of unknown race.

[b] 187 pediatric influenza deaths were of either Non-Hispanic or unknown ethnicity: 62 Non-Hispanic Blacks, 34 other/unknown Non-Hispanic, and 85 children of unknown ethnicity.

Table 3.4. Pediatric influenza mortality ratios by age and race/ethnicity

Race and Age	Unadjusted Mortality Ratio (N=173,017)	95% CI	Adjusted Mortality Ratio[a] (N=173,017)	95% CI
Age <5 years				
White	REF		REF	
Black	1.66	1.11, 2.48	1.53	1.02, 2.31
Age 5-17 years				
White	Ref		Ref	
Black	1.15	0.71, 1.86	1.05	0.71, 1.56
Ethnicity and Age	(N=118,090)		(N=118,090)	
Age <5 years				
Hispanic/Latino	2.76	1.77, 4.31	2.27	1.46, 3.53
Non-Hispanic White	REF		REF	
Age 5-17 years				
Hispanic/Latino	1.64	1.08, 2.49	1.35	0.88, 2.05
Non-Hispanic White	REF		REF	

[a] Adjusted for categorical percentage of persons with a college degree and continuous percentage of persons living in an urban area and the percentage of children under 19 years of age without insurance.

References

1. Centers for Disease Control and Prevention (2003). "Severe morbidity and mortality associated with influenza in children and young adults--Michigan, 2003." MMWR Morb Mortal Wkly Rep 52(35): 837-840.

2. Bhat, N., J. G. Wright, et al. (2005). "Influenza-associated deaths among children in the United States, 2003-2004." N Engl J Med 353(24): 2559-2567.

3. Centers for Disease Control and Prevention. "FluView Interactive." National Center for Immunization and Respiratory Disease, 7 Dec. 2012. Last accessed Feb. 12, 2013. http://www.cdc.gov/flu/weekly/fluviewinteractive.htm

4. Blanton, L., G. Peacock, et al. (2012). "Neurologic disorders among pediatric deaths associated with the 2009 pandemic influenza." Pediatrics 130(3): 390-396.

5. Cox, C. M., L. Blanton, et al. (2011). "2009 Pandemic influenza A (H1N1) deaths among children--United States, 2009-2010." Clin Infect Dis 52 Suppl 1: S69-74.

6. Weycker, D., J. Edelsberg, et al. (2005). "Population-wide benefits of routine vaccination of children against influenza." Vaccine 23(10): 1284-1293.

7. Thompson, W. W., L. Comanor, et al. (2006). "Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease." J Infect Dis 194 Suppl 2: S82-91.

8. Centers for Disease Control and Prevention (2010). "Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010." MMWR Recomm Rep 59(rr08): 1-62.

9. Dee, D. L., D. M. Bensyl, et al. (2011). "Racial and ethnic disparities in hospitalizations and deaths associated with 2009 pandemic Influenza A (H1N1) virus infections in the United States." Ann Epidemiol 21(8): 623-630.

10. Yousey-Hindes, K. M. and J. L. Hadler (2011). "Neighborhood socioeconomic status and influenza hospitalizations among children: New Haven County, Connecticut, 2003-2010." Am J Public Health 101(9): 1785-1789.

11. Iwane, M. K., K. M. Edwards, et al. (2004). "Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children." Pediatrics 113(6): 1758-1764.

12. Chowell, G., A. Ayala, et al. (2012). "Risk factors for mortality among 2009 A/H1N1 influenza hospitalizations in Maricopa County, Arizona, April 2009 to March 2010." Comput Math Methods Med 2012: 914196.

13. Centers for Disease Control and Prevention (2009). "2009 pandemic influenza A (H1N1) virus infections - Chicago, Illinois, April-July 2009." MMWR Morb Mortal Wkly Rep 58(33): 913-918.

14. Centers for Disease Control and Prevention (2009). "Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/Alaska Natives - 12 states, 2009." MMWR Morb Mortal Wkly Rep 58(48): 1341-1344.

15. Krieger, N., P. D. Waterman, et al. (2003). "Monitoring socioeconomic inequalities in sexually transmitted infections, tuberculosis, and violence: geocoding and choice of area-based socioeconomic measures--the public health disparities geocoding project (US)." Public Health Rep 118(3): 240-260.

16. Krieger, N., J. T. Chen, et al. (2005). "Painting a truer picture of US socioeconomic and racial/ethnic health inequalities: the Public Health Disparities Geocoding Project." Am J Public Health 95(2): 312-323.

17. Soto, K., S. Petit, et al. (2011). "Changing disparities in invasive pneumococcal disease by socioeconomic status and race/ ethnicity in Connecticut, 1998-2008." Public Health Rep 126 Suppl 3: 81-88.

18. Colosia, A. D., A. Masaquel, et al. (2012). "Residential crowding and severe respiratory syncytial virus disease among infants and young children: a systematic literature review." BMC Infect Dis 12: 95.

19. Levy, N. S., T. Q. Nguyen, et al. (2013). "Disparities in the severity of influenza illness: a descriptive study of hospitalized and nonhospitalized novel H1N1 influenza-positive patients in New York City: 2009-2010 influenza season." J Public Health Manag Pract 19(1): 16-24.

20. Lowcock, E. C., L. C. Rosella, et al. (2012). "The social determinants of health and pandemic H1N1 2009 influenza severity." Am J Public Health 102(8): e51-58.

21. O'Brien, M. A., T. M. Uyeki, et al. (2004). "Incidence of outpatient visits and hospitalizations related to influenza in infants and young children." Pediatrics 113(3 Pt 1): 585-593.

22. Rutter, P. D., O. T. Mytton, et al. (2012). "Socio-economic disparities in mortality due to pandemic influenza in England." Int J Public Health 57(4): 745-750.

23. Thompson, D. L., J. Jungk, et al. (2011). "Risk factors for 2009 pandemic influenza A (H1N1)-related hospitalization and death among racial/ethnic groups in New Mexico." Am J Public Health 101(9): 1776-1784.

24. Centers for Disease Control and Prevention. “Nationally Notifiable Diseases Surveillance System (NNDSS).” Public Health Surveillance and Informatics Program Office, 7 Dec. 2012. Last accessed Feb. 12, 2013. http://wwwn.cdc.gov/nndss/

25. U.S. Census Bureau. “Census tracts and block numbering areas.” U.S. Census Bureau, Geography Division, 19 Apr. 2000. Last accessed Feb. 12, 2013. http://www.census.gov/geo/www/cen_tract.html

26. U.S. Department of Health and Human Services. “Area Resource File (ARF): National County-level Health Resource Information Database.” Health Resources and Services Administration. Last accessed Feb. 12, 2013. http://arf.hrsa.gov/overview.htm

27. U.S. Census Bureau. “Statistical Brief: Poverty Areas.” U.S. Census Bureau, 31 Oct. 2011. Last accessed Feb. 12, 2013. http://www.census.gov/population/socdemo/statbriefs/povarea.html

28. Adler, NE and K Newman. Socioeconomic disparities in health: pathways and policies. Health Aff (Millwood). 2013;21(2):60-76.

29. Sanders, L.M., Federico, S., et al. (2009). “Literacy and child health: a systematic review.” Arch Pediatr Adolesc Med. 163(2):131-140.

30. National Center for Health Statistics. Health, United States, 2011: With special feature on socioeconomic status and health. Hyattsville, MD. 2012.

31. Newacheck, P. W., J. J. Stoddard, et al. (1998). "Health insurance and access to primary care for children." N Engl J Med 338(8): 513-519.

32. Wisk, LE and WP Witt. Predictors of delayed or forgone needed health care for families with children. Pediatrics. 2012;130:1027-1037.

33. Uwemedimo, OT, Findley, SE, Andres, R, Irigoyen, M, Stockwell, MS. Determinants of influenza vaccination among young children in an inner-city community. J Community Health 2012;37:663-672.

34. Rosenbaum, S. The patient protection and affordable care act: implications for public health policy and practice. Public Health Rep. 2011;126(1):130-135.

35. Mayer, D.K. (2013). “What does the affordable care act mean for you?” Clin J Oncol Nurs 17(1):13.

36. Peebles, P. J., R. Dhara, et al. (2011). "Influenza-associated mortality among children - United States: 2007-2008." Influenza Other Respi Viruses 5(1): 25-31.

37. Finelli, L., A. Fiore, et al. (2008). "Influenza-associated pediatric mortality in the United States: increase of Staphylococcus aureus coinfection." Pediatrics 122(4): 805-811.

38. Sachedina, N. and L. J. Donaldson (2010). "Paediatric mortality related to pandemic influenza A H1N1 infection in England: an observational population-based study." Lancet 376(9755): 1846-1852.

39. Viboud, C., P. Y. Boelle, et al. (2004). "Risk factors of influenza transmission in households." Br J Gen Pract 54(506): 684-689.

40. Piedra, P. A., M. J. Gaglani, et al. (2005). "Herd immunity in adults against influenza-related illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children." Vaccine 23(13): 1540-1548.

41. Piedra, P. A., M. J. Gaglani, et al. (2007). "Trivalent live attenuated intranasal influenza vaccine administered during the 2003-2004 influenza type A (H3N2) outbreak provided immediate, direct, and indirect protection in children." Pediatrics 120(3): e553-564.Rehkopf, D. H., L. T. Haughton, et al. (2006). "Monitoring socioeconomic disparities in death: comparing

individual-level education and area-based socioeconomic measures." Am J Public Health 96(12): 2135-2138.

42. Krieger, N., P. Waterman, et al. (2002). "Zip code caveat: bias due to spatiotemporal mismatches between zip codes and US census-defined geographic areas--the Public Health Disparities Geocoding Project." Am J Public Health 92(7): 1100-1102.

43. Krieger, N., J. T. Chen, et al. (2003). "Race/ethnicity, gender, and monitoring socioeconomic gradients in health: a comparison of area-based socioeconomic measures--the public health disparities geocoding project." Am J Public Health 93(10): 1655-1671.

44. Krieger, N., J. T. Chen, et al. (2006). "Race/ethnicity and changing US socioeconomic gradients in breast cancer incidence: California and Massachusetts, 1978-2002 (United States)." Cancer Causes Control 17(2): 217-226.

45. Chen, J. T., D. H. Rehkopf, et al. (2006). "Mapping and measuring social disparities in premature mortality: the impact of census tract poverty within and across Boston neighborhoods, 1999-2001." J Urban Health 83(6): 1063-1084.

46. Rehkopf, D.H., Haughton, L.T., et al. (2006). “Monitoring socioeconomic disparities in death: comparing individual-level education and area-based socioeconomic measures.” Am J Public Health. 96(12):2135-2138.

CHAPTER IV

Neighborhood Contribution to the Timing of Influenza Illness Onset and Progression to Death in Children

INTRODUCTION

Annual epidemics of influenza lead to infection of 15% to 42% of pre-school and school-aged children and result in an estimated 92 deaths per influenza season.[1-3] The direct medical cost of clinic visits and hospitalization amounts to more than 151 million dollars for children under 18 years of age.[4] The annual influenza burden does not equally impact all children. Individual level risk factors such as those with a high-risk medical condition, defined by the Advisory Committee on Immunization Practices (ACIP), disproportionately make up a higher percentage of children who are hospitalized and die from influenza.[5-10] Neighborhood level poverty has also been shown to disproportionately impact hospitalization rates for influenza in children, regardless of concurrent high-risk medical condition.[11]

Neighborhood characteristics have been used to help describe the burden of several respiratory diseases in addition to influenza, including RSV, pneumococcal disease, and tuberculosis.[12-15]The most examined outcome of influenza has been hospitalization.[16-19] Specific neighborhood factors assessed include poverty, crowding, education, and composite measures of deprivation.[16-19] Very few studies have examined the contribution of neighborhood factors to the risk of influenza infection and timing.[19-20]

In addressing the timing of influenza acquisition, studies have yielded disparate results with one study finding young children aged <4 years were more likely to have an earlier emergency department visit than older children aged 13-17 years and young adults aged 18-39 years and another study finding older children aged 10-19 years and young adults aged 20-29 years as the ages with an earliest diagnosis of laboratory-confirmed influenza.[21-22] The hypothesis that children are drivers of influenza transmission is supported by high clinical attack rates in children and high social contact rates in schools.[22-26] One study has examined this hypothesis by assessing the impact of the size of the pediatric population within zip codes on influenza outcome. This study found that the population of young children aged 3-4 years, in particular, was inversely associated with the timing of adult emergency department visits for fever and respiratory chief complaints, as a proxy for influenza.[20] While there is some evidence that children aged <4 years are the drivers of local influenza transmission, the existing studies have not accounted for other neighborhood factors such as poverty and crowding, which have been shown to influence the rate of influenza-related hospitalizations and could potentially increase the risk of influenza infection.[16-17,27]

Once influenza illness begins, it is unknown whether neighborhood factors contribute to the interval between onset and death in the same way they influence the risk of hospitalization and death. In studies of pediatric influenza mortality in the United States, the interval from influenza illness onset to death has been described to vary by individual factors. Specifically, differences in the interval from influenza illness onset to death have been reported across influenza seasons, by the presence of chronic medical conditions including neurologic disorders, and by the presence of a *Staphylococcus aureus* co-infection.[9,28-31] The interval from influenza illness onset to death has only been assessed using simple descriptive statistics and has not been

presented using multivariable methods to help explain the differences in the interval from influenza illness onset to death by incorporating individual and neighborhood characteristics that may impact the interval.

In this study, we examined whether neighborhood factors, including poverty, crowding, education, and access to medical care, modified the timing of influenza acquisition using illness onset date and the length of the interval from influenza illness onset to death, while controlling for individual-level factors such as age, influenza vaccination status, and ACIP-defined high-risk conditions. Our first hypothesis is that children from lower socioeconomic neighborhoods will experience an onset of influenza illness earlier in the epidemic curve than children from higher socioeconomic neighborhoods, among children who have ultimately died from influenza. Second, we hypothesized that the interval from influenza illness onset to death will be shorter for children from low socio-economic neighborhoods than for high socioeconomic neighborhoods. To address these questions, state surveillance data from influenza-associated pediatric mortality cases was linked to U.S. Census Bureau data via the census tract.

METHODS

Data Sources

Pediatric influenza mortality data. We contacted the State Epidemiologist in 23 states to request their state's influenza-associated pediatric mortality case data. We choose these states because twenty of the states had high cumulative incidence, comprising 80% of all pediatric influenza deaths by the end of the 2010-2011 influenza season and three additional states with low case counts were approached to be more broadly representative of the United States population based on geography and incidence. Of these 23 approached, 18 State Epidemiologists

(78%) agreed to participate. These 18 participating states included Arizona, California, Iowa, Illinois, Michigan, Minnesota, New Mexico, New York (including the New York City Health Department), North Carolina, Ohio, Oklahoma, Pennsylvania, South Carolina, South Dakota, Tennessee, Virginia, Washington, and Wisconsin. Three of these states represent 43% of the cases in our sample reported to the Centers for Disease Control (CDC) from the 2004-2005 through the 2010-2011 influenza seasons and the remaining 15 states represent 57% of cases reported to CDC during the same interval. The beginning of the reporting period, the 2004-2005 influenza season, was chosen because it was the first year influenza-associated pediatric mortality became nationally reportable.[32] Inclusion criteria were defined as a child <18 years of age residing in a participating state who died from influenza or its complications with laboratory evidence of influenza virus infection with no recovery to baseline, according to the Centers for Disease Control/Council for State and Territorial Epidemiologist influenza-associated pediatric case definition, and reported to a state health department between October 2004 and April 2011.[33]

Individual race and ethnicity data were collected on all pediatric influenza deaths and categorized as non-Hispanic White, non-Hispanic Black, non-Hispanic American Indian, non-Hispanic Asian, and Hispanic ethnicity of any race. Age was categorized as <1 year old, 1-4 years old, 5-11 years old, and 12-17 years old. Seasonal influenza vaccination status was available for 307 (74%) of the 416 pediatric influenza deaths. Data on the receipt of monovalent H1N1 vaccine during the 2009-2010 influenza season showed only 3 (1%) children were vaccinated out of the 187 pediatric influenza deaths reported during the season so receipt of monovalent H1N1 vaccination was not included in this analysis. A dichotomous variable was created for the presence of 1 or more ACIP-defined high-risk conditions: neurological disorder,

pulmonary disease, cardiac disease, renal disease, hemoglobinopathy, metabolic or endocrine disorders, immunosuppression, cancer or hematologic malignancy, obesity, or congenital musculoskeletal condition. ACIP-defined high risk conditions were also evaluated individually. Neurologic disorders included neurodevelopmental disorders (e.g., cerebral palsy, moderate/severe developmental delay, and other congenital or chronic neurologic disorders), seizure disorders (e.g., epilepsy), and neuromuscular disorders (e.g., muscular dystrophy, spinal muscular atrophy, and mitochondrial disorders). Pulmonary diseases included broncho-pulmonary dysplasia, restrictive lung disease, pulmonary hypertension, and cystic fibrosis; asthma was excluded. Renal diseases included adrenal insufficiency and hydronephrosis. Metabolic/endocrine disorders included diabetes, maple syrup urine disease, Zellweger syndrome, and dysmetabolic syndrome; mitochondrial disorders were excluded. The immunosuppression category included steroid use, chemotherapy, and radiation therapy. Cancer/hematologic malignancy included leukemia, metastatic osteosarcoma, alveolar rhabdomyosarcoma, and brain stem tumor with metastasis. Obesity was defined as a body mass index at or above the 95^{th} percentile for children of the same age and sex. Congenital musculoskeletal conditions included scoliosis, arthrogyposis, and Pierre-Robin syndrome.

In constructing our final dataset for analysis, three data sources were added to the pediatric influenza mortality data. First, influenza-associated pediatric mortality data were linked, using the census tract, to the 2000 Decennial Census. Next, influenza-associated pediatric mortality data were linked, via the county, to the 2011-2012 Areas Resource File (ARF). Finally, influenza-associated pediatric mortality data were linked to the CDC's viral surveillance data using influenza season, region, and week of laboratory test.

Census Data. The 2000 Decennial Census at the tract level was used as the level of aggregation for the neighborhood-level characteristics. The census tract is defined as a county subdivision with "…between 2,500 and 8,000 persons and, when first delineated, are designed to be homogeneous with respect to population characteristics, economic status, and living conditions."[34] Census tract data in this analysis included: overcrowding, defined as the percentage of households in a census tract with greater than 1.01 people per room; severe overcrowding, defined as the percentage of households in a census tract with greater than 1.51 people per room; the percentage of individuals living in an urban area; and average household size. Census tract socio-demographic characteristics included median household income, the percentage of households living below the federal poverty line, the percentage of individuals with a high school or college degree, the percentage of unemployed individuals, and the percentage of persons of White or Black race. The percentage of households living below the federal poverty line was defined in the 2000 Census as income less than $17,050 for a family of four.

Areas Resource File (ARF) Data. The Health Resources and Services Administration (HRSA) ARF contains over 6,000 county variables on "health facilities, health professions, measures of resource scarcity, health status, economic activity, health training programs, and socioeconomic and environmental characteristics."[35] Four county variables were included in the analysis: the number of hospitals in a county, the number of primary care physicians in a county, the percentage of children under 19 years of age without health insurance, and a whole, part, or none designation of the county as a Health Professional Shortage Area (HPSA). HPSAs are designated for areas with less than 1 primary care provider per 3,500 population or less than 1

primary care provider per 3,000 population if there are unusually high needs or insufficient existing capacity in primary care services.[36]

Epidemic timing. CDC aggregated viral surveillance data, publicly-available from the FluView Interactive site, were obtained by influenza season, Health and Human Services (HHS) Region, and week of laboratory test.[37] Viral surveillance data included the week during which specimens were collected, the total number of specimens collected, the total number of positive specimens tested, percentage of specimens that were positive, and further typing and subtyping information on the specimens that tested positive. The HHS Regions divide the United States into 10 distinct areas as shown in Figure 4.1.

Four periods describing the epidemic curve were created based on the week in which the incidence of laboratory-confirmed influenza peaked: early, middle, late, and inter-epidemic. The peak in influenza incidence was identified as the week when the total number of positive influenza specimens was greatest during each influenza season. Because the spread of influenza differs by geography, localized peaks in influenza incidence were determined for each HHS region.[38-39] The middle epidemic period was defined as the three week period (week of peak incidence plus or minus 1 week) centered on the week of peak incidence. The three weeks immediately preceding the middle epidemic period were designated as the early epidemic period. The three weeks immediately following the middle epidemic period were designated as the late epidemic period. The remainder of an influenza season was designated as the inter-epidemic period. The date of influenza illness onset of the pediatric influenza deaths was plotted against the epidemic curve by influenza season and HHS region in order to categorize the onset dates into the four epidemic curve periods. The 2009-2010 influenza season is the one exception where

two influenza laboratory-confirmed peak weeks were identified in a single season. The two-peak season occurred in 8 of the 10 HHS regions: Regions 1 to 6 and Regions 9 and 10.

Timing to influenza illness onset was also examined in number of days, starting from the week when five laboratory-confirmed influenza cases tested positive in a community, termed as an "increase in laboratory-confirmed influenza tests" in a localized area, to pediatric influenza illness onset. Ten localized areas were created across the U.S. according to the HHS regions and CDC viral surveillance data were used to determine an increased number of cases. Because two epidemic peaks, spring/summer and fall/winter, were observed in 8 of the 10 HHS regions during the 2009-2010 influenza season and there was sustained influenza activity between the two peaks unlike the six other influenza seasons in our data, the 2009-2010 influenza season was excluded from the linear regression analysis.

Interval from Onset to Death. The interval from influenza illness onset to death was calculated as the difference, in days, between the onset and death dates for the 416 pediatric influenza deaths. The date of onset was reported by a child's caregiver at the time of medical encounter or interview with public health officials and represents the earliest date influenza symptoms were identified.

The study was designated as not regulated by the University of Michigan Institutional Review Board (IRB) due to the use of data on deceased individuals [HUM00034214]. Reliance on the IRB determination and, as necessary, additional state IRB approval was received prior to analysis.

Statistical Analysis

Epidemic timing. The outcome was the timing of influenza illness onset in the epidemic curve period for pediatric influenza deaths. Descriptive statistics were calculated for neighborhood characteristics, the main predictor. Multinomial logistic regression models produced odds ratios and 95% confidence interval for the likelihood of an influenza illness onset during the middle versus early epidemic period and late versus early epidemic period given a neighborhood factor. The global Wald test identified variables significantly associated with the outcome in the unadjusted analysis.

Linear regression analyses were performed with the outcome as days between an increase in laboratory-confirmed influenza tests and illness onset. Neighborhood factors such as poverty, educational attainment, and area-level insurance status were the main predictors. Plots of variables associated with the outcome in the adjusted model are presented in Figure 4.2. Both the best subset method and backward selection identified the covariates retained in the adjusted model. Two plots, one of the distribution of the residuals and a second of the studentized residuals against their influence showed a good model fit. (Figure 4.3)

Interval from Onset to Death. Interval from influenza illness onset to death in days was the outcome. Descriptive statistics were calculated for neighborhood factors, the main predictor, and included the mean and standard deviation for individual and neighborhood variables. P-values for differences in mean intervals were calculated using the GLM procedure in SAS. Negative binomial regression models were used to calculate the rate of increase in the interval from influenza illness onset to death for pediatric influenza deaths by neighborhood measures. Neighborhood and individual level factors considered confounders either *a priori* or during the unadjusted analysis were included in the adjusted model. Findings were reported as incidence

rate ratios and 95% confidence interval. Likelihood ratio tests were used during model development.

Model Diagnostics. For the negative binomial regression models, the Pearson chi-square statistic, a goodness of fit measure, was obtained from the negative binomial models and evaluated for over-dispersion (>1.0). A graph of the observed proportions in the data along with the Poisson and negative binomial probabilities for a count variable were assessed to verify our choice in the count model. (Figure 4.4) Standardized Pearson residuals were plotted to examine the relationship to the predicted values. (Figure 4.5) SAS 9.2 and STATA 12 were used in the analysis.

RESULTS

Study sample. A total of 455 pediatric influenza deaths were reported to public health officials in the 18 participating states during the study period, October 2004 through April 2011. In relation to the United States population, the sample was similar with children <18 years of age comprising 28.6% for both the sample and nationally; percent White race was 73.8% in the sample and 75.1% nationally, percent Black race was 11.4% in the sample and 12.3% nationally, and the percent Hispanic was 13.2% in the sample and 12.5% nationally. Of the 455 deaths reported, 416 (91%) contained an illness onset date, when influenza symptoms were first identified, for inclusion in this analysis; 39 (9%) of deaths were excluded from analysis for lack of an illness onset date. Geo-coding information was available for 326 (78%) of the 416 pediatric influenza deaths in order to link with the U.S. Census Bureau census tracts to construct the neighborhood variables. The 90 (22%) pediatric influenza deaths lacking census tract information were excluded from the multivariable analyses.

Neighborhood factors. Neighborhood characteristics at the census tract and county levels are shown in Table 4.1 for neighborhoods with a pediatric influenza death. For the 326 neighborhoods in which a pediatric influenza death occurred, the mean household size was 2.8. Neighborhoods had a mean of 84% of residents living in urban areas, 68% of residents indicated their race as White and 15% of residents indicated their race as Black. Mean unemployment in neighborhoods with a pediatric influenza death was 4% and the mean graduation rate for high school and college was 77% and 21%, respectively. Median household income was $43,418 and the mean percentage of households living below the federal poverty line was 14%. The mean percentages of neighborhoods with crowded and severely crowded living conditions were 9% and 2%, respectively. For neighborhoods with a pediatric influenza death, the mean number of primary care doctors per 100,000 population was 1,238 and the mean number of hospitals per 100,000 population was 20. A total of 280 (86%) pediatric influenza deaths occurred in counties with a Health Provider Shortage Area designation covering the whole (n=180, 55%) or part (n=100, 31%) of the county, whereas just 47 (14%) of death occurred in counties with no HPSA designation.

Individual factors. Of the 416 pediatric influenza deaths, most were identified as White (42%) followed by Hispanic (25%), Black (18%), Asian (6%), American Indian (3%), and other/unknown (6%). A breakdown of deaths by age categories showed 73 (18%) were <1 year old, 73 (18%) were 1-4 years old, 156 (38%) were 5-11 years old, and 110 (27%) were 12-17 years old. Males had slightly more influenza deaths reported, 230 (55%) versus females with 185 (45%) deaths; 1 death lacked a sex identifier. Of the 307 pediatric influenza deaths for whom seasonal influenza vaccination status is known, 61 (20%) were vaccinated; 8 (12%) children aged <1 year, 9 (14%) children aged 1-4 years, 23 (21%) children aged 5-12 years, and 26 (30%)

children aged 13-17 years received an influenza vaccination. ACIP-defined high-risk conditions were present in 210 (50%) of the pediatric influenza deaths with history of any neurologic disorder being most prevalent, characterizing 110 (26%) of the deaths. Counts and percentages of the ACIP-defined high-risk conditions are out of the 416 total deaths since conditions are not mutually exclusive. Neurodevelopmental disorder was most frequent of the neurological disorders with 72 (17%) deaths followed by seizure disorder with 58 (14%) deaths and neuromuscular disorder with 46 (11%) deaths. Other ACIP-high risk conditions included asthma with 60 (14%) deaths, pulmonary disease with 49 (12%) deaths, and cardiac disease with 42 (10%) deaths. Conditions reported less frequently with pediatric influenza deaths included immunosuppressive conditions (26 deaths), metabolic/endocrine disorders (21), congenital musculoskeletal disorders (15), renal diseases (13), obesity (9), cancer/hematologic malignancy (7), and hemoglobinopathy (4). A bacterial co-infection or viral co-infection was identified in 75 (18%) and 15 (4%) pediatric influenza deaths, respectively. Complications were common among pediatric influenza deaths with 272 (65%) reporting at least one complication; 120 (29%) reported a single complication, 96 (23%) reported two complications, 40 (10%) reported three complications, and 16 (4%) reported four or more complications.

Epidemic timing. Influenza illness onset for pediatric influenza deaths occurred early in the epidemic for 79 (19%) cases, in the middle of the epidemic for 138 (33%) cases, late in the epidemic for 74 (18%) cases, and during the inter-epidemic period for 125 (30%) cases. (Table 4.1) The inter-epidemic period comprises both the time from the beginning of the influenza season in October to the start of the early epidemic period and the time after the late epidemic period. Due to the lack of distinction in the definition of the inter-epidemic period, i.e., including

the weeks both before and after each season's influenza epidemic, results from this period can't be interpreted with any reliability.

Most of the neighborhood factors were similar across the epidemic periods. (Table 4.1) Neighborhoods with a higher mean percentage of high school graduates had influenza illness onset later in the epidemic (80%) compared to early (78%) or middle (78%) in the epidemic. A higher mean percentage of severely crowded neighborhoods was found among those children with early illness onset (2.1%) compared to middle (1.3%) or late (1.7%) onset. The mean percentage of children lacking health insurance was marginally significant with a greater percentage of illness onsets occurring late (9.3%) in the epidemic versus early (8.6%) or middle (8.5%) in the epidemic.

The timing of influenza illness onset for pediatric influenza deaths was similarly distributed across the epidemic periods for all race/ethnic groups with the exception of American Indians. (Table 4.1) American Indians had a higher percentage of illness onsets occurring late (42%) in the epidemic compared to Whites (19%), Blacks (17%), Hispanics (17%), and Asians (22%), although this difference was not statistically significant. Illness onset for males was slightly earlier than for females with 20% of males versus 18% of females with early illness onset, 35% of males versus 31% of females with illness onset in the middle of the epidemic, and 15% of males versus 21% of females with late illness onset. For illness onset by age, no trend was observed except that more children had illness onset in the middle of the epidemic.

Of pediatric influenza deaths, receipt of influenza vaccination decreased the percentage with onset dates observed in the early (8% vaccinated; 21% unvaccinated) compared to the middle (43% vaccinated; 32% unvaccinated) and late (20% vaccinated; 15% unvaccinated)

epidemic periods. (Table 4.1) Presence of one or more ACIP-defined high-risk condition was not associated with the timing of onset dates for pediatric influenza deaths. The majority of pediatric influenza deaths with one or more ACIP-defined high-risk conditions had onset dates occurring during the middle (32%) epidemic period than the early (17%) or late (18%) epidemic period. Of the ACIP-defined high-risk conditions, none were associated with the timing of influenza illness onset dates for pediatric influenza deaths: neurodevelopmental disorder, seizure disorder, neuromuscular disorder, pulmonary disease, asthma, or cardiac disease. Differences in the number of pediatric influenza deaths with onset dates in the early, middle, and late epidemic periods could not be assessed for statistical significance due to small cell counts for several ACIP-defined high-risk conditions including renal disease (n=13), sickle cell anemia (n=4), metabolic/endocrine disorder (n=21), immunosuppressive conditions (n=26), cancer/hematologic malignancy (n=7), obesity (n=9), and congenital musculoskeletal disorder (n=15).

In unadjusted multinomial logistic regression models, the percentage of high school graduates comparing middle versus early (OR=0.99, 95% CI [0.80, 1.22]) and late versus early (OR=1.12, 95% CI [0.87, 1.45]) illness onset, the percentage of severely crowded neighborhoods comparing middle versus early (OR=0.64, 95% CI [0.31, 1.30]) and late versus early (OR=0.85, 95% CI [0.41, 1.76]) illness onset, and the percentage of children without health insurance comparing middle versus early (OR=0.99, 95% CI [0.90, 1.08]) and late versus early (OR=1.05, 95% CI [0.95, 1.16]) illness onset were significantly associated with the epidemic timing of illness onset using a global Wald test. However, none of the area-level factors, high school graduates, severe crowding, or children lacking health insurance, predicted the timing of illness onset of pediatric influenza deaths. No other neighborhood factors and no individual factors were

associated with the timing of influenza illness onset of pediatric influenza deaths. No adjusted analysis was conducted based on the findings in the unadjusted analyses.

The time from an increase in laboratory-confirmed influenza tests in a locality to influenza illness onset for children aged 6-23 months was a mean of 118 days, for 24-59 month-olds the mean was 108 days, for children 5-12 years the mean was 142 days, and for 13-17 year-olds was a mean of 166 days. (Figure 4.2) For children with a high-risk condition, only presence of pulmonary disease or an immunosuppressive condition were significantly associated with the time from an increase in laboratory-confirmed influenza tests to illness onset. For children with pulmonary disease compared to no disease, the mean number of days was 229 compared to 123. For children with an immunosuppressive condition versus no condition, the mean number of days was 205 versus 132. The continuous county-level factor, percent children without health insurance, was examined in simple linear regression and a 1% increase was positively associated with the time from an increase in laboratory-confirmed influenza tests to influenza illness onset ($p<0.0001$), increasing the time by 9.54 days.

In the adjusted linear regression analysis, age as a continuous predictor with a one year increase showed an additional 2.54 days from an increase in laboratory-confirmed influenza tests to influenza illness onset. (Table 4.2) An age squared term was added to the adjusted model in addition to age, but the age squared term was not statistically significant. Two high-risk conditions increased the time from an increase in laboratory-confirmed influenza tests to influenza illness onset with presence of a pulmonary disease showing an increase of 68.76 days and presence of immunosuppression with an increase of 86.22 days. For a 1% increase in the percent children without health insurance in a county, the mean number of days from an increase in laboratory-confirmed influenza tests to influenza illness onset increased 7.47 days.

Days from onset to death. The mean interval from influenza illness onset to death for all pediatric influenza deaths was 10.9 days. (Table 4.1) A child's age was associated with the influenza illness onset to death interval. The mean interval for children <1 year of age was 9.6 days, children 1-4 years old was 10.6 days, children 5-11 years old was 8.3 days, and children 12-17 years old was 15.1 days. The presence of 1 or more ACIP-defined high-risk medical condition was significantly associated with increasing the mean interval from influenza illness onset to death from 7.4 days to 14.3 days. The specific ACIP-defined high-risk conditions associated with influenza illness onset to death are shown in Table 4.3 and include any neurologic disorder or neurodevelopmental disorder, pulmonary disease, cardiac disease, immunosuppressive condition, and cancer/hematologic malignancy. The presence of 1 or more complication resulting from influenza infection was also associated with increasing the influenza illness onset to death interval from 5.3 days to 13.8 days.

In unadjusted negative binomial regression models, the neighborhood factors associated with the mean interval from influenza illness onset to death included the percentage of Black raced residents and the number of hospitals per 100,000 population in a county. Neighborhoods with more (>15%) Black residents had a 45% shorter mean interval compared to fewer (<5%) Black residents. Increase of a single hospital per 100,000 population was associated with a 5% increase in the mean interval from influenza illness onset to death. Individual factors associated with the mean interval included age, neurodevelopmental disorder, seizure disorder, pulmonary disease, immunosuppressive condition, and the number of complications. By age, children <1 year old had a 40% shorter mean interval, children 1-4 years old had a 28% shorter mean interval, and children 5-11 years had a 43% shorter interval than compared to children 12-17 years of age. Presence of 1 or more ACIP-defined high-risk medical condition increased the

mean interval from influenza illness onset to death by 62%. Specifically, neurodevelopmental disorders were associated with a 46% longer mean interval, seizure disorders with a 41% longer mean interval, pulmonary disease with a 104% longer mean interval, and immunosuppressive conditions with a 101% longer mean interval from influenza illness onset to death. The number of complications resulting from influenza illness was also associated with the mean interval and an increase of one complication resulted in a 40% longer mean interval.

The adjusted model included all significant associations from the unadjusted models and included race/ethnicity *a priori*. The association with the neighborhood factors was attenuated with the percentage of Black residents still significantly associated with the mean interval. Comparing neighborhoods with more (>15%) Black residents versus fewer (<5%) Black residents, the mean interval from influenza illness onset to death was 37% shorter. A 37% shorter mean interval is equivalent to a decrease in the mean interval of 3.8 days. The findings by age categories were attenuated with children <1 year old having a 5% shorter mean interval (-0.5 days), children 1-4 years having a 6% shorter interval (-0.6 days), and children 5-11 years old having a 33% shorter mean interval (-3.4 days) than children 12-17 years of age. Of the ACIP-defined high-risk conditions retaining significance in the association with the mean interval from influenza illness onset to death, pulmonary disease had a 76% longer mean interval (+7.9 days) and immunosuppressive conditions had a 109% longer mean interval (+11.3 days). The number of complications was also significantly associated with the mean interval in the adjusted analysis. An increase of one in the number of complications had a 42% greater mean interval (+4.4 days).

CONCLUSIONS

This study found that a higher percentage of Black race residents within census tracts was associated with a shorter interval between influenza onset to time of death. In addition, we found that an increase in the number of hospitals per 100,000 county population was associated with a longer interval between influenza illness onset to death. However, after adjusting for individual risk factors for influenza mortality, only the percentage of Black residents was statistically significantly associated with the interval from influenza illness onset to death. The findings from this study, the first to incorporate neighborhood factors to address the interval from influenza illness onset to death, show a newly-recognized disparity for children living in neighborhoods with a high concentration of Black residents had a shorter mean interval to death than children from neighborhoods with a lower concentration of Black residents. These findings have a number of implications, including the possibility that racial segregation or discrimination may impact access to care, time to seek care, and treatment, regardless of availability of hospitals per county population.

Our findings differed between the two analyses of influenza illness onset. Using linear regression, child's age, the chronic medical conditions pulmonary disease and immunosuppressive condition, and the county-level percentage of children without insurance were significantly associated with the number of days from an increase in laboratory-confirmed influenza tests to pediatric influenza illness onset. In comparison, using multinomial logistic regression none of the individual- or neighborhood-level factors examined were associated with early versus middle or late illness onset. This may be due to several factors including the methodological approach and the number of cases included in the analyses. Across influenza seasons, the epidemic peak can vary by month and within a single season the epidemic peak can vary by 2-5 weeks based on geographic location.[39-40] It is necessary to account for the changing

transmission burden and in the linear regression analysis, the number of days from an increase in laboratory-confirmed influenza tests to illness onset was used. This approach differed from the multinomial logistic regression analysis which accounted for the changing transmission burden by examining only the nine weeks during the peak of the influenza epidemic curve. The linear regression analysis allowed us to more fully discuss risk of illness onset across the influenza season rather than just the weeks surrounding the influenza epidemic curve.

In the multinomial analysis of the timing to influenza illness onset, no neighborhood or individual factors predicted middle or late versus early illness onset. This is not entirely surprising given our small sample size (n=416) and specific population of pediatric influenza deaths. Other studies have relied on much larger samples of laboratory-confirmed influenza cases or emergency department visits on individuals of all ages.[20-22] Another factor that may have contributed to our null findings is that the methods employed differ from those used in other studies. Peak incidence was chosen to represent transmission burden in a locality while other studies have used the epidemic midpoint method, i.e. the midpoint of the total positive influenza tests for the influenza season is designated at the center of the epidemic curve, or Pearson cross-correlation coefficient method, i.e. the center of the epidemic curve is determined by the highest Pearson correlation coefficient between two sets of data, to compare epidemic curves. However, our sample size of pediatric influenza deaths was not sufficiently large to use the Pearson cross-correlation coefficient method and when using the epidemic midpoint method, no statistically significant results were obtained for the timing to influenza illness onset. (data not shown)

In the linear regression analysis of the timing to influenza illness onset, increasing age of a child by a single year delayed illness onset by 3 days. This is may be due to the naïve immune

system in young children gradually increasing immune functioning in the body's ability to respond to influenza virus exposure and/or infection. Two high-risk medical conditions, pulmonary disease and immunosuppression, were associated with a greater number of days to illness onset, with 69 days and 86 days delay of illness onset, respectively. While this result seems counter-intuitive to findings indicating children with these conditions are at higher risk of infection and complication, part of the delay to illness onset may be explained by risk messaging to parents that is reinforced during routine visits for the child's medical condition.[41-42] The finding may also be explained by vigilance on the part of parents who institute disease prevention measures such as vaccinating family members to limit household introduction of influenza and emphasizing hand hygiene (including alcohol-based hand gel) at home and at school. There is also evidence that school-based educational interventions are important in helping children manage their chronic illness.[43-44] Research is needed that examines the education provided to parents and children on managing their chronic disease, including risk reduction measures, to elucidate what is underlying our findings.

The finding that a 1% increase in the county-level percentage of children without health insurance delays influenza illness onset by 7 days could be partly explained by recall bias of the onset date for the child's illness by parents. It can be hypothesized that a parent presenting a child for medical care who is severely ill may underestimate the length of time the child has been ill. The misreporting of illness onset could have occurred because of parental anxiety, stress, and guilt over not seeking care earlier in the illness or the societal pressure of appropriate care-seeking behavior to report the child's illness as being more proximal the healthcare visit.[45] Because children with no insurance have been shown more likely to have no medical home for continuous care and more likely to delay presentation of an illness because of no preventive care,

there would be no medical records to corroborate illness onset in these children during the public health investigation.[46-49] Future studies could use healthcare visit data in the time before a child's death to examine differences in healthcare utilization for children with and without current health insurance. There are implications for the Affordable Care Act because expanding health insurance coverage could help children receive influenza vaccination to prevent influenza and allow ill children to visit their healthcare provider in the early stages of their influenza illness.[50]

The disparity in the interval from influenza illness onset to death for neighborhoods with a high concentration of Black residents compared to neighborhoods with a low concentration of Black residents may be explained by inequalities in receiving appropriate treatment including antiviral medications or hospitalization.[51] Increased clinic and emergency department visits have been observed in minority populations with respiratory illness due to care-seeking behaviors.[52-53] Treatment inequalities may have blunted any benefit of the increased healthcare usage by diminishing the quality of any medical care received, resulting in more adverse health outcomes for Blacks and others living in predominately Black neighborhoods. An increase in the number of hospitals per 100,000 population was associated with an increase in the mean interval from influenza illness onset to death in the unadjusted analysis. Presence of a hospital in a community decreases the physical barrier of medical access but does not alter the need for primary care physicians and clinics, which may partly explain the marginally significant association of the number of primary care physicians per 100,000 population with the mean interval from influenza illness onset to death. The association between the number of hospitals and mean interval from influenza illness onset to death did not persist in the adjusted analysis. In addressing neighborhood factors, our intended purpose was to include a number of neighborhood factors in order to identify modifiable neighborhood risk factors that could be the focus for interventions or

policy. We were unable to find an association with the potentially modifiable factors of neighborhood poverty, education, crowding, or medical access factors, suggesting that other social determinants, such as segregation or discrimination may account for the findings regarding race. Further studies examining the impact of segregation and discrimination on influenza onset and time to death are warranted. It is also possible that our measure of medical access was more of a proxy for access to care than actual individual level access to care, such as health insurance. It is noteworthy that 86% of the pediatric influenza deaths occurred in a county with an HPSA designation of a whole or partial shortage of primary care physicians. In comparison, states in our sample of pediatric influenza deaths had an HPSA designation for 75% of counties (whole, 45%; part, 30%). Study findings may be biased toward a null effect, for at least the HPSA measure, because of the disparity of county designations in our sample. The Affordable Care Act aims to increase health insurance coverage and thereby improve access to primary care services with the expectation of diminishing adverse health effects, including influenza mortality, and improving overall health.[50,54] Implementation of the Affordable Care Act will expand delivery of medical care to populations previously uninsured, such as race/ethnic minorities, those with chronic medical conditions previously denied coverage, and low-income households. The disparity in the interval from influenza illness onset to death for neighborhoods with a high percentage of Black race residents could theoretically be reduced if the Affordable Care Act enhances medical monitoring for children from these at-risk neighborhoods through expansions in healthcare delivery. The Affordable Care Act also aims to enlarge primary care professional recruitment programs and increase the number community health centers. However, findings from our study showed that these activities may only have limited effects on the health of Americans in relation to pediatric influenza since the number of hospitals, number of primary

care physicians, and county designation as a health provider shortage area were not associated with the duration from influenza illness onset to death.[50]

Among individual factors, the finding that children aged 5-11 years had a shorter mean interval from influenza onset to death than 12-17 year olds deserves further consideration. The mean intervals of children aged <1 years, 1-4 years, and 12-17 years were similar and only 5-11 year olds were observed with a shorter mean interval (-3.4 days). We lacked data to assess several hypotheses, i.e. time from illness onset to medical encounter, time from medical encounter to hospitalization, or number of medical visits in the past year that may have explained the shorter mean interval for 5-11 year olds. Our finding that children with the ACIP-defined high-risk conditions pulmonary disease and immunosuppression had a longer mean interval from influenza illness onset to death was not surprising. Children with these conditions typically require careful monitoring and timely interventions such as hospitalization and early antiviral treatment.[55-57] The use of interventions in children with ACIP-defined high risk conditions was supported by Blanton et al. where their study found that the mean interval from influenza illness onset to death was 8 days for children with any neurologic disorder and 4 days with no high-risk condition.[30] The study by Blanton et al. also found children with neurologic conditions were more likely to die in the hospital than at home. We hypothesized that being in a hospital decreased the time to medical intervention following respiratory failure compared to children in the home and that early intervention, including mechanical ventilation and extracorporeal membrane oxygenation, either increased the interval from influenza illness onset to death or prevented death. The longer duration from onset to death for children with pulmonary disease or immunosuppression found in our analysis indicates these high-risk conditions may theoretically lead to enhanced monitoring or early intervention more often than children with neurological

conditions. The number of complications resulting from an influenza illness was also associated with the mean duration from influenza illness onset to death. Development of pneumonia, acute respiratory distress syndrome, croup, seizures, bronchiolitis, encephalitis, Reye syndrome, shock, sepsis, and myocarditis was included in the list of complications. Hospitalization following development of an influenza complication is likely as the complication, e.g., pneumonia, would require enhanced medical management including antibiotic treatment, antiviral treatment, and/or mechanical ventilation. Hospitalization for complications likely increased the interval from influenza illness onset to death through the enhanced medical management.

Limitations

Our findings are limited by several factors including the potential for reporting bias across states. The case definition for influenza-associated pediatric mortality required a positive laboratory test for influenza and this may have been a barrier to diagnosis due to a low prevalence of testing for influenza by clinicians. If a clinician did test for influenza, a rapid antigen tests provides the quickest results, but the rapid antigen tests are known for low sensitivity and specificity for detecting influenza. If an influenza test was positive and the child died, it was incumbent on the clinician and/or hospital to report the diagnosis to public health. Differences across states in the likelihood of a clinician to test a child for influenza or the type of test performed (polymerase chain reaction [PCR] versus enzyme-linked immunoassay [EIA] test) or report an influenza-associated pediatric death would bias our study sample. Specific to the timing of influenza illness onset, we were unable to account for differences in the circulating influenza subtypes when identifying the peak incidence. Several studies have rectified the difference in circulating strains by focusing on only the influenza seasons in which a single strain

dominated. This was not possible with our data because of our small sample size and limit of seven years of data since influenza-associated pediatric mortality first became reportable.

For assessing the interval from influenza illness onset to death, we were unable to account for three medical interventions the pediatric influenza deaths may have received which could impact the mean interval from influenza illness onset to death, namely hospitalization, antiviral treatment, and antibiotic treatment. Capture of antibiotics and antivirals prescribed after influenza illness onset was limited prior to the 2010-2011 influenza season and antibiotic and antiviral use was more likely in hospitalized children according to Blanton et al.[30] Children with an ACIP-defined high-risk condition had increased odds for a hospital stay greater than 6 days compared to children without a high-risk condition.[5] Without accounting for hospitalization in our analysis, part of the findings of a longer mean interval from influenza onset to death among children with the ACIP-defined high-risk conditions pulmonary disease and immunosuppression may have been due to receipt of antibiotic treatment, antiviral treatment, and/or hospitalization.

The use of census-derived measures in our analysis of neighborhoods was a proxy for more specific social and physical features that were causatively related to our study of influenza illness onset and interval to death of the pediatric influenza deaths. Despite this limitation, our findings highlighted at-risk neighborhoods to allow for more focused investigations. County-level neighborhood factors pertaining to medical care access were included to more specifically address proximal causes of influenza illness onset and interval to death. Our measure of medical access was only a surrogate for true access to medical care. For example, the number of hospitals per 100,000 county population does not differentiate between hospitals with no pediatrics department and those with pediatrics departments and pediatric intensive care units with highly experienced professionals. A more accurate measure might be the number of hospitals with a

pediatrics department or number of pediatricians with a subspecialty, such as pediatric critical care medicine, pediatric pulmonology, or pediatric cardiology. Future studies should assess various measures of access to investigate whether multiple facets of access, from the individual to the neighborhood, explain the disparity in the interval influenza from illness onset to death we observed for predominantly Black neighborhoods.

Strengths

Our use of neighborhood characteristics of pediatric influenza deaths represented the first time these factors have been used to describe the timing to influenza illness onset and interval from illness onset to death. In the timing to influenza illness onset analyses, we showed how different methods produced varied results. With the multinomial logistic regression analysis finding no association with the timing to illness onset but the linear regression analysis identifying child's age, the high-risk medical conditions pulmonary disease and immunosuppression, and the county-level factor percentage of children <19 years old without health insurance as being associated with the timing to illness onset. In the interval from influenza illness onset to death analysis, we were able to examine neighborhood factors as defined by census tracts and, using multivariable models, include other factors identified to modify the interval from influenza illness onset to death, including presence of high-risk medical conditions and bacterial co-infections. Use of existing public health surveillance data with a uniform case definition for this retrospective cohort study increased the internal validity of our results by increasing the likelihood that case investigations and determinations were conducted similarly across all participating states.

Conclusion

County-level percentage of children without health insurance was associated with the number of days from an increase in laboratory-confirmed influenza tests to influenza illness onset. Increasing the percentage of children without health insurance delayed the onset of influenza illness. Our finding may be subject to recall bias in the reporting of illness onset for children without health insurance. The Affordable Care Act is designed to increase health insurance coverage and may improve outcomes for severely ill children with influenza by increasing medical care access and decreasing the time to seeking care. An investigation of healthcare utilization preceding pediatric influenza deaths and whether children without health insurance delay seeking healthcare would help explain the process underlying the association between the percentage of children without health insurance in a county and the time to influenza illness onset.

Census tract-level percentage of Black residents was predictive of the mean interval from influenza illness onset to death. Having a higher percentage of Black residents in a census tract was associated with a shorter interval from influenza illness onset to death. This neighborhood association highlights a previously unrecognized disparity in pediatric influenza deaths in which children living in neighborhoods with a high concentration of Black residents are adversely affected. Our research suggests that other factors that we were unable to account for, such as individual level access to care, segregation, or discrimination may impact on the survival time for children with serious influenza illness. The Affordable Care Act offers a potential solution by increasing healthcare coverage and thereby access to quality medical care to individuals from neighborhoods with a high concentration of Black residents. Further evaluation of these findings is warranted and should include studies of segregation, discrimination, and access to care as it

related to the interval from influenza illness onset to clinical endpoints like hospitalization, admission to the intensive care unit, or antiviral treatment.

Figure 4.1. Map of the United States comprising 10 Health and Human Services Regions

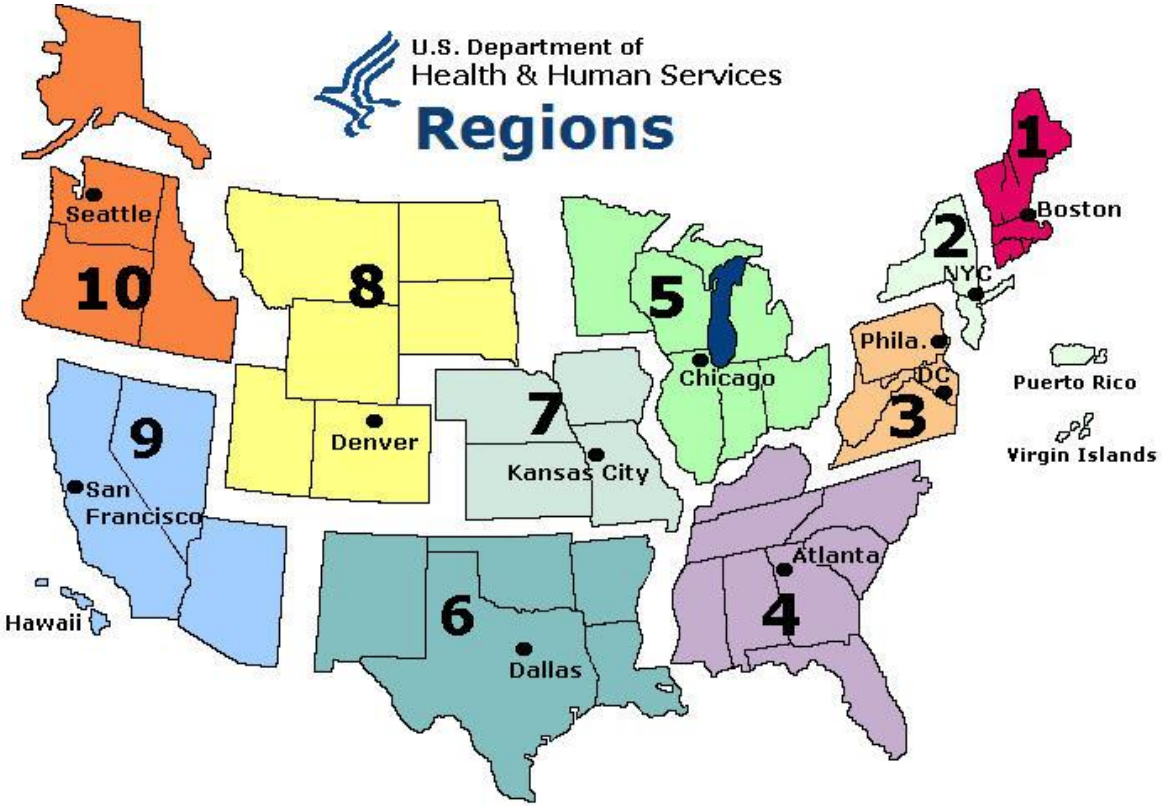


Figure 4.2. Individual and Neighborhood factors associated with the number of days to illness onset

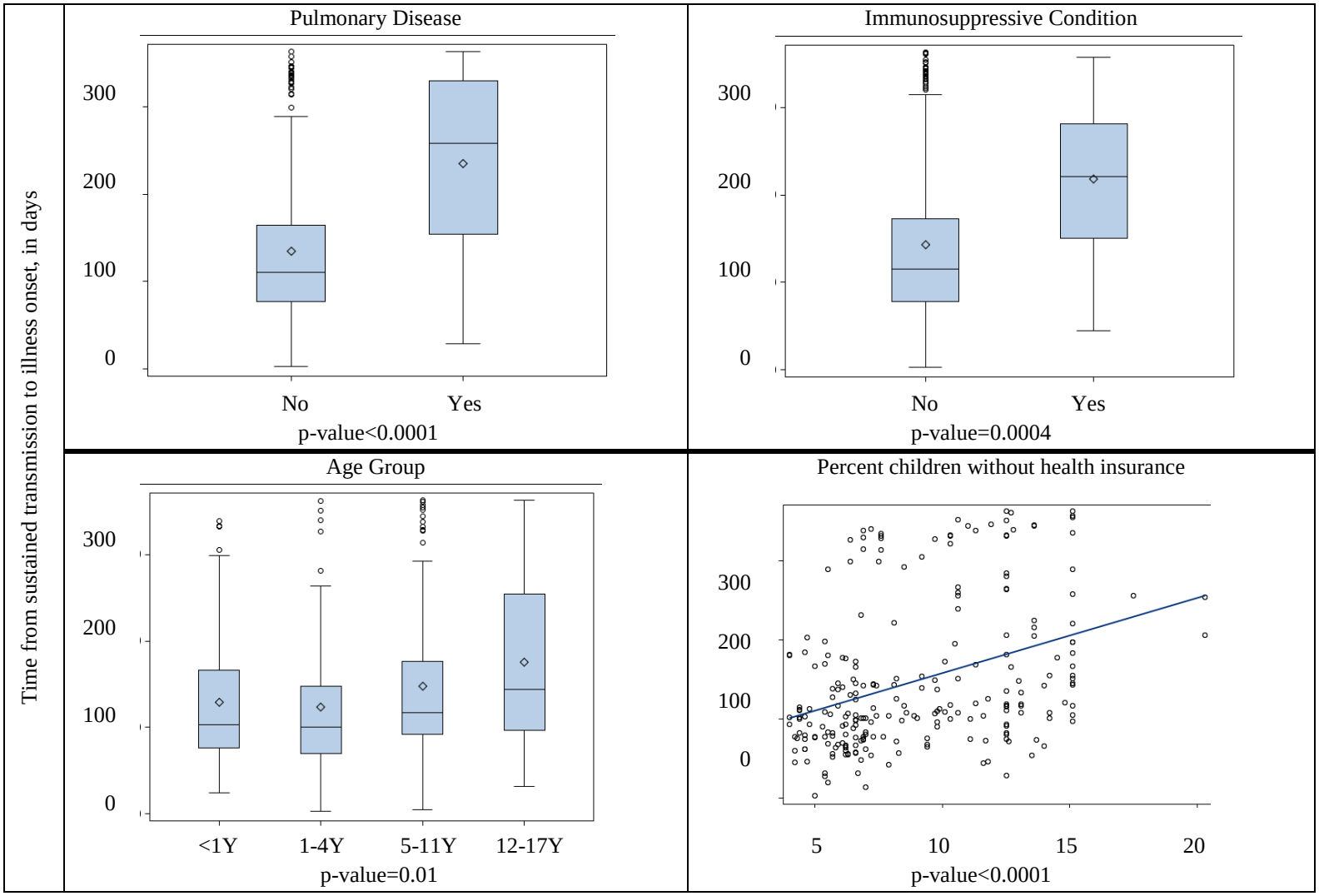


Figure 4.3. Residual plots of the number of days to illness onset

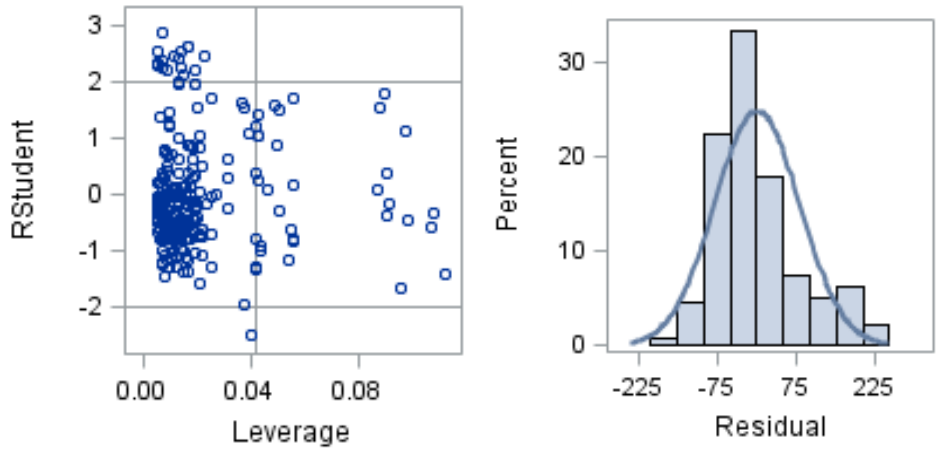


Figure 4.4. Probability distributions for days from influenza illness onset to death implied by the Poisson and negative binomial models against actual days

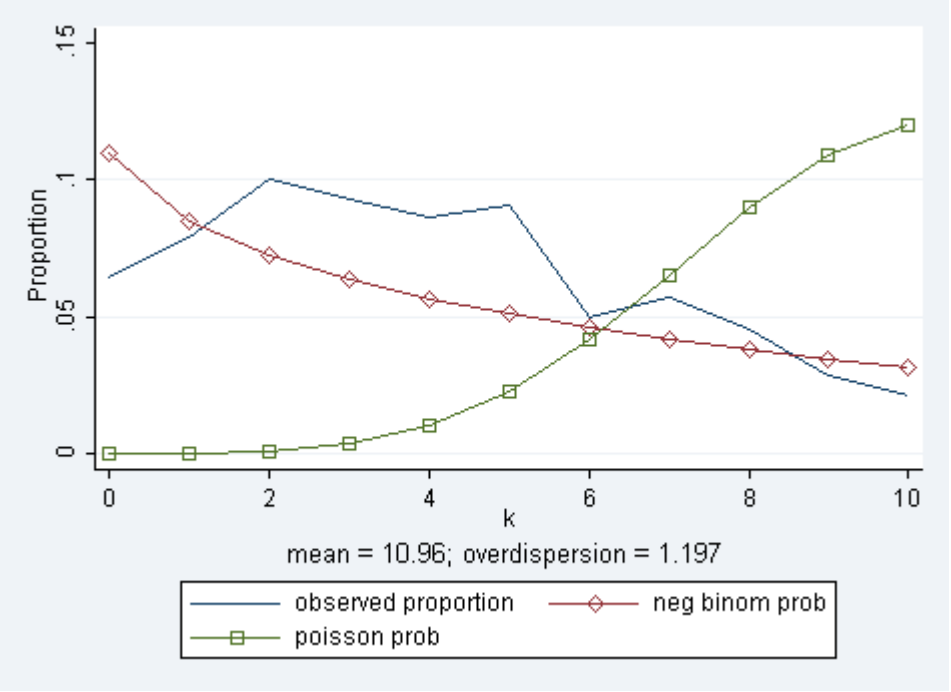


Figure 4.5 Plot of standardized Pearson residuals against predicted incidence rate ratios

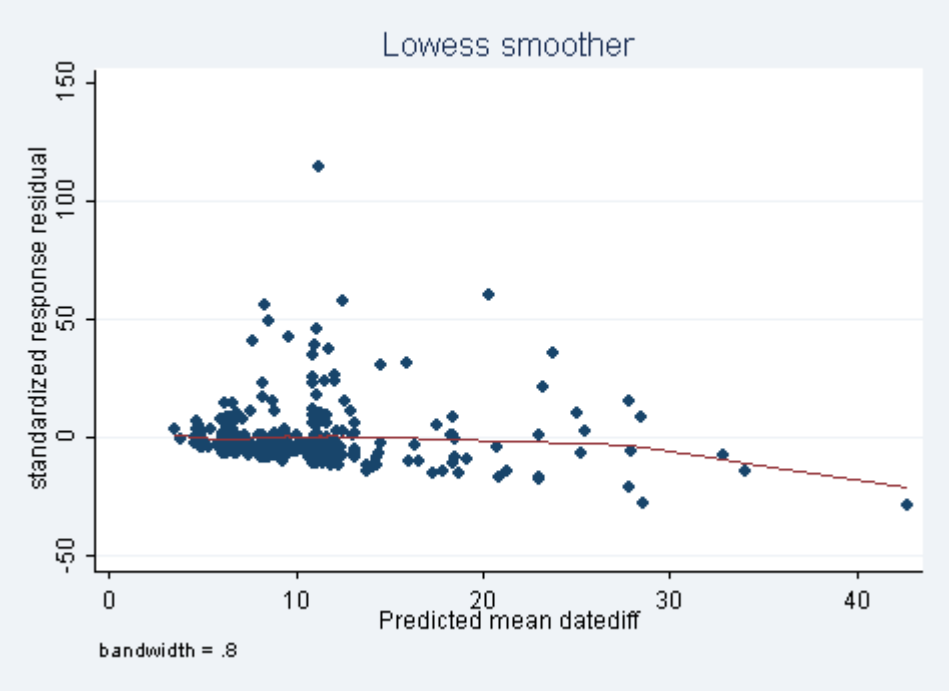


Table 4.1. Epidemic timing of influenza illness onset and mean days from onset to death (N=416)

	Total N (%)	Early	Middle	Late	Inter-epidemic	Chi-square p-value	Interval from Onset to Death, Mean Days [SD]
TOTAL	416 (100)	79 (19)	138 (33)	74 (18)	125 (30)		10.9 [16.0]
Race/ethnicity						0.24[a]	
-White	175 (42)	37 (21)	63 (36)	33 (19)	42 (24)		12.2 [18.7]
-Black	76 (18)	14 (18)	25 (33)	13 (17)	24 (32)		8.2 [12.0]
-Hispanic	106 (25)	17 (16)	32 (30)	18 (17)	39 (37)		12.3 [16.6]
-American Indian	12 (3)	2 (17)	2 (17)	5 (42)	3 (25)		9.2 [10.1]
-Asian	23 (6)	2 (9)	7 (30)	5 (22)	9 (39)		6.3 [6.3]
-Other/unknown	24 (6)	7 (29)	9 (7)	0 (0)	8 (33)		8.8 [8.2]
Age						0.95	
-<1 year	73 (18)	11 (15)	25 (34)	12 (16)	25 (35)		9.6 [19.7] [d]
-1-4 years	73 (18)	13 (18)	22 (30)	15 (21)	23 (32)		10.6 [14.7] [d]
-5-11 years	156 (38)	32 (21)	55 (35)	29 (19)	40 (26)		8.3 [10.5] [d]
-12-17 years	110 (27)	22 (20)	36 (33)	18 (16)	34 (31)		15.1 [19.0] [d]
Sex[f]						0.46	
-Male	230 (55)	45 (20)	80 (35)	35 (15)	70 (30)		11.3 [18.4]
-Female	185 (45)	34 (18)	57 (31)	39 (21)	55 (30)		10.4 [12.5]
Seasonal influenza vaccination[g]						0.08	
-Yes	61 (20)	5 (8)	26 (43)	12 (20)	18 (30)		11.3 [12.1]
-No	246 (80)	51 (21)	79 (32)	36 (15)	80 (33)		10.7 [17.0]
1 or more high-risk condition						0.49	
-Yes	210 (50)	35 (17)	68 (32)	38 (18)	69 (33)		14.3 [18.3] [d]
-No	206 (50)	44 (21)	70 (34)	36 (17)	56 (27)		7.4 [12.4] [d]
Any neurological disorders						0.58	
-Yes	110 (26)	17 (15)	41 (37)	18 (16)	34 (31)		14.2 [19.7] [c]
-No	306 (74)	62 (20)	97 (32)	56 (18)	91 (30)		9.7 [14.3] [c]
-Neurodevelopmental disorder						0.46	
-Yes	72 (17)	9 (13)	27 (38)	14 (19)	22 (31)		16.6 [23.3] [d]
-No	344 (83)	70 (20)	111 (32)	60 (17)	103 (30)		9.7 [13.7] [d]
-Seizure disorder						0.85	

-Yes	58 (14)	9 (16)	20 (34)	12 (21)	17 (29)		14.6 [18.0]
-No	358 (86)	70 (20)	118 (33)	62 (17)	108 (30)		10.3 [15.6]
-Neuromuscular disorder						0.82	
-Yes	46 (11)	7 (15)	17 (37)	7 (15)	15 (33)		13.7 [15.9]
-No	370 (89)	72 (19)	121 (33)	67 (18)	110 (30)		10.5 [16.0]
Pulmonary disease						0.31	
-Yes	49 (12)	8 (16)	12 (24)	9 (18)	20 (41)		21.4 [24.9] [d]
-No	367 (88)	71 (19)	126 (34)	65 (18)	105 (29)		9.5 [13.9] [d]
Asthma						0.66	
-Yes	60 (14)	14 (23)	21 (35)	8 (13)	17 (28)		14.3 [19.6]
-No	356 (86)	65 (18)	117 (33)	66 (19)	108 (30)		10.3 [15.3]
Cardiac disease						0.28	
-Yes	42 (10)	9 (21)	9 (21)	7 (17)	17 (40)		17.5 [22.9] [d]
-No	374 (90)	70 (19)	129 (34)	67 (18)	108 (29)		10.1 [14.9] [d]
Renal disease						0.57[a]	
-Yes	13 (3)	3 (23)	3 (23)	4 (31)	3 (23)		12.2 [11.4]
-No	403 (97)	76 (19)	135 (34)	70 (17)	122 (30)		10.8 [16.1]
Sickle cell anemia						0.36[a]	
-Yes	4 (1)	0 (0)	1 (25)	2 (50)	1 (25)		9.0 [9.2]
-No	412 (99)	79 (19)	137 (33)	72 (17)	124 (30)		10.9 [16.1]
Metabolic/Endocrine disorder						0.78[a]	
-Yes	21 (5)	4 (19)	5 (24)	4 (19)	8 (38)		14.7 [20.7]
-No	395 (95)	75 (19)	133 (34)	70 (18)	117 (30)		10.7 [15.7]
Immunosuppressive condition						0.09[a]	
-Yes	26 (6)	4 (15)	4 (15)	5 (19)	13 (50)		20.3 [20.2] [d]
-No	390 (94)	75 (19)	134 (34)	69 (18)	112 (29)		10.2 [15.5] [d]
Cancer/hematologic malignancy						0.36[a]	
-Yes	7 (2)	0 (0)	2 (29)	1 (14)	4 (57)		25.6 [12.7] [c]
-No	409 (98)	79 (19)	136 (33)	73 (18)	121 (30)		10.6 [15.9] [c]
Obesity						0.66[a]	
-Yes	9 (2)	3 (33)	2 (22)	2 (22)	2 (22)		19.4 [20.6]
-No	407 (98)	76 (19)	136 (33)	72 (18)	123 (30)		10.7 [15.9]
Congenital musculoskeletal disorder						0.90[a]	
-Yes	15 (4)	2 (13)	6 (40)	3 (20)	4 (27)		14.3 [16.2]

-No	401 (96)	77 (19)	132 (33)	71 (18)	121 (30)		10.7 [16.0]
Bacterial co-infection						--	
-Yes	75 (18)	--	--	--	--		13.1 [18.7]
-No	341 (82)	--	--	--	--		10.4 [15.3]
Viral co-infection						--	
-Yes	15 (4)	--	--	--	--		17.3 [20.2]
-No	401 (96)	--	--	--	--		10.6 [15.8]
Complications						--	
-Yes	272 (65)	--	--	--	--		13.8 [18.2] [d]
-No	144 (35)	--	--	--	--		5.3 [8.1] [d]

N=326	Mean(SD)					
	Total	Early	Middle	Late	Inter-epidemic	p-value
Mean household size	2.8 (0.5)	2.8 (0.4)	2.7 (0.5)	2.7 (0.6)	2.9 (0.6)	0.63
Pct. household below poverty	13.7 (11.6)	13.2 (11.7)	13.4 (11.1)	12.2 (11.4)	15.6 (12.2)	0.33
Pct. urban	83.8 (30.8)	82.4 (32.4)	84.9 (29.4)	85.6 (28.7)	82.2 (33.0)	0.87
Pct. Black	14.6 (23.9)	18.5 (26.5)	13.2 (22.7)	13.5 (24.2)	14.3 (23.1)	0.52
Pct. White	68.3 (27.6)	66.6 (30.6)	71.5 (26.3)	68.9 (27.1)	65.0 (27.3)	0.38
Pct. graduated from high school	77.0 (15.4)	78.0 (14.9)	77.7 (13.6)	80.2 (12.9)	73.1 (18.9)	0.04
Pct. graduated from college	20.7 (15.4)	21.8 (16.0)	20.1 (15.7)	23.3 (14.0)	18.7 (14.5)	0.29
Pct. individuals unemployed	4.0 (2.7)	4.0 (3.0)	4.0 (2.1)	3.8 (3.2)	4.2 (2.7)	0.85
Median household income, $	43,418 (19,035)	45,081 (17,211)	42,440 (18,617)	47,168 (20,700)	40,447 (19,910)	0.16
Pct. crowding	9.1 (13.2)	9.1 (12.4)	7.4 (10.3)	8.1 (11.4)	12.3 (17.6)	0.06
Pct. severe crowding	2.2 (5.6)	2.1 (5.1)	1.3 (3.6)	1.7 (3.6)	3.8 (8.5)	0.02
# primary care doctors[b,e]	1238 (1809)	1222 (1872)	1117 (1569)	1188 (1740)	1453 (2097)	0.62
# hospitals[b,e]	20 (29)	20 (30)	18 (25)	19 (28)	23 (33)	0.68
Pct. children lacking insurance[e]	9.0 (3.6)	8.6 (3.7)	8.5 (3.4)	9.3 (3.6)	9.8 (3.7)	0.05
HPSA[e]						0.14
-Whole county	180 (55)	31 (17)	71 (39)	25 (14)	53 (29)	
-Part of county	100 (31)	21 (21)	31 (31)	26 (26)	22 (22)	

-None of county	47 (14)	12 (26)	16 (34)	8 (17)	11 (23)

-ACIP-defined high-risk conditions are not mutually exclusive

[a] Uninterpretable due to small count sizes of cells

[b] Per 100,000 population

[c] Statistically significant difference at a p-value <0.05

[d] Statistically significant difference at a p-value <0.01

[e] County-level factors

[f] Sex data was not available for 1 child

[g] Influenza vaccination data was not complete for all children (N=307)

Table 4.2. Linear regression of the number of days to illness onset (N=228)

R^2=0.25	Adjusted β estimate	p-value
Intercept	53.253	--
Pct. children lacking insurance	7.473	<0.0001
Age (continuous)	2.542	0.02
Pulmonary disease	68.755	<0.0001
Immunosuppressive condition	86.216	0.0008

Table 4.3. Negative binomial regression of mean days from influenza illness onset to death (N=329)

	Unadjusted Incidence Rate Ratio (IRR)	95% CL	Adjusted Incidence Rate Ratio (IRR)	95% CL	Change in Mean Days from Onset to Death (Mean=10.4)
Neighborhood factors					
Mean household size	1.21	(1.00, 1.48)	--		
Pct. household below poverty	0.90	(0.81, 1.00)	--		
Pct. urban	0.98	(0.95, 1.02)	--		
Pct. Black		p-value=0.0002[c]		p-value=0.01 [c]	
->15% vs. <5%	0.55	(0.42, 0.73)	0.63	(0.45, 0.89)	-3.8
->15% vs. 5%-15%	0.74	(0.54, 1.02)	0.74	(0.55, 1.00)	-2.7
Pct. White	1.08	(1.03, 1.12)	--		
Pct. graduated from high school	0.98	(0.91, 1.05)	--		
Pct. graduated from college	0.98	(0.91, 1.06)	--		
Pct. individuals unemployed	0.65	(0.42, 1.02)	--		
Median household income, $	1.06	(0.99, 1.13)	--		
Pct. crowding	1.04	(0.96, 1.12)	--		
Pct. severe crowding	1.16	(0.96, 1.41)	--		
# primary care doctors[b]	1.01	(1.00, 1.01)	--		
# hospitals[b]	1.05	(1.01, 1.10)	1.02	(0.98, 1.07)	
Pct. children lacking insurance	1.03	(1.00, 1.06)	--		
HPSA		p-value=0.09 [c]			
-Whole county vs none	0.74	(0.52, 1.04)	--		
-Part county vs none	0.67	(0.46, 0.97)	--		
Individual factors					
Race/ethnicity		p-value=0.10 [c]		p-value=0.28 [c]	

-White	Ref		Ref		
-Black	0.67	(0.48, 0.93)	0.86	(0.58, 1.26)	
-Hispanic	0.98	(0.73, 1.31)	0.81	(0.60, 1.09)	
-American Indian	0.97	(0.43, 2.20)	1.46	(0.67, 3.16)	
-Asian	0.60	(0.33, 1.08)	0.89	(0.51, 1.55)	
-Other/unknown	0.63	(0.36, 1.11)	0.57	(0.33, 0.98)	
Age		p-value=0.002 [c]		p-value=0.02 [c]	
<1 year	0.60	(0.42, 0.87)	0.95	(0.66, 1.36)	-0.5
1-4 years	0.72	(0.50, 1.04)	0.94	(0.66, 1.33)	-0.6
5-11 years	0.57	(0.42, 0.77)	0.67	(0.51, 0.89)	-3.4
12-17 years	Ref		Ref		
Sex [Male vs. Female]	1.08	(0.85, 1.38)	--		
Seasonal influenza vaccination[a]	1.29	(0.92, 1.80)	--		
1 or more high-risk condition	1.62	(1.28, 2.04)	--		
Any neurological disorders	1.28	(0.98, 1.66)	--		
-Neurodevelopmental	1.46	(1.07, 1.98)	0.80	(0.55, 1.16)	
-Seizure	1.41	(1.01, 1.96)	1.26	(0.85, 1.85)	
-Neuromuscular	1.21	(0.84, 1.75)	--		
Pulmonary disease	2.04	(1.43, 2.91)	1.76	(1.26, 2.48)	+7.9
Asthma	1.36	(0.97, 1.89)	--		
Cardiac disease	1.46	(0.99, 2.17)	--		
Renal disease	1.09	(0.55, 2.16)	--		
Sickle cell anemia	0.86	(0.29, 2.55)	--		
Metabolic/Endocrine disorder	1.07	(0.62, 1.85)	--		
Immunosuppressive condition	2.01	(1.21, 3.33)	2.09	(1.30, 3.35)	+11.3
Cancer/hematologic malignancy	2.06	(0.72, 5.93)	--		
Obesity	1.65	(0.74, 3.70)	--		

Congenital musculoskeletal disorder	0.77	(0.40, 1.50)	--		
Bacterial co-infection	1.08	(0.80, 1.46)	--		
Viral co-infection	1.50	(0.81, 2.80)	--		
# of complications[d]	1.40	(1.26, 1.56)	1.42	(1.28, 1.57)	+4.4

[a] Of 329 pediatric influenza deaths with individual and neighborhood factors, only 239 (73%) also contain influenza vaccination data.

[b] Number in a county per 100,000 population

[c] p-values for categorical variables are likelihood ratio chi-square test p-values.

[d] Complications include pneumonia, acute respiratory distress syndrome, croup, seizures, bronchiolitis, encephalitis, Reye syndrome, shock, sepsis, hemorrhagic pneumonia, and myocarditis.

- Pearson chi-square Goodness of Fit ranged from 1.52 to 1.89.

References

1. Glezen WP, Couch RB. Interpandemic influenza in the Houston area, 1974-76. N Engl J Med. 1978;298(11):587-592.

2. Neuzil KM, Zhu Y, Griffin MR, et al. Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study. J Infect Dis. 2002;185(2):147-152.

3. Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. J Infect Dis. 2006;194 Suppl 2:S82-91.

4. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine. 2007;25(27):5086-5096.

5. Coffin SE, Zaoutis TE, Rosenquist AB, et al. Incidence, complications, and risk factors for prolonged stay in children hospitalized with community-acquired influenza. Pediatrics. 2007;119(4):740-748.

6. Ampofo K, Gesteland PH, Bender J, et al. Epidemiology, complications, and cost of hospitalization in children with laboratory-confirmed influenza infection. Pediatrics. 2006;118(6):2409-2417.

7. Hassan F, Lewis TC, Davis MM, Gebremariam A, Dombkowski K. Hospital utilization and costs among children with influenza, 2003. Am J Prev Med. 2009;36(4):292-296.

8. Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003-2004. N Engl J Med. 2005;353(24):2559-2567.

9. Cox CM, Blanton L, Dhara R, Brammer L, Finelli L. 2009 Pandemic influenza A (H1N1) deaths among children--United States, 2009-2010. Clin Infect Dis. 2011;52 Suppl 1:S69-74.

10. Fowlkes AL, Arguin P, Biggerstaff MS, et al. Epidemiology of 2009 pandemic influenza A (H1N1) deaths in the United States, April-July 2009. Clin Infect Dis. 2011;52 Suppl 1:S60-68.

11. Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infections on persons with chronic underlying conditions. JAMA. 2000;283(4):499-505.

12. Colosia AD, Masaquel A, Hall CB, Barrett AM, Mahadevia PJ, Yogev R. Residential crowding and severe respiratory syncytial virus disease among infants and young children: a systematic literature review. BMC Infect Dis. 2012;12:95.

13. Soto K, Petit S, Hadler JL. Changing disparities in invasive pneumococcal disease by socioeconomic status and race/ ethnicity in Connecticut, 1998-2008. Public Health Rep. 2011;126 Suppl 3:81-88.

14. Krieger N, Waterman PD, Chen JT, Soobader MJ, Subramanian SV. Monitoring socioeconomic inequalities in sexually transmitted infections, tuberculosis, and violence: geocoding and choice of area-based socioeconomic measures--the public health disparities geocoding project (US). Public Health Rep. 2003;118(3):240-260.

15. Krieger N, Chen JT, Waterman PD, Rehkopf DH, Subramanian SV. Painting a truer picture of US socioeconomic and racial/ethnic health inequalities: the Public Health Disparities Geocoding Project. Am J Public Health. 2005;95(2):312-323.

16. Yousey-Hindes KM, Hadler JL. Neighborhood socioeconomic status and influenza hospitalizations among children: New Haven County, Connecticut, 2003-2010. Am J Public Health. 2011;101(9):1785-1789.

17. Levy NS, Nguyen TQ, Westheimer E, Layton M. Disparities in the severity of influenza illness: a descriptive study of hospitalized and nonhospitalized novel H1N1 influenza-positive patients in New York City: 2009-2010 influenza season. J Public Health Manag Pract. 2013;19(1):16-24.

18. Lowcock EC, Rosella LC, Foisy J, McGeer A, Crowcroft N. The social determinants of health and pandemic H1N1 2009 influenza severity. Am J Public Health. 2012;102(8):e51-58.

19. Charland KM, Brownstein JS, Verma A, Brien S, Buckeridge DL. Socio-economic disparities in the burden of seasonal influenza: the effect of social and material deprivation on rates of influenza infection. PloS One. 2011;6(2):e17207.

20. Brownstein JS, Mandl KD. Pediatric population size is associated with geographic patterns of acute respiratory infections among adults. Ann Emerg Med. 2008;52(1):63-68.

21. Schanzer D, Vachon J, Pelletier L. Age-specific differences in influenza A epidemic curves: do children drive the spread of influenza epidemics? Am J Epidemiol. 2011;174(1):109-117.

22. Olson DR, Heffernan RT, Paladini M, Konty K, Weiss D, Mostashari F. Monitoring the impact of influenza by age: emergency department fever and respiratory complaint surveillance in New York City. PLoS Med. 2007;4(8):e247.

23. Longini IM, Jr., Koopman JS, Haber M, Cotsonis GA. Statistical inference for infectious diseases. Risk-specific household and community transmission parameters. Am J Epidemiol. 1988;128(4):845-859.

24. Glass LM, Glass RJ. Social contact networks for the spread of pandemic influenza in children and teenagers. BMC Public Health. 2008;8:61.

25. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med. 2008;5(3):e74.

26. Wallinga J, Teunis P, Kretzschmar M. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. Am J Epidemiol. 2006;164(10):936-944.

27. Thompson DL, Jungk J, Hancock E, et al. Risk factors for 2009 pandemic influenza A (H1N1)-related hospitalization and death among racial/ethnic groups in New Mexico. Am J Public Health. 2011;101(9):1776-1784.

28. Finelli L, Fiore A, Dhara R, et al. Influenza-associated pediatric mortality in the United States: increase of Staphylococcus aureus coinfection. Pediatrics. 2008;122(4):805-811.

29. Sachedina N, Donaldson LJ. Paediatric mortality related to pandemic influenza A H1N1 infection in England: an observational population-based study. Lancet. 2010;376(9755):1846-1852.

30. Blanton L, Peacock G, Cox C, Jhung M, Finelli L, Moore C. Neurologic disorders among pediatric deaths associated with the 2009 pandemic influenza. Pediatrics. 2012;130(3):390-396.

31. Peebles PJ, Dhara R, Brammer L, Fry AM, Finelli L. Influenza-associated mortality among children - United States: 2007-2008. Influenza Other Respi Viruses. 2011;5(1):25-31.

32. Centers for Disease Control and Prevention. Notice to Readers: Mid-year addition of influenza-associated pediatric mortality to the list of nationally notifiable diseases, 2004. MMWR Morb Mortal Wkly Rep. 2003;53(40):951-952.

33. Centers for Disease Control and Prevention. Nationally Notifiable Disease Surveillance System (NNDSS): NNDSS Home. 2013; http://wwwn.cdc.gov/nndss/. Accessed February 25th, 2013.

34. United States Census Bureau. Census tracts and block numbering areas. 2000; http://www.census.gov/geo/www/cen_tract.html. Accessed February 12th, 2013, 2013.

35. United States Department of Health and Human Services. Area Resource File (ARF): National County-level Health Resource Information Database. 2013; http://arf.hrsa.gov/overview.htm. Accessed February 25th, 2013.

36. United States Department of Health and Human Services. Primary Medical Care HPSA Designation Criteria. 2013; http://bhpr.hrsa.gov/shortage/hpsas/designationcriteria/primarycarehpsacriteria.html. Accessed February 25th, 2013.

37. Centers for Prevention Control and Prevention. FluView Interactive. 2012; http://www.cdc.gov/flu/weekly/fluviewinteractive.htm. Accessed February 12, 2013, 2013.

38. Wenger JB, Naumova EN. Seasonal synchronization of influenza in the United States older adult population. PloS One. 2010;5(4):e10187.

39. Schanzer DL, Langley JM, Dummer T, Aziz S. The geographic synchrony of seasonal influenza: a waves across Canada and the United States. PloS One. 2011;6(6):e21471.

40. Centers for Disease Control and Prevention. Seasonal Influenza: Clinical Signs and Symptoms of Influenza. 2013; http://www.cdc.gov/flu/professionals/acip/clinical.htm. Accessed February 25th, 2013.

41. Cabana, MD, Rand, CS, Becher, OJ, Rubin, HR. Reasons for pediatrician nonadherence to asthma guidelines. Arch Pediatr Adolesc Med. 2001;155(9):1057-1062.

42. O'Laughlen, MC, Rance, K, Rovnyak, V, Hollen, PJ, Cabana, MD. National asthma education prevention program: survey of nurse practitioners' knowledge, attitudes, and behaviors. J Pediatr Health Care. 2013;27(2):Epub.

43. Clark, NM, Shah, S, Dodge, JA, Thomas, LJ, Andridge, RR, Little, R. An evaluation of asthma interventions for preteen students. J Sch Health. 2010;80(2):80-87.

44. Bruzzese, JM, Bonner, S, et al. Asthma education: the adolescent experience. Patient Educ Couns. 2004;55(3):396-406.

45. Wray, J, Lee, K, Dearmun, N, Franck, L. Parental anxiety and stress during children's hospitalization: the StayClose study. J Child Health Care. 2011;15(3):163-174.

46. Wisk, LE, Witt, WP. Predictors of delayed or forgone needed health care for families with children. Pediatrics. 2013;130(6):1027-1037.

47. Uwemedimo, OT, Findley, SE, Andres, R, Irigoyen, M, Stockwell, MS. Determinants of influenza vaccination among young children in an inner-city community. J Community Health 2012;37:663-672.

48. National Center for Health Statistics. Health, United States, 2011: With special feature on socioeconomic status and health. Hyattsville, MD. 2012.

49. Newacheck, P. W., J. J. Stoddard, et al. (1998). "Health insurance and access to primary care for children." N Engl J Med 338(8): 513-519.

50. Rosenbaum, S. The patient protection and affordable care act: implications for public health policy and practice. Public Health Rep. 2011;126(1):130-135.

51. Smedley BD, Stith AY, Nelson AR, eds. Unequal treatment: confronting racial and ethnic disparities in health care. Washington, DC: National Academies Press, 2003.

52. Shi L, Lu N. Individual sociodemographic characteristics associated with hospitalization for pediatric ambulatory care sensitive conditions. J Health Care Poor Underserved. 2000;11(4):373-384.

53. Christakis DA, Mell L, Koepsell TD, Zimmerman FJ, Connell FA. Association of lower continuity of care with greater risk of emergency department use and hospitalization in children. Pediatrics. 2001;107(3):524-529.

54. United States Department of Health and Human Services. The Health Care Law & You: Key Features of the Law. 2013; http://www.healthcare.gov/law/features/index.html. Accessed February 25th, 2013.

55. Ortiz JR, Neuzil KM, Victor JC, Wald A, Aitken ML, Goss CH. Influenza-associated cystic fibrosis pulmonary exacerbations. Chest. 2010;137(4):852-860.

56. Tasian SK, Park JR, Martin ET, Englund JA. Influenza-associated morbidity in children with cancer. Pediatr Blood Cancer. 2008;50(5):983-987.

57. Lieu TA, Quesenberry CP, Jr., Capra AM, Sorel ME, Martin KE, Mendoza GR. Outpatient management practices associated with reduced risk of pediatric asthma hospitalization and emergency department visits. Pediatrics. 1997;100(3 Pt 1):334-341.

CHAPTER V

Conclusion

Influenza poses an annual challenge to provide both the recommended influenza vaccination to prevent illness and the appropriate and timely use of antiviral medication and hospital care to prevent untimely death in children with influenza illness. Included in the challenge is the opportunity to diminish the individual and neighborhood disparities related to prevention and treatment. Toward that end, this dissertation contributes to the existing literature in several ways--

Analysis 1 – Neighborhood risk factors of pediatric influenza vaccination

We examined if neighborhood factors were associated with pediatric influenza vaccination and whether the findings were robust after controlling for individual-level factors. The county-level factors neighborhood poverty, income, and racial density were associated with pediatric influenza vaccination. However, none of the neighborhood factors retained statistical significance after controlling for individual-level factors including type of provider and type of insurance. Public providers were shown to have lower pediatric influenza vaccination rates than private providers and Vaccines for Children program recipients were identified as having lower influenza vaccination rates than children privately insured. This analysis is one of the first to incorporate multi-level modeling to understand the effect of the neighborhood, at the county level, on the likelihood of pediatric influenza vaccination and was useful in identifying geographic variability of influenza vaccination. Our analysis also looked at how race/ethnicity

influenced influenza vaccination but only for children under 5 years of age. The finding that children of White mothers had higher influenza vaccination rates than children of Black mothers highlights the presence of a racial disparity in receipt of influenza vaccine in Michigan children.

Public Health Implications. There are several public health implications of these findings. The county-level measures of neighborhood showed that the socioeconomic environment does influence pediatric influenza vaccination, but not as much as more proximal factors of vaccination such as the type of provider or type of insurance. One potential reason for the finding that children receiving care from public providers had lower influenza vaccination rates than those from private providers could be a lower continuity of care in the patient-provider relationship among children seeing public providers. When public providers interact with children for other vaccinations, well child visits, or any health need, it is essential that they communicate the importance of timely vaccinations, and, in the case of influenza, seasonal vaccination. The limitations of public providers in fulfilling the continuity of care role for children should be noted, such as not offering episodic care for children with particular medical problems or having reduced days or hours of operation. It will be important to monitor the effects of the Affordable Care Act on the population of children served by public providers to identify how increases in health insurance coverage may affect the child/provider relationship and subsequently influenza vaccination. The mean influenza vaccination rate by county varied considerably in our study. The county-level variation in influenza vaccination rate strengthens the findings from previous studies that geographic area plays a role in both influenza vaccination and routine childhood vaccination. Interventions should thusly be tailored to a particular geographic area and the use of large-scale interventions or initiatives may vary in their success.

Future directions. One future avenue of research includes analyzing data from the 2012-2013 influenza season to document the effect of the newly-instituted reporting requirement in August 2012 in Michigan. The recent change extends required reporting of influenza vaccination to all vaccine providers and not just providers participating in the Vaccines for Children program. This would allow us to assess any change in the observed association between neighborhood-level factors and pediatric influenza vaccination following the change in reporting requirements. Additionally, our analysis failed to account for several known individual factors associated with receipt of vaccines including the family stressors of being a single-family household and flexibility to take time off work, parental education to understand the importance of vaccines and comprehend the immunization schedule, individual and social perceptions of vaccine effectiveness, and economic barriers such as presence of health insurance. Conducting a study on the individual barriers and perceptions of influenza vaccines in Michigan would provide background on the spectrum of barriers influencing annual influenza vaccination overall and whether barriers vary by neighborhood factors. A clinic-based study to evaluate where children receive their non-immunization-related care, such as episodic care for particular medical conditions or illnesses, could help identify whether acute care clinics or other urgent care settings could increase child influenza immunization rates by carrying state-funded influenza vaccine. Finally, research that compares pre- and post-implementation of the Affordable Care Act would identify the impact of expanded health insurance coverage on a child's choice of medical home, public versus private provider, which our research has shown to influence pediatric influenza vaccination.

Analysis 2 – Neighborhood risk factors of pediatric influenza mortality

We examined if neighborhood factors were associated with pediatric influenza mortality and whether those neighborhood factors could help explain the race/ethnic disparities in pediatric mortality. For the first time to our knowledge, we showed that several neighborhood factors measured at the census level including the percentage of residents with a college degree, percentage of residents living in an urban area, and the percentage of children without insurance helped explain the rate of pediatric influenza mortality. Neighborhood factors were also found to attenuate the observed race/ethnic disparity in pediatric influenza mortality in our analysis. To our knowledge, the percentage of children less than 19 years of age residing in a county, which was assessed as a neighborhood factor, had not been previously identified as significantly contributing to the risk of influenza or other infectious disease morbidity and mortality.

Public Health Implications. Through the identification of neighborhoods at higher risk for experiencing pediatric influenza mortality, we pave the way for improved prevention strategies by enabling targeted implementation of prevention efforts. In counties with a greater number of uninsured children we observed increased risk of pediatric influenza mortality. This finding reinforces previous research and helps inform the debate on healthcare reform and the Affordable Care Act. It is unknown how the Affordable Care Act will change a child's overall health by expanding health insurance coverage and increasing the number of covered preventive services for both public and private insurance, but the changes can theoretically decrease pediatric influenza mortality. Our findings provide a baseline examination of the neighborhood factors and race/ethnic disparities in pediatric influenza mortality to conduct before/after comparative studies of the Affordable Care Act.

Future directions. Public health surveillance systems should begin to collect individual level income and education data and simple objective factors of the neighborhood during public

health case investigations. The collection of these data would add socioeconomic measures to our understanding of disease occurrence, likely diminish the observed race/ethnic associations with adverse health outcomes, and allow for a more coherent interpretation of neighborhood health findings. Pediatric influenza mortality is a relatively rare condition and the need for additional studies aggregating multiple years of data are necessary to achieve sufficient statistical power to study these occurrences.

Analysis 3 – Neighborhood risk factors of influenza illness onset and time to death

The timing of influenza illness onset and the interval from influenza illness onset to death were examined and we report a previously unidentified disparity in pediatric influenza mortality. The interval from influenza illness onset to death was shorter for children living in neighborhoods with a high percentage of Black residents. No association was found between neighborhood factors and the risk of influenza illness onset.

Public Health Implications. Our findings indicate an unidentified disparity in the interval from influenza illness onset to death. We also identify the neighborhood and individual level risk factors that should be used to focus medical monitoring and rapid treatment, including antivirals and hospitalization, to minimize the risk of child death and early death. While tradition risk factors such as the presence of an ACIP-defined high-risk condition have been associated with poorer health outcomes including longer hospital stays, this longer interval from onset to death provides the opportunity for medical interventions that are not afforded to those children live in certain neighborhoods and have rapid onset to death.

Future directions. Our finding of a disparity in the interval from influenza illness onset to death is inhibited by at least two unmeasured mediators. Future studies should be conducted with

consideration given to collecting antiviral medication use and timing to hospital care to determine how much of the effect of the individual- and neighborhood-level factors that was identified in our study resulted from differences in the medical care received. Understanding the process underlying the association between the neighborhood factor, percentage of Black raced residents, and the interval from influenza onset to death can help reduce or eliminate this newly identified neighborhood disparity. Our analysis included area-level measures of medical access and socioeconomic status that were not found to be associated with the interval from onset to death. However, use of individual-level measurements of insurance coverage and family income would add detail for analysis and discussion.

Taken together, the analyses in this dissertation suggest the added value of using immunization information systems and public health surveillance data for research purposes beyond their originally intended public health use. Collaborations between public health agencies and academic institutions could provide a mutually beneficial relationship with public health practitioners being able to gain analytic expertise to answer important public health questions while providing academic researchers a quality source of data on a myriad of public health conditions. The societal benefit is the monitoring of public health conditions and their race/ethnic disparities for changes in trends over time and through interventions.

The research findings presented in this concluding chapter have identified several factors to help designate at-risk neighborhoods for expanded surveillance, public health interventions, and to inform policy change. In terms of enhancing surveillance, we have identified several risk factors not previously recognized in the current literature through linkage with census data that will help in monitoring under-immunization and mortality using immunization information systems and public health surveillance systems. Toward the prospect of advancing public health

interventions, we offer insight into several areas of focus for increasing pediatric influenza immunizations and decreasing pediatric influenza mortality. The neighborhood factors are simple census-derived measures that lay the groundwork for direct measurement of neighborhoods. Informing policy change can only be done after the extent of the problem has been characterized and research has made its case by providing a strong body of evidence. This dissertation research highlights the relevance of neighborhood factors to influence infectious disease morbidity and mortality.