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Examining Parental Perceptions and Decisions to Uptake Child Influenza Immunizations: Assessing Pandemic and Policy Impacts on Vaccination Rates Following the H1N1 Pandemic, and the ACIP LAIV Preferential Recommendation Revocation

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EXAMINING PARENTAL PERCEPTIONS AND DECISIONS TO UPTAKE CHILD INFLUENZA IMMUNIZATIONS: ASSESSING PANDEMIC AND POLICY IMPACTS ON VACCINATION RATES FOLLOWING THE H1N1 PANDEMIC, AND THE ACIP LAIV PREFERENTIAL RECOMMENDATION REVOCATION

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ABSTRACT

Introduction

2009 H1N1 Pandemic: The historical 2009 H1N1 Influenza pandemic, which had a CDC estimated accrued disease burden of 100.5 million illnesses, 936,000 hospitalizations, and 75,000 deaths from 2009 to 2018, resulted in a declared state of emergency nationally, with ensuing diminished vaccine confidence and amplified fears of infection, prompting some to pursue flu vaccination, and others to forego. Although the Centers for Disease Control and Prevention (CDC), and its Advisory Committee on Immunization Practices (ACIP) recommend an annual flu vaccine for individuals 6 months of age and older as the "first and best" defense against influenza, a low percentage of children are vaccinated, and parental decisions are not fully understood. Examining previous literature, a void exists in relation to parental perceptions and decisions for child immunizations, particularly concerning the U.S. nationally, with most studies being international. Furthermore, there is evidence of varied results with inadequate and conflicting conclusions, specifically for children.

2015 LAIV Policy Shift: The 2015 Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) retraction of its original preferential recommendations for usage of the live attenuated influenza vaccine (LAIV), which is the intra-nasal version of the vaccine, has resulted in varied responses, with fluctuations in ensuing CDC vaccine advisements affecting its implementation and uptake among children. Although the CDC's ACIP recommend an annual flu vaccine for

individuals 6 months of age and older as the "first and best" defense against influenza, a low percentage of children are vaccinated, and parental decisions are not completely comprehended, particularly in regards to the LAIV formulation. Reviewing the literature, in certain studies a decline in flu vaccine uptake was concluded, whereas in other instances, it conversely increased, or remained static, yielding inconsistent outcomes. Furthermore, there exists a great void in the number, scale, and scope of studies published, with none being nationally representative, and examining parental perspectives, decisions, and responses in regard to child flu vaccine uptake following the 2015 ACIP LAIV policy shift.

Methods

2009 H1N1 Pandemic: To assess impacts of the 2009 H1N1 pandemic on decisions to uptake influenza vaccines for children age 6 months to 17 years of age, data from NIS was used as a series of weighted consecutive annual surveys in order to synthesize a longitudinal panel dataset spanning from 2003 to 2018. Population adjusted measures of influenza like illness (ILI) by state and season procured from CDC's FluView application and ILI Net from 2008 to 2018 was used in order to supplement the primary NIS dataset. Quasi-experimental (QE) approaches in the form of segmented interrupted time series (ITS), and fixed effects model (FEM) logistic estimations were executed on the integrated dataset yielding logistic regression coefficients and post-estimation marginal effects signifying the impact of the pandemic on child influenza vaccine uptake (CIVU). ITS regressions examined both level and trend changes due to pandemic occurrence via binary and continuous pandemic incidence variables

respectively. FEM regressions examined fluctuations in CIVU as a function of influenza disease progression across seasons and geographic jurisdictions.

2015 LAIV Policy Shift: To assess impacts of the 2015 ACIP LAIV preferential recommendation revocation on decisions to uptake influenza vaccines for children age 6 months to 17 years of age, data from NIS was used as a series of weighted consecutive annual surveys in order to synthesize a longitudinal panel dataset spanning from 2003 to 2018. Quasi-experimental (QE) approaches in the form of segmented interrupted time series (ITS), and difference in differences (DID) logistic estimations were executed on the integrated dataset yielding logistic regression coefficients and post-estimation marginal effects signifying the impact of the 2015 ACIP LAIV policy shift on child influenza vaccine uptake (CIVU). ITS regressions examined both level and trend changes due to policy shift occurrence via binary and continuous policy shift incidence variables respectively. DID regressions incorporated LAIV eligibility indicators to ascertain the level and trend differences in CIVU between LAIV eligible (age 2 years and greater), and LAIV ineligible (age 6 to 23 months) individuals, pre and post policy shift. This additionally allowed for ascertainment of spillover effects and impacts of the policy shift on individuals who were only eligible for the injected influenza vaccine (IIV) formulation. Vaccine specific ITS estimations for individual formulations were executed applying previous procedures, in addition to regressions assessing heterogeneity effects.

Results

2009 H1N1 Pandemic: The interrupted time series (ITS) regression for the NIS-Child sample yielded statistically significant coefficients. Post-estimation average marginal effects (AMEs) were as follows. The H1N1 pandemics occurrence yielded a

12.57 percentage point (pp), 95% CI [10.28, 14.32], immediate level change increase in the probability of a child being immunized, on average. It also yielded a 3.77 pp, 95% CI [-4.32, -2.55], sustained slope change decrease in the probability of a child being immunized annually, on average. Pre-pandemic, a 1.64 pp, 95% CI [1.47, 1.81], sustained increase in the probability of a child being immunized annually, on average, was evident. Restricted scale epidemic (RSE) occurrences of the influenza virus yielded post-estimation AMEs that were statistically significant for RSEs on 2012, 2013, and 2014. These coefficients were a 1.79 pp, 95% CI [-2.22, 0.38], 5.23 pp, 95% CI [-6.27, -4.77], and 1.92 pp, 95% CI [2.74 1.10], decrease in the probability of a child being immunized, on average, respectively. The respective trend change increases post RSE occurrences were 0.85 pp, 95% CI [0.74, 0.96], 0.34 pp, 95% CI [0.28, 0.40], and 1.24 pp, 95% CI [1.12 1.35], on average, in the probability of the same outcome. Sensitivity analysis fixed effects model (FEM) regressions yielded logit and AME coefficients that were statistically insignificant with the exception of a single variable in subgroup 5, which indicated a decrease of 2.29 pp, on average, in immunization rates during peak season weeks registering at a ILI intensity magnitude of 9 or greater. FEM regressions for the NIS-Teen sample yielded logit and AME coefficients that were statistically insignificant with the exception of three variables in subgroup 5. The initial variable indicated a 1.31 pp increase, and the subsequent variables indicated a 0.135 pp, and a 0.212 pp decrease, on average, in immunization rates respectively.

2015 LAIV Policy Shift: The interrupted time series (ITS) regression for the NIS-Child sample yielded statistically significant coefficients. Post-estimation average marginal effects (AMEs) were as follows. The LAIV preferential recommendation

revocation yielded a 3.01 percentage point (pp), 95% CI [2.54, 4.74], immediate level change increase in the probability of a child being immunized, on average. It also yielded a 2.41 pp, 95% CI [-2.62, -2.11], sustained slope change decrease in the probability of a child being immunized annually, on average. Pre-policy shifts, a 2.06 pp, 95% CI [1.91, 2.22], sustained increase in the probability of a child being immunized annually, on average, was evident. The LAIV preferential recommendation of 2014, and the subsequent LAIV recommendation rescindment of 2016, respectively yielded a 5.25 pp decrease, 95% CI [-7.05, -3.25], and a 1.02 pp increase, 95% CI [0.55, 1.12], in the probability of a child being immunized, on average. The respective trend changes post-policy shifts were a 1.21 pp increase, 95% CI [1.11, 1.31], and a 5.30 pp decrease, 95% CI [-6.22, -4.38], on average. The sensitivity analysis difference in differences (DID) estimation yielded statistically significant coefficients. Comparing the differences between LAIV-eligible and LAIV-ineligible individuals, pre and post 2015 policy shift, yielded a DID of 20.70 pp, 95% CI [19.52, 21.88], indicating an increase occurred in the probability of a LAIV-eligible child being immunized as compared to an LAIV-ineligible child, on average, following the 2015 policy shift. Examining the LAIV-eligibility indicator's AME, it is evident that an LAIV-eligible child experiences a 1.34 pp, 95% CI [0.64, 2.03], increase in the probability of being immunized, on average, as compared to an LAIV-ineligible child. The interrupted time series (ITS) regression for the NIS-Teen sample yielded statistically significant coefficients. Post-estimation AMEs are as follows. The LAIV preferential recommendation revocation yielded a 4.25 pp, 95% CI [2.31, 6.22], immediate level change increase in the probability of a teen being immunized, on average. It also yielded a 3.02 pp, 95% CI [-4.77, -2.33], sustained slope change decrease

in the probability of a teen being immunized annually, on average. Pre-policy shifts, a 2.70 pp, 95% CI [2.12, 3.16], sustained increase in the probability of a teen being immunized annually, on average, was evident. The LAIV preferential recommendation of 2014, and the subsequent LAIV recommendation rescindment of 2016, respectively yielded a 8.41 pp decrease, 95% CI [-10.35, -6.41], and a 6.52 pp decrease, 95% CI [-8.21, -4.42], in the probability of a teen being immunized, on average. The respective trend changes post-policy shifts were a 7.17 pp increase, 95% CI [6.11, 8.58], and a 2.84 pp increase, 95% CI [1.96, 3.71], on average.

Conclusion

2009 H1N1 Pandemic: Preliminary escalations in the probability of child immunization uptake are evident following the pandemic. This is possibly linked to immediate vaccination promoting factors connected to the pandemics occurrence, but cannot be ascertained. These factors are possibly paramount in the initial post-pandemic phase, and gradually diminish with the progression of time, theoretically yielding reductions in uptake rates in the long term. Public health immunization professionals should expect preliminary increases in uptake behavior, followed by gradual decreases in the same outcome for influenza pandemics such as H1N1. They should anticipate decreases in uptake behavior following smaller scale epidemics. For pandemic intensity ILI seasons, uptake behavior is not sensitive to weekly fluctuations in ILI severity for children, but slightly sensitive for teens during peak and late phases of the influenza season, with fluctuating uptake behavior associated with peak season phases, and consistent increases for late season phases. This study contributes to the existing literature by enhancing the understanding of how vaccine uptake rates change following

pandemic and epidemic events. However it is limited in determining why these changes occur, and due to what factors and mechanisms specifically, which future studies should attempt to discern and ascertain.

2015 LAIV Policy Shift: The 2015 policy shift was associated with preliminary increases in vaccine uptake, followed by annual declines, for both children and teens. Reductions in overall immunization uptake following the preceding 2014 policy shift, and subsequent 2016 policy shift were evident, for both samples for 2014, and teens for 2016. Public health policies concerning influenza immunization for children and adolescents should concentrate on refraining from issuing preferential advisements for either vaccine formulation if possible. Immunization policies should focus on consistent and stable annual advisements, which may promote greater trust in immunization policies. This study contributes to the existing literature by enhancing the understanding of how vaccine uptake rates change following policy shifts. However it is limited in determining why these changes occur, and due to what factors and mechanisms specifically, which future studies should attempt to discern and ascertain.

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CHAPTER 1

INTRODUCTION

1.1. Project Background, Significance, and Innovation

Each year millions of children in the U.S. experience influenza-related illness. Although most children infected with influenza viruses recover within a week, serious complications can result in hospitalization or death.[1] Currently, the Centers for Disease Control and Prevention (CDC), and its Advisory Committee on Immunization Practices (ACIP) recommend an annual flu vaccine for individuals 6 months of age and older as the "first and best" defense against influenza.[2,3] Nevertheless, only 45.6% of children 6 months to 17 years of age received the vaccine in 2018 – 2019, and even less at 38.8% in 2017-2018.[4] Understanding parental attitudes and barriers associated with uptake of childhood immunization is a crucial national public health priority. This process is complex, as numerous socioeconomic, psychological, demographic, and contextual factors influence vaccine uptake rates.[5–9] Doubts regarding vaccine benefits,[10] concerns regarding side-effects and safety,[5,11–17] perceived disease seriousness and risk assessment,[11,15,16,18,19] uncertainties about vaccine effectiveness,[8,11,12,20,21] and healthcare access and costs,[7,8,14,22,23] are prime influencers and factors affecting immunization uptake.

The effects of policy shifts and pandemic occurrences on parental perceptions and decisions to uptake immunizations in the U.S. are not completely understood, with

conflicting, and inconsistent conclusions, [5,11,19,23–26] specifically for child flu vaccines. This study overcame these shortcomings and contributes to a better understanding of how parental perceptions and decisions are affected by these aforementioned factors by examining the historical 2009 H1N1 pandemic, and the 2015 ACIP live attenuated influenza vaccine (LAIV) preferential advisement revocation. These events served as points of analysis to determine how parental decision-making and perceptions regarding child flu vaccines may shift through mechanisms such as perceived disease risk and erosion of vaccine confidence. This study has parallels to past research that has examined the controversies regarding other diseases, health conditions, and vaccine formulation elements. These include the measles, mumps, rubella and Autism dilemma, and thimerosal presence in vaccines debate, where child vaccination rates shifted due to false scares, ensuing spillover effects, incorrect conclusions, and parental inability to critically analyze and decipher vaccine information.[5,13,24,27]

1.1.1. 2009 H1N1 Influenza Pandemic

The occurrence of the historical 2009 H1N1 Influenza pandemic, which had a CDC estimated accrued disease burden of 100.5 million illnesses, 936,000 hospitalizations, and 75,000 deaths from 2009 to 2018,[28] resulted in a declared state of emergency nationally. For the U.S. in 2009 alone, the pandemic resulted in approximately 270,000 hospitalizations and 12,270 mortalities, with 1,270 of those deaths being under age 18.[29] Examining previous literature, a void exists in relation to parental perceptions and decisions for their children, particularly concerning influenza for the U.S. nationally, with most studies having been completed internationally. Furthermore, there is evidence of varied results with inadequate and conflicting

conclusions, specifically for children. In certain studies, flu vaccine rates decreased following the pandemic,[11,16,30] while in others it increased,[31,32] with the measured magnitude of change being vastly different, with certain publications reporting substantial fluctuations,[11,31,32] and others stating milder effects, regardless of directionality. There also exists a lack of a comprehensive nationwide study that is representative and all encompassing.

Given the aforementioned, the question arises as to what was the impact of the historical 2009 H1N1 pandemic on overall child influenza vaccination uptake rates in the U.S.? This study is novel and innovative in that it is the first nationally representative and comprehensive study that examines the impacts of the 2009 H1N1 pandemic on overall child flu vaccine rates over a significant time span using an extensive vaccine-focused data source in the form of the National Immunization Survey (NIS). It is the first to assess how parental uptake of child influenza immunizations is affected nationally across diverse segments of the population, while yielding improved results with public health implications. This is significant, as it allows for a better understanding of parental cognitive and behavioral responses to pandemics in relation to decision making for uptake of child flu vaccines within the United States. This is significant, as it ultimately allows for U.S. public health policymakers to increase future child flu vaccine uptake by understanding how parental perspectives and decisions shift following a pandemic.

1.1.2. 2015 Retraction of Preferential Recommendations for LAIV

The 2015 CDC ACIP retraction of its original preferential recommendations for usage of the LAIV, which is the intra-nasal version of the vaccine for children, [21,25,26,33–37] has resulted in varied parental responses, with fluctuations in ensuing CDC vaccine

advisements affecting its implementation and uptake among children.[25,33,38,39] Reviewing the literature, in certain studies a decline in flu vaccine uptake was concluded,[33] whereas in other instances, it conversely increased,[26] or remained static,[25] yielding inconsistent outcomes. There is a void in the number, scale, and scope of studies published with none being nationally representative and examining parental perspectives, decisions, and responses in regard to child flu vaccine uptake following the ACIP LAIV withdrawal.

Given the aforementioned, the question arises as to what was the policy impact of the 2015 ACIP LAIV withdrawal on overall child influenza vaccination uptake rates in the U.S.? This study is novel and innovative as it is the first nationally extensive study assessing the potential impacts of the 2015 LAIV withdrawal on overall child flu vaccine rates over a substantial time range using the National Immunization Survey (NIS) focusing specifically on children. It is the first to evaluate parental decisions to vaccinate their children against the flu by considering changes in parental uptake of child influenza immunizations, following consecutive and evolving ACIP recommendations and advisements. This study is significant, as it is an improved assessment of the LAIV withdrawals, and assists in addressing the shortcomings of predecessor publications. It is significant, as it provides a preliminary understanding of how CDC policy shifts may impact decision making for uptake of child flu vaccines within the U.S., permitting public health policymakers to increase future child flu vaccine uptake by anticipating how parental perspectives and decisions may alter following future ACIP advisements and recommendations.

1.2. Project Specific Aims and Hypotheses

Given the absence of knowledge regarding the broader question of how parental decisions and perspectives to adopt child influenza vaccines are impacted by macroscopic phenomenon and events, this study will aim to answer this conundrum, and rectify this quandary, by specifically examining 2 macro-scale events of diverse origin in relation to their respective effects on decisions to uptake influenza vaccines among children. The first of these events is in the form of a pandemic occurrence, such as the historical H1N1 pandemic of 2009, and the second is in the form of a major flu vaccine related policy shift, such as the CDC ACIP LAIV preferential advisement reversals of 2015. Concepts involved in decision processes such as hesitancy to complete vaccines, and confidence erosion regarding vaccine effectiveness will be applied in order to explain why behaviors relative to parental flu vaccine adoption altered following event occurrences. The following are the primary goals and objectives of this study and their hypotheses.

Specific Aim 1: To ascertain the effects of the 2009 H1N1 pandemic on overall child influenza vaccination uptake rates in the U.S. by assessing changes in the likelihood that a child is vaccinated for influenza following the pandemic event.

H_1: The 2009 H1N1 pandemic is expected to increase the likelihood of overall child influenza vaccine uptake. In accordance with the previous literature, and this studies conceptual model, vaccine uptake stimulating factors related to disease severity and susceptibility to infection will drive the expected increases in flu immunization uptake.

Specific Aim 2: To ascertain the policy effects of the 2015 ACIP LAIV preferential recommendation revocation on overall child influenza vaccination uptake

rates in the U.S. by assessing changes in the likelihood that a child is vaccinated for influenza following the policy shift event.

H_2: The 2015 ACIP LAIV preferential recommendation revocation is expected to decrease the likelihood of overall child influenza vaccine uptake. In accordance with the previous literature, and this studies conceptual model, provider dissemination of immunization information, based on ACIP advisements, will likely reduce vaccine uptake, since LAIV will not be recommended as the preferred option to parents by providers.

CHAPTER 2

LITERATURE REVIEW

2.1. U.S. Immunization Program: Public Health Strategy and Mission

2.1.1. Primary Objectives

The United States immunization strategy has consistently been to increase immunization rates for vaccine preventable diseases, and to minimize the morbidity and mortality rates resulting from vaccine preventable infectious diseases, through completion of immunizations for eligible individuals.[29] Part of this approach is to allocate special attention to higher risk populations and susceptible groups such as children and the elderly.[29]

2.1.2. Successes and Failures

Overall increases in life expectancy and reductions in infectious disease induced mortalities have been observed during the 20th century, chiefly due to improvements and enhancements in vaccines and optimized implementation of immunizations nationally.[29] Despite technological advancements in immunizations and vaccine applications, there still exists a great degree of disease burden attributable to infectious diseases within the U.S., primarily resulting from diseases such as influenza, tuberculosis, and viral hepatitis, which are the leading causes of illnesses and mortalities due to infectious diseases in the United States.[29] Among the respiratory vaccine preventable infectious diseases, the disease burden of influenza nationally amounts to 200,000 hospitalizations, and 36,000

mortalities overall annually.[29] The H1N1 influenza pandemic of 2009 resulted in approximately 270,000 hospitalizations, and 12,270 mortalities, among which 1,270 were children in one year's time following the outbreak.[29]

In addition to the aforementioned mortality and morbidity rates linked to vaccine preventable infectious disease burdens, there also exist major accompanying expenditures and costs which can be avoided if immunizations are administered appropriately.[29] Vaccines have been demonstrated to be an exceedingly effective and exceptionally cost efficient method of clinical prevention of infectious diseases with child immunizations being influential in this area, since they have been demonstrated to increase survival rates among the population and diminish disease related expenditures overall.[29] For each birth cohort of routine child immunization series that are administered and completed for the U.S., child vaccines have been observed to prevent 33,000 mortalities, 14 million instances of disease, decrease costs directly associated with health care by $9.9 billion, and by $33.4 billion indirectly.[29]

2.1.3. Future Prognosis

Through vaccine preventable infectious disease surveillance, monitoring, screening, and prevention via immunizations, it is possible to circumvent consequences, such as vaccine preventable disease induced morbidity and mortality, and associated costs.[29] The public health strategy for dealing with vaccine preventable infectious diseases in the future will be dependent upon the execution and degree of coordination present between disease detection, control, and prevention via immunizations.[29] Expanding pathways to achieve and accomplish these objectives, and attain these results is dependent upon improving current understanding of vaccine preventable diseases as

well as determinants and factors that serve as facilitators and barriers to immunization adoption and vaccine uptake and completion by the population.[29]

2.2. Determinants Affecting Immunization Decisions and Uptake

Vaccination for children is a highly effective and prominent disease prevention and control strategy in the field of public health, yet deficiencies in immunization uptake and variations in vaccine practices persist with ensuing consequences.[37,40] The effects of policy shifts and pandemic occurrences on vaccination rates, perceptions, and uptake of immunizations in the U.S. are not completely understood with conflicting, uncertain, and inconsistent results.[5,11,19,23–26] Various determinants have been demonstrated to affect vaccination decisions by parents both in the U.S. and globally.

2.2.1. General Determinant Classification by Category

These elements include socioeconomic, psychological, demographic, and contextual factors. These variables have been demonstrated to influence vaccine uptake rates through different mechanisms, producing complexities in determining policy and pandemic effects.[5–9] Additionally, ascertaining the magnitude of effect of these numerous factors is difficult as well.

2.2.2. General Vaccine Uptake Decision Influencing Factors

Hesitancy regarding vaccine benefits,[10,30,40,41] level of vaccine confidence,[30,42,43] degree of vaccine information and knowledge,[9,15,42] safety concerns, and apprehensions regarding side-effects,[5,11–17] perceived disease seriousness and risk assessment,[11,15,16,18,19] uncertainties in vaccine effectiveness,[8,11,12,20,21] and healthcare accessibility, availability, and costs,[7,8,14,22,23,44] are prime influencers and barriers to immunization uptake. These determinants serve as mechanisms that affect the parental decision to vaccinate their

children broadly for various immunizations and disease types (refer to *Figure 2.1* for visual illustration).

2.2.3. Specific Vaccine Uptake Predictive Variables

Demographic and socioeconomic predictors that have been demonstrated to impact vaccination uptake decisions include the mother's education level,[5,13,24,30,45] marital status,[46,47] age,[30,45] ethnicity or racial background,[12,30,31,33,34,44,48] geographic location,[18,36,45] overall income level,[5,30,34,45] health care access,[14,23] and parental vaccine knowledge.[12,45,49] Specific determinants attributed to the child include gender,[30,44] order of birth,[46] age,[30,44] ethnicity or racial background,[12,30,31,33,34,44,48] and insurance type and status.[7,30,33,34] Immunization specific factors such as perceived vaccine effectiveness, efficiency, safety, and disease susceptibility and vulnerability impact vaccine completion rates.[50] Contextual predictors, and external non-individualized factors related to regional, or state specific policies and mandates, their temporal implementation, the social beliefs and norms of the population, as well as patient and clinician relationships and interactions, and facility types where these interactions occur, also affect vaccine decisions.[50]

Differences and disparities in these characteristics impact vaccine uptake rates to varying degrees. This is particularly the case in relation to the provider's and clinician's roles in recommending and administering required immunizations, specifically for minority and marginalized subgroups, who are the most vulnerable to experiencing differences and disparities in vaccine completions (refer to *Figure 2.1* for visual illustration).

Parent, Child, and Family Specific Factors:

Child Associated Predictors

Age Subgroup: Child's age has been demonstrated to influence vaccine uptake minimally.[30,44] It is expected that this studies analyses will yield consistent results. It is possible that increases in age yield increases in uptake for certain age groups as compared to others for specific vaccine types, hence this factor is correlated with uptake rates.

Gender: Child's gender has been demonstrated to influence vaccine uptake minimally in certain instances for specific immunizations.[30,44] It is expected that this studies analyses will yield consistent results and exhibit minimal disparities. Certain genders as compared to others, may be more likely to receive vaccines for particular immunization types and experience disparities in this respect, hence this factor is correlated with uptake rates.

Ethnic and Racial Background: Child's ethnicity has been demonstrated to influence vaccine uptake,[12,30,31,33,34,44,48] with Caucasians experiencing greater uptake as compared to other ethnicities, with African Americans and Hispanics experiencing lower uptake rates. It is expected that this studies analyses will yield consistent results. Disparities in vaccine accessibility and availability are linked to ethnicity, among other differences, hence this factor is correlated with uptake rates.

Birth Order Status: Childs birth order status has been demonstrated to influence vaccine uptake,[46] with first born status children experiencing greater uptake as compared to non-first born children. It is expected that this studies analyses will yield consistent results. Mothers may be more risk averse to the first born child and pursue vaccines to a

greater extent for them, with the degree of attention and concern diminishing for the subsequent children, hence this factor is correlated with uptake rates.

Mobility and Relocation: Childs relocation status has been demonstrated to influence vaccine uptake,[51] with children who relocated from a different geographic region generally experiencing lower uptake as compared to those who did not. It is expected that this studies analyses will yield consistent results. Children who relocate are more likely to experience disruptions in vaccination completion due to shifting to a different clinician or facility. This may result in declines in the subsequent access to vaccines, or availability of immunizations, hence this factor is correlated with uptake rates.

Insurance Status: Child's insurance type has been demonstrated to influence uptake of vaccines,[7,30,33,34,48] with children possessing health insurance experiencing greater uptake rates as compared to those who are uninsured. It is expected that this studies analyses will yield consistent results. Insurance status permits parents to attain greater access to vaccines and related immunization resources, hence this factor is correlated with uptake rates.

Maternal Associated Predictors

Age Subgroup: Maternal age has been demonstrated to influence vaccine uptake,[30,45] with uptake for children generally increasing with mothers age for certain ranges. It is expected that this studies analyses will yield consistent results. It is possible that older mothers are more risk averse and more likely to pursue preventive measures such as vaccination, hence this factor is correlated with uptake rates.

Education Level: Maternal educational achievement has been demonstrated to influence vaccine uptake,[5,13,24,30,45,48] with uptake generally increasing for children with more educated mothers beyond university degree completion. It is expected that this studies analyses will yield consistent results. It is possible that mothers with higher educational attainment are more knowledgeable or informed about the importance of vaccines, and more likely to pursue medical information and possess access to it, in addition to absorbing it more effectively, hence this factor is correlated with uptake rates.[24]

Marital Status: Maternal marital status has been demonstrated to influence vaccine uptake,[46–48] with married mothers exhibiting greater uptake for their children. It is expected that this studies analyses will yield consistent results. Married mothers may pursue uptake at greater levels due to availability of vaccine related resources, hence this factor is correlated with uptake rates.

Family Associated Predictors

Total Number of Children Present: Number of children in the family unit has been linked to variations in uptake,[12,47] with greater number of children beyond a certain number being linked to differences in vaccine uptake. It is expected that this studies analyses will yield consistent results. Its predicted that a greater number of children beyond a certain point may reduce parental capability in attaining vaccinations for their children, due to limitations in resources available to them, hence this factor is correlated with uptake rates.

Income Level and Economic Status: Income category and as a function of the Federal Poverty Line (FPL) has been demonstrated to affect vaccine uptake,[5,30,34,45,48]

with increases in percentage of the FPL being linked to greater uptake generally for certain ranges. It is expected that this studies analyses will yield consistent results. Differences in economic status affect the ability of the parent to obtain access to immunizations, with greater poverty status reducing this capability, hence this factor is correlated with uptake rates.

Vaccine Specific Factors:

Characteristics related to the vaccine itself have been demonstrated to be linked with vaccine uptake rates. Immunization specific aspects such as the perceived effectiveness of the immunization, the vaccines efficiency, clinical safety, and capability in reducing disease susceptibility are associated with vaccine uptake decisions.[50] The concerns regarding the side effects and disadvantages of the vaccine as compared to its benefits have also been linked to vaccine uptake decisions.[50] For this study, these vaccine specific aspects are not measured or accounted for when performing the study, and are a limitation of this study.

External Factors:

Provider Associated Predictors

Provider Facility Type: Provider and clinician facility classification has been demonstrated to influence vaccine uptake,[50,52] with supply, distribution, and availability of immunizations influencing uptake rates.[50,53] with private practices exhibiting greater uptake as compared to other facilities. It is expected that this studies analyses will yield consistent results. Variations in facility type generate variations in availability and accessibility of vaccines, and potentially their sub-formulations, hence this predictor influences uptake rates.

Clinicians and health care providers possess a major role in vaccine uptake decisions by parents since they are the individual that is explaining vaccine information, disseminating immunization options based on ACIP advisements and in correspondence with ACIP protocols and recommendations for the season, as well as influencing parental vaccination decisions by discussing their suggestions for which immunization formulation to pursue.[50] The degree of vaccine knowledge acquired by the parent from the clinician affects the decision process as well as whether the information was related to vaccine policy shifts and to what depth it was discussed.[50] The level of trust and confidence that exists for the provider-patient relationship additionally influences the decision process, with parents accepting clinician suggestions from providers they have known and visited for a longer time in the past. This degree of familiarity with the clinician or provider may decrease hesitancy to uptake vaccines. Provider and clinician facility type may also determine a particular vaccine types accessibility and availability which influences the vaccine uptake decision process as well.[50]

Event Associated Predictors

Pandemic and Epidemic Occurrences: Pandemic and epidemic events have been demonstrated to affect vaccination rates, with alterations in parental perceptions of disease risk and benefits of vaccination exhibited in certain studies.[11,16,30] Vaccine uptake decision processes may theoretically alter following these occurrences as well, and can be influenced by variations in CDC ACIP advisements and guidance, as well as clinician dissemination of information relative to the risks of the disease, and advantages of vaccination. These events are anticipated to amplify the concerns and fears associated

with disease infection and contraction, and are expected to increase vaccine uptake rates as a consequence.

Vaccine Policy Shifts: Vaccine policy advisements and recommendations have been demonstrated to affect immunization rates, with ensuing changes in parental immunization uptake exhibited in certain studies.[25,33] Policy shifts could theoretically induce changes in a physician's clinical practice and the information they discuss and disseminate to parents, and their vaccine recommendations following a vaccine policy shift. This may then induce changes in a parent's perceptions of the relative risks versus benefits of immunization. It is expected that vaccine policy shifts could affect immunization uptake for this studies analysis as well, consistent with the previous literature.

Factors related to supply and distribution of influenza vaccines and their subtypes is also associated with immunization uptake rates, with shortages in vaccine supply during particular time periods or geographic locations affecting vaccine availability and accessibility.[53] This can lead to increases in vaccine costs as well as rationing, reprioritization, and reallocation of existing dosages to high risk individuals and to cope with population demands.[53] This issue was observed in the 2004 influenza season where the nation experienced vaccine shortages for the influenza immunization, and is the main occurrence of this type during this studies time period.[53] Vaccine shortage occurrences would decrease overall immunization uptake rates nationally due to limited vaccine availability and accessibility eliminating the populations ability to receive the immunization.

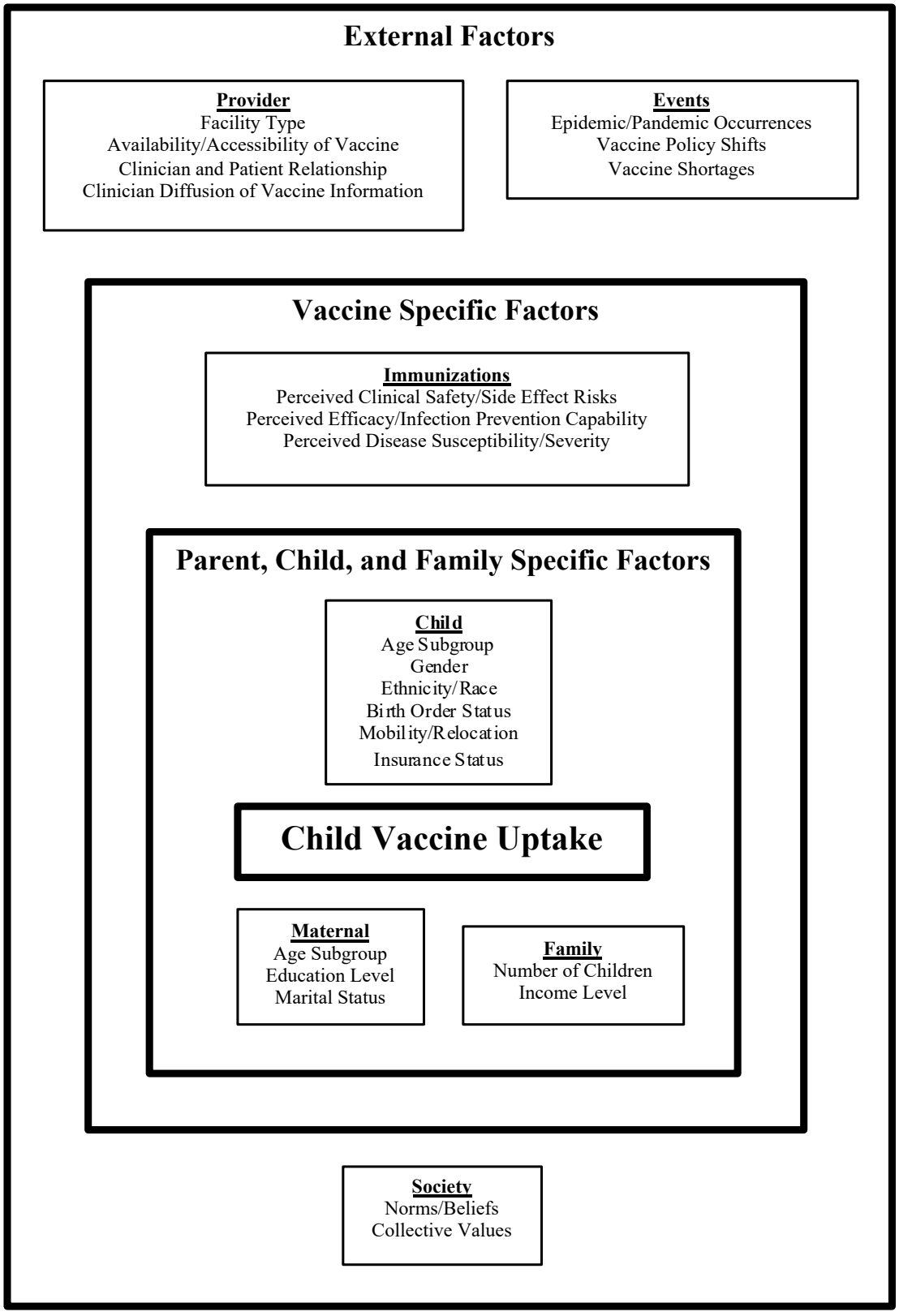

Figure 2.1 – Vaccine Uptake Conceptual Diagram

2.3. Conceptual Rational and Theoretical Underpinnings

Certain vaccine related occurrences have been demonstrated to adversely impact parental perceptions and decision-making regarding vaccinating their child through mechanisms of perceived disease risk,[54] benefits versus costs,[55] hesitancy and doubt,[56] safety concerns and risk of side-effects,[5] and loss of confidence in vaccine effectiveness.[57] This was exhibited in the Measles, Mumps, Rubella and Autism controversy where child vaccination rates declined for MMR and overall, due to spillover effects, based on false conclusions and parental inability to critically analyze and decipher vaccine information.[5,13,24] This was also observed in the case of false claims that thimerosal being in vaccines could potentially cause harm resulting in declines in overall vaccine rates due to the inability of parents to delineate the accuracy of these conclusions.[27] In the case of the H1N1 outbreak and LAIV recommendations revocations, our aforementioned hypotheses are reinforced by these types of studies, and rooted in previous observational trends and patterns that are parallel to our proposed study (refer to *Figure 2.1* for conceptual framework and hierarchical stratification illustration).

2.3.1. Protection Motivation Theory (PMT)

2.3.1.a. Principal Description and Conceptual Application

Protection Motivation Theory (PMT), as demonstrated in *Figure 2.2*,[58] (refer to *Figure 2.2* for PMT composition diagram), can be subdivided into two core mechanisms of action and processes, threat appraisal and coping appraisal.[59] The threat appraisal cognitive process emphasizes a source of hazard, and how certain variables would increase or decrease the probability of maladaptive reactions.[59] The subjects' perceptions of susceptibility and vulnerability to the hazard source, and the hazards severity dictate

the level of inhibition of the maladaptive responses.[59] In the case of the 2009 H1N1 Pandemic, the threat source is the pandemic occurrence, and the maladaptive reaction would be avoiding influenza vaccination completion. In this instance, individuals escalating fear in relation to the pandemic would theoretically inhibit the evasion of influenza vaccines in order to guarantee self-preservation and protection from the disease, hence vaccine uptake rates would theoretically increase following the pandemic by this logic.

The coping appraisal cognitive process emphasizes the coping methods for reacting to the source of hazard, and variables that would affect the probability of adaptive responses occurring.[59] This process is subdivided into response efficacy and self-efficacy, which are the degree to which the individual believes a response behavior will minimize the threat level relative to them, and the degree to which they can achieve the suggested response behavior successfully, respectively.[59] In the case of the 2009 H1N1 Pandemic, the coping response would be receiving the influenza vaccine, the threat source would be the pandemic occurring and ensuing risk of disease, the response efficacy portion of the coping mechanism would be the believed potency of the vaccine in reducing contraction of the influenza virus, and the self-efficacy portion would be the degree to which the individual believes they can accomplish completion of the vaccine. Based on this part of the theoretical concept, the occurrence of the pandemic would lead to increases in the coping response, which is the uptake of influenza vaccines, in order to maximize survival from the hazard source, and minimize risk of disease contraction. The degree of coping response exemplified by different individuals may vary in reaction to the pandemic stimulus source.

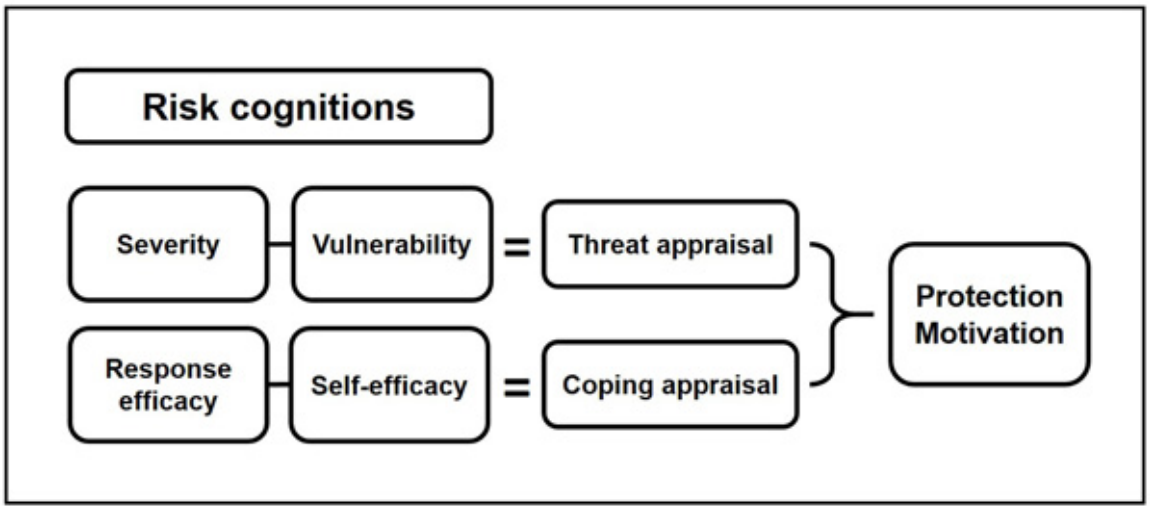

Figure 2.2 - PMT Composition Schematic

2.3.1.b. Extended Scrutiny of PMT Derivation

Dissecting the PMT model and its core components further, and delving into the sub-elements that contribute to the PMT's principal appraisal developments, there are three types of sub-concepts that exist.[60] These include intra-personal characteristics, such as social norms, attitudes, and beliefs.[60] Previous experiences with the hazard source and treatment response, including past infection with the disease in question by the child, relative, or known individual, and the degree of adversity with side effect production for these individuals.[60] Information sources regarding the hazard or threat, including public health institution declarations, clinician dissemination, media coverage, and internet promulgation.[60]

The PMT model, specifically relative to the threat appraisal core component, is contributed to through fear appeal pathways, which consist of the magnitude of noxiousness of the threat, the perceived probability of its occurrence, and the potency of the protective response in alleviating the threat.[61] These fear appeals affect the attitudes the individual possesses relative to the threat, and decisions they will ultimately

produce.[61] These fear modulating avenues serve as channels through which the degree of anxiety regarding the threat or hazard source is propagated.[61] The intensity of this transmission dictates the proliferation of concern regarding the hazard source and how the threat is processed through the threat appraisal mechanism of PMT.[61]

2.3.2. Diffusion of Innovation (DOI) Theory

The Diffusion of Innovation (DOI) theory is a principle that applies to this study in terms of the expected trend and anticipated patterns of influenza immunization adoption, specifically in the case of development and implementation of the LAIV version of the vaccine that is FluMist. The inception of this vaccine formulation in 2003 serves as the initiation point of the LAIV technological innovation with subsequent years of its existence theoretically following the DOI adoption curve,[62] as illustrated below in the diagram, with a progression occurring in the stated sequence, at the stated percentages.[62] With the application of this concept, and stages of the curve successively, it is possible to forecast from 2003 onward the fashion in which FluMist would have been potentially accepted and adopted by users hypothetically. It is exhibited by the DOI curve that by the time the 2009 H1N1 Pandemic and the 2015 ACIP recommendations would have been reached, the vast majority of users would have been aware of FluMist, and would have theoretically adopted or rejected this vaccine innovation. Furthermore, the DOI function demonstrates the different subgroups that would theoretically complete adoption of immunizations with the progression of time. The function emulates the trend of the normal curve and adheres to a similar appearance and is symmetrical. (refer to *Figure 2.3* for graphical illustration of the DOI function).[62]

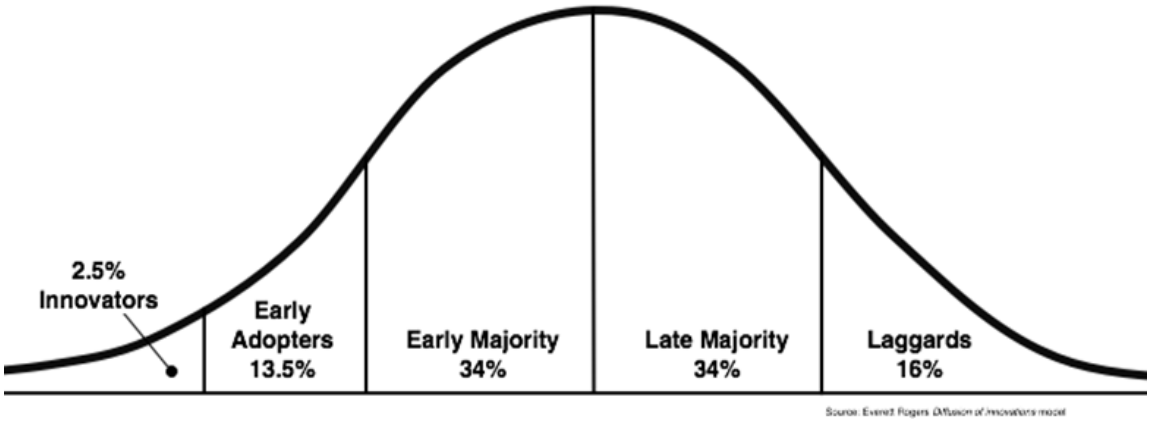

Figure 2.3 - DOI Adoption Curve

2.4. The Influenza Virus Pathogen Composition

Influenza is a severely contagious respiratory disease that can be transmitted directly or indirectly through infected droplets that are contaminated with the virus.[63] These are ejected during respiratory activity including coughing and sneezing episodes.[63] Individuals of all age ranges can become infected with the virus with certain subpopulations such as elderly over 65 years of age and infants being the most vulnerable.[63,64] Medically susceptible and immuno-compromised individuals are also at greater risk of being infected by the pathogen.[65]

The pathogenic influenza virus can be subdivided into 3 primary subtypes consisting of influenza type A, B, and C. Influenza type A is observed in both humans and animal organisms and is highly adaptable.[63] Influenza type A can be further divided into subclasses based on antigen components located on the surface of the pathogens exterior.[63] Hemagglutinin (HA) and neuraminidase (NA) are two such antigens that allow the virus to attach to and penetrate the target cells respectively.[63] The evolutionary and adaptive vigor of this pathogen is attributable to the minor and major mutations, designated as antigenic drift and shift respectively, which occur in relation to the

aforementioned pathogen surface antigens.[63] Influenza type B is observed in humans only and targets mainly children who are the major transmission vectors for the virus, and can remain contagious for a time period greater than 10 days.[63] Influenza type B produces a moderate degree of illness in infected individuals.[63] Influenza type C is a minor cause of illness in human subjects and less important as a pathogenic agent in relation to human subjects.[63]

2.5. Influenza Immunizations and Vaccines

In response to the inception of the influenza pathogenic agent, and its distinct ability to mutate and adapt continuously and rapidly, influenza vaccines with varying compositions were, and have since been continuously developed, and annually adjusted, modified, and approved for usage in attempts to correspond to the specific annual strain.[63,64] This task has been the joint responsibility of the World Health Organization (WHO) Collaborating Centre for Reference and Research on Influenza, the Federal Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC).[63,64] The CDC Advisory Committee on Immunization Practices (ACIP) is the primary agency at the federal level responsible for vaccine advisements and recommendations, with state public health agencies being responsible for individual states.

2.5.1. Vaccine Structural Compositions and Functional Mechanisms

Influenza vaccines can be trivalent or quadrivalent in composition, consisting of 2 type A strains and 1 type B strain, or 2 type A and 2 type B strains, respectively.[39,63,64,66] The vaccines function through a mechanism of viral surface antigen inhibition, through the release and subsequent attachment of antibodies that target HA and NA virus surface

antigens.[63] This suppresses the virus's ability to survive and proliferate.[63] The vaccines effectiveness is characterized primarily by the degree of HA inhibition.[63]

2.5.2. Vaccine Formulations and Sub-Classes

There are two major formulations of the influenza vaccination, the inactivated form of the influenza vaccine (IIV), and the live attenuated influenza vaccine (LAIV).[39,63,64,66] IIV class influenza vaccines are the most universally available and have been produced and implemented historically since the mid-1900's.[39,63,64,66] IIV's are intramuscularly injected and abide the standard convention of vaccine administration.[39,63,64,66] LAIV class influenza vaccines are the modern version of the vaccine, and are administered intra-nasally as opposed to intramuscularly, mimicking the viruses infiltration and infection pathway.[39,63,64,66] IIV's contain influenza viruses in a completely inactivated state, whereas LAIV's contain viruses in a weakened state.[39,63,64,66] IIV's stimulate both a local and systemic immune response, whereas LAIV's trigger a local mucosal immune response.[63,64] Neither vaccine type infects the individual with the virus, but may cause ensuing symptoms and side-effects to occur.[39,63,64,66]

2.6. Influenza Vaccine Recommendations Overview

The Centers for Disease Control and Prevention (CDC) assesses and evaluates annual influenza infection rates and vaccination rates, as well as vaccine effectiveness and safety in order to ascertain what immunization recommendations are most appropriate for the anticipated season.[65,67] Specifically, the Advisory Committee on Immunization Practices (ACIP), located within the CDC, is responsible for these

recommendations regarding annual influenza vaccinations, and providing advisements and guidance in relation to influenza immunizations.[68,69]

2.6.1. Inactivated Influenza Vaccine (IIV) Advisements

The CDC's ACIP has long recommended flu vaccines for children. Prior to 2002, it was advised only for those with severe risks for contraction of the disease.[31] In 2002, individuals 6-23 months were advised to receive flu vaccines routinely regardless of medical predisposition, with ACIP explicitly stating in 2004 that this age range should universally receive the standard IIV version of the immunization, on a consistent annual basis.[31,39,65–69] The upper limit of the age range was extended to 59 months in 2006, and 18 years in 2008.[31] In relation to IIV, this recommendation by ACIP has been sustained, and IIV has been routinely advised and established as the primary version of the vaccine.[39,65–69] All individuals 6 months and older, for whom it is not contraindicated, are currently recommended to receive the annual flu vaccine. (refer to *Figure 2.4* for a complete visual illustration of recommendation and advisement chronology)

2.6.2. Live Attenuated Influenza Vaccine (LAIV) Advisements

In 2003, the FDA reviewed and approved the usage of the LAIV formulation of the immunization, titled as the pharmaceutical product FluMist, which is the quadrivalent intra-nasally administered version of the flu vaccine.[35] From its inception, this subclass of the vaccine has resulted in fluctuations in the annual ACIP recommendations concerning its application, particularly as it pertains to the age ranges eligible for it, what medical conditions qualify or disqualify an individual from receiving it, and whether LAIV's are acceptable, or preferential and advantageous as compared to IIV's, or not recommended

at all.[67,68] (refer to *Figure 2.4* for a complete visual illustration of recommendation and advisement chronology)

In the year after its conception and approval for implementation nationally by the FDA, ACIP recommended LAIV's for ages 5-49 years in 2004.[67–70] This persisted until 2008, at which point ACIP extended the lower age limit boundary to 2 years of age, and the age bracket spanned from 2-49 years of age, with indications that children 2-4 years of age who had wheezing in past 12 months, or in later years asthma or respiratory medical issues should not receive the formulation.[65,68–70] Until 2014, ACIP maintained the majority of its regulations consistently, except it advised a preferential recommendation for LAIV as compared to IIV, suggesting it's the advantageous formulation of the immunization.[26,35,68–70] This was based on initial assessments of its performance and evaluations of its effectiveness which were deemed superior as compared to IIV.[25,33] In the following year of 2015, ACIP revoked and rescinded the LAIV preferential recommendations as compared to IIV's, and the phase of regular LAIV recommendation resumed.[26,35,68–71]

This persisted until 2016, when ACIP completely advised against the usage of LAIV's, and does not recommend LAIV's application.[25,26,33,35,68–70,72] This was due to concerns about decreased effectiveness of the vaccine formulation in combating the A(H1N1)pdm09 strain of the influenza virus, which was circulating in the U.S. during the two previous seasons. Following these series of advisements, in 2019, ACIP again recommends LAIV's as acceptable alternatives to the IIV's for those 2 to 49 years of age, with similar medical contraindications as those suggested in 2008.[35,68–70] The aforementioned fluctuations in ACIP LAIV recommendations and advisements since

2003 indicate a potential lack of consistent consensus on the merits of the LAIV formulation, and its potency and efficacy in adequately preventing the annually evolving influenza virus. This alludes to the potential existence of vacillation as to how appropriate LAIV's are as alternative influenza vaccine options. It is also important to recognize that parents who previously used the LAIV formulation for themselves or their children, or who adhered strictly to LAIV related advisements in the past, may also be more likely to be impacted directly by subsequent LAIV specific policy shifts, or ACIP recommendations and decisions.

2.7. Influenza Pandemics and Restricted Scale Epidemics

Influenza is a cyclical and seasonal disease, with certain periods of the season exhibiting greater degrees of infection as compared to other time periods.[73] It follows that particular years exhibit greater infection rates throughout the season, due to certain strains being more potent in their virulence, and the inability of the vaccine to counteract the strain effectively, resulting in a localized and actively spreading epidemic, or a national, or global scale pandemic of greater magnitude and intensity occurring.[16,73]

The most notable influenza pandemic that has occurred in the U.S. is the historical Spanish flu of 1918, with 675,000 U.S. mortalities confirmed.[74] Most recently, the A(H1N1) virus outbreak of 2009 was highly notable for the United States, as well as globally.[28] The occurrence of the 2009 H1N1 influenza pandemic, with a CDC estimated accrued disease burden of 100.5 million illnesses, 936,000 hospitalizations, and 75,000 deaths from 2009 to 2018,[28] is considered one of the most prominent influenza pandemics to have affected the United States. The severe repercussions were experienced on a national scale, and its reverberations are still felt years later in the form of the accrued

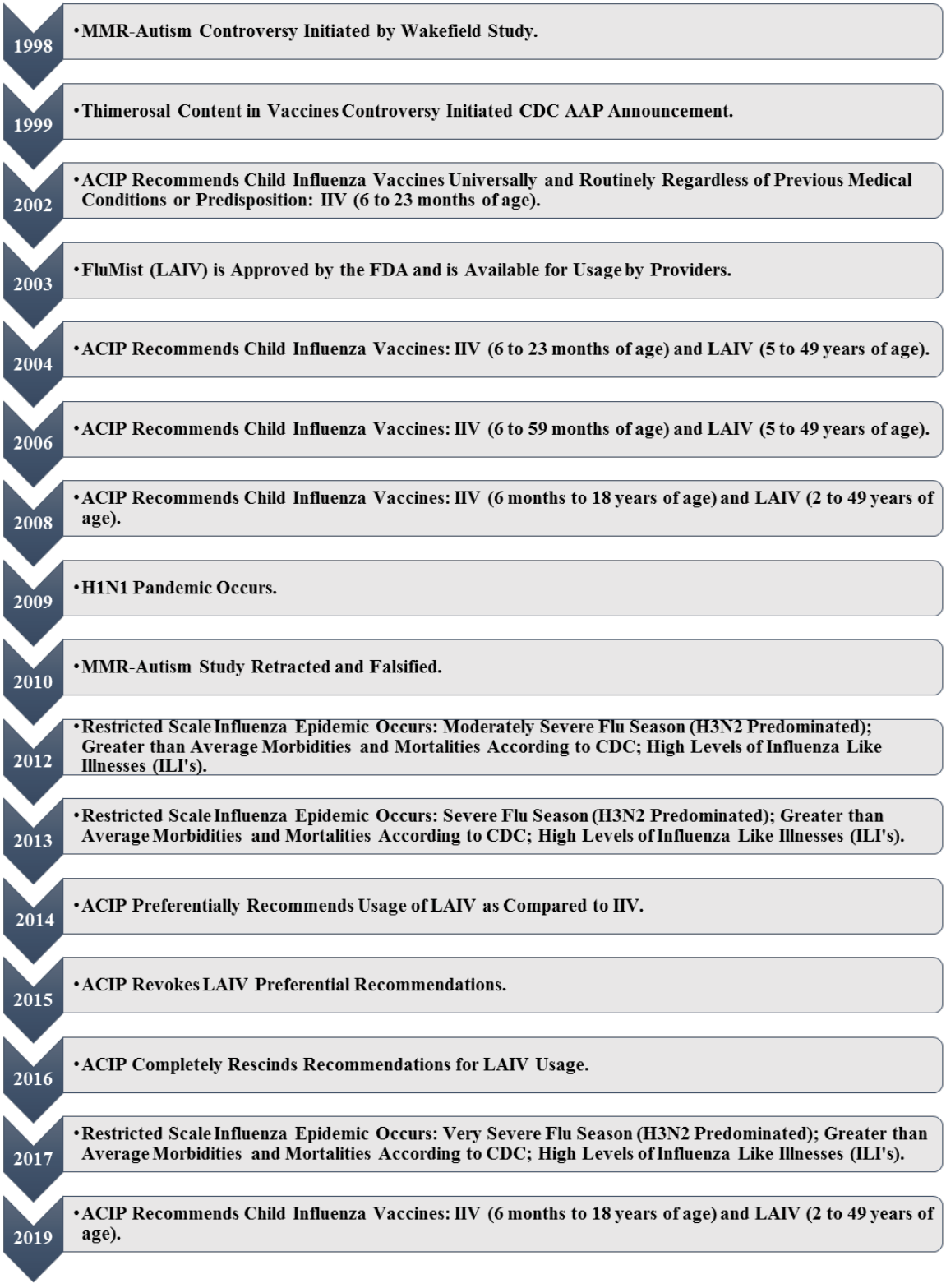

Figure 2.4 - Chronological Sequence of Events

disease burden aftermath, mortalities, morbidities, and individual level attitudes and concerns about the flu virus.[28]

Surrounding the A(H1N1) viral pandemic of 2009, lesser magnitude and intensity, restricted scale epidemics (RSE's), where greater than average influenza infection rates, morbidities, and mortalities were observed and reported by the CDC, occurred in 2012-2013, 2013-2014, and 2017-2018.[75–78] During these miniature epidemics, the influenza season was labeled as either highly severe, such as in 2017-2018, severe, such as in 2013-2014, or moderately severe, such as in 2012-2013, with higher than regular mortalities and morbidities being observed during all three time periods.[75–78] These time periods exhibited severe degrees of influenza like illnesses (ILI's), and ambulatory clinic and emergency department visits, as well as hospitalizations.[75–78] In these time periods, the Influenza A virus subtype H3N2 predominated as opposed to the Influenza A virus subtype H1N1.[75–78] These restricted magnitude epidemic occurrences resulted in their respective consequences similar to the A(H1N1)pdm09 (refer to *Figure 2.4* for a complete diagram of flu pandemic and restricted scale epidemic chronology).

2.8. Review of Existing and Associated Literature

Reviewing the existing literature broadly as it pertains to vaccine decision making and determinants, it is evident that numerous publications exist for various immunization types with a plethora of diverse determinants being assessed in different studies. The studies span from those evaluating parental attitudes and decisions regarding MMR vaccines, and related controversies, barriers, and influeners,[5,13,24,42,79] to those examining uptake and decisions surrounding HPV vaccines [7,12,80,81] and associated determinants. Additional routine child immunization studies are included as well, examining similar

predictors and factors. The studies are dispersed internationally and domestically with focuses divided between the studies, which evaluate different age groups, ethnicities and races, socioeconomic levels, and regional and geographic disparities to name a few. It is evident by the extensive literature, that the relationship between vaccination decisions and predictive factors and determinants has been analyzed substantially across numerous diverse groups, with questions linked to many of the major determinant categories.

Given this, a deeper level of scrutiny of existing publications related to influenza vaccine uptake decisions for pediatric populations yields a different literary landscape. This is evident specifically in relation to the H1N1 Influenza pandemic of 2009, and the CDC ACIP LAIV recommendations revocation of 2015, and their respective impacts on overall child influenza vaccination rates, and decisions by parents to uptake influenza immunizations in the United States. It is evident that a void in knowledge exists in the literature for these particular topics. The quantity of publications available in relation to these topics specifically is scarce, in particular for the United States.

The majority of existing publications that examine vaccine uptake rates, and decisions to complete vaccines, are focused on an entirely different vaccine type, for a different disease class, or they are examining a different phenomenon or event in relation to a completely different outcome. Furthermore, the vast majority were vaccine studies conducted internationally in different continents such as Europe, South America, Asia, Africa, and Australia and excluded North America.

2.8.1. 2009 H1N1 Influenza Pandemic

Examining existing publications related to vaccine uptake following the 2009 H1N1 pandemic, it is evident that the majority of studies evaluated focus on international

populations and samples, with post pandemic uptake rates analyzed for much of the central and south American nations broadly for all age groups,[82] and seasonal uptake rates specifically for adults for 12 different European nations including Austria, Czech Republic, France, England, Finland, Germany, Ireland, Italy, Poland, Portugal, Spain, and Netherlands.[45] A smaller number focused on East Asian nations such as China and Japan.[45] The vast majority of these studies were cross sectional with a minority of longitudinal studies, and an even greater minority of RCT's, and CRCT's. Of the U.S. based studies in existence, the majority examined the adult population with adequate, but limited sample sizes, that were less than several thousand, with some being CRCT's and RCT's, and possessing strong methodology and study design.[45] The studies in existence overall examined barriers and uptake factors well with a vast array of predictors that encompassed nearly all determinant categories. Of studies that examined children specifically, a study conducted for Western Australia in relation to parental decisions to uptake for infants,[11] and the U.S.,[31] which focused primarily on uptake trends, and percentage coverage over time for IIV eligible infants only.

2.8.2. 2015 LAIV Preferential Advisement Revocation

Examining existing publications related to vaccine uptake following the 2015 LAIV preferential recommendation revocations, a few studies were focused in Europe, with a study in England assessing LAIV uptake rates in different geographic regions based on program implementations and analysis of coverage percentages overall.[36] Of the several studies that focus on subpopulations within the U.S., they concentrated on particular states or regions only, and overall flu vaccine rates. Examples include a study conducted among children in Pennsylvania, that evaluated the impacts of the complete

withdrawal of the LAIV, by analyzing 2016-2017 data only, and applying logistic regression. The study concluded declines in uptake occurred when comparing the initial and late time periods of the flu season for pediatric flu vaccine uptake within the state.[33] Another study examined the same LAIV policy shift and ensuing uptake rates for children of a broad age group for the state of Oregon, and concluded unchanged uptake rates overall for pediatric flu vaccines.[25]

A final example includes a study that examined LAIV uptake following the 2014 ACIP preferential recommendations among the multistate pediatric samples of Michigan, Minnesota, New York, Wisconsin, Oregon, and North Dakota, and concluded increases in uptake had occurred for LAIV following the policy implementation.[26] These studies were overall well designed, with application of logistic regressions for the single statewide analysis studies,[25,33] and analysis of percentage fluctuations in coverages for the multistate study example.[26] These studies yielded results that can be extended, and further expanded upon by future studies in relation to child vaccine uptake rates, particularly in relation to the 2015 revocations of the ACIP preferential recommendations for LAIV usage over IIV's, which was the policy point least evaluated for its consequences as compared to the 2014 preferential recommendations, and the 2016 complete withdrawal of recommendations for LAIV usage by ACIP.

2.8.3. Disadvantages of Existing Literature

Of the existing studies that examine influenza vaccines specifically, the majority are external and exclude the United States, and are evaluating different outcomes, variables of interest, predictors, or policy shifts and occurrences. Of the existing studies conducted for the U.S. in relation to influenza vaccination rates, the majority are either

assessing different determinants and chief variables of interest, or focus on a different subpopulation such as adolescents, adults, and the elderly. They are limited in scope and scale, and are distinct and confined to only a particular city, county, region, or state, and are not nationally conducted and representative. They employ the use of data sources that are not designed specifically for influenza vaccine assessment, or are collected by less robust means. They examine and assess limited time spans that are not substantial, sufficient, or ample enough to produce decisive conclusions. They implement the use of methodological approaches that do not establish cause and effect relationships and are less rigorous in nature. They examine locations that lack diversity in observations and subjects evaluated, with small sample sizes limiting their statistical power.

Of the literary works that specifically focus on the occurrence of the historical 2009 H1N1 Influenza pandemic, and the 2015 CDC Advisory Committee on Immunization Practice's (ACIP) retraction of its original recommendations for preferential usage of the live attenuated influenza vaccine (LAIV),[21,25,26,33–35] the majority yield conclusions whose explanations of the exact impacts on overall child influenza vaccine rates and uptake decisions are relatively uncertain, inconsistent, and contradictory.[16,25,26,31,33,34,44,83] Certain studies report a decline in influenza vaccine rates as a consequence of these occurrences,[11,16,30,33] while in other studies, there are reports that the opposite happened, and state that it conversely increased.[26,31,32] Additionally, certain studies report that the vaccination uptake remained static and did not fluctuate considerably.[25] Assessing the studies in existence overall, it is notable that variations are exhibited in the range of implications concluded by different studies.

2.8.4. Prime Publication Examples

2.8.4.a. ACIP LAIV Advisements

There are few existing publications that attempt to examine similar questions to what this study is proposing. The closest study currently, for examining CDC ACIP LAIV policy revocations, is the study by Robison et al. that analyzes 5 years of flu seasons consecutively from 2012 to 2017, for a cohort of individuals located specifically in Oregon, and focuses on ages 2-17 years excluding those 6 months to just under 2 years. The outcome of IIV receipt was assessed for both IIV and LAIV eligible patients. The study concluded that the 2016 withdrawal of the recommendations for LAIV usage had minimal to no impact on the immunization rates overall, with minimal associated fluctuations observed over the evaluated seasons.

This study is limited in that it examines the state of Oregon alone, which is limited in diversity and ethnic representation and narrow in this arena, and the study is not nationally distributed with respect to its sampled subjects. This study only examines one year following the policy shift point of 2015-2016 and is limited in this aspect. It is debatable, as to whether it follows the post policy shift time period sufficiently, and amply enough to produce the most meaningful, decisive, and robust conclusions with valid implications. This study's time span of analysis is less symmetric with its observation years heavily skewed towards pre-policy shift time periods, as compared to post policy time periods, affecting its post-policy analysis portion and associated statistical estimations.

This ultimately results in conclusions that were extrapolated from those regression estimations that may not be optimal. Furthermore, this study uses statewide immunization

data that lacks the rigor of a nationally representative comprehensive data source, and may lack the extent of variables that are accessible for analysis. Additionally, the methodology implemented for this study establishes correlative and associative linkages as opposed to cause and effect relationships resulting in a connection being established that possesses lesser connotations. This study does not examine the influences of intermediary ACIP recommendation alterations in the examined time spans, and only focuses on the 2016 complete revocation of the recommendations for LAIV usage and the associated 2016-2017 season. It does not incorporate the 2014 preferential advisements for LAIV over IIV usage, and the subsequent 2015 rescindment of preferential advisements. The lack of integration of these critical policy points may have resulted in unmeasured immediate and lagging impacts that may have occurred and ensued respectively for the target sample evaluated.

2.8.4.b. H1N1 Influenza Pandemic

The closest study for examining the impact of the H1N1 pandemic is the study by Santibanez et al. that analyzes 10 consecutive influenza seasons from 2002 to 2012 using NIS data for 6 to 23 month old children. This study concluded that a significant escalation in total influenza vaccination coverage occurred from the start of the study period to its termination using Kaplan-Meier survival analyses. Although this study is national in its scope, and examines an extensive time span in years, it is limited in several ways. This study examines only two seasons of post pandemic occurrence years and eight years pre-pandemic and is heavily asymmetrical and skewed towards pre-pandemic analysis resulting in a limited number of observations to be available for post pandemic assessment, and impact estimation.

This study's methodology does not establish causative relationships and primarily reports fluctuations in percentages and descriptive information that is a weaker foundation for inference generating. Furthermore, this study analyzes a limited range of child age groups with its boundaries spanning only 17 months and excludes all individuals two years and older who are prime candidates for other formulations of the vaccine such as LAIV's which were introduced and approved in 2003. It follows that the definition of total vaccine coverage in this study is flawed and incomplete, since its definition excludes individuals who were eligible for, and were administered LAIV's, as opposed to IIV's, from 2003 onward. The authors of this study justified this age exemption because this age group was designated as the highest risk subgroup for influenza related complications, they were the first child subgroup to have routine flu vaccines recommended for them, and because provider reported immunization histories were available in NIS specifically for this age group, whereas other ages were parent reported.

This study is also narrowly focused on ethnic disparities and incorporates a nominal degree of predictors and covariates potentially weakening the statistical estimation. It is missing determinants that are present as controls in the regressions of the majority of other publications, especially for the primary decision maker for vaccine uptake, and other socioeconomic, psychosocial, and contextual factors. This study also lacks incorporation of minor scale influenza epidemics that occurred during the time periods of analysis. This may bias estimates of the impact of the 2009 H1N1 pandemic, and its ensuing effects on immunization status and influenza vaccination rates.

Another study examining the relationship between influenza season severity and vaccine effectiveness in prior and current time periods with influenza immunization rates in the current season concluded that no statistically significant association was evident,[84] with minimal decreases in uptake observed for seasons following low vaccine effectiveness years.[84] This study also concluded that current season severity was not associated with immunization rates when comparing different age groups. This study indicated the need for future studies in order to determine and ascertain additional conclusions.

2.9. Proposed Study

Given the review of the existing literature, and comparisons of previously published studies, it is evident that a void in the literature exists in its current state. This mandates the need for additional studies that will fill current voids and supplement existing publications.

2.9.1. Primary Goal and Proposed Research Questions

The research questions proposed would be examining the two major pandemic and policy events, and their respective impacts on overall influenza vaccination rates and uptake among U.S. children. Specifically, the questions would be assessing how the occurrence of the 2009 H1N1 influenza pandemic, and the 2015 ACIP LAIV preferential recommendations revocations, impacted overall child flu vaccine uptake rates in the United States.

2.9.2. Hypotheses

H_1: The 2009 H1N1 pandemic is expected to increase the likelihood of overall child influenza vaccine uptake. In accordance with the previous literature, and this studies

conceptual model, vaccine uptake stimulating factors related to disease severity and susceptibility to infection will drive the expected increases in flu immunization uptake.

H_2: The 2015 ACIP LAIV preferential recommendation revocation is expected to decrease the likelihood of overall child influenza vaccine uptake. In accordance with the previous literature, and this studies conceptual model, provider dissemination of immunization information, based on ACIP advisements, will likely reduce vaccine uptake, since LAIV will not be recommended as the preferred option to parents by providers.

2.9.3. Advantages and Contributions of this Study

This study is the first nationally representative and comprehensive study that examines the impacts of the 2009 H1N1 pandemic, and the 2015 ACIP LAIV policy revocations on overall influenza vaccination rates among children in the United States. This study is the first to analyze these occurrences over an extensive time continuum, and examine their impacts respectively, in separate and distinct literary works. Its scope, comprehensiveness, depth, and representation will supersede that of existing studies. Previous studies for the U.S. generally focused on a limited region or state. To reiterate, the majority of previous studies where completed on populations internationally and abroad and excluded U.S. territories.[6,11,20,36,37,82] This study overcame this and is designed specifically for the United States. Additionally, this study examined a time span that is greater than existing studies, and ample enough to generate profound results and conclusions.

Previous studies were focused on children of varying age groups, with some concentrating on certain ranges, but excluding others, that this study encompasses, and

analyzes specifically in relation to overall influenza vaccine uptake decisions following occurrence of the pandemic and policy event points. Furthermore, of the LAIV policy shifts examined, very few had focused on the 2015 preferential advisement retractions, and instead evaluated the 2014 preferential advisements, or the complete retractions of 2016. They also did not use a data source such as the National Immunization Survey (NIS), and its variations (NIS-Child and NIS-Teen), which are designed specifically for tracking vaccination data for select age subpopulations. This study achieved this, and combines elements of these NIS data sources to improve its strength and harness its advantages.

The methodology of this study is more rigorous in terms of its results and implications. It attempts to establish a strong correlational relationship, as well as examine marginal effects, as opposed to previous studies that established a weaker relationship in the form of basic associations, and descriptive results, producing a stage for less prominent inferences and extrapolations. Furthermore, this study implemented auxiliary estimations in the form of additional quasi experimental estimations in order to reinforce primary computations.

On aggregate, the extensive and comprehensive nationally representative dataset used for this study, its specificity combined with the substantial time range examined, in conjunction with the rigor of the methodology implemented, allowed for a critical analysis of the consequences of the historic H1N1 pandemic, and the recent CDC LAIV policy revocations, on overall child influenza vaccination rates in the United States.

Ultimately this study overcame the lack of consistency in the ascertainment of the impacts of the H1N1 pandemic, and CDC LAIV recommendations revocation on overall

child influenza vaccination rates. It supplements the literature, and assisted in overcoming the deficiency in the number, scale, and scope of studies performed for the U.S., and addresses the void that is the absence of a comprehensive nationally representative study focused on children in the United States.

2.9.4. Public Health Implications and Utility of this Study

2.9.4.a. Universally

Conclusions attained by this study would be vital for CDC and public health policy development and formation as they pertain to child influenza vaccinations in the future, by ascertaining behavioral responses to policy shifts and pandemics and decision making for uptake of child influenza vaccines within the United States. This would ultimately allow for public health policymakers in the U.S. to increase future child influenza vaccination coverage by understanding how parental perspectives about influenza vaccines are impacted by influenza epidemics and policy shifts.

In summary, these criteria make this proposed study a necessary addition to the literature that would reconcile inadequacies that currently exist among the limited child Influenza vaccine studies, and enhance the child immunization research area of the field of public health. The results and outcomes of this study essentially provide an in depth viewpoint on the relationship between adoption of child influenza vaccines and parental perspectives, allowing for better predictions and forecasts of what is to come, and how to be ready for it. Examples of potential applications of this study's results include and are not limited to the following based on each specific aim.

2.9.4.b. H1N1 Influenza Pandemic

Results could be used by policymakers to target specific subgroups that were more vulnerable and susceptible in not completing flu vaccines in post pandemic, such as children of lower education, lower income parents, or of a certain age group or ethnic background. Results could be used to develop strategies that would allow for attention to be directed or diverted accordingly to different subgroups based on how the subgroup responded in reaction to the pandemic, saving resources, and allowing for more efficient use of those resources.

Results could be used to improve capabilities to anticipate fluctuations in flu vaccine uptake for children following pandemics, allowing CDC officials to strengthen campaigns to encourage flu vaccine uptake, or to inform clinics and medical facilities of such expected fluctuations, permitting them to reallocate clinical staffing accordingly, and prepare for surges in patients seeking flu vaccines. Results can be used to yield improved patient flu vaccine achievement, by implementing the use of health information technology, and patient-provider health communication pathways. These would include electronic, and digital correspondences, telemedicine and telehealth interfaces, and flu vaccine quick-sheets, and fact-sheets, during post pandemic flu seasons. Results can be integrated into use for flu monitoring apps such as CDC's Flu View, Flu Near You, and Flu Defender, which can be enhanced operationally and functionally by this studies outcomes in order to improve influenza epidemic and pandemic surveillance, prevention, and control by public health institutions.

2.9.4.c. ACIP LAIV Advisements

Results could be used by policymakers to target specific subgroups that were more vulnerable and susceptible in not completing flu vaccines in post policy shift years, such as children of lower socioeconomic status parents, or of a certain age range, or racial subgroup. Results could be used to develop tactics that would allow for attention to be reallocated to more susceptible groups, depending on reactions of those particular groups to policy decisions, promoting optimal and efficient use of limited resources. Results could be used to enhance capabilities to anticipate fluctuations in flu vaccine uptake for children following policy events, permitting public health professionals to increase flu immunization rates, by notifying health institutions of such projected influxes of vaccine seekers. Reallocation of clinical personnel would ensue correspondingly in order to prepare for surges in patients seeking flu vaccines.

Policies could be developed guiding clinicians, such as family doctors and pediatricians, that would assist them in explaining flu vaccine recommendations and advisements better, and with more concerted efforts with patients, specifically following revocation years where greater confusion may be present, in order to improve parental decision making abilities. Clinicians can be informed to focus more on target parental groups that are more prone to avoiding flu vaccines, even when flu vaccine rates have increased overall, or targeting post-policy revocation years with stronger vaccine interventions, pamphlet distribution, and advertising, in order to counteract the anticipated decreases in flu vaccines that would occur in post-withdrawal years.

Results can be used to yield improved patient flu vaccine completion rates, and achievement outcomes, by using patient portal email correspondences, telemedicine and

telehealth communication pathways and interfaces, and flu vaccine quick-sheets and fact-sheets during anticipated low uptake seasons following ACIP recommendations. Results can be used to promote performance of flu vaccine related activities in the education systems nationally, including implementing and incorporating kindergarten, preschool, and school based flu vaccine interventions, programs, and memorandum distribution in order to increase uptake in post policy shift years that may be deficient for immunization completion.

CHAPTER 3

METHODOLOGY

3.1. Description of Project Design and Methodological Approach

The primary purpose of this project is to advance understanding of how influenza pandemics and policy shifts affect the likelihood of parents getting their children immunized against the influenza virus. By examining marginal effects for completion of child flu vaccines following the occurrence of the pandemic and policy shift events respectively, we plan to evaluate these impacts. Analysis was achieved by executing logistic regression models, specifically by implementing an interrupted time-series (ITS) empirical approach, which is a quasi-experimental design strategy for the estimations, using STATA 16 statistical software. Provider-verified immunization histories from a state and nationally representative dataset will serve as the basis for performing these statistical estimations. Vaccine formulation specific measures served as the basis for execution of a series of auxiliary ITS regressions for the LAIV policy analysis, that assisted in reinforcing and corroborating the primary ITS estimations evaluating overall immunization uptake. All ITS regressions are predicated on clinician validated responses.

The 15-year time span from 2003 to 2018 was examined for this study, encompassing both the 2009 H1N1 pandemic and the 2015 ACIP LAIV withdrawal completely and sufficiently. The time period of analysis commences in 2003, since that is the preliminary year the IIV formulation was universally recommended by ACIP.

It is also the year where the LAIV formulation of the immunization was accepted and authorized for usage by the ACIP. The time period of analysis terminates in 2018 as that is the most recent year available for analysis. The data was aggregated, and compiled for analysis by merging separate annual surveys consecutively into a single dataset. The final version of the data was a series of repeated cross-sections based on annually completed NIS surveys. This generated dataset emulates longitudinal and panel data sources, and allows for minimization of bias, while reinforcing estimation of a correlation relationship that is representative of a larger scale heterogeneous population.[85]

Sensitivity analyses, including fixed effects estimations for the H1N1 pandemic analysis, and difference in differences (DID) estimations for the LAIV policy analysis, were performed in order to corroborate and validate results yielded by the primary logistic regressions.

Specific Aim 1: To ascertain the effects of the 2009 H1N1 pandemic on overall child influenza vaccination uptake rates in the U.S. by assessing changes in the likelihood that a child is vaccinated for influenza following the pandemic event.

H_1: The 2009 H1N1 pandemic is expected to increase the likelihood of overall child influenza vaccine uptake. In accordance with the previous literature, and this studies conceptual model, vaccine uptake stimulating factors related to disease severity and susceptibility to infection will drive the expected increases in flu immunization uptake.

Specific Aim 2: To ascertain the policy effects of the 2015 ACIP LAIV preferential recommendation revocation on overall child influenza vaccination uptake rates in the U.S. by assessing changes in the likelihood that a child is vaccinated for influenza following the policy shift event.

H_2: The 2015 ACIP LAIV preferential recommendation revocation is expected to decrease the likelihood of overall child influenza vaccine uptake. In accordance with the previous literature, and this studies conceptual model, provider dissemination of immunization information, based on ACIP advisements, will likely reduce vaccine uptake, since LAIV will not be recommended as the preferred option to parents by providers.

3.1.1. Data Sources

The data source used for this study was the National Immunization Survey (NIS), which is conducted by the CDC's National Center for Immunization and Respiratory Diseases (NCIRD) in order to monitor immunization coverage. It is nationally representative and comprehensive including flu vaccination data for children 6 months – 17 years of age for all 50 states and additional U.S. territories.[86] NIS consists of a combination of NIS-Child (ages 19-35 months), and NIS-Teen (ages 13-17 years).[86] NIS offers national, state, and local level data, provided directly from the child's providers (NIS-Child and NIS-Teen consist of provider-verified immunization measures), bolstering its accuracy and validity.[86] It contains information regarding the types of vaccines administered to children, their dates and dosages, demographic, socioeconomic, geographic, and insurance data, as well as administrative data related to providers and facilities where the procedures were performed.[86]

The CDC published surveillance reports of influenza disease activity, in the form of the National Notifiable Diseases Surveillance System (NNDSS), was the data source used in conjunction with the aforementioned NIS population data, in order to execute sensitivity analysis estimations for the H1N1 pandemic. CDC's FluView and generated

report data from ILI Net was used as well in order to achieve this sensitivity analysis. This was accomplished by examining measures such as population-adjusted ILI incidence and prevalence rates, for each state, on an annual basis.

3.1.1.a. NIS Sampling Procedures and Weighting Approach

NIS-Child and NIS-Teen conduct sampling in a two phased and tiered approach. In phase one, the data collection procedure is to attain immunization information for a national probability sample of children, by performing random digit dialing (RDD) within each of the statistical sampling strata in order to identify eligible subjects.[86] The interviewers request permission to contact the vaccination provider of the qualified child, and subsequently, a mailed survey is sent to the designated clinician. In phase two, the provider record check (PRC) survey is completed, and allows for confirmation and verification of the phase one questionnaire responses.[86] Overall this allows for vaccination statistics that are comparable across geographic territories, with the progress of time, and promotes minimization of bias that may exist.[86]

NIS-Child and NIS-Teen possess weighting processes and procedures that adjust for variation in sampling rates, differences and discrepancies in response rates, and variations in representation in the sample relative to the overall population being assessed.[86] This allows for improved accuracy of estimates at various sampling levels. The estimates and variance approximations are generated for separate areas, states, and sampling subdivisions. Weight imputations are performed for the survey as necessary.[86]

3.1.1.b. NIS Response Rates

The anticipated NIS-Child sample size for completed interviews is approximately 25,000 addresses, on average.[86] The annual response rate of NIS-Child is approximately

65 percent of eligible subjects within the sample, on average, for the parent response segment.[86] The rate of children with adequate provider data available is approximately 70 percent, on average.[86]

The anticipated NIS-Teen sample size for completed interviews is approximately 35,000 addresses, on average.[86] The annual response rate of NIS-Teen is approximately 60 percent of eligible subjects within the sample, on average, for the parent response segment.[86] The rate of children with adequate provider data available is approximately 70 percent, on average.[86]

3.1.2. Quasi-Experimental Design Overview and Primary Application

Although randomized controlled trials (RCTs) are considered the top echelon or gold standard for conducting a study, they are not always feasible, possible, or ethical, and in certain cases, not the optimal design option, as they may focus on a specified cohort of individuals, and are not generalizable to the population level which is heterogeneous in composition.[85] RCTs are the gold standard for clinical trials concerning the efficacy of an intervention, treatment, or program, but are not appropriate for many other types of studies. Instances where overall population level effects of a vaccine program or related event are being evaluated, and examined, as opposed to individual level effects, require the implementation of quasi-experimental strategies, as opposed to RCTs or cluster RCTs (CRCTs), which are incapable of assessing such impacts.

Quasi-experimental designs are optimal to use in instances where assessment is being performed for a previously used vaccine formulation, or previously implemented vaccine intervention or program. They also preserve the ethical aspect of the experiment completely providing protection for participants in this regard. They are also

advantageous to apply to cases where time constraints and cost limits exist. This aspect does not directly benefit this study, and is not significantly advantageous for this instance, hence providing minor value in this capacity. Quasi-experimental approaches are also optimal when examining the impacts of a vaccine related event, such as a pandemic, policy, or intervention, in relation to vaccine uptake rates. They allow for evaluation of the overall impacts of the occurrence on health service outcomes in natural settings and real world scenarios.[87]

Quasi-experimental designs, unlike RCTs, do not incorporate randomized assignment to control and treatment groups in order to enhance their internal validity, and reinforce the approximation of the true counterfactual phenomenon, which is at the core of evaluation study designs, and symbolizes what would have been observed if the event or intervention had not occurred and was absent. The true counterfactual is unknown and can only be approximated, with more accurate approximations improving the legitimacy and internal validity of the analysis. Precise mimicry of the true counterfactual is central and chief to strengthening the statistical approach if the quasi-experimental design.

Quasi-experimental designs, unlike experimental designs, that directly assign participants to comparison groups, take advantage of exogenous sources to accomplish this, termed as a natural experiment. This allows the quasi-experimental design to retain the majority of advantages and superior aspects of the RCT and CRCT designs without directly allocating subjects to comparison groups, and instead indirectly accomplishing the same task through exogenous factors. In essence, the quasi-experimental design is a natural experiment that achieves the objectives of an RCT without being randomized directly in its assignment process, and instead achieves this quality through other external

means. They possess similar characteristics, and design attributes as compared to RCTs, but are distinct and unique.[87]

These exogenous sources include location differences in event occurrences, where one location exhibits the event while another was restricted from experiencing it. Threshold differences, where a marker may limit groups from exposure to a phenomenon, and serve as natural boundaries. Finally, time point occurrences which divide groups naturally into pre and post segments, allowing for comparison of the two segments, while retaining natural assignment to the pre and post groupings due to exposure being divided by the time point barrier. This latter category is what will be applied as the exogenous source for this study, with pre-pandemic and pre-policy shift trends being used to accurately approximate the true counterfactual, or the phenomenon that would have been observed in the absence of the pandemic or policy shift. Because the subjects examined in this study are not in control of assignment to the pre and post time point segments of our analysis, this eliminates volunteer selection bias.[87] This type of bias is of minor concern for this project, with contemporaneous event occurrence being of chief concern.

The major assumption that exists with this study is that the pre-event trend serves as the comparison control group for non-exposure to the event, and that the post-event serves as the treatment group for exposure to the event, with differences and fluctuations in vaccination uptake being attributable distinctly to the event occurrences and exposure to the event time points. This relies on the pre-event trends, which serve as the true counterfactual, persisting consistently past the event exposure time point, with minimal deviation. If the counterfactual is erroneous, then measured increases or decreases in flu vaccine uptake rates, following the event occurrences, will also inherit flaws that were

generated from the approximation stage of the true counterfactual. This is because the assumed baseline for post event comparison is predicated on the assumed counterfactual, which is the expected trajectory that will be adhered to in the absence of the treatment or exposure. Hence it follows that changes that are computed in the post event phase that are attributed to the events impact become inaccurate, since the changes are being compared to a falsely established baseline trend, and incorrectly presumed anticipated unobservable trajectory. This assumption is at the crux of this approach, and is its weakest point.[87]

In order to minimize the potential for violation of this chief assumption, methodological countermeasures can be strategically employed in order to maintain the accuracy of the true counterfactual. Tactics include augmenting the regression formula, and integrating countermeasures in the form of additional control factors, and indicator variables signifying concomitant incidents, such as simultaneous policy fluctuations or epidemic occurrences, that may alter the true counterfactuals trend assumption. Incorporating these aspects assists in maintaining stability with regards to the counterfactual trends anticipated trajectory past the point of exposure, and allows for deviations that the unobserved true counterfactual may encounter, to be compensated for adequately, hence improving the accuracy of the actual effect estimation.

For this studies estimation, the threats that would potentially cause deviations in the assumed counterfactuals expected unobservable trajectory, from the correct course, are mitigated by insertion of control variables within the regression function. These control elements include state level policy and mandate differences, state characteristics and unique attributes, indicators of time proximal influenza related policy shifts, and indicators of restricted scale epidemic occurrences of the influenza virus. The hazards to

this studies counterfactual assumption and potential violation are mainly in the form of simultaneously or proximally occurring state and national vaccine uptake related policy shifts and events.

For the 2009 H1N1 pandemic analysis these primarily include the restricted scale influenza epidemics (RSE's) that occurred in the aftermath of the H1N1 pandemic, which will be compensated and adjusted for via augmentation of the regression equation as described above. This will mitigate the interference of the RSE's influences on flu vaccine uptake rates in the post H1N1 pandemic phase of the analysis. The RSE's could decrease uptake rates by exacerbating preexisting erosions in vaccine confidence, or by initiating attritions in vaccine confidence levels. The RSE's could increase uptake rates by amplifying preexisting concerns of disease exposure, or by initiating intensified awareness of disease risk.

For the 2015 LAIV policy shift analysis, these primarily include the following. First, the lagging effects of the 2014 LAIV preferential advisements, which could possibly affect the pre 2015 policy shift segment of the analysis, by causing increases in overall flu vaccine uptake, and delayed effects that are realized proximate to the 2015 policy point of interest. Second, the aftermath of the 2016 LAIV complete rescindment advisements, which could potentially affect the post 2015 policy shift segment of the analysis, by causing decreases in overall flu vaccine uptake, and immediate effects that are realized proximate to the 2015 policy point of interest.

A quasi-experimental design is advantageous for this study due to potential, but minor, cost and time constraints, which are inherent in epidemic, pandemic, and seasonal flu vaccination scenarios. Additionally, RCTs would be unethical for this study due to the

outcome being examined, and the events being assessed for their impacts, hence a quasi-experimental design is most appropriate. Also the fact that both the LAIV and IIV immunizations have previously been implemented and applied, disqualifying the use of RCTs or CRCTs as they are not possible to use in these instances. Quasi-experimental designs are also necessary for our study because we are evaluating an outcome that could not be examined in initial vaccine trials, such as the uptake of influenza vaccines, among a specific subpopulation such as children. A quasi-experimental design provides the advantage of being relatively unaffected by the absence of a direct randomization process, since allocation to comparison groupings is based on eligibility resulting from naturally existing barriers, which in this case is the time point that divides subgroups based on their exposure to the event.[87]

3.1.3. Interrupted Time-Series (ITS) Overview and Primary Application

The interrupted time-series design is a sub-design category of the quasi-experimental design approach. In the ITS design, the exogenous variable that is responsible for ensuring assignment is time. With the ITS design, pre and post event time-point observations are analyzed in order to assess changes in the trends of the outcome variable that occur over time. This is achieved by comparing the outcomes trends before and after the time point of interest, and assessing the changes in the outcome variable that ensue following the occurrence of the time point of interest. The alteration in the slope of the trend function being analyzed symbolizes the impact of the event on the outcome variable.

Explicated in regression analysis terms, the slope of the outcome function can be compared before and after the time point of interest to determine the degree of impact of

the event in question. If the regression analysis yields an immediate fluctuation in the outcome variable, it is termed a change in intercept, while if a consistent and sustained fluctuation is detected, then it is defined as a change in slope.[88] The selection and designation of the ITS model should be accomplished a priori while considering the type of outcome variable being examined as well as the time point of interest.[87]

The primary advantage of the ITS design is that it is best implementable in scenarios where a true unaffected control group is not available, and when the overall impacts of an event are being assessed in a pre and post time point manner. The ITS design is advantageous for population level analyses due to the fact that it controls for preexisting trends, and selection bias due to population level differences, and heterogeneity that exists.[87]

The primary disadvantage and limitation of the ITS design is its inability to eliminate and exclude the effects of simultaneous and coinciding phenomenon such as pandemics and epidemics, policy shifts, or interventions that are occurring parallel to the target phenomenon concomitantly. This limitation is termed history bias, and exists with all ITS design approaches, suppressing its ability and reliability in extrapolation of trends and patterns. It follows for this study that phenomenon occurring alongside the 2009 H1N1 pandemic and 2015 LAIV policy shifts could be either directly or indirectly influencing differences in child influenza vaccine uptake rates simultaneously, and overlapping of effects could potentially be occurring that cannot be isolated with the ITS design approach.

If the history bias that exists is sufficiently influential, to the degree that it alters the forecasted counterfactual trend, and violates the presumed counterfactual assumption,

then the computation of the effect in the post event phase of the estimation becomes defective. Conceptually stated, if the contemporaneous phenomenon's expected impact directionality is the same, and co-aligned with the event in question, then overestimation of the events impact is yielded. If the contemporaneous phenomenon's expected impact directionality opposes and contradicts that of the event in question, then underestimation of the events impact is yielded.

If the history bias affects the unobserved actual trend in a way that it alters the functions slope magnitude, and increases it as compared to the assumed counterfactuals slope magnitude, then the computed event effect is greater in quantity than the actual impact magnitude, and the approximation is incorrect due to overestimation of the impact magnitude.

Conversely, if the history bias alters the unobserved actual trend in a way that it alters the functions slope magnitude, and decreases it as compared to the assumed counterfactuals slope magnitude, then the computed event effect is lesser in quantity than the actual impact magnitude, and the approximation is incorrect due to underestimation of the impact magnitude.

If history bias sufficiently influences the unobserved actual trend, such that the initial intercept point immediately following the event exposure time point is altered, then errors can arise as well for the estimation. If the initial intercept, or baseline, point following the event exposure was actually greater in magnitude than the assumed counterfactuals, then the effect magnitude computed is flawed, due to overestimation of the impact magnitude. That is, the estimations computed effect was erroneously greater than the actual effect, and the events true impact was over-credited.

If the initial intercept, or baseline, point following the event exposure was actually lesser in magnitude than the assumed counterfactuals, then the effect magnitude computed is flawed, due to underestimation of the impact magnitude. That is, the estimations computed effect was erroneously lesser than the actual effect, and the events true impact was under-credited.

Table 3.1 - Effect Estimation Fallacies Due to Assumed Counterfactual Violations

Effect (E) Estimation Fallacy	Slope (S) Comparison	Intercept (I) Comparison
Overestimated ($E_{Computed} > E_{Actual}$)	$\lvert S_{Actual}\rvert > \lvert S_{Counterfactual}\rvert$	$\lvert I_{Actual}\rvert > \lvert I_{Counterfactual}\rvert$
Underestimated ($E_{Computed} < E_{Actual}$)	$\lvert S_{Actual}\rvert < \lvert S_{Counterfactual}\rvert$	$\lvert I_{Actual}\rvert < \lvert I_{Counterfactual}\rvert$

The potential for history bias for the 2009 H1N1 pandemic is moderate, prior to adjusting the regression function accordingly, due to the multiyear distancing of the preliminary RSE, of the three RSE sequence, relative to the pandemic itself. If the ensuing two RSEs (2012-2013, 2013-2014) are potent in their immediate effects, then flu vaccine uptake rates could increase if perceived disease risks are intensified, or conversely decrease if vaccine confidence is diminished. The former would generate bias manifested as overestimation of the pandemics effect, and the latter would generate bias manifested as underestimation of the pandemics effect.

The potential for history bias for the 2015 LAIV policy shift is more prominent, prior to adjusting the regression function accordingly, due to proximate LAIV linked advisements in 2014 and 2016, as well as the final RSE in 2017-2018. The hypothetical biased scenarios that would be exhibited in relation to the LAIV advisements are as

follows. These particular hypothetical scenarios are predicated on predecessor publication results that were most significant.

The 2014 preferential advisements for the LAIV may have improved overall flu vaccine uptake rates, resulting in lagged effects, that may bias the 2015 analysis by inducing underestimation of 2015 post policy effects. This is due to 2014 post policy effect directionality opposing the directionality of the 2015 policies, and the counterfactuals trajectory deviating from the actual trajectory. This subsequently leads to the post 2015 policy point computed effect being smaller than the actual effect.

The 2016 complete withdrawal advisements for the LAIV may have reduced overall flu vaccine uptake rates, resulting in immediate effects, that may bias the 2015 analysis by inducing overestimation of 2015 post policy effects. This is due to the anticipated 2016 post policy effect directionality co-aligning with the directionality of the 2015 policy, and the counterfactual trajectory deviating from the actual trajectory. This subsequently leads to the post 2015 policy point computed effect being greater than the actual effect.

The 2017-2018 RSE may have increased or decreased overall flu vaccine uptake rates. If the RSE increased uptake rates, then the 2015 analysis may be biased, and underestimation of effects may be yielded. This is due to the presumed counterfactual trajectory's slope being different than the actual trajectory's slope, leading to a computed effect that is smaller than the actual effect. This is similar to the anticipated biased effects yielded by the 2014 LAIV policy shift.

If the RSE decreased uptake rates, then the 2015 analysis may be biased, and overestimation of effects may be yielded. This is due to the presumed counterfactual

function's slope being different than the actual function's slope, leading to a computed effect that is greater than the actual effect. This is similar to the anticipated biased effects yielded by the 2016 LAIV policy shift.

A milder limitation that is inherent with all time and history based design strategies is the presence of instrumentation fluctuation interferences if the outcome was measured differently or in a varying manner over the time periods being examined. This limitation is minimal in this study, as flu vaccine uptake has been measured as an outcome consistently by the same entity, the CDC, over time with consistent conventions historically.[87]

General Empirical Form Regression Model: $CIVU_{tis} = \beta_0 + [\beta_1 (P_{ts})] + [\beta_2 (\mathbf{X}_{tis})] + [\beta_3 (Z_{ts})] + [\beta_4 (M_{ts})] + [\beta_5 (SFE_s)] + [\beta_6 (TFE_t)] + [\beta_7 (RSE_{ts})] + e_{tis}$

Regression models were executed using the formulation described above, with one corresponding to the pandemic event (2009 H1N1), and one to the policy shift event (2015 LAIV withdrawal). For each respective event point, the major regression estimations were performed based on the provider-verified responses. Variations of the regression equation were applied in the auxiliary estimations.

Outcome (Dependent) Variable: CIVU (Child Influenza Vaccine Uptake) denotes whether the child was administered and received the influenza vaccine. This is a binary "Yes" or "No" outcome measure represented by 1 or 0 respectively.

Primary Variable of Interest: P (Event of Interest) denotes the occurrence of the policy shift or pandemic. This is binary and symbolizes incidence of the H1N1 pandemic or the LAIV preferential advisement rescindment accordingly.

Predictive (Independent) Variables: Child sex, age, birth order, race/ethnicity, relocation/mobility comparing state of birth and current location, maternal age, education level, marital status, insurance type, family income level, and provider/clinician facility type. These covariates are in concordance with previously applied conventions among predecessor studies, and are standard across previously completed studies published in the literature. They are represented by the vector "**X".**

Additional Control Factors: SFE = State Fixed Effects; TFE = Time Fixed Effects; Z = State level characteristics that vary with time; M = State level policy and mandate differences; RSE = Restricted Scale Epidemic Occurrences of the Influenza Virus. Time-variant state level attributes specifically include: Unemployment rates, retrieved from the Bureau of Labor Statistics (BLS); Poverty rates, retrieved from the U.S. Census; Health insurance coverage rates subdivided between percentage private, public, and uninsured, retrieved from the U.S. Census; Medicaid income eligibility thresholds as a function of a percentage of the Federal Poverty Level (FPL), retrieved from the Kaiser Family Foundation (KFF). These will be merged into the primary data source via each states Federal Information Processing Standard (FIPS) code identifiers, which will serve as channels for cross matching state by year control data.

Associated Terms: β_0 = Constant term; $\beta_{1\text{-}7}$ = Beta coefficients specifying the marginal effect of their corresponding variable in regards to the outcome variable CIVU; e = Error term.

Cross Sections Examined (Subscripts): t = year; i = individual; s = state; These subscripts denote cross sections used in the aforementioned regression equation, and subsequent auxiliary estimations.

Primary Coefficient Measure: The chief quantitative value that was interpreted in order to determine the impact of P relative to CIVU, is the beta coefficient (β_1).

Covariate Coefficient Measures: Covariate coefficients were examined, and subsequently interpreted, in order to assess if baseline disparities existed, and if further disparities existed beyond those due to standard inherent heterogeneity for certain covariates. This signified if the disparities and heterogeneity were attributable to the event occurrences specifically, or if they were naturally occurring by default.

Interpretation of Coefficients: The interpretation of the beta coefficients are as follows. If the marginal effect yielded is a positive value, this indicates that the event of interest increased the predicted probability of the outcome occurring, which is child flu vaccine uptake by parents. If the marginal effect yielded is a negative value, this indicates that the event decreased the predicted probability of the outcome occurring. If the marginal effect equals zero, or is nearly zero, this signifies the event had no impact, or minimal impact respectively. The magnitude of the marginal effect regardless of directionality and sign exemplifies the degree of impact of the event of interest on the outcome, with greater measures corresponding to larger impacts, without exceeding the limit of 1 as the maximum value.

3.2. Sensitivity Analyses

Aim 1 Robustness: Since 2003, the CDC publishes weekly surveillance reports of influenza activity, in the form of the National Notifiable Diseases Surveillance System (NNDSS). The CDC also integrates surveillance data into FluView, which synthesizes nationally representative reports for indicators and measures of disease, such as morbidity rates, mortality rates, and population-adjusted ILI incidence and prevalence rates, for

each state, on an annual basis. By replacing the binary variable P, symbolizing the event of interest, with a continuous measure of influenza burden, labeled variable I, we exploited the specific timing and intensity of the H1N1 outbreak across the United States. This sensitivity analysis was accomplished by implementing a fixed effects model (FEM) that controls for temporal and state fixed effects. These factors are elements that are intrinsic to this studies FEM estimations, and are essential fixed effects control variables. This procedure supplemented the primary ITS estimation and provided reaffirmation of its results. This statistical method was applied previously in a study examining pertussis infections nationally, and has been previously tested with success.[19,89]

Aim 2 Robustness: We estimated a difference-in-differences model using children age 6 months to 23 months as an untreated comparison group, or control group, since LAIV was previously recommended for children age 2 years and older, but never for children below 2 years of age. Children greater than or equal to the 2 year age threshold will serve as the treatment group for LAIV recommendation, and those below this threshold age point are disqualified from treatment exposure, due to ACIP never approving or recommending the LAIV formulation for usage among this age range. Spillover effects of the ACIP LAIV policy shifts in relation to the LAIV ineligible individuals (IIV eligible only individuals) were assessed and examined as a byproduct of this sensitivity analysis and execution of the DID statistical procedure.

3.2.1. Difference in Differences (DID) Overview and Application

The difference in differences (DID) is a quasi-experimental design applied as an alternative to costlier and less feasible RCTs in order to establish causal relationships and produce causal inferences. The DID regression computation examines in its basic form 2

subgroups and 2 time periods, those being the control and treatment subgroups, and the pre and post event point time ranges respectively. The DID technique calculates the difference between the computed difference between the treatment and control subgroups outcome measures, pre and post time point of interest, and compares the outcome values for the subgroups both within and across time phases.[90]

In this study, the treatment group is individuals who were eligible for LAIV receipt (ages 2 years and greater), and who would theoretically be affected by LAIV related policy shifts, and the control group is individuals who were ineligible for LAIV receipt but eligible for IIV (ages 6 to 23 months of age), and who would theoretically be unaffected directly by LAIV based policy recommendations, but may be indirectly impacted by linked spillover effects.

The time periods are divided into pre and post LAIV preferential recommendation rescindment, also called LAIV withdrawal. The pre policy point time range will serve as the unaffected time phase, and the post policy point time range will serve as the affected time phase. Measures for overall influenza vaccine completion will be examined for both LAIV eligible and non-eligible subgroups respectively, and compared for fluctuations before and after the 2015 ACIP LAIV revocations. The outcome variable CIVU (child influenza vaccine uptake) will be examined for both treatment (symbolized by the subscript T) and control (symbolized by the subscript C) during the pre-policy shift time phase (designated by the numeral 0), and the post-policy shift time phase (designated by the numeral 1), and subsequently compared for differences in order to yield the DID value (Table C.6).

The DID estimation expression will possess a treatment (LAIV-eligible) versus control (LAIV-ineligible) cohort assignment variable, LAIV Eligible, that will perform this segregation predicated on the individuals age. The expression will also consist of a DID variable that compares the LAIV eligible versus ineligibles vaccine completion rates pre and post policy implementation. The empirical estimation equation is listed below.

Difference in Differences Regression Equation (DID): $\text{Logit}\,(CIVU_{tis}) = \beta_0 + [\beta_1\,(H1N1_{ts})] + [\beta_2\,(\text{LAIV 2014}_{ts})] + [\beta_3\,(\text{LAIV 2015}_{ts})] + [\beta_4\,(\text{LAIV 2016}_{ts})] + [\beta_5\,(\text{LAIV Eligible}_{tis})] + [\beta_6\,(DID_{tis})] + [\beta_7\,(\mathbf{RSE}_{ts})] + [\beta_8\,(\mathbf{X}_{tis})] + [\beta_9\,(\mathbf{State\ Factors}_{ts})] + e_{tis}$

Similar to RCT's, the DID approach has the advantages of possessing distinct treatment and control subgroups, with established pre and post treatment, or exposure time periods, allowing for profound comparisons to be attained. Furthermore the population being examined and the criteria and conditions are well recognized when designing the experiment. The dissimilarity with the DID technique, as contrasted with RCT's, is that it lacks direct randomized assignment of participants to treatment versus control subgroupings, and hence must use other means in order to eliminate bias that may arise at this stage due to confounding effects influencing both the outcome variable and exposure to treatment. Instead, DID relies on assumptions in the form of constraints on confounding factors that may exist.

These assumptions include the supposition that confounder variation due to subgroup types, does not exhibit variation across time, and that confounder variation due to time progression, does not exhibit variation across subgroups. These dual assumptions on aggregate synthesize the greater common trend assumption, which is similar to the true counterfactual assumption in ITS analyses.[90]

The common trend assumption is at the core of the DID method, and violation of this assumption could potentially negatively affect its application and results yielded. If either of the primary assumption's subcomponents are violated, then issues may arise. Meaning that unmeasured factors involved with the DID estimation must be restricted to group specific characteristics that are time invariant, or time specific characteristics that are group invariant, otherwise the analysis may be flawed, and inferences made using the DID technique are limited.[90]

Another assumption that the DID approach relies on in order for its estimation mechanism to function properly is that the treatment exposure must be statistically independent from the anticipated outcomes and their pattern of occurrence. That is, overlapping effects of treatment exposure and other similarly timed events should be avoided, and timing of other phenomenon that may affect the outcome should be considered, with expected outcome fluctuations due to timing of parallel events being compensated for. This concept is termed strict exogeneity, and if not adhered to can yield validity issues with the DID estimation.[90]

Ultimately the DID method relies most on the parallel trends assumption in order to ensure its validity, which states that in the absence of exposure to the treatment, the treatment and control groups should possess constant variations in relation to the outcome variable, with the progression of time, and should not deviate from this trend. Additionally, the pre-treatment time period trends should ideally be identical, if not very similar, for the subgroups being compared, since this trend is assumed to persist consistently for the treatment subgroup past the treatment point, and into the post treatment time period, where it is used to calculate the actual effects of the treatment.

This serves as the basis for usage of the unobserved counterfactual in the post event time phase portion of the DID analysis, which is responsible for establishing the baseline for comparison, in order to compute the true impact of the event of interest on the outcome for the treatment subgroup (refer to *Figure 3.1* for graphical diagram of the DID estimation).[91]

In order to protect the parallel trends assumption from violation, the pre 2015 policy phase trends for the LAIV eligible (2 years and up) and the LAIV ineligible (6 – 23 months) should be similar in relation to the outcome (overall flu vaccine completion). The greater the amount of time, within the pre 2015 policy phase, that the LAIV eligible (treatment) and LAIV ineligible (control) trajectories mimic and emulate each other's trends, the greater the degree of reinforcement for the DID estimations parallel trends assumption, and its potential for violation is minimized. This is due to the concept that the greater the amount of time of trend emulation, and degree of trend mimicry, prior to treatment exposure point (2015 policy shift), the more probable it is that the assumed unobservable counterfactuals trajectory (based on the LAIV ineligibles trend), post treatment exposure, is an accurate depiction of the actual trajectory that the LAIV eligible subgroup would have experienced in the absence of the 2015 policy shift.

Additional assumptions for the DID method include that the outcome variable should not dictate the occurrence of the treatment in question, and outcome and treatment application were initially unrelated. Also that for repeated cross sectional analyses, the composition of the subgroupings should remain consistent and stable over time, with the consistency of the treatment and control groups not varying substantially with subsequent cross sections, and maintaining a sustained conformation.[91]

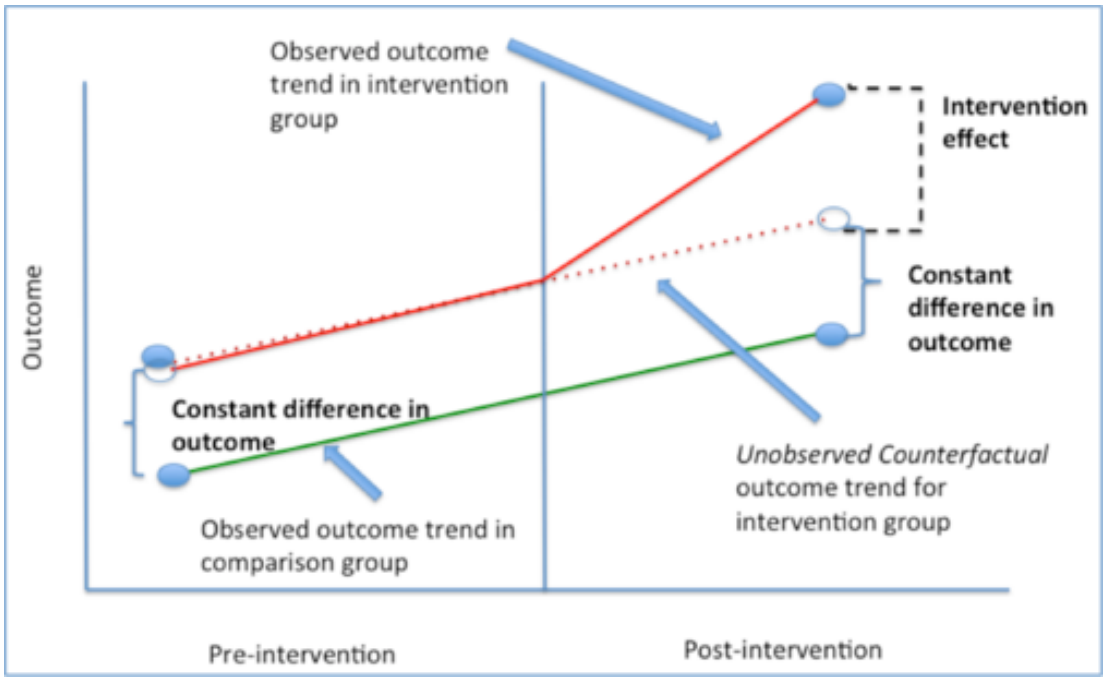

Figure 3.1 - Difference in Differences (DID) Method Graphical Depiction

3.2.2. Fixed Effects Modelling Overview and Application

In attempts to confirm causal relationships associated between event exposures and specific outcomes, estimations may suffer from bias attributable to selection, confounding, and measurement of observations. Both observed (known), and unobserved (unknown) factors lead to measured and unmeasured confounding respectively, which diminish the estimations validity and potential for producing legitimate causal inferences associated with exposure instigating outcome. Differences that occur with the progression of time are composed of 2 primary subcomponents, those being intra-individual alterations (time invariant modifications), not controlled for in this study, and inter-individual alterations (time variant modifications). Fixed effects models generally control for and regulate the time invariant changes inherent to the estimation, and hence limit the effects of time invariant unmeasured confounding that may exist.

They operate with the assumption of the aforementioned strict exogeneity concept, which states that lagging effects of previous outcomes cannot influence current covariates, and that current outcomes cannot influence future covariates. It also states that previous covariate quantities cannot affect currently measured outcomes, and current covariate values cannot affect future outcome values independently.[85]

This approach is limited in that in cannot regulate for bias resulting from time variant unmeasured confounding, and reverse causation. Additionally, because the fixed effects model is limited in controlling for these variations that are intrinsic to the estimation, it fails to completely compensate for other sources of temporal variation, and can yield declines in precision level. These characteristics of the fixed effects model are a disadvantage, because they limit its precision level and efficiency, which mixed models cope with better. This approach is limited also due to the fact that temporal parameters that are time variant cannot be completely adjusted for, and there will be differences in exposure levels due to temporal factors. This is critical to the fixed effects models estimation, since it only incorporates observations where the exposure altered as part of its computation of estimates.[85]

The FEM model for this study include temporal fixed effects in addition to state fixed effects in the form of fixed effects for all study years. Although the incorporation of the year fixed effects will adjust and control for a degree of unobserved time varying factors, such as national level trends, it cannot completely achieve this, and hence is a limitation of this approach.

Fixed effects models are optimal for application in situations like this study, where exposure to a pandemic event is being assessed relative to the causation of changes

in influenza vaccine uptake over time. This is achieved by the model by adjusting for both measured and unmeasured time invariant confounding, and measured time variant confounding, and usage of a data source with minimal attrition, sustained stability over time of observations, with exhibited differences in exposures, and maintenance of the strict exogeneity condition.[85] The fixed effects model estimation was applied as a sensitivity analysis and supplementary analysis that reaffirmed results yielded by the primary ITS estimation.

The CDC's National Notifiable Diseases Surveillance System (NNDSS), which provides statewide counts of influenza cases annually, was merged with existing NIS population data in order to produce influenza disease rates. The original logistic regression estimation for the H1N1 pandemic had the binary event point variable of interest P, replaced by the continuous influenza disease epidemic variable of interest I, and temporal and state level fixed effects were incorporated into the equation, in order to mitigate the potential for biased estimates. Once this level of regulation was achieved using the fixed effects integration, and confounding factors were controlled for, the beta coefficient associated with the influenza disease epidemic variable I, signified the variations in CIVU rates that occurred with respective changes in the influenza disease risk progression across states for different individuals. This exhibited how child flu vaccine uptake rates were impacted as a function of H1N1 influenza disease incidence and progression with time across states. Refer to regression equation below for the mathematical expression of the aforementioned.

CIVU as a Function of Influenza Disease Outbreak: $CIVU_{tis} = \beta_0 + [\beta_1 (I_{ts})] + [\beta_2 (\mathbf{X}_{tis})] + [\beta_3 (Z_{ts})] + [\beta_4 (M_{ts})] + [\beta_5 (SFE_s)] + [\beta_6 (TFE_t)] + e_{tis}$

CHAPTER 4

THE 2009 H1N1 PANDEMIC:

ASSESSING IMPACTS ON IMMUNIZATION[1]

[1]A.H. Mehrabi, N.L. Hair, C.M. Andrews, S.E. Harrison, R.D. Horner. To be submitted to *American Journal of Public Health.*

Abstract

Introduction: The historical 2009 H1N1 Influenza pandemic, which had a CDC estimated accrued disease burden of 100.5 million illnesses, 936,000 hospitalizations, and 75,000 deaths from 2009 to 2018, resulted in a declared state of emergency nationally, with ensuing diminished vaccine confidence and amplified fears of infection, prompting some to pursue flu vaccination, and others to forego. Although the Centers for Disease Control and Prevention (CDC), and its Advisory Committee on Immunization Practices (ACIP) recommend an annual flu vaccine for individuals 6 months of age and older as the "first and best" defense against influenza, a low percentage of children are vaccinated, and parental decisions are not fully understood. Examining previous literature, a void exists in relation to parental perceptions and decisions for child immunizations, particularly concerning the U.S. nationally, with most studies being international. Furthermore, there is evidence of varied results with inadequate and conflicting conclusions, specifically for children.

Methods: To assess impacts of the 2009 H1N1 pandemic on decisions to uptake influenza vaccines for children age 6 months to 17 years of age, data from NIS was used as a series of weighted consecutive annual surveys in order to synthesize a longitudinal panel dataset spanning from 2003 to 2018. Population adjusted measures of influenza like illness (ILI) by state and season procured from CDC's FluView application and ILI Net from 2008 to 2018 were used in order to supplement the primary NIS dataset. Quasi-experimental (QE) approaches in the form of segmented interrupted time series (ITS), and fixed effects model (FEM) logistic estimations were executed on the integrated dataset yielding logistic regression coefficients and post-estimation marginal effects

signifying the impact of the pandemic on child influenza vaccine uptake (CIVU). ITS regressions examined both level and trend changes due to pandemic occurrence via binary and continuous pandemic incidence variables respectively. FEM regressions examined fluctuations in CIVU as a function of influenza disease progression across seasons and geographic jurisdictions.

Results: The segmented interrupted time series (ITS) regression for the NIS-Child sample yielded statistically significant coefficients. Post-estimation average marginal effects (AMEs) were as follows. The H1N1 pandemics occurrence yielded a 12.57 percentage point (pp), 95% CI [10.28, 14.32], immediate level change increase in the probability of a child being immunized, on average. It also yielded a 3.77 pp, 95% CI [-4.32, -2.55], sustained slope change decrease in the probability of a child being immunized annually, on average. Pre-pandemic, a 1.64 pp, 95% CI [1.47, 1.81], sustained increase in the probability of a child being immunized annually, on average, was evident. Restricted scale epidemic (RSE) occurrences of the influenza virus yielded post-estimation AMEs that were statistically significant for RSEs on 2012, 2013, and 2014. These coefficients were a 1.79 pp, 95% CI [-2.22, 0.38], 5.23 pp, 95% CI [-6.27, -4.77], and 1.92 pp, 95% CI [2.74 1.10], decrease in the probability of a child being immunized, on average, respectively. The respective trend change increases post RSE occurrences were 0.85 pp, 95% CI [0.74, 0.96], 0.34 pp, 95% CI [0.28, 0.40], and 1.24 pp, 95% CI [1.12 1.35], on average, in the probability of the same outcome.

Sensitivity analysis fixed effects model (FEM) regressions yielded logit and AME coefficients that were statistically insignificant with the exception of a single variable in

subgroup 5, which indicated a decrease of 2.29 pp, on average, in immunization rates during peak season weeks registering at a ILI intensity magnitude of 9 or greater.

FEM regressions for the NIS-Teen sample yielded logit and AME coefficients that were statistically insignificant with the exception of three variables in subgroup 5. The initial variable indicated a 1.31 pp increase, and the subsequent variables indicated a 0.135 pp, and a 0.212 pp decrease, on average, in immunization rates respectively.

Conclusion: Preliminary escalations in the probability of child immunization uptake are evident following the pandemic. This is possibly linked to immediate vaccination promoting factors connected to the pandemics occurrence, but cannot be ascertained. These factors are possibly paramount in the initial post-pandemic phase, and gradually diminish with the progression of time, theoretically yielding reductions in uptake rates in the long term. Public health immunization professionals should expect preliminary increases in uptake behavior, followed by gradual decreases in the same outcome for influenza pandemics such as H1N1. They should anticipate decreases in uptake behavior following smaller scale epidemics. For pandemic intensity ILI seasons, uptake behavior is not sensitive to weekly fluctuations in ILI severity for children, but slightly sensitive for teens during peak and late phases of the influenza season, with fluctuating uptake behavior associated with peak season phases, and consistent increases for late season phases. This study contributes to the existing literature by enhancing the understanding of how vaccine uptake rates change following pandemic and epidemic events. However it is limited in determining why these changes occur, and due to what factors and mechanisms specifically, which future studies should attempt to discern and ascertain.

4.1. Introduction

Each year millions of children in the U.S. experience influenza-related illness. Although most children infected with influenza viruses recover within a week, serious complications can result in hospitalization or death.[1] Currently, the Centers for Disease Control and Prevention (CDC), and its Advisory Committee on Immunization Practices (ACIP) recommend an annual flu vaccine for individuals 6 months of age and older as the "first and best" defense against influenza.[2,3] Nevertheless, only 45.6% of children 6 months to 17 years of age received the vaccine in 2018 – 2019, and even less at 38.8% in 2017-2018.[4] Understanding parental attitudes and barriers associated with uptake of childhood immunization is a crucial national public health priority. This process is complex, as numerous socioeconomic, psychological, demographic, and contextual factors influence vaccine uptake rates.[5–9] Doubts regarding vaccine benefits,[10] concerns regarding side-effects and safety,[5,11–17] perceived disease seriousness and risk assessment,[11,15,16,18,19] uncertainties about vaccine effectiveness,[8,11,12,20,21] and healthcare access and costs,[7,8,14,22,23] are prime influencers and factors affecting immunization uptake.

The effects of epidemic and pandemic occurrences on parental perceptions and decisions to uptake immunizations in the U.S. are not completely understood, with conflicting, and inconsistent conclusions, [5,11,19,23–26] specifically for child flu vaccines. This study overcame these shortcomings and contributes to a better understanding of how parental perceptions and decisions are affected by these aforementioned factors by examining the historical 2009 H1N1 pandemic. The pandemic served as a point of analysis to determine how parental decision-making and perceptions regarding child flu

vaccines may have shifted through mechanisms such as perceived disease risk and erosion of vaccine confidence. This study has parallels to past research that has examined the controversies regarding other diseases, health conditions, and vaccine formulation elements. These include the measles, mumps, rubella and Autism dilemma, and thimerosal presence in vaccines debate, where child vaccination rates shifted due to false scares, ensuing spillover effects, incorrect conclusions, and parental inability to critically analyze and decipher vaccine information.[5,13,24,27]

The occurrence of the historical 2009 H1N1 Influenza pandemic, which had a CDC estimated accrued disease burden of 100.5 million illnesses, 936,000 hospitalizations, and 75,000 deaths from 2009 to 2018,[28] resulted in a declared state of emergency nationally. For the U.S. in 2009 alone, the pandemic resulted in approximately 270,000 hospitalizations and 12,270 mortalities, with 1,270 of those deaths being under age 18.[29] Examining previous literature, a void exists in relation to parental perceptions and decisions for their children, particularly concerning influenza for the U.S. nationally, with most studies having been completed internationally. Furthermore, there is evidence of varied results with inadequate and conflicting conclusions, specifically for children. In certain studies, flu vaccine rates decreased following the pandemic,[11,16,30] while in others it increased,[31,32] with the measured magnitude of change being vastly different, with certain publications reporting substantial fluctuations,[11,31,32] and others stating milder effects, regardless of directionality. A study examining the relationship between influenza season severity and vaccine effectiveness, with influenza immunization rates, concluded that no statistically significant association was evident,[84] with minimal decreases in uptake observed for

seasons following low vaccine effectiveness years.[84] There also exists a lack of a comprehensive nationwide study that is representative and all encompassing.

Given the aforementioned, the question arises as to what was the impact of the historical 2009 H1N1 pandemic on overall child influenza vaccination uptake rates in the U.S.? It is postulated that the 2009 H1N1 pandemic increased overall child Influenza vaccine uptake rates due to stimulation of parental fears, and the perceived disease risk being greater. The shock and awe of the pandemic and heightened sense of hazard would supersede and overwhelm the erosion in vaccine confidence that ensued.

This study is novel and innovative in that it is the first nationally representative and comprehensive study that will examine the impacts of the 2009 H1N1 pandemic on overall child flu vaccine rates over a significant time span using an extensive vaccine-focused data source in the form of the National Immunization Survey (NIS). It is the first to assess how parental uptake of child influenza immunizations is affected nationally across diverse segments of the population, while yielding improved results with public health implications. This is significant, as it allows for a better understanding of parental cognitive and behavioral responses to pandemics in relation to decision making for uptake of child flu vaccines within the United States. This is significant, as it ultimately allows for U.S. public health policymakers to increase future child flu vaccine uptake by understanding how parental uptake rates alter following a pandemic. By possessing insight regarding the pandemic and epidemic associated trend alterations for immunization, public health professionals and authorities can adapt better to the evolving disease contagions progression and influences it has on vaccination. Vaccine campaigns can then be designed and implemented accordingly based on forecasted patterns.

4.2. Description of Project Design and Methodological Approach

The primary purpose of this project is to advance understanding of how influenza epidemics and pandemics affect parental perspectives and decisions regarding child flu vaccine uptake. By examining marginal effects for completion of child flu vaccines following the occurrence of the 2009 H1N1 pandemic we evaluated these impacts. Analysis was achieved by executing logistic regression models, specifically by implementing an interrupted time-series (ITS) empirical approach, with a quasi-experimental design strategy for the estimations, using STATA 16 statistical software. Provider-verified immunization histories from a state and nationally representative dataset served as the basis for performing these statistical estimations.

The 15-year time span from 2003 to 2018 was examined for this study, encompassing the 2009 H1N1 pandemic completely and sufficiently. The time period of analysis commenced in 2003, since that is the preliminary year where the IIV formulation's universal recommendation and application would be realized following the ACIP's decision. It is also the year the LAIV formulation of the immunization was accepted and authorized for usage by the ACIP. The time period of analysis terminates in 2018 as that is the most recent year available for analysis. The data was aggregated, and compiled for analysis by merging separate annual surveys consecutively into a single dataset. The final version of the data was a series of repeated cross-sections based on annually completed NIS surveys. This generated dataset emulated longitudinal and panel data sources, and allowed for minimization of bias, while reinforcing estimation of a correlation relationship that was representative of a larger scale heterogeneous population.[85] Sensitivity analysis in the form of auxiliary estimations using fixed effects

models were performed in order to corroborate and validate results yielded by the primary ITS logistic regressions.

Specific Aim 1: To ascertain the effects of the 2009 H1N1 pandemic on overall child influenza vaccination uptake rates in the U.S. by assessing changes in the likelihood that a child is vaccinated for influenza following the pandemic event.

H_1: The 2009 H1N1 pandemic is expected to increase the likelihood of overall child influenza vaccine uptake. In accordance with the previous literature, and this studies conceptual model, vaccine uptake stimulating factors related to disease severity and susceptibility to infection will drive the expected increases in flu immunization uptake.

4.2.1. Data Sources

The data source used for this study was the National Immunization Survey (NIS), which is conducted by the CDC's National Center for Immunization and Respiratory Diseases (NCIRD) in order to monitor immunization coverage. It is nationally representative and comprehensive including flu vaccination data for children 6 months – 17 years of age for all 50 states and additional U.S. territories.[86] NIS consists of a combination of NIS-Child (ages 19-35 months), and NIS-Teen (ages 13-17 years).[86] NIS offers national, state, and local level data, provided directly from the child's providers (NIS-Child and NIS-Teen consist of provider-verified immunization measures), bolstering its accuracy and validity.[86] It contains information regarding the types of vaccines administered to children, their dates and dosages, demographic, socioeconomic, geographic, and insurance data, as well as administrative data related to providers and facilities where the procedures were performed.[86]

The CDC published surveillance reports of influenza disease activity, in the form of the National Notifiable Diseases Surveillance System (NNDSS), was the data source used in conjunction with the aforementioned NIS population data, in order to execute sensitivity analysis estimations for the H1N1 pandemic.[92] CDC's FluView and generated report data from ILI Net, were used as well in order to achieve this sensitivity analysis.[93] This was accomplished by examining measures related to intensity levels for population-adjusted ILI incidence and prevalence rates, for each state, on an annual basis.[92]

4.2.2. NIS Sampling Procedures, Weighting, and Response Rates

NIS-Child and NIS-Teen conduct sampling in a two phased and tiered approach. In phase one, the data collection procedure is to attain immunization information for a national probability sample of children, by performing random digit dialing (RDD) within each of the statistical sampling strata in order to identify eligible subjects.[86] The interviewers request permission to contact the vaccination provider of the qualified child, and subsequently, a mailed survey is sent to the designated clinician. In phase two, the provider record check (PRC) survey is completed, and allows for confirmation and verification of the phase one questionnaire responses.[86] Overall this allows for vaccination statistics that are comparable across geographic territories, with the progress of time, and promotes minimization of bias that may exist.[86]

NIS-Child and NIS-Teen possess weighting processes and procedures that adjust for variation in sampling rates, differences and discrepancies in response rates, and variations in representation in the sample relative to the overall population being assessed.[86] This allows for improved accuracy of estimates at various sampling levels.

The estimates and variance approximations are generated for separate areas, states, and sampling subdivisions. Weight imputations are performed for the survey as necessary.[86]

The anticipated NIS-Child sample size for completed interviews is approximately 25,000 addresses, on average.[86] The annual response rate of NIS-Child is approximately 65 percent of eligible subjects within the sample, on average, for the parent response segment.[86] The rate of children with adequate provider data available is approximately 70 percent, on average.[86]

The anticipated NIS-Teen sample size for completed interviews is approximately 35,000 addresses, on average.[86] The annual response rate of NIS-Teen is approximately 60 percent of eligible subjects within the sample, on average, for the parent response segment.[86] The rate of children with adequate provider data available is approximately 70 percent, on average.[86]

4.2.3. General Regression Model Components and Estimation Elements

Outcome (Dependent) Variable: CIVU (Child Influenza Vaccine Uptake) denotes whether the child was administered and received the influenza vaccine. This is a binary "Yes" or "No" outcome measure represented by 1 or 0 respectively.

Primary Variables of Interest: H1N1, denotes the initial occurrence of the pandemic, with its coefficient demonstrating the immediate level change with respect to CIVU. This is binary and symbolizes the incidence of the H1N1 pandemic. The H1N1 slope change factor, is a continuous variable arising from the interaction between the normalized time variable (T) and the pandemic indicator variable H1N1. It denotes the ensuing trend occurrence in the post pandemic phase, with its coefficient demonstrating the subsequent slope change with respect to CIVU.

Predictive (Independent) Variables: Child sex, age, birth order, race/ethnicity, relocation/mobility comparing state of birth and current location, maternal age, education level, marital status, insurance type, family income level, and provider/clinician facility type. These covariates are in concordance with previously applied conventions among predecessor studies, and are standard across previously completed studies published in the literature.

Additional Control Factors: State fixed effects (SFE), time fixed effects (TFE), state level characteristics that vary with time, state level policy and mandate differences, restricted scale epidemic occurrences of the influenza virus (RSEs), and CDC ACIP influenza vaccine policy shifts. Time-variant state level attributes specifically include: Unemployment rates, retrieved from the Bureau of Labor Statistics (BLS); Poverty rates, retrieved from the U.S. Census; Health insurance coverage rates subdivided between percentage private, public, and uninsured, retrieved from the U.S. Census; Medicaid income eligibility thresholds as a function of a percentage of the Federal Poverty Level (FPL), retrieved from the Kaiser Family Foundation (KFF). These will be merged into the primary data source via each states Federal Information Processing Standard (FIPS) code identifiers, which will serve as channels for cross matching state by year control data.

Associated Terms: Beta coefficients specify the impact, or marginal effect, of their corresponding variable in regards to the outcome variable CIVU.

Cross Sections Examined: Individuals are examined in conjunction with time progression in years for different states.

Covariate Coefficient Measures: Coefficients were examined, and subsequently interpreted, in order to assess if baseline disparities existed, and if further disparities existed beyond those due to standard inherent heterogeneity for certain covariates. This signified if the disparities and heterogeneity were attributable to the event occurrence specifically, or if they were naturally occurring by default.

Interpretation of Coefficients: The interpretation of the beta coefficients are as follows. If the marginal effect yielded is a positive value, this indicates that the event of interest increased the predicted probability of the outcome occurring, which is child flu vaccine uptake by parents. If the marginal effect yielded is a negative value, this indicates that the event decreased the predicted probability of the outcome occurring. If the marginal effect equals zero, or is nearly zero, this signifies the event had no impact, or minimal impact respectively. The magnitude of the marginal effect regardless of directionality and sign exemplifies the degree of impact of the event of interest on the outcome, with greater measures corresponding to larger impacts, without exceeding the limit of 1 as the maximum value.

4.2.4. Regression Model Structures, Designations, and Specifications

The interrupted time series and fixed effects models are the two primary methodological designations that were implemented in order to execute the logistic regressions on the immunization data. Following the logistic regression estimations, post estimation commands for predicted probability and marginal effect computations were executed.

4.2.4.a. Segmented Interrupted Time Series Estimation: NIS - Child

The segmented interrupted time series estimation was executed on NIS-Child data for individuals across the entire age range (19-35 months) for consecutive years initiating in 2003 and terminating in 2018. Due to the difficulty in isolating the effects of the 2009 pandemic individually, it was necessary to account for the three restricted scale epidemics (RSE 1, RSE 2, RSE 3) corresponding to the 2012-2013, 2013-2014, and 2017-2018 influenza seasons respectively. In order to accomplish this, the ITS estimation was executed as a segmented or piecewise regression as opposed to a regular ITS estimation. The segmented ITS regression incorporates multiple temporal periods (pre-2009, 2009 to 2012, 2012 to 2013, 2013 to 2017, and post-2017) in order to compute the estimates for both level and slope changes for individual pandemic and epidemic severity seasons. This model allows for slope as well as intercept changes to be calculated for each of the three RSE points, as well as the main pandemic point, while controlling for concomitant factors.

The regression equation included concomitant event control indicators for the three CDC ACIP vaccine policy advisements (LAIV 2014, LAIV 2015, LAIV 2016) corresponding to the LAIV 2014 preferential recommendation, LAIV 2015 revocation of preferential recommendations, and LAIV 2016 complete rescindment of recommendations. All contemporaneous influenza vaccination influencing events are coded as categorical variables corresponding to the initial year of the contemporaneous events season of occurrence.

This is due to the NIS survey design being such that it is conducted from the January of the initial year to the February of the subsequent year, hence the year variable

represents the interview year, or the year survey conduction commenced.[86,94] This is the initial year of the influenza season, which is of interest, since the vast majority of vaccination happens during the months of September to February of each influenza season.[95,96] This allows for capturing of influenza vaccine uptake behavior during the major vaccine completion portion of the year, spanning this intra-season time period. Specifically for the H1N1 pandemic, the first monovalent vaccine formulation became available to be administered October 2009,[97] hence the 2009-2010 season, designated by interview year 2009, would capture this occurrence. This also allows the post policy period effects of the contemporaneous policy shifts to be captured effectively since the ACIP policy decisions are completed in the preceding summer months, and regulations and protocols are subsequently disseminated to clinicians and providers for the upcoming season, permitting ample time for the effects of the policy shift to be realized.[70,98] Predecessor vaccine studies have implemented this convention for analysis purposes, as it is established in the literature.

The outcome variable representing CIVU is defined as an child who is completely vaccinated and immunized based on CDC ACIP guidelines and regulations. Meaning that completion of required dosages and injection sequences are incorporated into formulation of this outcome measure as described in the CDC NIS user guide protocols and definitions based on vaccine season recommendations from ACIP. An individual is reported by providers as immunized when they are up-to-date for their vaccinations. This is denoted in the NIS-Child data by a series of provider verified up-to-date (UTD) variables specifically related to the influenza vaccine. To reflect CDC ACIP decisions and adjustments in advisements, the final immunization variable used in this estimation is

comprised of different up-to-date variables recorded in NIS-Child. From the time period between 2003 to 2006, one variable is used, followed by another from 2007 to 2013, in order to reflect the revised definition of vaccinated by ACIP, followed by a final variable from 2014 to 2018, which was synthesized based on ACIP chart guidelines defining complete immunization. This was achieved by using the intermediate variable denoting the provider reported measure for total number of vaccinations completed per cycle to date.

The alternative outcome variable that was implemented in supplementary ITS estimations used the provider verified immunization measure for the total number of shots completed. The outcome in the alternative regressions was coded as a binary variable with 0 corresponding to no dosages received, and 1 corresponding to greater than or equal to 1 dosage received.

The additional covariates used in the regression were selected based on ubiquity and frequency of previous usage among predecessor literary works and publications, as well as pertinence predicated on CDC NIS user guide definitions and recommendations. Covariates representing child characteristics include age group of the child, gender, race/ethnicity, birth order status, and translocation from a different state. Covariates linked to maternal attributes include marriage status, age group, and education level. Family characteristics included total number of children present, income level category as a function of a percentage of the federal poverty line. Provider characteristics included the providers facility classification type. State attributes included percentage poverty rate, percentage unemployment rate, percentage uninsured below 65 years of age, percentage

with public health insurance below 65 years of age, and Medicaid eligibility thresholds for parents, and infants 0 to 1 and 1 to 5 years of age respectively.

Interrupted Time Series Regression Equation (ITS): $\text{Logit}(CIVU_{tis}) = \beta_0 + [\beta_1 (T_{ts})] + [\beta_2 (\text{H1N1 Level}_{ts})] + [\beta_3 (\text{H1N1 Slope}_{ts})] + [\beta_4 (\mathbf{RSE\ 1}_{ts})] + [\beta_5 (\mathbf{RSE\ 2}_{ts})] + [\beta_6 (\mathbf{RSE\ 3}_{ts})] + [\beta_7 (\mathbf{Policy\ Shifts}_{ts})] + [\beta_8 (\mathbf{X}_{tis})] + [\beta_9 (\mathbf{State\ Factors}_{ts})] + e_{tis}$

4.2.4.b. Fixed Effects Model Estimation: NIS - Child

The fixed effects model for NIS-Child examined the same age range as the ITS model for NIS-Child using a different time period that spans from 2008 to 2018 instead. This is due to fixed effects models not requiring a substantial pre event time phase to serve as the baseline trend for comparison, whereas their ITS counterparts necessitate this time period to be sufficient. Also due to the fact that the influenza like iIlness (ILI) data from CDC's FluView application not going past 2008.

By accessing the CDC Weekly U.S. Influenza Surveillance Report data through the FluView interactive application's ILI Activity Indicator Map and ILI Net, it is possible to obtain information regarding the weekly ILI activity level intensity by state for each influenza season.[92,93] The ILI activity levels are calculated using the proportion of outpatient clinician and provider visits for ILI, and assigning an ILI intensity level for different measures. The data is population adjusted for each jurisdiction.[92]

ILI intensity levels are predicated on the percentage of ambulatory visits for ILI for different jurisdictions, compared to the average percentage for weeks that are minimal or nonexistent for influenza circulation for those same jurisdictions.[92] ILI activity levels compare the mean percent of visits for ILI's for a week in question to a non-circulation influenza weeks value.[92] ILI intensity levels are computed based on the number of

standard deviations for the current mean value as compared to the non-circulation mean value.[92] ILI activity levels are classified as four categories, those being minimal (intensity levels 1-3), low (intensity levels 4-5), moderate (intensity levels 6-7), and high (intensity levels 8-10).[92]

Data for all states spanning from the 2008-2009 to 2017-2018 influenza season were obtained, with each season possessing the total number of annual weeks. The aggregated population adjusted data was coded in order to identify the maximum ILI activity level for each state per season. This intermediary variable was then used to generate a variable to determine whether the maximum ILI activity level was classified at an epidemic or pandemic intensity based on CDC, WHO, and predecessor literary works and publications.[92,99] ILI intensity levels that are considered severe for an influenza season, and at epidemic or pandemic magnitudes, exceed a threshold ILI activity level of 5 or greater,[92,99] hence variables were generated to measure these. Following this procedure, a time dimension was integrated by generating variables that measures the number of weeks the ILI activity level exceeded a certain magnitude, which was used as an intermediary to synthesize variables representing the aggregate number of influenza weeks that an ILI intensity level was achieved for each state by season. These variables serve as the measure for ILI progression with time across geographic jurisdictions across the nation. A further variable designating intra-season time phases was generated to indicate early, late, and peak time periods of the season and interacted with the previous variable. This final variable serves as the primary variable of interest for the pandemic fixed effect model (FEM) regression equations. The ILI analysis data following

processing, augmentation, and refinement was merged with the primary NIS data via state identifier codes and year markers for statistical estimation computations.

The FEM estimations possess two fixed effect control variables, those being for states, and for seasons. The FEM regression equations possess identical covariates as compared to the ITS regression equations. The difference is the substitution of the influenza disease progression variables individually for the binary variable denoting the H1N1 pandemic's occurrence, and the insertion of the state and time fixed effects, and the deletion of the normalized time progression variable, and H1N1 trend fluctuation variable.

To perform the sensitivity analysis segment of this study, the experimental measures of influenza season severity, using various ILI intensity level variables, were developed and tested by conducting separate fixed effects model regressions for individual ILI severity variables. The experimental variables were generated for ILI intensity levels ranging from 5 to 10, as these magnitudes correspond to greater severity seasons,[92,99] with variations in threshold limit calculation and time period designation. Threshold limit types were classified as singular limit thresholds exhibiting whether the intensity level was surpassed or not. Total number of weeks threshold limit being surpassed or not, by individual weekly increments for different segments of the season, divided as early season, weeks initiating in September and terminating in November,[95,96] late season, weeks initiating in March and terminating in May,[95,96] and peak season, weeks initiating in December and terminating in February,[95,96] These variables were generated by interacting intra-season time phases with previously defined variables for total number of week ILI intensity level variables. Selection of the final ILI intensity

level variable, representing influenza season severity as a progression of time across geographical regions, is predicated on logistic regression coefficient and marginal effect statistical significance levels, as determined by minimum standard error and p-value computations, and confidence interval tests.

Fixed Effects Model Regression Equation (FEM): $\text{Logit}\,(CIVU_{tis}) = \beta_0 + [\beta_1\,(\text{ILI Intensity Variable}_{ts})] + [\beta_2\,(\mathbf{SFE}_s)] + [\beta_3\,(\mathbf{TFE}_t)] + [\beta_4\,(\mathbf{X}_{tis})] + [\beta_5\,(\mathbf{State\ Factors}_{ts})] + e_{tis}$

4.2.4.c. Fixed Effects Model Estimation: NIS - Teen

The fixed effects model for NIS-Teen was executed on data for individuals across the entire age range (13-17) for consecutive years initiating in 2008 and terminating in 2018. The outcome variable representing CIVU is defined as a teen who is completely vaccinated and immunized based on CDC ACIP guidelines and regulations. Meaning that completion of required dosages and injection sequences are incorporated into formulation of this outcome measure as described in the CDC NIS user guide protocols and definitions based on vaccine season recommendations from ACIP. An individual is reported by providers as immunized when they are up-to-date for their vaccinations. This is denoted in the NIS-Teen data by a series of UTD variables specifically related to the influenza vaccine for each season. For individuals with adequate provider vaccination information available, the seasonal variables were combined and integrated annually, using each year systematically from 2008 to 2018, to generate a final measure of complete vaccination. This variable symbolizes CIVU in the regression equation.

The FEM estimations possess two fixed effect control variables, those being for states, and for seasons. The primary variable of interest will be as previously explained

for NIS-Child, and will be the influenza disease progression variable. The sensitivity analysis will be achieved using the exact systematic approach described for NIS-Child.

The additional covariates used in the regression were selected based on ubiquity, pertinence, and frequency of previous usage among predecessor literary works and publications, as well as pertinence predicated on CDC NIS user guide definitions and recommendations. Covariates representing teen characteristics include age of the teen, gender, race/ethnicity, insurance type, and translocation from a different state. Covariates linked to maternal attributes include marriage status, age group, and education level. Family characteristics included total number of children present, income level category as a function of a percentage of the federal poverty line. Provider characteristics included the providers facility classification type. State attributes included percentage poverty rate, percentage unemployment rate, percentage uninsured below 65 years of age, percentage with public health insurance below 65 years of age, and Medicaid eligibility thresholds for parents, and infants 0 to 1 and 1 to 5 years of age respectively.

Fixed Effects Model Regression Equation (FEM): $\text{Logit}(CIVU_{tis}) = \beta_0 + [\beta_1 (\text{ILI Intensity Variable}_{ts})] + [\beta_2 (\mathbf{SFE}_s)] + [\beta_3 (\mathbf{TFE}_t)] + [\beta_4 (\mathbf{X}_{tis})] + [\beta_5 (\mathbf{State\ Factors}_{ts})] + e_{tis}$

Rational and decisions for regression variable and factor usage, formulation, application, and incorporation were enhanced based on information and explanations acquired regarding NIS data from electronic correspondence and consultation with data experts and analysts at NORC. The empirical approach was enhanced based on similar procedures performed in the previous literature, and predecessor studies which implemented expressions similar to this studies estimation equations.

4.3. Results

4.3.1. Descriptive and Summary Analysis

4.3.1.a. NIS-Child

The data sample for individuals ages 19 - 35 months consisted of 698,157 total observations, with 29.34 % (204,855) between 19 - 23 months, 33.78 % (235,812) between 24 - 29 months, and 36.88 % (257,490) between 30 - 35 months. Among the sample, 26.35 % (183,982) received the influenza vaccine and possessed complete and adequate provider records. Among this subsample, 32.77 % (60,294) were considered immunized against the influenza virus as defined by ACIP regulations and protocols for vaccine dosage sequence and administration. The division in frequency of observations for the age ranges (19 - 23 months, 24 - 29 months, and 30 - 35 months) among this subsample was 31.30% (18,870), 37.37 % (22,534), and 31.33 % (18,890) respectively.

Among immunized children with adequate provider verified vaccine records, 48.86 % (29,457) were female and 51.14 % (30,837) were male. Among the same sample, 16.13 % (9,728) were Hispanic, 65.32 % (39,385) were Caucasian, 5.89 % (3,553) were African American, and 12.65 % (7,628) were of another ethnicity. With regard to first born status, 45.78 % (27,602) were the first child, and 54.22 % (32,692) were not. With regard to relocation and mobility, 8.26 % (4,979) had relocated from another state, and 91.74 % (55,312) had not.

With regard to marriage status of the mother and age, 81.25 %, (48,988) were children of married mothers, and 18.75 % (11,306) were not, with 74.01 % (44,624) of those mothers being over 30 years of age, and 25.99 % (15,670) being under 30 years of age. Mothers education level was divided at 7.32 % (4,411) for less than high school

achievement, 13.10 % (7,899) for high school graduate achievement, 20.12 % (12,132) for some degree of university achievement, and 59.46 % (35,852) for university graduate achievement.

With regards to the number of total children within the family unit, 29.87 % (18,012) were single child families, 61.01% (36,786) were families with 2 to 3 children, and 9.12 % (5,496) were families with 4 or more children. With regard to income to FPL ratio status, 14.67 % (8,371) were below 100% of the FPL, 13.99 % (7,982) were between 100 % to 199 % of the FPL, 13.50 % (7,706) were between 200 % to 299 % of the FPL, and 57.84 % (33,005) were at or above 300 % of the FPL.

The provider facility type the child was administered the vaccine at was divided such that 7.26 % (4,380) were at a public facility, 13.66 % (8,235) were at a hospital facility, 62.08 % (37, 429) were at a private practice, 4.56 % (2,752) were at a military or other type of facility, and 12.44 % (7,498) were at a hybrid or mixed facility.

4.3.1.b. NIS-Teen

The data sample for individuals ages 13 - 17 years consisted of 414,708 total observations, with 19.52 % (80,956) at 13 years of age, 20.38 % (84,531) at 14 years of age, 20.24 % (83,918) at 15 years of age, 20.58 % (85,359) at 16 years of age, and 19.28 % (79,944) at 17 years of age. Among the sample, 49.57 % (205,576) received the influenza vaccine and possessed complete and adequate provider records. Among this subsample, 21.35 % (43,895) were considered immunized against the influenza virus as defined by ACIP regulations and protocols for vaccine dosage sequence and administration. The frequency of observations based on ages (13 to 17 years) among this

subsample was 23.95% (10,511), 22.21 % (9,750), 19.77 % (8,679), 18.60 % (8,163), and 15.47 % (6,792) respectively.

Among immunized children with adequate provider verified vaccine records, 48.23 % (21,171) were female and 51.77 % (22,724) were male. Among the same sample, 15.01 % (6,587) were Hispanic, 65.53 % (28,765) were Caucasian, 8.53 % (3,746) were African American, and 10.93 % (4,797) were of another ethnicity. With regard to relocation and mobility, 22.42 % (9,840) had relocated from another state, and 77.58 % (34,055) had not.

With regard to marriage status of the mother and age, 75.20 %, (33,010) were children of married mothers, and 24.80 % (10,885) were not, with 7.28 % (3,197) of those mothers being at or under 34 years of age, and 39.26 % (17,233) being between 35 and 44 years of age inclusive, and 53.46 % (23,465) being at or above 45 years of age. Mothers education level was divided at 10.14 % (4,449) for less than high school achievement, 15.22 % (6,682) for high school graduate achievement, 24.18 % (10,616) for some degree of university achievement, and 50.46 % (22,148) for university graduate achievement.

With regards to the number of total children within the family unit, 35.29 % (15,490) were single child families, 55.00 % (24,143) were families with 2 to 3 children, and 9.71 % (4,262) were families with 4 or more children. With regard to income to FPL ratio status, 15.61 % (6,459) were below 100% of the FPL, 15.12 % (6,254) were between 100 % to 199 % of the FPL, 13.10 % (5,419) were between 200 % to 299 % of the FPL, and 56.17 % (23,240) were at or above 300 % of the FPL.

The provider facility type the child was administered the vaccine at was divided such that 10.38 % (4,555) were at a public facility, 10.52 % (4,617) were at a hospital facility, 48.17 % (21,143) were at a private practice, 8.11 % (3,561) were at a military or other type of facility, and 22.82 % (10,019) were at a hybrid or mixed facility.

4.3.2. NIS-Child: Logistic Regression Analysis

4.3.2.a. Primary Analysis: Interrupted Time Series

The interrupted time series (ITS) regression targeting the H1N1 pandemic of 2009 yielded statistically significant coefficients for the primary variables of interest. Execution of the delta-method margins procedure yielded post-estimation average marginal effects (AMEs) for the primary variables of interest associated with the pandemics occurrence. The H1N1 pandemics occurrence yielded a 12.57 percentage point, 95% CI [10.28, 14.32], immediate level change increase in the probability of a child being immunized, on average. It also yielded a 3.77 percentage point, 95% CI [-4.32, -2.55], sustained slope change decrease in the probability of a child being immunized annually, on average. Prior to the H1N1 pandemics occurrence, a 1.64 percentage point, 95% CI [1.47, 1.81], sustained increase in the probability of a child being immunized annually, on average, was evident.

Restricted scale epidemic occurrences of the influenza virus yielded post-estimation AMEs that were statistically significant. Occurrence of RSE 1 in 2012 yielded a 1.79 percentage point, 95% CI [-2.22, 0.38], decrease in the probability of a child being immunized, on average, followed by a 0.85 pp slope increase. Occurrence of RSE 2 in 2013 yielded a 5.23 percentage point, 95% CI [-6.27, -4.77], decrease in the probability of a child being immunized, on average, followed by a 0.34 pp slope increase.

Occurrence of RSE 3 in 2017 yielded a 1.92 percentage point, 95% CI [-2.74, -1.10], decrease in the probability of a child being immunized, on average, followed by a 1.24 pp slope increase. Refer to table 4.1 for ITS regression results pertaining to chief variables of interest.

Table 4.1 – NIS Child H1N1 Pandemic ITS Regression: Variables of Interest

Pandemic Variables	AME	SE	z	P > z	[95%	CI]
Pre-H1N1 2009 Trend	0.0164	0.0009	18.83	0.0000	0.0147	0.0181
H1N1 2009 Level	0.1257	0.0234	7.53	0.0000	0.1028	0.1432
Post-H1N1 2009 Trend	-0.0377	0.0030	-8.42	0.0000	-0.0432	-0.0255
RSE 1 2012 Level	-0.0179	0.0071	-1.46	0.1500	-0.0222	0.0038
Post-RSE 1 2012 Trend	0.0085	0.0005	15.58	0.0000	0.0074	0.0096
RSE 2 2013 Level	-0.0523	0.0092	-3.99	0.0000	-0.0627	-0.0477
Post-RSE 2 2013 Trend	0.0034	0.0003	11.3	0.0000	0.0028	0.0040
RSE 3 2017 Level	-0.0192	0.0073	-3.68	0.0000	-0.0274	-0.0110
Post-RSE 3 2017 Trend	0.0124	0.0006	21.45	0.0000	0.0112	0.0135

The AME coefficients for the pre and post pandemic and epidemic trends and their respective level changes are summarized above. The graphical depiction of the segmented ITS estimation is illustrated in Figure 4.1. The dashed lines indicate immediate level or intercept shifts, and solid lines signify trend or slope changes that occurred respectively for each event point.

Execution of the segmented ITS estimation using the alternative flu vaccination outcome (provider verified immunizations for the number of shots completed) yielded statistically significant AME coefficients that corroborated the up-to-date outcome regressions. The magnitude and direction of the AMEs for all pandemic and epidemic variables were in agreement for both level and trend values, with the AME values slightly greater in magnitude as compared to their counterparts (Table B.1).

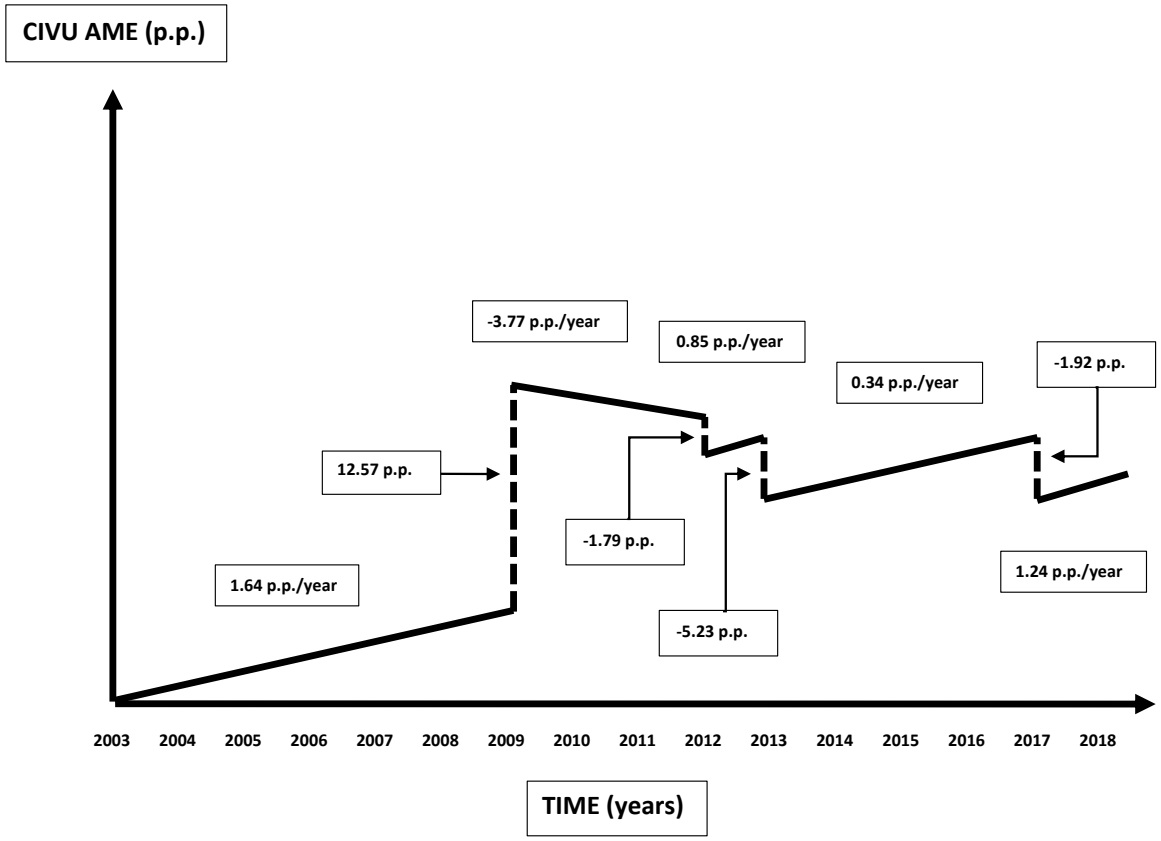

Figure 4.1 – Pandemic Piecewise ITS Regression Graphical Illustration

4.3.2.b. Sociodemographic Characteristics and Disparities (ITS):

The following segment is examining baseline differences relative to sociodemographic factors, with positive differences indicating greater likelihoods of immunization, and negative differences indicating lesser likelihoods of immunization, on average (Table 4.2). Comparing average marginal effects (AMEs) between age subgroups with 19-23 months as the reference category, ages 24-29 months experienced a 3.41% point greater likelihood of immunization on average, 95% CI [2.93, 3.89], and ages 30-35 months experienced a 6.63% point greater likelihood of immunization on average, 95% CI [6.05, 7.22]. With regards to gender differences, the AME was statistically insignificant and no discernable disparities existed.

With regards to ethnicity and race category, with Hispanic as the reference subgroup, Caucasians experienced a 1.40% point greater likelihood of immunization on average, 95% CI [0.75, 2.04], African Americans experienced a 5.59% point lesser likelihood of immunization on average, 95% CI [-6.48, -4.69], other non-Hispanic ethnicities possessed statistically insignificant differences.

Individuals who were the first born experienced a 4.00% point greater likelihood of immunization on average compared to non-first born individuals, 95% CI [3.37, 4.62]. Individuals who had relocated from another state experienced a 6.00% point lesser likelihood of immunization on average, 95% CI [-6.31, -4.89].

Mothers marital status being married was associated with a greater likelihood of immunization by 2.24% points, on average, 95% [1.63, 2.85], as did a mothers age being 30 years of age or greater, at 5.33% points on average, 95% CI [4.81, 5.85]. For mothers education level, with uneducated being the reference category, university graduates experienced a 5.27% point greater likelihood of immunization on average, 95% CI [4.31, 6.23], and high school graduation and some degree of university achievement experienced statistically insignificant differences.

For the number of children in the family unit, with one as the reference category, families with two to three children experienced statistically insignificant differences, and families with four or more experienced a 5.25% point on average lesser likelihood of immunization, 95% CI [-6.21, -4.29]. For income to FPL ratio category, with less than 100% as the reference category, 100% to 199% of the FPL experienced statistically insignificant differences, 200% to 299% of the FPL experienced a 1.93% point on average greater likelihood of immunization, 95% CI [1.10, 2.76], and 300% of the FPL or

greater experienced a 6.71% point on average greater likelihood of immunization, 95% CI [5.91, 7.51].

Table 4.2 – NIS Child H1N1 Pandemic ITS Regression: Covariates

Covariates	AME	SE	z	P > z	[95%	CI]
Age (Ref: 19-23 months)						
24-29 months	0.0341	0.0024	13.9400	0.0000	0.0293	0.0389
30-35 months	0.0663	0.0030	22.2800	0.0000	0.0605	0.0722
Gender (Ref: Male)						
Female	0.0001	0.0021	0.0600	0.9510	-0.0041	0.0043
Ethnicity (Ref: Hispanic)						
Non-Hispanic Caucasian	0.0140	0.0033	4.2500	0.0000	0.0075	0.0204
Non-Hispanic AA	-0.0559	0.0046	-12.2300	0.0000	-0.0648	-0.0469
Non-Hispanic Other	0.0049	0.0042	1.1700	0.2440	-0.0034	0.0132
Birth Order (Ref: No)						
First Born	0.0400	0.0032	12.5300	0.0000	0.0337	0.0462
Mobility (Ref: No)						
Relocated	-0.0560	0.0036	-15.4400	0.0000	-0.0631	-0.0489
Marital Status (Ref: No)						
Married	0.0224	0.0031	7.1600	0.0000	0.0163	0.0285
Mother's Age (Ref: < 30)						
30 years or over	0.0533	0.0026	20.1700	0.0000	0.0481	0.0585
Mother's Educ (Ref: < HS)						
High School	-0.0059	0.0046	-1.2800	0.2000	-0.0150	0.0031
Some College	0.0008	0.0046	0.1700	0.8630	-0.0083	0.0098
College Graduate	0.0527	0.0049	10.7600	0.0000	0.0431	0.0623
Num of Children (Ref: 1)						
2-3 Children	-0.0043	0.0035	-1.2400	0.2160	-0.0111	0.0025
4+ Children	-0.0525	0.0049	-10.7500	0.0000	-0.0621	-0.0429
Inc to FPL (Ref: < 100%)						
100 to 199% FPL	-0.0007	0.0037	-0.1800	0.8550	-0.0080	0.0066
200 to 299% FPL	0.0193	0.0042	4.5600	0.0000	0.0110	0.0276
300% FPL or greater	0.0671	0.0041	16.3700	0.0000	0.0591	0.0751
Facility Type (Ref: Public)						
Hospital Facility	0.0491	0.0047	10.4000	0.0000	0.0398	0.0583
Private Practice	0.0523	0.0039	13.3900	0.0000	0.0447	0.0600
Military/Other	0.0154	0.0056	2.7700	0.0060	0.0045	0.0264
Hybrid/Mixed	0.0427	0.0047	9.0300	0.0000	0.0334	0.0519

With regards to the provider facility type the vaccine was administered at, public facilities were the reference category, with hospital facilities experiencing a 4.91% point greater likelihood of immunization, on average, 95% CI [3.99, 5.83]. Private practices experienced a 5.23% point greater likelihood of immunization, on average, 95% CI [4.47, 6.00]. Military and other facility types experienced a 1.54% point greater likelihood of immunization, on average, 95% CI [0.45, 2.64]. Hybrid and mixed facilities experienced a 4.27% point greater likelihood of immunization, on average, 95% CI [3.34, 5.19]. Refer to table 4.2 for ITS regression results pertaining to control variables. Differences observed with regards to estimation covariates was consistent with expected and predicted coefficients, and adhered to anticipated trends.

The heterogeneity for the sample was computed by subdividing the sample for specific subgroups and executing logistic estimations for different subgroups separately. This was achieved by applying commands to segregate the sample based on income to FPL thresholds and ethnicity type (Table B.2). For ethnicity categories, with Hispanic as the reference subgroup, Caucasian children were more likely to experience immunization uptake, as were other ethnicities, and African Americans were less likely, on average. This is consistent with expectations for ethnicity based variations, with African Americans experiencing the least likelihood. For income to FPL ratio categories, with less than 100% being the reference subgroup, if the income to FPL percent was greater than 300%, the likelihood of experiencing immunization for a child increased substantially, with the remaining categories experiencing greater likelihoods as compared to the reference category, on average.

4.3.2.c. Sensitivity Analysis: Fixed Effects Model Estimation

Fixed effects estimations were completed using fixed effect indicators for seasons and states in addition to previously implemented covariates, and by substituting different experimental ILI disease intensity and progression variables. The five subclasses included activity levels greater than a certain threshold magnitude for disease intensity, the total number of weeks the threshold limit was surpassed, and variations in intra-season time periods divided as early, peak, and late respectively, and interacted with the other experimental variable subgroups. This was achieved for ILI intensity levels of 5 and greater, specifically symbolizing epidemic and pandemic magnitude levels.

Executing regressions by systematically inserting individual experimental variables measuring ILI intensity level and disease progression by state and season yielded logit and average marginal effect coefficient values that were statistically insignificant with the exception of a single variable in subgroup 5, which indicated a decrease of 2.29% points, on average, in immunization rates during peak season weeks registering at a ILI intensity magnitude of 9 or greater. Refer to Appendix A for sensitivity analysis FEM regression results.

4.3.3. NIS-Teen: Logistic Regression Analysis

4.3.3.a. Primary Analysis: Fixed Effects Model Estimation

Fixed effects regressions were performed for the teen age group by executing and implementing the same procedures and conventions. After executing regressions by systematically inserting individual experimental variables measuring ILI intensity level and disease progression by state and season yielded logit and average marginal effect coefficient values that were statistically insignificant with the exception of three variables

in subgroup 5. The first variable indicated a 1.31% point increase, on average, in immunization rates during peak season weeks registering at a ILI intensity magnitude of 9 or greater. The second and third variables indicated a 0.135% point, and a 0.212% point decrease, on average, in immunization rates during peak season weeks registering at a ILI intensity magnitude of 8 and greater, or 10 and greater respectively. Refer to Appendix B for primary analysis FEM regression results.

4.3.3.b. Sensitivity Analysis: Fixed Effects Model Estimation

Auxiliary fixed effects estimations were performed as an extension of primary fixed effects regressions in order to isolate and ascertain intra-season variations and effects of pandemic magnitude ILI intensity thresholds. This was achieved by systematically interacting intra-season time phases with ILI threshold variables. AMEs yielded following regressions for the maximum activity level, activity levels exceeding a magnitude of 8, and activity levels exceeding a magnitude of 9, were statistically significant during late segments of the influenza season. Respectively, AMEs were 0.2092% point, 95% CI [0.0038, 0.4145], 2.1965% point, 95% CI [0.0664, 4.3265], and 2.5850% point, 95% CI [0.2541, 4.9158], increases on average in immunization rates. The reference category were influenza seasons that were below the pandemic ILI intensity limit, and additionally did not surpass their specific maximum ILI intensity thresholds during early (E), peak (P), or late (L) segments of the influenza season. AMEs yielded following the remaining regressions were statistically insignificant and exhibited no statistically discernable differences. Refer to table 4.3 for sensitivity analysis FEM regression results.

Table 4.3 – NIS Teen H1N1 Pandemic Sensitivity Analysis: FEM Regression

Period	activitylevel_max	activitylevel_8plus	activitylevel_9plus	activitylevel_10plus
E	0.000177	0.001233	0.001984	0.000417
P	0.000352	0.002662	0.003367	-0.006183
L	0.0020919*	0.0219645*	0.0258495*	0.020051
E*P	0.000555	0.007595	0.006216	-0.000043
P*L	-0.000759	-0.002945	-0.004138	-0.004690
E*L	-0.000548	-0.004513	-0.003350	-0.003787
E*P*L	0.000560	0.004346	0.001812	0.003227

*** p < 0.05 ** p < 0.01 *** p < 0.001**

4.4. Discussion

4.4.1. Recapitulation and Interpretation

Based on statistically significant AME coefficients computed following the ITS regressions for the child sample, it is evident that the 2009 H1N1 pandemic was associated with an initial increase in the probability of overall influenza immunization uptake by parents, and subsequently followed by incremental annual decreases in the same immunization outcome. The AME magnitude for the level change increase was 12.57 percentage points, on average, in the probability of immunization uptake for children. The AME magnitude for the slope change decrease was 3.77 percentage points, on average, in the probability of immunization uptake for children. The baseline trend prior to the 2009 pandemic was a 1.64 percentage point, on average, increase in the probability of immunization uptake by parents, on an annual basis.

It is also evident by the statistically significant AME coefficients for the 2012-2013, 2013-2014, and 2017-2018 restricted scale epidemics, that influenza seasons of constrained epidemic scales yield level decreases in the probability of overall influenza immunization uptake by parents. As demonstrated by the AME coefficients for RSE 1 in

2012, RSE 2 in 2013, and RSE 3 in 2014, which demonstrate a 1.79 percentage point, 5.23 percentage point, and 1.92 percentage point, on average, decrease in the probability of immunization uptake for children, respectively. The ensuing trend change increases are 0.85 pp, 0.34 pp, and 1.24 pp, on average, respectively for each RSE.

Predicated on AME coefficients generated by the ITS estimation, it can be stated that the 2009 H1N1 pandemic initially increased the probability of influenza immunization uptake through psychological mechanisms of escalating fears of disease contraction, and concerns regarding viral infection.[18,30–32,83] It is also likely that shock and awe impacts of the pandemics occurrence heightened parents perceptions regarding the importance of the influenza vaccine and motivated them to pursue completion of influenza vaccinations for their children.[18] Uncertainties regarding potential clinical side-effects, and possible ineffectiveness of vaccine formulations was most probably of lesser concern as compared to the benefits of protection from infection from the influenza virus, and prevention of disease contraction and mortality.[100] It can additionally be speculated that following the subsiding of initial pandemic linked concerns and fears about disease contraction and ensuing morbidity, decision factors linked to assessment of influenza vaccine effectiveness, efficiency, and risk of clinical side-effects, among others, became incorporated in the immunization uptake decision process.[11,45,100] Subsequently, erosions in vaccine confidence and perceptions of effectiveness, diminished concerns regarding risks of viral infection, and desensitization to pandemic progression and public health warnings lead to incremental decreases in immunization uptake behavior.[11,45,100] Evaluating the costs versus benefits of the influenza vaccine became less influenced by initial pandemic trauma and distress.[11,45,100] The degree of doubt and hesitancy regarding

the vaccine likely escalated as well with the progression of time as individuals who were immunized might have still contracted the virus, and this information propagated throughout diffusion channels.[11,45,50,100]

For the RSE occurrences, the limited epidemics exhibit a converse relationship as compared to the pandemic, with anti-immunization factors prominent initially, followed by vaccination uptake promoting factors subsequently. The immediate intercept shifts are notable, and the trend changes pre and post RSE occurrences are minimal. The RSE occurrences relative to their vaccine uptake influences are in correspondence regardless of temporal distance, with the consecutive RSEs (2012 and 2013) exemplifying the same impact directionality as compared to the RSE of 2017.

Examining the sensitivity analysis FEM estimations for the child sample, it is evident that the AME coefficients were statistically insignificant for the vast majority of experimental variables for ILI intensity and disease progression by state and season. The single highly statistically significant experimental indicator is among the pandemic magnitude (high category ILI intensity level) variables during the peak intra-season phase of the flu year. Evaluating the regressions in totality, it can be surmised that for the child sample specifically, parental decisions to uptake influenza immunizations are not directly influenced by influenza disease severity and progression by season and state. It is more likely that vaccine uptake decisions and perceptions are influenced minimally by disease severity on a weekly basis, in different states and geographical regions, and more so on a national scale and larger scope basis. It is possible pandemics, with regards to parental vaccination decisions, are viewed as a periodic occurrence as opposed to a disrupted and dispersed occurrence.

Examining the FEM estimation for the teen sample, it is evident that the AME coefficients were statistically insignificant for the vast majority of experimental variables for ILI intensity and disease progression by state and season. The statistically significant experimental indicators are among the pandemic magnitude (high category ILI intensity level) variables during the peak intra-season phase of the flu year. The peak flu season segment, in conjunction with influenza weeks at pandemic ILI intensity levels of 8, 9, and 10, yield statistically significant AME coefficients with fluctuating direction, proceeding from decreasing to increasing to decreasing respectively. This demonstrates that peak portions of the pandemic severity seasons, may experience oscillating changes in vaccine uptake behavior for teens, and at minimum, that peak segments of pandemic seasons are associated with a degree of effects on immunization uptake by parents for their teens.

After evaluating the sensitivity analysis FEM estimations for the teen sample, it is evident that they are statistically significant, with consistent increases in the probability of immunization uptake occurring for pandemic severity seasons, specifically for their late intra-season phases. For a pandemic severity season, the maximum activity level week occurring during the late segment of the intra-season time phase yields a 0.21 percentage point increase, on average, in the probability of a teen being immunized. For a pandemic severity season in its late phase, the ILI activity level exceeding an 8 or 9 threshold is associated with a 2.20 percentage point, and a 2.59 percentage point, increase in the probability of a teen being immunized, on average. It can be surmised that for the teen sample specifically, parental decisions to uptake influenza immunizations are influenced by influenza disease severity and progression, by season and state, during

peak and late segments of pandemic severity seasons only. With regards to the intra-season timing aspects, peak season uptake behavior is sporadic, while late season uptake behavior is more consistent with minimal increases in the probability of a teen being immunized.

The previous literature evaluating pertussis disease outbreaks by different states attempted to exploit localized variations, and demonstrated escalating infection rates were linked to uptake increases.[23,89] This study determines that during severe influenza seasons, very small increases in influenza vaccine uptake rates for different states are evident, only for adolescents, with variations existing predominantly during later phases of high intensity ILI seasons. This study also determines that for children, no statistically significant effect is evident. This is different than the previous literature regarding pertussis.[23,89] As stated in the literature regarding pertussis outbreaks, perceptions of the disease risk being greater are associated with increases in immunization completion.[23,89] This association is not as evident for influenza pandemics, with escalating infection rates being correlated with very small increases in immunization uptake, by state and season, for adolescents only, and not for children.

The differences and discrepancies observed when comparing this study with the pertussis study may be attributable to the infectious diseases being examined, and it may be that pertussis affects vaccination uptake differently than influenza due to how the infectious disease is perceived or how it progresses. The discrepancies may also be due to the targeted age groups that were examined being different for the studies, with this study examining young children and teens. The discrepancies may additionally be due to this

study examining statewide measures of disease incidence as opposed to local instances which is how the pertussis study performed its analysis.[23,89]

In the pertussis literature, access and costs were said to be involved in determining vaccine uptake for severe seasons, and this may be the case for influenza as well.[23,89] In accordance with the previous literature regarding vaccine access and availability as well as provider facility types, factors such as facility classification, clinician-patient interactions, and vaccine availability may have influenced vaccine uptake, and likely played a role during pandemic severity influenza seasons.[50] Possibilities of vaccine shortages may have existed as well during these time periods, as has been observed in the previous literature.[53] These relationships however are postulated for this study and cannot be ascertained.

4.4.2. Limitations

Limitations inherently associated with this study provide challenges in generating definitive conclusions. The adjacent proximity of the consecutive LAIV advisements and recommendations spanning from 2014 to 2016 produce complexities in delineating the exact trend changes that exist pre and post policy implementation. Specifically for the 2014 post-policy phase, 2015 pre and post policy phases, and for the 2016 pre-policy phase, the trend time periods intersect and are difficult to isolate for the ITS estimations. This is a susceptibility of the ITS regression specification, and the ITS is vulnerable in this respect. Implementing a segmented or piecewise ITS approach minimizes this limitations effects and optimizes estimation results.

The study is limited by the absence of primary and secondary data measuring perceptions of vaccine specific elements such as clinical safety, side effect risks,

effectiveness, disease infection prevention capabilities, and disease susceptibility and severity. The absence of psychologic data measuring aspects such as vaccine confidence level, hesitancy, doubt, intent to vaccinate, concerns regarding infection by the virus, and amplified anxiety and fears induced by the pandemics and epidemics are also a limitation. Measurements for provider characteristics such as immunization availability and accessibility, clinician and patient relationships, and clinician diffusion and dissemination of vaccine information also limit this study. External factors such as societal norms and beliefs are also difficult to integrate into this study due to lack of data measurements for these aspects. The majority of these factors require qualitative study data that allow for in depth analysis of these aspects.

Limitations pertaining to specific vaccine version supply and availability data based on provider facility type and geographic region also reduce the ability to determine if supply and access shortages existed for particular interview survey years. Limitations pertaining to data source design aspects also generate complexities, such as interview years not being subdivided into incremental time periods allowing for a greater number of time points between consecutive annual time spans. This would permit for intra and inter year trends to be examined with a greater degree of scrutiny.

4.5. Conclusion

The 2009 H1N1 influenza pandemic was associated with statistically significant effects on parental decisions to uptake influenza immunizations for their children (ages19-35 months). The pandemic was associated with an initial level change increase in the probability of influenza immunization uptake, on average, for children. Subsequently, annual declines in vaccination uptake ensued, as exhibited by the decreasing trend post

pandemic. The baseline trend prior to the pandemic was a sustained annual increase, on average, in the probability of immunization uptake by parents for children.

Restricted scale epidemic occurrences in 2012-2013, 2013-2014, and 2017-2018, where the influenza season was constrained to epidemic scales, yielded decreases in the probability of immunization uptake for children initially, followed by minimal increases annually. Assessing the pandemic for children based on ILI intensity levels and disease progression, while controlling for fixed effects for states and seasons, yielded minimal to no effects on uptake behavior, with the exception of a single peak pandemic season indicator.

Assessing the pandemic for teens based on ILI intensity levels and disease progression, while controlling for fixed effects for states and seasons, yielded fluctuating effects on uptake behavior for peak segments of pandemic magnitude seasons (intensity levels 8, 9, and 10). Further sensitivity analysis examining intra-season phases in conjunction with seasonal disease severity yielded consistent increasing effects on uptake behavior for late segments of pandemic magnitude seasons.

The 2009 H1N1 influenza pandemic is linked to preliminary escalations in the probability of child immunization uptake likely due to immediate fears of disease contraction, concerns of viral infection, and trauma connected to shock and awe impacts of the pandemics occurrence. These factors likely are paramount in the initial post-pandemic decision phase, and supersede anti-uptake drivers such as uncertainties regarding potential clinical side-effects, possible ineffectiveness of vaccine formulations, and associated erosions in vaccine confidence, and ensuing hesitancy, and doubt. Heightened parental perceptions regarding the importance of the vaccine likely motivates

uptake initially, with the benefits of protection from infection from the influenza virus, and prevention of disease contraction and mortality of chief importance.

Subsequently, initial pandemic linked concerns and fears about disease contraction and ensuing morbidity subside, and decision factors linked to assessment of influenza vaccine effectiveness, efficiency, and risk of clinical side-effects, become integrated more prominently in the immunization uptake decision process, leading to erosions in vaccine confidence and perceptions of effectiveness, and increasing hesitancy and doubt regarding the vaccines advantages. Furthermore, it is speculated that evaluation of the costs versus benefits of the influenza vaccine become less influenced by initial pandemic trauma and distresses. This in conjunction with reduced concerns of viral infection, and desensitization to the pandemics progression lead to gradual declines in uptake behavior. Additionally, it is possible the degree of vaccine confidence declined with the progression of time as individuals who were immunized still contracted the virus and became infected.

Restricted scale epidemics are consistently associated with declines in immunization uptake behavior for children initially, followed by nominal increases annually. It is likely that RSEs do not generate the degree of initial trauma and shock that pandemics such as the H1N1 generate, hence assessments of vaccination merits are considered in the absence of pandemic linked distresses and fears. This possibly permits factors such as vaccine effectiveness, risk of clinical side-effects, and immunization hazards to supersede, in terms of importance, vaccine protection benefits from viral infection, and prevention of morbidity. This altered perception may produce the observed post RSE declines in uptake behavior for children.

Immunization uptake behavior for children is likely not sensitive to ILI severity and disease progression with respect to geography and time specifically, and may be perceived as a grander scale occurrence disconnected from individual state and season occurrences on a weekly basis. Immunization uptake behavior for teens is likely sensitive to ILI severity and disease progression with respect to geography and time specifically, with oscillating effects on uptake behavior exhibited for peak segments of pandemic magnitude seasons, and consistent positive effects on uptake behavior exhibited for late segments of pandemic magnitude seasons.

Public health immunization professionals and personnel should expect preliminary increases in child immunization uptake behavior, followed by gradual decreases in the same outcome for influenza pandemics such as H1N1. They should anticipate decreases in child immunization uptake behavior following smaller scale influenza epidemics. For pandemic intensity ILI seasons, immunization uptake behavior is not sensitive to weekly fluctuations in ILI severity for children, but sensitive for teens during peak and late phases of the influenza season, with fluctuating uptake behavior associated with peak season phases, and consistent increases in uptake behavior associated with late season phases.

This study contributes to the existing literature by enhancing the understanding of how vaccine uptake rates change following pandemic and epidemic events. However it is limited in determining why these changes occur, and due to what factors and mechanisms specifically, which future studies should attempt to discern and ascertain.

CHAPTER 5

THE 2015 LAIV POLICY SHIFT:

ASSESSING IMPACTS ON IMMUNIZATION[1]

[1]A.H. Mehrabi, N.L. Hair, C.M. Andrews, S.E. Harrison, R.D. Horner. To be submitted to *American Journal of Public Health.*

Abstract

Introduction: The 2015 Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) retraction of its original preferential recommendations for usage of the live attenuated influenza vaccine (LAIV), which is the intra-nasal version of the vaccine, has resulted in varied responses, with fluctuations in ensuing CDC vaccine advisements affecting its implementation and uptake among children. Although the CDC's ACIP recommend an annual flu vaccine for individuals 6 months of age and older as the "first and best" defense against influenza, a low percentage of children are vaccinated, and parental decisions are not completely comprehended, particularly in regards to the LAIV formulation. Reviewing the literature, in certain studies a decline in flu vaccine uptake was concluded, whereas in other instances, it conversely increased, or remained static, yielding inconsistent outcomes. Furthermore, there exists a void in the number, scale, and scope of studies published, with none being nationally representative, and examining parental perspectives, decisions, and responses in regard to child flu vaccine uptake following the 2015 ACIP LAIV policy shift.

Methods: To assess impacts of the 2015 ACIP LAIV preferential recommendation revocation on decisions to uptake influenza vaccines for children age 6 months to 17 years of age, data from NIS was used as a series of weighted consecutive annual surveys in order to synthesize a longitudinal panel dataset spanning from 2003 to 2018. Quasi-experimental (QE) approaches in the form of segmented interrupted time series (ITS), and difference in differences (DID) logistic estimations were executed on the integrated dataset yielding logistic regression coefficients and post-estimation

marginal effects signifying the impact of the 2015 ACIP LAIV policy shift on child influenza vaccine uptake (CIVU). ITS regressions examined both level and trend changes due to policy shift occurrence via binary and continuous policy shift incidence variables respectively. DID regressions incorporated LAIV eligibility indicators to ascertain the level and trend differences in CIVU between LAIV eligible (age 2 years and greater), and LAIV ineligible (age 6 to 23 months) individuals, pre and post policy shift. This additionally allowed for ascertainment of spillover effects and impacts of the policy shift on individuals who were only eligible for the injected influenza vaccine (IIV) formulation. Vaccine specific ITS estimations for individual formulations were executed applying previous procedures, in addition to regressions assessing heterogeneity effects.

Results: The segmented interrupted time series (ITS) regression for the NIS-Child sample yielded statistically significant coefficients. Post-estimation average marginal effects (AMEs) were as follows. The LAIV preferential recommendation revocation yielded a 3.01 percentage point (pp), 95% CI [2.54, 4.74], immediate level change increase in the probability of a child being immunized, on average. It also yielded a 2.41 pp, 95% CI [-2.62, -2.11], sustained slope change decrease in the probability of a child being immunized annually, on average. Pre-policy shifts, a 2.06 pp, 95% CI [1.91, 2.22], sustained increase in the probability of a child being immunized annually, on average, was evident. The LAIV preferential recommendation of 2014, and the subsequent LAIV recommendation rescindment of 2016, respectively yielded a 5.25 pp decrease, 95% CI [-7.05, -3.25], and a 1.02 pp increase, 95% CI [0.55, 1.12], in the probability of a child being immunized, on average. The respective trend changes post-

policy shifts were a 1.21 pp increase, 95% CI [1.11, 1.31], and a 5.30 pp decrease, 95% CI [-6.22, -4.38], on average.

The sensitivity analysis difference in differences (DID) estimation yielded statistically significant coefficients. Comparing the differences between LAIV-eligible and LAIV-ineligible individuals, pre and post 2015 policy shift, yielded a DID of 20.70 pp, 95% CI [19.52, 21.88], indicating an increase occurred in the probability of a LAIV-eligible child being immunized as compared to an LAIV-ineligible child, on average, following the 2015 policy shift. Examining the LAIV-eligibility indicator's AME, it is evident that an LAIV-eligible child experiences a 1.34 pp, 95% CI [0.64, 2.03], increase in the probability of being immunized, on average, as compared to an LAIV-ineligible child.

The segmented interrupted time series (ITS) regression for the NIS-Teen sample yielded statistically significant coefficients. Post-estimation AMEs are as follows. The LAIV preferential recommendation revocation yielded a 4.25 pp, 95% CI [2.31, 6.22], immediate level change increase in the probability of a teen being immunized, on average. It also yielded a 3.02 pp, 95% CI [-4.77, -2.33], sustained slope change decrease in the probability of a teen being immunized annually, on average. Pre-policy shifts, a 2.70 pp, 95% CI [2.12, 3.16], sustained increase in the probability of a teen being immunized annually, on average, was evident. The LAIV preferential recommendation of 2014, and the subsequent LAIV recommendation rescindment of 2016, respectively yielded a 8.41 pp decrease, 95% CI [-10.35, -6.41], and a 6.52 pp decrease, 95% CI [-8.21, -4.42], in the probability of a teen being immunized, on average. The respective

trend changes post-policy shifts were a 7.17 pp increase, 95% CI [6.11, 8.58], and a 2.84 pp increase, 95% CI [1.96, 3.71], on average.

Conclusion: The 2015 policy shift was associated with preliminary increases in vaccine uptake, followed by annual declines, for both children and teens. Reductions in overall immunization uptake following the preceding 2014 policy shift, and subsequent 2016 policy shift were evident, for both samples for 2014, and teens for 2016. Public health policies concerning influenza immunization for children and adolescents should concentrate on refraining from issuing preferential advisements for either vaccine formulation if possible. Immunization policies should focus on consistent and stable annual advisements, which may promote greater trust in immunization policies. This study contributes to the existing literature by enhancing the understanding of how vaccine uptake rates change following policy shifts. However it is limited in determining why these changes occur, and due to what factors and mechanisms specifically, which future studies should attempt to discern and ascertain.

5.1. Introduction

Each year millions of children in the U.S. experience influenza-related illness. Although most children infected with influenza viruses recover within a week, serious complications can result in hospitalization or death.[1] Currently, the Centers for Disease Control and Prevention (CDC), and its Advisory Committee on Immunization Practices (ACIP) recommend an annual flu vaccine for individuals 6 months of age and older as the “first and best” defense against influenza.[2,3] Nevertheless, only 45.6% of children 6 months to 17 years of age received the vaccine in 2018 – 2019, and even less at 38.8% in 2017-2018.[4] Understanding parental attitudes and barriers associated with uptake of

childhood immunization is a crucial national public health priority. This process is complex, as numerous socioeconomic, psychological, demographic, and contextual factors influence vaccine uptake rates.[5–9] Doubts regarding vaccine benefits,[10] concerns regarding side-effects and safety,[5,11–17] perceived disease seriousness and risk assessment,[11,15,16,18,19] uncertainties about vaccine effectiveness,[8,11,12,20,21] and healthcare access and costs,[7,8,14,22,23] are prime influencers and factors affecting immunization uptake.

The effects of policy shifts on parental perceptions and decisions to uptake immunizations in the U.S. are not completely understood, with conflicting, and inconsistent conclusions, [5,11,19,23–26] specifically for child flu vaccines. This study overcame these shortcomings and contributes to a better understanding of how parental uptake is affected by these aforementioned factors by examining the 2015 ACIP live attenuated influenza vaccine (LAIV) preferential advisement revocation. The policy shift served as a point of analysis to determine how parental uptake for child flu vaccines may have shifted through different mechanisms. This study has parallels to past research that has examined the controversies regarding other diseases, health conditions, and vaccine formulation elements. These include the measles, mumps, rubella and Autism dilemma, and thimerosal presence in vaccines debate, where child vaccination rates shifted due to false scares, ensuing spillover effects, incorrect conclusions, and parental inability to critically analyze and decipher vaccine information.[5,13,24,27]

The 2015 CDC ACIP retraction of its original preferential recommendations for usage of the LAIV, which is the intra-nasal version of the vaccine for children, [21,25,26,33–37] has resulted in varied responses, with fluctuations in ensuing CDC vaccine advisements

affecting its implementation and uptake among children.[25,33,38,39] Reviewing the literature, in certain studies a decline in flu vaccine uptake was concluded,[33] whereas in other instances, it conversely increased,[26] or remained static,[25] yielding inconsistent outcomes. There is a void in the number, scale, and scope of studies published with none being nationally representative and examining parental perspectives, decisions, and responses in regard to child flu vaccine uptake following the ACIP LAIV withdrawal.

Given the aforementioned, the question arises as to what was the policy impact of the 2015 ACIP LAIV withdrawal on overall child influenza vaccination uptake rates in the U.S.? It is postulated that the 2015 ACIP LAIV withdrawal increased overall child influenza vaccine uptake rates.

This study is novel and innovative as it is the first nationally extensive study assessing the potential impacts of the 2015 LAIV withdrawal on overall child flu vaccine rates over a substantial time range using the National Immunization Survey (NIS) focusing specifically on children. It is the first to evaluate parental decisions to vaccinate their children against the flu by considering changes in parental uptake of child influenza immunizations, following consecutive and evolving ACIP recommendations and advisements. This study is significant, as it is an improved assessment of the LAIV withdrawals, and assists in addressing the shortcomings of predecessor publications. It is significant, as it provides a preliminary understanding of how CDC policy shifts may impact decision making for uptake of child flu vaccines within the U.S., permitting public health policymakers to increase future child flu vaccine uptake by anticipating how parental perspectives and decisions may alter following future ACIP advisements and recommendations.

5.2. Description of Project Design and Methodological Approach

The primary purpose of this project is to advance understanding of how influenza immunization policy shifts affect parental perspectives and decisions regarding child flu vaccine uptake. By examining marginal effects for completion of child flu vaccines following the occurrence of the 2015 LAIV policy shift we evaluated these impacts. Analysis was achieved by executing logistic regression models, specifically by implementing an interrupted time-series (ITS) empirical approach, with a quasi-experimental design strategy for the estimations, using STATA 16 statistical software. Provider-verified immunization histories from a state and nationally representative dataset served as the basis for performing these statistical estimations.

The 15-year time span from 2003 to 2018 was examined for this study, encompassing the 2015 ACIP LAIV preferential recommendation revocation completely and sufficiently. The time period of analysis commences in 2003, since that is the preliminary year where the IIV formulation's universal recommendation and application would be realized following the ACIP's decision.

It is also the year where the LAIV formulation of the immunization was accepted and authorized for usage by the ACIP. The time period of analysis terminates in 2018 as that is the most recent year available for analysis. The data was aggregated, and compiled for analysis by merging separate annual surveys consecutively into a single dataset. The final version of the data was a series of repeated cross-sections based on annually completed NIS surveys. This generated dataset emulated longitudinal and panel data sources, and allowed for minimization of bias, while reinforcing estimation of a correlation relationship that is representative of a larger scale heterogeneous population.[85]

Sensitivity analyses in the form of auxiliary ITS estimations, implementing a difference in differences (DID) designation, for the LAIV policy shift, were performed in order to corroborate and validate results yielded by the primary logistic regressions.

Specific Aim 2: To ascertain the policy effects of the 2015 ACIP LAIV preferential recommendation revocation on overall child influenza vaccination uptake rates in the U.S. by assessing changes in the likelihood that a child is vaccinated for influenza following the policy shift event.

H_2: The 2015 ACIP LAIV preferential recommendation revocation is expected to decrease the likelihood of overall child influenza vaccine uptake. In accordance with the previous literature, and this studies conceptual model, provider dissemination of immunization information, based on ACIP advisements, will likely reduce vaccine uptake, since LAIV will not be recommended as the preferred option to parents by providers.

5.2.1. Data Sources

The data source used for this study was the National Immunization Survey (NIS), which is conducted by the CDC's National Center for Immunization and Respiratory Diseases (NCIRD) in order to monitor immunization coverage. It is nationally representative and comprehensive including flu vaccination data for children 6 months – 17 years of age for all 50 states and additional U.S. territories.[86] NIS consists of a combination of NIS-Child (ages 19-35 months), and NIS-Teen (ages 13-17 years).[86] NIS offers national, state, and local level data, provided directly from the child's providers (NIS-Child and NIS-Teen consist of provider-verified immunization measures), bolstering its accuracy and validity.[86] It contains information regarding the types of

vaccines administered to children, their dates and dosages, demographic, socioeconomic, geographic, and insurance data, as well as administrative data related to providers and facilities where the procedures were performed.[86]

5.2.2. NIS Sampling Procedures, Weighting, and Response Rates

NIS-Child and NIS-Teen conduct sampling in a two phased and tiered approach. In phase one, the data collection procedure is to attain immunization information for a national probability sample of children, by performing random digit dialing (RDD) within each of the statistical sampling strata in order to identify eligible subjects.[86] The interviewers request permission to contact the vaccination provider of the qualified child, and subsequently, a mailed survey is sent to the designated clinician. In phase two, the provider record check (PRC) survey is completed, and allows for confirmation and verification of the phase one questionnaire responses.[86] Overall this allows for vaccination statistics that are comparable across geographic territories, with the progress of time, and promotes minimization of bias that may exist.[86]

NIS-Child and NIS-Teen possess weighting processes and procedures that adjust for variation in sampling rates, differences and discrepancies in response rates, and variations in representation in the sample relative to the overall population being assessed.[86] This allows for improved accuracy of estimates at various sampling levels. The estimates and variance approximations are generated for separate areas, states, and sampling subdivisions. Weight imputations are performed for the survey as necessary.[86]

The anticipated NIS-Child sample size for completed interviews is approximately 25,000 addresses, on average.[86] The annual response rate of NIS-Child is approximately 65 percent of eligible subjects within the sample, on average, for the parent response

segment.[86] The rate of children with adequate provider data available is approximately 70 percent, on average.[86]

The anticipated NIS-Teen sample size for completed interviews is approximately 35,000 addresses, on average.[86] The annual response rate of NIS-Teen is approximately 60 percent of eligible subjects within the sample, on average, for the parent response segment.[86] The rate of children with adequate provider data available is approximately 70 percent, on average.[86]

5.2.3. General Regression Model Components and Estimation Elements

Outcome (Dependent) Variable: CIVU (Child Influenza Vaccine Uptake) denotes whether the child was administered and received the influenza vaccine. This is a binary "Yes" or "No" outcome measure represented by 1 or 0 respectively.

Primary Variables of Interest: The LAIV 2015 level change variable denotes the initial occurrence of the policy shift, with its coefficient demonstrating the immediate level change with respect to CIVU. This is binary and symbolizes the incidence of the policy shift. The LAIV 2015 slope change variable is a continuous variable arising from the interaction between the normalized time variable (T) and the policy point indicator variable. It denotes the ensuing trend occurrence in the post policy phase, with its coefficient demonstrating the subsequent slope change with respect to CIVU.

Predictive (Independent) Variables: Child sex, age, birth order, race/ethnicity, relocation/mobility comparing state of birth and current location, maternal age, education level, marital status, insurance type, family income level, and provider/clinician facility type. These covariates are in concordance with previously applied conventions among

predecessor studies, and are standard across previously completed studies published in the literature.

Additional Control Factors: State level characteristics that vary with time, state level policy and mandate differences, occurrence of the H1N1 influenza pandemic, restricted scale epidemic occurrences of the influenza virus (RSEs), and CDC ACIP influenza vaccine policy shifts. Time-variant state level attributes specifically include: Unemployment rates, retrieved from the Bureau of Labor Statistics (BLS); Poverty rates, retrieved from the U.S. Census; Health insurance coverage rates subdivided between percentage private, public, and uninsured, retrieved from the U.S. Census; Medicaid income eligibility thresholds as a function of a percentage of the Federal Poverty Level (FPL), retrieved from the Kaiser Family Foundation (KFF). These will be merged into the primary data source via each states Federal Information Processing Standard (FIPS) code identifiers, which will serve as channels for cross matching state by year control data.

Associated Terms: Beta coefficients specify the impact, or marginal effect, of their corresponding variable in regards to the outcome variable CIVU.

Cross Sections Examined: Individuals are examined in conjunction with time progression in years for different states.

Covariate Coefficient Measures: Coefficients were examined, and subsequently interpreted, in order to assess if baseline disparities existed, and if further disparities existed beyond those due to standard inherent heterogeneity, for certain covariates. This signified if the disparities and heterogeneity were attributable to the event occurrence specifically, or if they were naturally occurring by default.

Interpretation of Coefficients: The interpretation of the beta coefficients are as follows. If the marginal effect yielded is a positive value, this indicates that the event of interest increased the predicted probability of the outcome occurring, which is child flu vaccine uptake by parents. If the marginal effect yielded is a negative value, this indicates that the event decreased the predicted probability of the outcome occurring. If the marginal effect equals zero, or is nearly zero, this signifies the event had no impact, or minimal impact respectively. The magnitude of the marginal effect regardless of directionality and sign exemplifies the degree of impact of the event of interest on the outcome, with greater measures corresponding to larger impacts, without exceeding the limit of 1 as the maximum value.

5.2.4. Regression Model Structures, Designations, and Specifications

The interrupted time series and difference in difference models are the two primary methodological designations that were implemented in order to execute the logistic regressions on the immunization data. Following the logistic regression estimations, post estimation commands for predicted probability and marginal effect computations will be executed.

5.2.4.a. Segmented Interrupted Time Series Estimation: NIS - Child

The segmented interrupted time series estimation was executed on NIS-Child data for individuals across the entire age range (19-35 months) for consecutive years initiating in 2003 and terminating in 2018. Due to the difficulty in isolating the effects of the 2015 policy point individually, it is necessary to account for the 2014 and 2016 policy shifts as well. In order to accomplish this, the ITS estimation was executed as a segmented or piecewise regression as opposed to a regular ITS estimation. The segmented ITS

regression incorporates multiple temporal periods (pre-2014, 2014 to 2015, 2015 to 2016, and post-2016) in order to compute the estimates for both level and slope changes for individual policy shifts. This model allows for slope as well as intercept changes to be calculated for each of the three policy points, while controlling for concomitant factors.

The regression equation included concomitant event control indicators for the H1N1 influenza pandemic of 2009, and the three restricted scale epidemics (RSE 1, RSE 2, RSE 3) corresponding to the 2012-2013, 2013-2014, and 2017-2018 influenza seasons respectively. All contemporaneous influenza vaccination influencing events are coded as categorical variables corresponding to the initial year of the contemporaneous events season of occurrence.

This is due to the NIS survey design being such that it is conducted from the January of the initial year to the February of the subsequent year, hence the year variable represents the interview year, or the year survey conduction commenced.[86,94] This is the initial year of the influenza season, which is of interest, since the vast majority of vaccination happens during the months of September to February of each influenza season.[95,96] This allows for capturing of influenza vaccine uptake behavior during the major vaccine completion portion of the year, spanning this intra-season time period. This also allows the post policy period effects of the contemporaneous policy shifts to be captured effectively since the ACIP policy decisions are completed in the preceding summer months, and regulations and protocols are subsequently disseminated to clinicians and providers for the upcoming season, permitting ample time for the effects of the policy shift to be realized.[70,98] Predecessor vaccine studies have implemented this convention for analysis purposes, as it is established in the literature.

The outcome variable representing CIVU is defined as an child who is completely vaccinated and immunized based on CDC ACIP guidelines and regulations. Meaning that completion of required dosages and injection sequences are incorporated into formulation of this outcome measure as described in the CDC NIS user guide protocols and definitions based on vaccine season recommendations from ACIP. An individual is reported by providers as immunized when they are up-to-date for their vaccinations. This is denoted in the NIS-Child data by a series of provider up-to-date (UTD) variables specifically related to the influenza vaccine. To reflect CDC ACIP decisions and adjustments in advisements, the final up-to-date variable used in this estimation is comprised of different immunization variables recorded in NIS-Child. From the time period between 2003 to 2006, one variable is used, followed by another from 2007 to 2013, in order to reflect the revised definition of vaccinated by ACIP, followed by a final variable from 2014 to 2018, which was synthesized based on ACIP chart guidelines defining complete immunization. This was achieved using the intermediate variable denoting the provider reported measure for total number of vaccinations completed per cycle to date.

The alternative outcome variable that was implemented in supplementary ITS estimations used the provider verified immunization measure for the total number of shots completed. The outcome in the alternative regressions was coded as a binary variable with 0 corresponding to no dosages received, and 1 corresponding to greater than or equal to 1 dosage received.

The additional covariates used in the regression were selected based on ubiquity, appositeness, and frequency of previous usage among predecessor literary works and

publications, as well as pertinence predicated on CDC NIS user guide definitions and recommendations. Covariates representing child characteristics include age group of the child, gender, race/ethnicity, birth order status, and translocation from a different state. Covariates linked to maternal attributes include marriage status, age group, and education level. Family characteristics included total number of children present, income level category as a function of a percentage of the federal poverty line. Provider characteristics included the providers facility classification type. State attributes included percentage poverty rate, percentage unemployment rate, percentage uninsured below 65 years of age, percentage with public health insurance below 65 years of age, and Medicaid eligibility thresholds for parents, and infants 0 to 1 and 1 to 5 years of age respectively.

Interrupted Time Series Regression Equation (ITS): $\text{Logit}(CIVU_{tis}) = \beta_0 + [\beta_1 (T_{ts})] + [\beta_2 (H1N1_{ts})] + [\beta_3 (\mathbf{LAIV\ 2014}_{ts})] + [\beta_4 (\text{LAIV 2015 Level}_{ts})] + [\beta_5 (\text{LAIV 2015 Slope}_{ts})] + [\beta_6 (\mathbf{LAIV\ 2016}_{ts})] + [\beta_7 (\mathbf{RSE}_{ts})] + [\beta_8 (\mathbf{X}_{tis})] + [\beta_9 (\mathbf{State\ Factors}_{ts})] + e_{tis}$

5.2.4.b. Difference in Differences Estimation: NIS - Child

The difference in differences (DID) estimation function executed on NIS-Child was identical to the ITS estimation function executed on NIS-Child except the DID regression equation integrated additional treatment versus control subgrouping variables in conjunction with the pre-existing ITS time phase variables. The treatment cohort is designated as those individuals who are eligible to receive the LAIV formulation in addition to the standard IIV version (infants greater than 2 years or 24 months of age). The control cohort is designated as those individuals who are candidates to receive the IIV formulation only (infants 6 to 23 months of age).

To establish these cohort divisions necessary for the DID estimation, a binary categorical treatment (LAIV eligible) vs control (LAIV non-eligible) cohort assignment variable is generated, with a value of 0 corresponding to individuals in the age range between 19 to 23 months, and a value of 1 corresponding to individuals in the age range between 24 to 35 months. The intermediary variable for age subgroup was used to achieve this segregation. The treatment versus control subgroup assignment variable's beta coefficient symbolizes the baseline difference comparing LAIV eligible to non-eligible individuals, with respect to the outcome variable CIVU.

The variable DID is generated to compute the trend difference between LAIV eligible versus non-eligible individuals, pre and post policy point, also termed the difference between differences comparing treatment versus control subgroups, across the time phases. The DID variable is synthesized by interacting the policy point time phase variable, with the LAIV eligibility variable. The beta coefficient for the DID variable symbolizes the difference in trends comparing LAIV eligible to non-eligible individuals, pre and post 2015 policy shift, with respect to the outcome variable CIVU. The calculated beta coefficient value signifies the degree of impact of the policy on vaccination rates for LAIV eligible individuals, and also ascertain whether spillover effects were experienced by LAIV non-eligible individuals with respect to CIVU, as an unintended consequence of the 2015 LAIV advisement.

Difference in Differences Regression Equation (DID): $\text{Logit}\,(\text{CIVU}_{tis}) = \beta_0 + [\beta_1\,(\text{H1N1}_{ts})] + [\beta_2\,(\text{LAIV 2014}_{ts})] + [\beta_3\,(\text{LAIV 2015}_{ts})] + [\beta_4\,(\text{LAIV 2016}_{ts})] + [\beta_5\,(\text{LAIV Eligible}_{tis})] + [\beta_6\,(\text{DID}_{tis})] + [\beta_7\,(\mathbf{RSE}_{ts})] + [\beta_8\,(\mathbf{X}_{tis})] + [\beta_9\,(\mathbf{State\ Factors}_{ts})] + e_{tis}$

5.2.4.c. Segmented Interrupted Time Series Estimation: NIS - Teen

The segmented interrupted time series estimation for teens was executed on NIS-Teen data for individuals across the entire age range (13 to 17 years) for consecutive years initiating in 2008 and terminating in 2018. Due to the difficulty in isolating the effects of the 2015 policy point individually, it was necessary to account for the 2014 and 2016 policy shifts as well. In order to accomplish this, the ITS estimation was executed as a segmented or piecewise regression as opposed to a regular ITS estimation. The segmented ITS regression incorporates multiple temporal periods (pre-2014, 2014 to 2015, 2015 to 2016, and post-2016) in order to compute the estimates for both level and slope changes for individual policy shifts. This model allows for slope as well as intercept changes to be calculated for each of the three policy points, while controlling for concomitant factors.

The regression equation included concomitant event control indicators for the H1N1 influenza pandemic of 2009, and the three restricted scale epidemics (RSE 1, RSE 2, RSE 3) corresponding to the 2012-2013, 2013-2014, and 2017-2018 influenza seasons respectively. All contemporaneous influenza vaccination influencing events are coded as categorical variables corresponding to the initial year of the contemporaneous events season of occurrence.

This is due to the NIS survey design being such that it is conducted from the January of the initial year to the February of the subsequent year, hence the year variable represents the interview year, or the year survey conduction commenced.[86,94] This is the initial year of the influenza season, which is of interest, since the vast majority of vaccination happens during the months of September to February of each influenza

season.[95,96] This allows for capturing of influenza vaccine uptake behavior during the major vaccine completion portion of the year, spanning this intra-season time period. This also allows the post policy period effects of the contemporaneous policy shifts to be captured effectively since the ACIP policy decisions are completed in the preceding summer months, and regulations and protocols are subsequently disseminated to clinicians and providers for the upcoming season, permitting ample time for the effects of the policy shift to be realized.[70,98] Predecessor vaccine studies have implemented this convention for analysis purposes, as it is established in the literature.

The outcome variable representing CIVU is defined as a teen who is completely vaccinated and immunized based on CDC ACIP guidelines and regulations. Meaning that completion of required dosages and injection sequences are incorporated into formulation of this outcome measure as described in the CDC NIS user guide protocols and definitions based on vaccine season recommendations from ACIP. An individual is reported by providers as immunized when they are up-to-date for their vaccinations. This is denoted in the NIS-Teen data by a series of provider verified up-to-date variables specifically related to the influenza vaccine for each season. For individuals with adequate provider vaccination information available, the seasonal up-to-date variables were combined and integrated annually, using each year systematically from 2008 to 2018, to generate a final measure of complete vaccination. This variable symbolizes CIVU in the regression equation.

The alternative outcome variable that was implemented in supplementary ITS estimations used the provider verified immunization measure for the total number of shots completed. The outcome in the alternative regressions was coded as a binary

variable with 0 corresponding to no dosages received, and 1 corresponding to greater than or equal to 1 dosage received.

The additional covariates used in the regression were selected based on ubiquity, appositeness, and frequency of previous usage among predecessor literary works and publications, as well as pertinence predicated on CDC NIS user guide definitions and recommendations. Covariates representing teen characteristics include age of the teen, gender, race/ethnicity, insurance type, and translocation from a different state. Covariates linked to maternal attributes include marriage status, age group, and education level. Family characteristics included total number of children present, income level category as a function of a percentage of the federal poverty line. Provider characteristics included the providers facility classification type. State attributes included percentage poverty rate, percentage unemployment rate, percentage uninsured below 65 years of age, percentage with public health insurance below 65 years of age, and Medicaid eligibility thresholds for parents, and infants 0 to 1 and 1 to 5 years of age respectively.

Interrupted Time Series Regression Equation (ITS): $\text{Logit}\,(CIVU_{tis}) = \beta_0 + [\beta_1 (T_{ts})] + [\beta_2 (H1N1_{ts})] + [\beta_3 (\mathbf{LAIV\ 2014}_{ts})] + [\beta_4 (\text{LAIV 2015 Level}_{ts})] + [\beta_5 (\text{LAIV 2015 Slope}_{ts})] + [\beta_6 (\mathbf{LAIV\ 2016}_{ts})] + [\beta_7 (\mathbf{RSE}_{ts})] + [\beta_8 (\mathbf{X}_{tis})] + [\beta_9 (\mathbf{State\ Factors}_{ts})] + e_{tis}$

Rational and decisions for regression variable and factor usage, formulation, application, and incorporation were enhanced based on information and explanations acquired regarding NIS data from electronic correspondence and consultation with data experts and analysts at NORC. The empirical approach was enhanced by similar procedures implemented by predecessor studies.

5.3. Results

5.3.1. Descriptive and Summary Analysis

5.3.1.a. NIS-Child

The data sample for individuals ages 19 - 35 months consisted of 698,157 total observations, with 29.34 % (204,855) between 19 - 23 months, 33.78 % (235,812) between 24 - 29 months, and 36.88 % (257,490) between 30 - 35 months. Among the sample, 26.35 % (183,982) received the influenza vaccine and possessed complete and adequate provider records. Among this subsample, 32.77 % (60,294) were considered immunized against the influenza virus as defined by ACIP regulations and protocols for vaccine dosage sequence and administration. The division in frequency of observations for the age ranges (19 - 23 months, 24 - 29 months, and 30 - 35 months) among this subsample was 31.30% (18,870), 37.37 % (22,534), and 31.33 % (18,890) respectively.

Among immunized children with adequate provider verified vaccine records, 48.86 % (29,457) were female and 51.14 % (30,837) were male. Among the same sample, 16.13 % (9,728) were Hispanic, 65.32 % (39,385) were Caucasian, 5.89 % (3,553) were African American, and 12.65 % (7,628) were of another ethnicity. With regard to first born status, 45.78 % (27,602) were the first child, and 54.22 % (32,692) were not. With regard to relocation and mobility, 8.26 % (4,979) had relocated from another state, and 91.74 % (55,312) had not.

With regard to marriage status of the mother and age, 81.25 %, (48,988) were children of married mothers, and 18.75 % (11,306) were not, with 74.01 % (44,624) of those mothers being over 30 years of age, and 25.99 % (15,670) being under 30 years of age. Mothers education level was divided at 7.32 % (4,411) for less than high school

achievement, 13.10 % (7,899) for high school graduate achievement, 20.12 % (12,132) for some degree of university achievement, and 59.46 % (35,852) for university graduate achievement.

With regards to the number of total children within the family unit, 29.87 % (18,012) were single child families, 61.01% (36,786) were families with 2 to 3 children, and 9.12 % (5,496) were families with 4 or more children. With regard to income to FPL ratio status, 14.67 % (8,371) were below 100% of the FPL, 13.99 % (7,982) were between 100 % to 199 % of the FPL, 13.50 % (7,706) were between 200 % to 299 % of the FPL, and 57.84 % (33,005) were at or above 300 % of the FPL.

The provider facility type the child was administered the vaccine at was divided such that 7.26 % (4,380) were at a public facility, 13.66 % (8,235) were at a hospital facility, 62.08 % (37, 429) were at a private practice, 4.56 % (2,752) were at a military or other type of facility, and 12.44 % (7,498) were at a hybrid or mixed facility.

5.3.1.b. NIS-Teen

The data sample for individuals ages 13 - 17 years consisted of 414,708 total observations, with 19.52 % (80,956) at 13 years of age, 20.38 % (84,531) at 14 years of age, 20.24 % (83,918) at 15 years of age, 20.58 % (85,359) at 16 years of age, and 19.28 % (79,944) at 17 years of age. Among the sample, 49.57 % (205,576) received the influenza vaccine and possessed complete and adequate provider records. Among this subsample, 21.35 % (43,895) were considered immunized against the influenza virus as defined by ACIP regulations and protocols for vaccine dosage sequence and administration. The frequency of observations based on ages (13 to 17 years) among this

subsample was 23.95% (10,511), 22.21 % (9,750), 19.77 % (8,679), 18.60 % (8,163), and 15.47 % (6,792) respectively.

Among immunized children with adequate provider verified vaccine records, 48.23 % (21,171) were female and 51.77 % (22,724) were male. Among the same sample, 15.01 % (6,587) were Hispanic, 65.53 % (28,765) were Caucasian, 8.53 % (3,746) were African American, and 10.93 % (4,797) were of another ethnicity. With regard to relocation and mobility, 22.42 % (9,840) had relocated from another state, and 77.58 % (34,055) had not.

With regard to marriage status of the mother and age, 75.20 %, (33,010) were children of married mothers, and 24.80 % (10,885) were not, with 7.28 % (3,197) of those mothers being at or under 34 years of age, and 39.26 % (17,233) being between 35 and 44 years of age inclusive, and 53.46 % (23,465) being at or above 45 years of age. Mothers education level was divided at 10.14 % (4,449) for less than high school achievement, 15.22 % (6,682) for high school graduate achievement, 24.18 % (10,616) for some degree of university achievement, and 50.46 % (22,148) for university graduate achievement.

With regards to the number of total children within the family unit, 35.29 % (15,490) were single child families, 55.00 % (24,143) were families with 2 to 3 children, and 9.71 % (4,262) were families with 4 or more children. With regard to income to FPL ratio status, 15.61 % (6,459) were below 100% of the FPL, 15.12 % (6,254) were between 100 % to 199 % of the FPL, 13.10 % (5,419) were between 200 % to 299 % of the FPL, and 56.17 % (23,240) were at or above 300 % of the FPL.

The provider facility type the child was administered the vaccine at was divided such that 10.38 % (4,555) were at a public facility, 10.52 % (4,617) were at a hospital facility, 48.17 % (21,143) were at a private practice, 8.11 % (3,561) were at a military or other type of facility, and 22.82 % (10,019) were at a hybrid or mixed facility.

5.3.2. NIS-Child: Logistic Regression Analysis

5.3.2.a. Primary Analysis: Interrupted Time Series

The interrupted time series (ITS) regression targeting the LAIV preferential recommendation revocation of 2015 yielded statistically significant coefficients for the primary variables of interest. Execution of the delta-method margins procedure yielded post-estimation average marginal effects (AMEs) for the primary variables of interest associated with the policy shifts occurrence. The LAIV preferential recommendation revocation yielded a 3.01 percentage point, 95% CI [2.54, 4.74], immediate level change increase in the probability of a child being immunized, on average. It also yielded a 2.41 percentage point, 95% CI [-2.62, -2.11], sustained slope change decrease in the probability of a child being immunized annually, on average. Prior to the policy shifts occurrence, a 2.06 percentage point, 95% CI [1.91, 2.22], sustained increase in the probability of a child being immunized annually, on average, was evident.

The LAIV preferential recommendation of 2014, and the subsequent LAIV recommendation rescindment of 2016, yielded post-estimation AMEs that were statistically significant. Occurrence of the 2014 policy shift yielded a 5.25 percentage point, 95% CI [-7.05, -3.25], decrease in the probability of a child being immunized, on average, followed by a 1.21 pp sustained slope increase. Occurrence of the 2016 policy

shift yielded a 1.02 percentage point, 95% CI [0.55, 1.12], increase in the probability of a child being immunized, on average, followed by a 5.30 pp sustained slope decrease. Refer to table 5.1 for ITS regression results pertaining to chief variables of interest.

Table 5.1 – NIS Child LAIV Policy Shift ITS Regression: Variables of Interest

Policy Variables	AME	SE	z	P > z	[95%	CI]
Pre-LAIV 2014 Trend	0.0206	0.0079	26.08	0.0000	0.0191	0.0222
LAIV 2014 Level	-0.0525	0.0056	-14.73	0.0000	-0.0705	-0.0325
Post-LAIV 2014 Trend	0.0121	0.0052	23.49	0.0000	0.0111	0.0131
LAIV 2015 Level	0.0301	0.0052	7.47	0.0000	0.0254	0.0474
Post-LAIV 2015 Trend	-0.0241	0.0006	-25.78	0.0000	-0.0262	-0.0211
LAIV 2016 Level	0.0102	0.0052	2.46	0.0140	0.0055	0.0112
Post-LAIV 2016 Trend	-0.0530	0.0047	-11.30	0.0000	-0.0622	-0.0438

Examining the policy variables specifically with regards to their temporal aspects pertaining to intercept and trend shifts yields statistically significant AME values following execution of a segmented ITS regression for NIS-Child. The AME coefficients for the pre and post policy trends as well as their respective level changes are summarized above. The graphical depiction of the segmented ITS estimation is illustrated in Figure 5.1. The pre and post policy shift trends are indicated by solid graph lines, and the policy shift intercept changes are exhibited by dashed graph lines. The trend changes are demonstrated by percentage point fluctuations annually with respect to the outcome, and the level changes are demonstrated by immediate percentage point intercept shifts.

Execution of the segmented ITS estimation using the alternative flu vaccination outcome (provider verified immunizations for the number of dosages completed) yielded statistically significant AME coefficients that corroborated the up-to-date outcome regressions. The magnitude and direction of the AMEs for all policy shift variables were in agreement for both level and trend values (Table C.5).

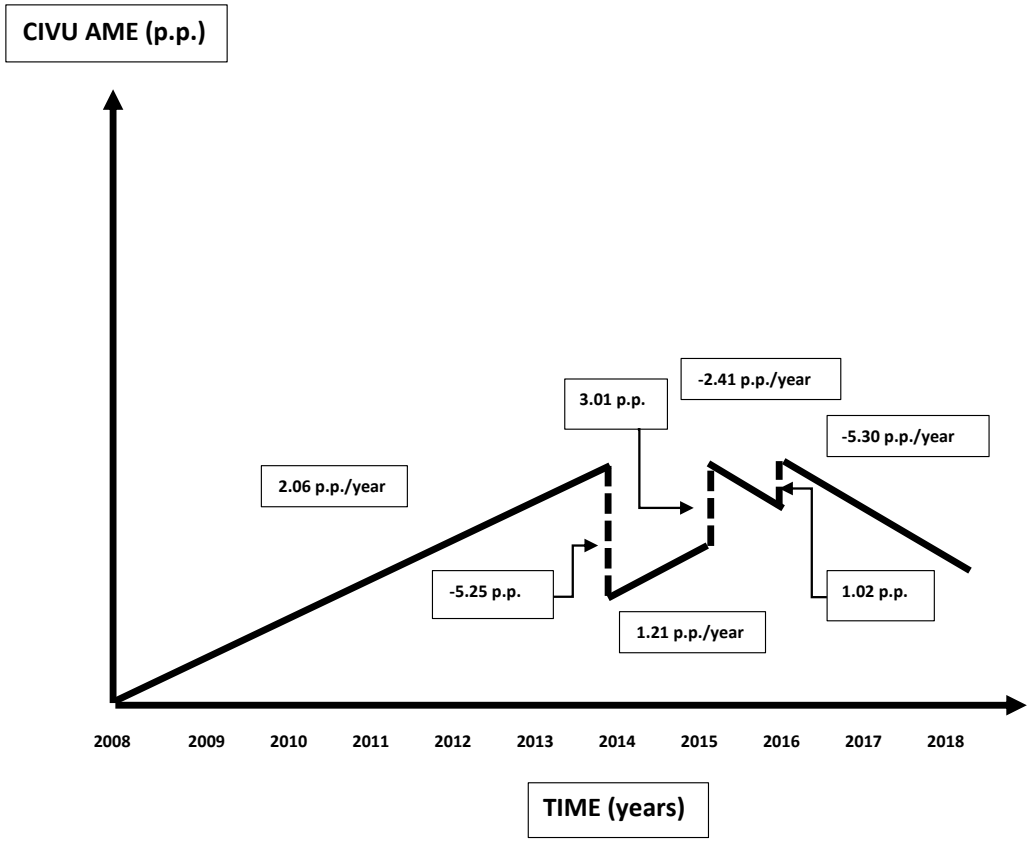

Figure 5.1 – NIS Child Policy Specific Piecewise ITS Regression Graph

5.3.2.b. Sociodemographic Characteristics and Disparities (ITS)

The following segment is examining baseline differences relative to sociodemographic factors, with positive differences indicating greater likelihoods of immunization, and negative differences indicating lesser likelihoods of immunization, on average (Table 5.2). Comparing average marginal effects (AMEs) between age subgroups with 19-23 months as the reference category, ages 24-29 months experienced a 3.40% point greater likelihood of immunization on average, 95% CI [2.92, 3.88], and ages 30-35 months experienced a 6.60% point greater likelihood of immunization on average, 95% CI [6.01, 7.18]. With regards to gender differences, the AME was statistically insignificant and no discernable disparities existed.

With regards to ethnicity and race category, with Hispanic as the reference subgroup, Caucasians experienced a 1.38% point greater likelihood of immunization on average, 95% CI [0.74, 2.03], African Americans experienced a 5.55% point lesser likelihood of immunization on average, 95% CI [-6.44, -4.65], other non-Hispanic ethnicities possessed statistically insignificant differences.

Individuals who were the first born experienced a 4.22% point greater likelihood of immunization on average compared to non-first born individuals, 95% CI [3.60, 4.85]. Individuals who had relocated from another state experienced a 5.60% point, on average, lesser likelihood of immunization, 95% CI [-6.31, -4.89].

Mothers marital status being married was associated with a greater likelihood of immunization by 2.24% points, on average, 95% [1.63, 2.85], as did a mothers age being 30 years of age or greater, at 5.37% points on average, 95% CI [4.85, 5.89]. For mothers education level, with uneducated being the reference category, university graduates experienced a 5.21% point greater likelihood of immunization, 95% CI [4.25, 6.17], and high school graduation and some degree of university achievement experienced statistically insignificant differences.

For the number of children in the family unit, with one as the reference category, families with two to three children experienced statistically insignificant differences, and families with four or more experienced a 5.06 % point, on average, lesser likelihood of immunization, 95% CI [-6.01, -4.10]. For income to FPL ratio category, with less than 100% as the reference category, 100% to 199% of the FPL experienced statistically insignificant differences, 200% to 299% of the FPL experienced a 1.94% point on average greater likelihood of immunization, 95% CI [1.11, 2.77] and 300% of the FPL or

greater experienced a 6.75% point on average greater likelihood of immunization, 95% CI [5.94, 7.55].

Table 5.2 – NIS Child LAIV Policy Shift ITS Regression: Covariates

Covariates	AME	SE	z	P > z	[95%	CI]
Age (Ref: 19-23 months)						
24-29 months	0.0340	0.0024	13.8700	0.0000	0.0292	0.0387
30-35 months	0.0660	0.0030	22.1600	0.0000	0.0601	0.0718
Gender (Ref: Male)						
Female	0.0001	0.0021	0.0600	0.9520	-0.0041	0.0043
Ethnicity (Ref: Hispanic)						
Non-Hispanic Caucasian	0.0138	0.0033	4.2100	0.0000	0.0074	0.0203
Non-Hispanic AA	-0.0555	0.0046	-12.1400	0.0000	-0.0644	-0.0465
Non-Hispanic Other	0.0048	0.0042	1.1400	0.2550	-0.0035	0.0131
Birth Order (Ref: No)						
First Born	0.0422	0.0032	13.2800	0.0000	0.0360	0.0485
Mobility (Ref: No)						
Relocated	-0.0560	0.0036	-15.4500	0.0000	-0.0631	-0.0489
Marital Status (Ref: No)						
Married	0.0224	0.0031	7.1500	0.0000	0.0163	0.0285
Mother's Age (Ref: < 30)						
30 years or over	0.0537	0.0026	20.3400	0.0000	0.0485	0.0589
Mother's Educ (Ref: < HS)						
High School	-0.0063	0.0046	-1.3600	0.1750	-0.0154	0.0028
Some College	0.0008	0.0046	0.1700	0.8620	-0.0082	0.0099
College Graduate	0.0521	0.0049	10.6300	0.0000	0.0425	0.0617
Num of Children (Ref: 1)						
2-3 Children	-0.0025	0.0035	-0.7100	0.4750	-0.0092	0.0043
4+ Children	-0.0506	0.0049	-10.3700	0.0000	-0.0601	-0.0410
Inc to FPL (Ref: < 100%)						
100 to 199% FPL	-0.0006	0.0037	-0.1700	0.8660	-0.0079	0.0066
200 to 299% FPL	0.0194	0.0042	4.5800	0.0000	0.0111	0.0277
300% FPL or greater	0.0675	0.0041	16.4600	0.0000	0.0594	0.0755
Facility Type (Ref: Public)						
Hospital Facility	0.0488	0.0047	10.3600	0.0000	0.0396	0.0581
Private Practice	0.0527	0.0039	13.4900	0.0000	0.0450	0.0604
Military/Other	0.0159	0.0056	2.8500	0.0040	0.0050	0.0268
Hybrid/Mixed	0.0427	0.0047	9.0300	0.0000	0.0334	0.0519

With regards to the provider facility type the vaccine was administered at, public facilities were the reference category, with hospital facilities experiencing a 4.89% point greater likelihood of immunization, on average, 95% CI [3.96, 5.81]. Private practices experienced a 5.27% point greater likelihood of immunization, on average, 95% CI [4.51, 6.04]. Military and other facility types experienced a 1.59% point greater likelihood of immunization, on average, 95% CI [0.50, 2.68]. Hybrid and mixed facilities experienced a 4.27% point greater likelihood of immunization, on average, 95% CI [3.34, 5.19]. Refer to table 5.2 for ITS regression results pertaining to control variables.

The heterogeneity for the sample was computed by subdividing the sample for specific subgroups and executing logistic estimations for different subgroups separately. This was achieved by applying commands to segregate the sample based on income to FPL thresholds and ethnicity type (Table C.3). For ethnicity categories, with Hispanic as the reference subgroup, Caucasian children were more likely to experience immunization uptake, as were other ethnicities, and African Americans were less likely, on average. This is consistent with expectations for ethnicity based variations, with African Americans experiencing the least likelihood. For income to FPL ratio categories, with less than 100% being the reference subgroup, as the income to FPL percent increased, the likelihood of experiencing immunization for a child increased, on average, and is consistent with expectation.

5.3.2.c. Sensitivity Analysis: Difference in Differences Estimation

Examination of child observations for the sample (289,712) yielded 71.24 % (206,381) eligible to be administered the LAIV formulation, and 28.76 % (83,331) ineligible to receive the LAIV formulation. Among the LAIV eligible individuals

(77,348), 46.24 % (35,769) were specified as immunized with adequate provider verified vaccination records, and 53.76 % (41,579) were specified as not completely immunized, and had adequate provider verified vaccination records.

Among the LAIV ineligible individuals (42,798), 65.48 % (14,775) were specified as immunized with adequate provider verified vaccination records, and 34.52 % (28,023) were specified as not completely immunized, and had adequate provider verified vaccination records.

The difference in differences (DID) estimation targeting the effects of the LAIV preferential recommendation revocation of 2015 for LAIV-eligible children (treatment) versus LAIV-ineligible children (control) yielded statistically significant coefficients. Execution of the delta-method margins procedure yielded post-estimation average marginal effects (AMEs) for the DID primary variable of interest and associated LAIV-eligibility indicator. Comparing the differences between LAIV-eligible and LAIV-ineligible individuals, pre and post 2015 LAIV preferential recommendation revocation, yielded a difference in differences of 20.70 percentage points, 95% CI [19.52, 21.88]. This indicates that a 20.70 percentage point increase occurred in the probability of a LAIV-eligible child being immunized as compared to an LAIV-ineligible child, on average, following the 2015 policy shift. Examining the LAIV-eligibility indicator's AME, it is evident that an LAIV-eligible child experiences a 1.34 percentage point, 95% CI [0.64, 2.03], increase in the probability of being immunized, on average, as compared to an LAIV-ineligible child. Refer to table 5.3 for sensitivity analysis DID regression results.

Table 5.3 – NIS Child LAIV Policy Shift: Difference in Differences Regression

Sensitivity Analysis	AME	SE	z	P > z	[95%	CI]
LAIV Eligible	0.0134	0.0036	3.7600	0.0000	0.0064	0.0203
Difference in Differences	0.2070	0.0060	34.4300	0.0000	0.1952	0.2188

5.3.2.d. Sensitivity Analysis: Formulation Specific ITS Estimations

Auxiliary ITS estimations specifically aiming at assessing the influences of the 2015 policy point with respect to vaccine formulation type were executed. This was performed by alternating the dependent variable measuring overall uptake, and instead substituting the provider verified measures for immunization completion for each version of the vaccine individually (IIV and LAIV). Following regression procedures, the preliminary logit coefficients and post-estimation average marginal effect (AME) coefficients were statistically significant (Table C.1). Examining the IIV formulation singularly yielded a 4.43 pp sustained annual increase, on average, in the probability of a child being immunized, pre-policy implementation. For the 2015 policy immediate level change, a 4.17 pp increase, on average, was evident in the probability of the outcome, followed by a 1.98 pp sustained annual decrease, on average, in the probability of the outcome, post-policy implementation.

For the 2014 policy point, a 13.31 pp decrease, on average, in the probability of the outcome was evident, and for the 2016 policy point, the AME was statistically insignificant. The H1N1 pandemic yielded a 1.51 pp increase, on average, in the probability of the outcome, with RSE 1 and RSE 2 yielding a 4.76 pp and a 8.45 pp decrease, on average, in the probability of the outcome, respectively.

Examining the LAIV formulation singularly yielded a 2.02 pp sustained annual increase, on average, in the probability of a child being immunized, pre-policy

implementation. For the 2015 policy immediate level change, a 23.43 pp increase, on average, was evident in the probability of the outcome, followed by a 1.42 pp sustained annual decrease, on average, in the probability of the outcome, post-policy implementation.

For the 2014 policy point, a 4.00 pp decrease, on average, in the probability of the outcome was evident, and for the 2016 policy point, a 13.01 pp increase, on average, in the probability of the outcome was evident. The H1N1 pandemic yielded a 2.09 pp increase, on average, in the probability of the outcome, with RSE 1 and RSE 2 yielding a 1.89 pp and a 3.08 pp decrease, on average, in the probability of the outcome, respectively.

Evaluating LAIV uptake with respect to segregated provider facility types, public establishments experienced a 17.17 pp level increase, on average, in the probability of the outcome, followed by a 4.20 pp sustained annual decrease, on average, after inception of the 2015 policy shift. Private practices experienced a 24.06 pp level increase, on average, in the probability of the outcome, followed by a 7.05 pp sustained annual decrease, on average, after inception of the 2015 policy shift (Table C.1).

5.3.3. NIS-Teen: Logistic Regression Analysis

5.3.3.a. Primary Analysis: Interrupted Time Series

The interrupted time series (ITS) regression targeting the LAIV preferential recommendation revocation of 2015 yielded statistically significant coefficients for the primary variables of interest. Execution of the delta-method margins procedure yielded post-estimation average marginal effects (AMEs) for the primary variables of interest associated with the policy shifts occurrence. The LAIV preferential recommendation

revocation yielded a 4.25 percentage point, 95% CI [2.31, 6.22], immediate level change increase in the probability of a teen being immunized, on average. It also yielded a 3.02 percentage point, 95% CI [-4.77, -2.33], sustained slope change decrease in the probability of a teen being immunized annually, on average. Prior to the policy shifts occurrence, a 2.70 percentage point, 95% CI [2.12, 3.16], sustained increase in the probability of a teen being immunized annually, on average, was evident.

The LAIV preferential recommendation of 2014, and the subsequent LAIV recommendation rescindment of 2016, yielded post-estimation AMEs that were statistically significant. Occurrence of the 2014 policy shift yielded a 8.41 percentage point, 95% CI [-10.35, -6.41], decrease in the probability of a teen being immunized, on average, followed by a sustained slope increase of 7.17 pp. Occurrence of the 2016 policy shift yielded a 6.52 percentage point, 95% CI [-8.21, -4.42], decrease in the probability of a teen being immunized, on average, followed by a sustained slope increase of 2.84 pp. Refer to table 5.4 for ITS regression results pertaining to chief variables of interest.

Table 5.4 – NIS Teen LAIV Policy Shift ITS Regression: Variables of Interest

Policy Variables	AME	SE	z	P > z	[95%	CI]
Pre-LAIV 2014 Trend	0.0270	0.0018	14.63	0.0000	0.0212	0.0316
LAIV 2014 Level	-0.0841	0.0084	-11.96	0.0000	-0.1035	-0.0641
Post-LAIV 2014 Trend	0.0717	0.0047	15.21	0.0000	0.0611	0.0858
LAIV 2015 Level	0.0425	0.0047	5.62	0.0000	0.0231	0.0622
Post-LAIV 2015 Trend	-0.0302	0.0018	-14.53	0.0000	-0.0477	-0.0233
LAIV 2016 Level	-0.0652	0.0122	-7.06	0.0000	-0.0821	-0.0442
Post-LAIV 2016 Trend	0.0284	0.0044	6.38	0.0000	0.0196	0.0371

The graphical depiction of the segmented ITS estimation is illustrated in Figure 5.2, with dashed lines signifying level or intercept shifts, and solid lines indicating trend or slope shifts.

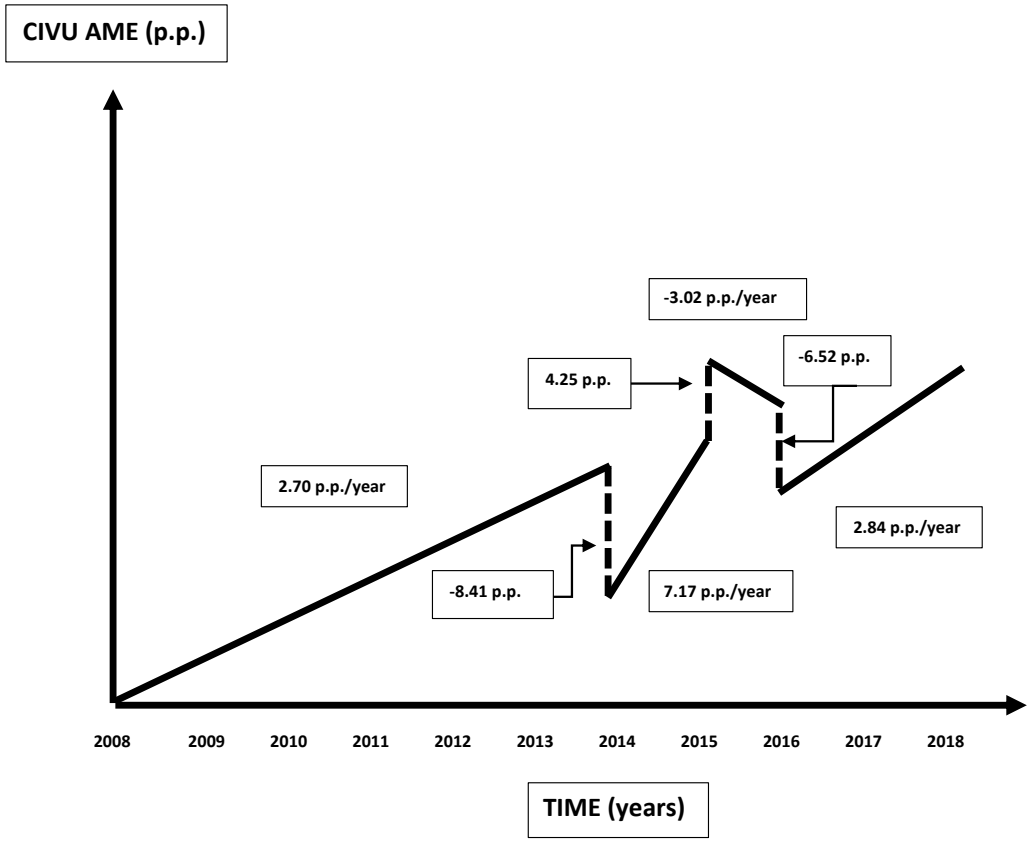

Figure 5.2 – NIS Teen Policy Specific Piecewise ITS Regression Graph

Execution of the segmented ITS estimation using the alternative flu vaccination outcome (provider verified immunizations for the number of dosages completed) yielded statistically significant AME coefficients that corroborated the up-to-date outcome regressions. The magnitude and direction of the AMEs for all policy shift variables were in agreement for both level and trend values (Table C.5).

5.3.3.b. Sociodemographic Characteristics and Disparities (ITS)

The following is examining baseline differences relative to sociodemographic factors (Table 5.5). Comparing average marginal effects (AMEs) between age subgroups with 13 years of age as the reference category, 14 years of age experienced a 2.41% point lesser likelihood of immunization on average, 95% CI [-3.23, -1.60], 15 years of age

experienced a 4.32% point lesser likelihood of immunization on average, 95% CI [-5.14, -3.50], 16 years of age experienced a 5.59% point lesser likelihood of immunization on average, 95% CI [-6.41, -4.77], 17 years of age experienced a 7.15% point lesser likelihood of immunization on average, 95% CI [-7.99, -6.32]. With regards to gender differences, the AME was statistically insignificant and no discernable disparities existed.

With regards to ethnicity and race category, with Hispanic as the reference subgroup, Caucasians experienced a 2.86% point greater likelihood of immunization on average, 95% CI [1.99, 3.73], African Americans experienced a 2.53% point lesser likelihood of immunization on average, 95% CI [-3.70, -1.36], other non-Hispanic ethnicities possessed statistically insignificant differences.

For insurance type, private insurance was the reference category, individuals with only Medicaid experienced a 2.52% point greater likelihood of immunization on average, 95% CI [1.59, 3.45], uninsured individuals experienced a 7.92% lesser likelihood of immunization on average, 95% CI [-10.63, -5.22], individuals covered by S-Chip or alternative plans possessed statistically insignificant differences. Individuals who had relocated from another state experienced a 1.18% point, on average, lesser likelihood of immunization, 95% CI [-1.78, -0.59].

Mothers marital status being married was associated with a greater likelihood of immunization by 0.83% points, on average, 95% [0.18, 1.48]. For mothers age, with 34 years of age or younger being the reference category, mother between 35 to 44 years of age experienced statistically insignificant differences, and mothers 45 years of age or greater experienced a 3.15% point, on average, greater likelihood of immunization, 95% CI [2.10, 4.21]. For mothers education level, with uneducated being the reference

category, children of mothers who were university graduates experienced statistically insignificant differences, children of mothers who were high school graduates experienced a 2.22% point, on average, lesser likelihood of immunization, 95% CI [-3.32, -1.12], children of mothers with some degree of university achievement experienced a 2.38% point, on average, lesser likelihood of immunization, 95% CI [-3.45, -1.31].

For the number of children in the family unit, with one as the reference category, families with two to three children experienced a 2.72% point, on average, greater likelihood of immunization, 95% CI [2.15, 3.29], and families with four or more experienced a 2.03 % point, on average, greater likelihood of immunization, 95% CI [1.04, 3.01]. For income to FPL ratio category, with less than 100% as the reference category, 100% to 199% of the FPL experienced a 1.53% point, on average, lesser likelihood of immunization, 95% CI [-2.47, -0.58], 200% to 299% of the FPL experienced a 1.56% point, on average, lesser likelihood of immunization, 95% CI [-2.67, -0.46], and 300% of the FPL or greater experienced a 2.69% point, on average, greater likelihood of immunization, 95% CI [1.57, 3.80].

For provider facility type, public facilities were the reference category, with hospital facilities experiencing a 6.60% point greater likelihood of immunization, on average, 95% CI [5.53, 7.68]. Private practices experienced a 4.94% point greater likelihood of immunization, on average, 95% CI [4.18, 5.70]. Military and other facility types experienced a 4.84% point greater likelihood of immunization, on average, 95% CI [3.73, 5.95]. Hybrid and mixed facilities experienced a 9.10% point greater likelihood of immunization, on average, 95% CI [8.22, 9.98].

Table 5.5 – NIS Teen LAIV Policy Shift ITS Regression: Covariates

Covariates	AME	SE	z	P > z	[95%	CI]
Age (Ref: 13)						
14	-0.0241	0.0042	-5.8000	0.0000	-0.0323	-0.0160
15	-0.0432	0.0042	-10.3400	0.0000	-0.0514	-0.0350
16	-0.0559	0.0042	-13.4100	0.0000	-0.0641	-0.0477
17	-0.0715	0.0042	-16.8800	0.0000	-0.0798	-0.0632
Gender (Ref: Male)						
Female	0.0045	0.0026	1.7500	0.0810	-0.0005	0.0095
Ethnicity (Ref: Hispanic)						
Non-Hispanic Caucasian	0.0286	0.0044	-6.4300	0.0000	0.0199	0.0373
Non-Hispanic AA	-0.0253	0.0060	-4.2500	0.0000	-0.0370	-0.0136
Non-Hispanic Other	0.0077	0.0061	1.2700	0.2040	-0.0042	0.0197
Mobility (Ref: No)						
Relocated	-0.0118	0.0030	-3.9100	0.0000	-0.0178	-0.0059
Insurance (Ref: Private)						
Medicaid Only	0.0252	0.0047	5.3100	0.0000	0.0159	0.0345
S-Chip or Other Plan	0.0058	0.0050	1.1700	0.2400	-0.0039	0.0155
Uninsured	-0.0792	0.0138	-5.7500	0.0000	-0.1062	-0.0522
Mother's Age (Ref: <= 34)						
35 to 44 years	0.0088	0.0051	1.7400	0.0830	-0.0011	0.0187
>= 45 years	0.0315	0.0054	5.8500	0.0000	0.0210	0.0421
Marital Status (Ref: No)						
Married	0.0083	0.0033	2.4900	0.0130	0.0018	0.0148
Mother's Educ (Ref: < HS)						
High School	-0.0222	0.0056	-3.9500	0.0000	-0.0331	-0.0112
Some College	-0.0238	0.0055	-4.3500	0.0000	-0.0345	-0.0131
College Graduate	0.0112	0.0058	1.9400	0.0530	-0.0001	0.0225
Inc to FPL (Ref: < 100%)						
100 to 199% FPL	-0.0152	0.0048	-3.1500	0.0020	-0.0247	-0.0058
200 to 299% FPL	-0.0156	0.0056	-2.7800	0.0060	-0.0267	-0.0046
300% FPL or greater	0.0269	0.0057	4.7200	0.0000	0.0157	0.0380
Num of Children (Ref: 1)						
2-3 Children	0.0272	0.0029	9.3800	0.0000	0.0215	0.0329
4+ Children	0.0203	0.0050	4.0300	0.0000	0.0104	0.0301
Facility Type (Ref: Public)						
Hospital Facility	0.0660	0.0055	12.0500	0.0000	0.0553	0.0768
Private Practice	0.0494	0.0039	12.7900	0.0000	0.0418	0.0570
Military/Other	0.0484	0.0057	8.5600	0.0000	0.0373	0.0595
Hybrid/Mixed	0.0910	0.0045	20.2600	0.0000	0.0822	0.0998

The heterogeneity for the sample was computed by subdividing the sample for specific subgroups and executing logistic estimations for different subgroups separately. This was achieved by applying commands to segregate the sample based on income to FPL thresholds and ethnicity type (Table C.4). For ethnicity categories, with Hispanic as the reference subgroup, Caucasian children were more likely to experience immunization uptake, as were other ethnicities, and African Americans were less likely, on average. This is consistent with expectations for ethnicity based variations, with African Americans experiencing the least likelihood. For income to FPL ratio categories, with less than 100% being the reference subgroup, as the income to FPL percent increased, the likelihood of experiencing immunization for a child increased, on average, and is consistent with expectation.

5.3.3.c. Sensitivity Analysis: Formulation Specific ITS Estimations

Auxiliary ITS estimations specifically aiming at assessing the influences of the 2015 policy point with respect to vaccine formulation type were executed. This was performed by alternating the dependent variable measuring overall uptake, and instead substituting the provider verified measures for immunization completion for the LAIV version of the vaccine separately. Following regression procedures, the preliminary logit coefficients and post-estimation average marginal effect (AME) coefficients were statistically significant (Table C.2).

Examining the LAIV formulation singularly yielded a 6.39 pp sustained annual increase, on average, in the probability of a child being immunized, pre-policy implementation. For the 2015 policy immediate level change, a 4.53 pp increase, on average, was evident in the probability of the outcome, followed by a 3.04 pp sustained

annual decrease, on average, in the probability of the outcome, post-policy implementation.

For the 2014 policy point, a 10.67 pp decrease, on average, in the probability of the outcome was evident, and for the 2016 policy point, a 7.75 pp decrease, on average, in the probability of the outcome was evident. The H1N1 pandemic yielded a statistically insignificant AME coefficient, while RSE 1 and RSE 2 yielding a 5.02 pp and a 8.55 pp decrease, on average, in the probability of the outcome, respectively.

Evaluating LAIV uptake with respect to segregated provider facility types, public establishments experienced a 2.98 pp level increase, on average, in the probability of the outcome, followed by a 2.33 pp sustained annual decrease, on average, after inception of the 2015 policy shift. Private practices experienced a 4.05 pp level increase, on average, in the probability of the outcome, followed by a 3.03 pp sustained annual decrease, on average, after inception of the 2015 policy shift (Table C.2).

5.4. Discussion

5.4.1. Recapitulation and Interpretation

Based on statistically significant AME coefficients computed following the ITS regressions for the child and teen samples, it is evident that in both samples, that the 2015 preferential advisement rescindment was associated with an initial increase in the probability of overall influenza immunization uptake by parents, and subsequently followed by incremental annual decreases in the same immunization outcome. The AME magnitudes for the level change increases for both samples were similar at 3.01 percentage points on average for children, and 4.25 percentage points on average for teens. The AME magnitudes for the slope change decreases were also in agreement with

2.41 percentage points on average for children, and 3.02 percentage points on average for teens. Baseline trends pre-2014 policy point were in accordance as well with a 2.06 percentage point, and a 2.70 percentage point on average increase in the probability of immunization uptake by parents on an annual basis.

With regard to the juxtaposed LAIV policy points, the AME magnitudes and direction for the 2014 preferential advisement were in accordance with decreases of 5.25 percentage points and 8.41 percentage points for children and teens respectively. The post-2014 trend changes were in agreement at 1.21 pp and 7.17 pp respectively. The AME magnitudes and direction however were opposites with regards to the 2016 non-recommendation of LAIV with a 1.02 percentage point increase on average for children, and a 6.52 percentage point decrease for teens. The post-2016 trend changes were different directionally at a 5.30 pp decrease for children, and a 2.84 pp increase for teens.

The trends and fluctuations exhibited in influenza immunization uptake by parents following the policy points can be rationalized in various hypothetical and theoretical ways. Theoretically, changes in a physician's clinical practices, including alterations in the information they discuss with parents, and their vaccine recommendations, could influence changes in parental perceptions of the relative risks versus benefits of immunizations, and their particular formulations.[10,50] It is possible that vaccine formulations are being recommended as options by providers and clinicians differently following the occurrence of the ACIP policy decisions, due to clinicians and providers altering suggestions for which formulation to pursue based on that years ACIP advisement.[10,50] This is due to providers being informed regarding recent adjustments to immunization policies and protocols, hence providers adapt their recommendations

appropriately, including what formulation options they present to the parent during appointments or informational sessions.[10,50] It is unlikely that parents are cognizant of minor revisions to ACIP LAIV policies on an annual basis, and are likely uninformed regarding such advisements or modifications of ACIP advisements, and instead are dependent on clinician and provider recommendations. The providers dissemination of vaccine related information is likely to be modified predicated on ACIP annual guidance as well, hence this leads to differences in the providers vaccination practices following each advisement, and the information they convey to parents.[9,10,50]

Preferential recommendation for LAIV over IIV in 2014 likely lead to the intra-nasal vaccine formulation being offered by providers as the optimal selection as compared to the IIV formulation.[26] The subsequent rescindment of the preferential advisement in 2015 likely lead to reductions in prescription of LAIV as compared to IIV by the child's providers.[10,26,50,101] The clinicians equally promoted both LAIV and IIV formulations as recommended influenza vaccine versions, possibly stimulating greater vaccination uptake in totality as a consequence.[10,26,50,101] This possibly lead to the increases in overall immunization uptake rates initially, since both formulations were being favored as opposed to a single version.[101] This rationalizes the initial increase in the probability of immunization uptake exhibited by the immediate level change difference following the 2015 policy shift, but cannot be ascertained.

It is possible that vacillating and fluctuating advisements by ACIP, and ultimately clinician dissemination of vaccine information regarding recommendations, may have led to decreased trust in health and medical authorities, inducing annual declines in influenza

immunization uptake with the progression of time.[9] This rationalizes the subsequent incremental decreases in overall influenza immunization uptake rates annually.

With regards to LAIV eligibility, the baseline difference between LAIV eligible and LAIV ineligible cohorts was minimal at 1.34 percentage points in favor of LAIV eligible children experiencing a greater probability of immunization uptake on average. Following the 2015 policy shift, the difference between LAIV eligible and ineligible cohorts was more prominent as exemplified by a difference in differences AME coefficient of 20.7 percentage points. Meaning that LAIV eligible individuals, as compared to non-eligible individuals, experienced a substantially greater probability of being immunized by their parents. This may be because the LAIV eligible individuals, who are also IIV eligible, experienced greater adoption of influenza vaccines in general, since both versions of the immunization were recommended to them by providers as options, meaning both formulation channels (LAIV and IIV) were considered as legitimate options by providers. This is demonstrated by the DID AME coefficient being substantially greater in magnitude for LAIV eligible individuals following the 2015 policy point.

It is also possible that LAIV eligible children, being older, are more likely to receive influenza vaccinations by predisposition, since a greater percentage of 24 month and older children were up to date for their influenza immunizations, and parents might be more likely to pursue immunizations for them, and be less sensitive about uncertainties. This would also potentially explain the difference observed pre and post between LAIV eligible and ineligible children, and the magnitude of the DID estimation coefficient.

Finally, it is possible that fluctuating recommendations and advisements by ACIP on an annual basis diminished parental trust relative to immunization authorities.[9] It is possible that this also directed attention towards the influenza vaccine overall, hence leading to more parents pursuing information regarding influenza immunizations from providers and clinicians.[9]

Assessing the vaccine formulations singularly corroborated the primary analysis results and rationalization of immunization uptake mechanisms. The IIV formulation estimation validated the core estimation by exhibiting an increasing pre-policy trend, followed by an immediate level change increase in the probability of the outcome for the 2015 policy point, followed by a sustained annual decrease, on average, during the post-policy phase. The LAIV formulation estimations validated the principal regressions by exemplifying a sustained increasing pre-policy trend, followed by an immediate level change increase in the probability of the outcome for the 2015 policy point, followed by a subsequent annual decrease, on average, during the post-policy phase. This trend sequence was evident for both child and teen samples, with the pre and post 2015 policy trends for both samples in agreement for magnitude and direction, as well as the intercept increases. The level change increase for the child sample was prominent for the LAIV specific estimation.

For the juxtaposed policy shifts of 2014 and 2016, the magnitude and directionality of the LAIV specific estimations were in agreement with the primary analysis regressions and corroborated the previous results. The formulation specific estimations indicate that the preferential advisements for the LAIV induce declines in uptake for both vaccine versions, particularly for IIV, and that subsequent rescindments

of the preferential recommendations stimulate increases in uptake for both formulations, specifically for IIV. This further corroborates the rationalizations and explanations for the overall influenza vaccine uptake results.

The provider facility type specific estimations that were executed for both child and teen samples exhibited immediate level change increases in the probability of the outcome, on average, followed by sustained annual decreases in the post-policy phase. This was evident for both child and teen samples and for both private and public facility types. However, private practices exhibited a more prominent level increase in vaccine uptake rates for both child and teen samples as compared to public facilities, with the difference being most noticeable for children specifically.

5.4.2. Limitations

Limitations inherently associated with this study provide challenges in generating definitive conclusions. The adjacent proximity of the consecutive LAIV advisements and recommendations spanning from 2014 to 2016 produce complexities in delineating the exact trend changes that exist pre and post policy implementation. Specifically for the 2014 post-policy phase, 2015 pre and post policy phases, and for the 2016 pre-policy phase, the trend time periods intersect and are difficult to isolate for the ITS estimations. This is a susceptibility of the ITS regression specification, and the ITS is vulnerable in this respect. Implementing a segmented or piecewise ITS approach minimizes this limitations effects and optimizes estimation results.

The study is limited by the absence of primary and secondary data measuring perceptions of vaccine specific elements such as clinical safety, side effect risks, effectiveness, disease infection prevention capabilities, and disease susceptibility and

severity. The absence of psychologic data measuring aspects such as vaccine confidence level, hesitancy, doubt, intent to vaccinate, concerns regarding infection by the virus, and amplified anxiety and fears induced by the pandemics and epidemics are also a limitation. Measurements for provider characteristics such as immunization availability and accessibility, clinician and patient relationships, and clinician diffusion and dissemination of vaccine information also limit this study. External factors such as societal norms and beliefs are also difficult to integrate into this study due to lack of data measurements for these aspects. The majority of these factors require qualitative study data that allow for in depth analysis of these aspects.

Limitations pertaining to specific vaccine version supply and availability data based on provider facility type and geographic region also reduce the ability to determine if supply and access shortages existed for particular interview survey years. Limitations pertaining to data source design aspects also generate complexities, such as interview years not being subdivided into incremental time periods allowing for a greater number of time points between consecutive annual time spans. This would permit for intra and inter year trends to be examined with a greater degree of scrutiny.

5.5. Conclusion

The 2015 LAIV preferential recommendation revocation was associated with statistically significant effects on parental decisions to uptake influenza immunizations for their children (ages19-35 months) and adolescents (ages 13 to 17 years). The policy shift was associated with an initial level change increase in the probability of influenza immunization uptake, on average, for children and teens. Subsequently, annual declines in vaccination uptake ensued, with slope change decreases in the probability of influenza

immunization uptake, on average, for children and teens. Baseline trends prior to the policy shift sequences exhibited a sustained annual increase, on average, in the probability of immunization uptake by parents for children and teens.

LAIV eligibility was associated with a minimal baseline difference between LAIV eligible and ineligible cohorts, with LAIV eligible children experiencing a 1.34 percentage point increase in the probability of immunization uptake, on average. Following the 2015 policy shift, the difference between LAIV eligible and ineligible cohorts was more prominent as exemplified by a difference in differences sensitivity analysis that yielded a 20.7 percentage point increase, on average, in the probability of a LAIV eligible child being immunized, as compared to a non-eligible child. This signifies a substantially greater probability of an LAIV eligible child being immunized by their parents following the policy shift as compared to their ineligible counterparts, who are IIV eligible only. Spillover effects in the form of reductions in the probability of immunization uptake for LAIV ineligible children is evident predicated on DID estimation outcomes.

Provider and clinician recommendations for the LAIV and IIV versions of the influenza immunization, based on ACIP advisements, including preferential recommendations, may have stimulated reductions in overall immunization uptake rates following the 2014 policy shift, which were counteracted by the 2015 policy shift initially, when both formulations were equally recommended by providers due to the elimination of the preferential statement. This possibly led to the increases in immunization uptake rates that were exhibited initially. Subsequently erosion in vaccine

uptake due to fluctuating annual LAIV advisements, and provider recommendations, may have induced the declining slope change trend post 2015 policy shift.

Public health policies concerning influenza immunization for children and adolescents should concentrate on refraining from issuing preferential advisements for either vaccine version if possible. Immunization policies should focus on recommending both formulations in order to maximize overall immunization uptake rates instead. Consistent and stable annual advisements, and minimizing vacillation of recommendations on an annual basis, may additionally increase parental trust in immunization policies and provider suggestions, and promote increases in child influenza vaccine uptake.

This study contributes to the existing literature by enhancing the understanding of how vaccine uptake rates change following policy shifts. However it is limited in determining why these changes occur, and due to what factors and mechanisms specifically, which future studies should attempt to discern and ascertain.

CHAPTER 6

CONCLUSION

6.1. The 2009 H1N1 Pandemic

The 2009 H1N1 influenza pandemic was associated with statistically significant effects on parental decisions to uptake influenza immunizations for their children (ages19-35 months). The pandemic was associated with an initial level change increase in the probability of influenza immunization uptake, on average, for children. Subsequently, annual declines in vaccination uptake ensued, as exhibited by the decreasing trend post pandemic. The baseline trend prior to the pandemic was a sustained annual increase, on average, in the probability of immunization uptake by parents for children.

Restricted scale epidemic occurrences in 2012-2013, 2013-2014, and 2017-2018, where the influenza season was constrained to epidemic scales, yielded decreases in the probability of immunization uptake for children initially, followed by minimal increases annually. Assessing the pandemic for children based on ILI intensity levels and disease progression, while controlling for fixed effects for states and seasons, yielded minimal to no effects on uptake behavior, with the exception of a single peak pandemic season indicator.

Assessing the pandemic for teens based on ILI intensity levels and disease progression, while controlling for fixed effects for states and seasons, yielded fluctuating effects on uptake behavior for peak segments of pandemic magnitude seasons

(intensity levels 8, 9, and 10). Further sensitivity analysis examining intra-season phases in conjunction with seasonal disease severity yielded consistent increasing effects on uptake behavior for late segments of pandemic magnitude seasons.

The 2009 H1N1 influenza pandemic is linked to preliminary escalations in the probability of child immunization uptake likely due to immediate fears of disease contraction, concerns of viral infection, and trauma connected to shock and awe impacts of the pandemics occurrence. These factors likely are paramount in the initial post-pandemic decision phase, and supersede anti-uptake drivers such as uncertainties regarding potential clinical side-effects, possible ineffectiveness of vaccine formulations, and associated erosions in vaccine confidence, and ensuing hesitancy, and doubt. Heightened parental perceptions regarding the importance of the vaccine likely motivates uptake initially, with the benefits of protection from infection from the influenza virus, and prevention of disease contraction and mortality of chief importance.

Subsequently, initial pandemic linked concerns and fears about disease contraction and ensuing morbidity subside, and decision factors linked to assessment of influenza vaccine effectiveness, efficiency, and risk of clinical side-effects, become integrated more prominently in the immunization uptake decision process, leading to erosions in vaccine confidence and perceptions of effectiveness, and increasing hesitancy and doubt regarding the vaccines advantages. Furthermore, it is speculated that evaluation of the costs versus benefits of the influenza vaccine become less influenced by initial pandemic trauma and distresses. This in conjunction with reduced concerns of viral infection, and desensitization to the pandemics progression lead to gradual declines in uptake behavior. Additionally, it is possible the degree of vaccine confidence declined

with the progression of time as individuals who were immunized still contracted the virus and became infected.

Restricted scale epidemics are consistently associated with declines in immunization uptake behavior for children initially, followed by nominal increases annually. It is likely that RSEs do not generate the degree of initial trauma and shock that pandemics such as the H1N1 generate, hence assessments of vaccination merits are considered in the absence of pandemic linked distresses and fears. This possibly permits factors such as vaccine effectiveness, risk of clinical side-effects, and immunization hazards to supersede, in terms of importance, vaccine protection benefits from viral infection, and prevention of morbidity. This altered perception may produce the observed post RSE declines in uptake behavior for children.

Immunization uptake behavior for children is likely not sensitive to ILI severity and disease progression with respect to geography and time specifically, and may be perceived as a grander scale occurrence disconnected from individual state and season occurrences on a weekly basis. Immunization uptake behavior for teens is likely sensitive to ILI severity and disease progression with respect to geography and time specifically, with oscillating effects on uptake behavior exhibited for peak segments of pandemic magnitude seasons, and consistent positive effects on uptake behavior exhibited for late segments of pandemic magnitude seasons.

Public health immunization professionals and personnel should expect preliminary increases in child immunization uptake behavior, followed by gradual decreases in the same outcome for influenza pandemics such as H1N1. They should anticipate decreases in child immunization uptake behavior following smaller scale

influenza epidemics. For pandemic intensity ILI seasons, immunization uptake behavior is not sensitive to weekly fluctuations in ILI severity for children, but sensitive for teens during peak and late phases of the influenza season, with fluctuating uptake behavior associated with peak season phases, and consistent increases in uptake behavior associated with late season phases.

This study contributes to the existing literature by enhancing the understanding of how vaccine uptake rates change following pandemic and epidemic events. However it is limited in determining why these changes occur, and due to what factors and mechanisms specifically, which future studies should attempt to discern and ascertain.

6.2. The 2015 LAIV Preferential Recommendation Revocation

The 2015 LAIV preferential recommendation revocation was associated with statistically significant effects on parental decisions to uptake influenza immunizations for their children (ages19-35 months) and adolescents (ages 13 to 17 years). The policy shift was associated with an initial level change increase in the probability of influenza immunization uptake, on average, for children and teens. Subsequently, annual declines in vaccination uptake ensued, with slope change decreases in the probability of influenza immunization uptake, on average, for children and teens. Baseline trends prior to the policy shift sequences exhibited a sustained annual increase, on average, in the probability of immunization uptake by parents for children and teens.

LAIV eligibility was associated with a minimal baseline difference between LAIV eligible and ineligible cohorts, with LAIV eligible children experiencing a 1.34 percentage point increase in the probability of immunization uptake, on average. Following the 2015 policy shift, the difference between LAIV eligible and ineligible

cohorts was more prominent as exemplified by a difference in differences sensitivity analysis that yielded a 20.7 percentage point increase, on average, in the probability of a LAIV eligible child being immunized, as compared to a non-eligible child. This signifies a substantially greater probability of an LAIV eligible child being immunized by their parents following the policy shift as compared to their ineligible counterparts, who are IIV eligible only. Spillover effects in the form of reductions in the probability of immunization uptake for LAIV ineligible children is evident predicated on DID estimation outcomes.

Provider and clinician recommendations for the LAIV and IIV versions of the influenza immunization, based on ACIP advisements, including preferential recommendations, may have stimulated reductions in overall immunization uptake rates following the 2014 policy shift, which were counteracted by the 2015 policy shift initially, when both formulations were equally recommended by providers due to the elimination of the preferential statement. This possibly led to the increases in immunization uptake rates that were exhibited initially. Subsequently erosion in vaccine uptake due to fluctuating annual LAIV advisements, and provider recommendations, may have induced the declining slope change trend post 2015 policy shift.

Public health policies concerning influenza immunization for children and adolescents should concentrate on refraining from issuing preferential advisements for either vaccine version if possible. Immunization policies should focus on recommending both formulations in order to maximize overall immunization uptake rates instead. Consistent and stable annual advisements, and minimizing vacillation of recommendations on an annual basis, may additionally increase parental trust in

immunization policies and provider suggestions, and promote increases in child influenza vaccine uptake.

This study contributes to the existing literature by enhancing the understanding of how vaccine uptake rates change following policy shifts. However it is limited in determining why these changes occur, and due to what factors and mechanisms specifically, which future studies should attempt to discern and ascertain.

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APPENDIX A

H1N1 PANDEMIC FEM ANALYSES

Table A.1 - NIS Child FEM Regressions

Experimental Variables Subgroup 1	**activitylevel_5plus**	**activitylevel_6plus**	**activitylevel_7plus**
ILI Intensity Level Logit Coefficient	-0.0345	-0.0143	-0.0259
ILI Intensity Level Marginal Effect	-0.00731	-0.00304	-0.00548
Experimental Variables Subgroup 2	**totalweeks_5plus**	**totalweeks_6plus**	**totalweeks_7plus**
ILI Intensity Level Logit Coefficient	-0.00245	-0.000756	-0.000587
ILI Intensity Level Marginal Effect	-0.000519	-0.000160	-0.000124
Experimental Variables Subgroup 3	**early_totalweeks_5plus**	**early_totalweeks_6plus**	**early_totalweeks_7plus**
ILI Intensity Level Logit Coefficient	-0.00184	-0.00145	-0.00155
ILI Intensity Level Marginal Effect	-0.000389	-0.000308	-0.000329
Experimental Variables Subgroup 4	**late_totalweeks_5plus**	**late_totalweeks_6plus**	**late_totalweeks_7plus**
ILI Intensity Level Logit Coefficient	0.00198	0.00218	0.00260
ILI Intensity Level Marginal Effect	0.000419	0.000461	0.000550
Experimental Variables Subgroup 5	**peak_totalweeks_5plus**	**peak_totalweeks_6plus**	**peak_totalweeks_7plus**
ILI Intensity Level Logit Coefficient	0.000664	0.000718	0.00117
ILI Intensity Level Marginal Effect	0.000141	0.000152	0.000248
*** p < 0.05 ** p < 0.01 *** p < 0.001**			

Experimental Variables Subgroup 1	**activitylevel_8plus**	**activitylevel_9plus**	**activitylevel_10plus**
ILI Intensity Level Logit Coefficient	-0.0132	-0.0275	0.00464
ILI Intensity Level Marginal Effect	-0.00280	-0.00582	0.000982
Experimental Variables Subgroup 2	**totalweeks_8plus**	**totalweeks_9plus**	**totalweeks_10plus**
ILI Intensity Level Logit Coefficient	0.000289	0.00201	0.000466
ILI Intensity Level Marginal Effect	0.0000612	0.000426	0.0000986
Experimental Variables Subgroup 3	**early_totalweeks_8plus**	**early_totalweeks_9plus**	**early_totalweeks_10plus**
ILI Intensity Level Logit Coefficient	-0.000557	0.000855	0.000900
ILI Intensity Level Marginal Effect	-0.000118	0.000181	0.000191
Experimental Variables Subgroup 4	**late_totalweeks_8plus**	**late_totalweeks_9plus**	**late_totalweeks_10plus**
ILI Intensity Level Logit Coefficient	0.00240	0.00174	0.00125
ILI Intensity Level Marginal Effect	0.000509	0.000368	0.000265
Experimental Variables Subgroup 5	**peak_totalweeks_8plus**	**peak_totalweeks_9plus**	**peak_totalweeks_10plus**
ILI Intensity Level Logit Coefficient	0.000372	-0.108***	-0.000606
ILI Intensity Level Marginal Effect	0.0000789	-0.0229***	-0.000128
*** p < 0.05 ** p < 0.01 *** p < 0.001**			

Table A.2 - NIS Teen FEM Regressions

Experimental Variables Subgroup 1	**activitylevel_5plus**	**activitylevel_6plus**	**activitylevel_7plus**
ILI Intensity Level Logit Coefficient	0.00564	0.000518	0.0218
ILI Intensity Level Marginal Effect	0.000899	0.0000826	0.00348
Experimental Variables Subgroup 2	**totalweeks_5plus**	**totalweeks_6plus**	**totalweeks_7plus**
ILI Intensity Level Logit Coefficient	-0.00187	-0.00151	-0.000609
ILI Intensity Level Marginal Effect	-0.000297	-0.00024	-0.000097
Experimental Variables Subgroup 3	**early_totalweeks_5plus**	**early_totalweeks_6plus**	**early_totalweeks_7plus**
ILI Intensity Level Logit Coefficient	-0.00131	-0.00209	-0.00256
ILI Intensity Level Marginal Effect	-0.000209	-0.000333	-0.000408
Experimental Variables Subgroup 4	**late_totalweeks_5plus**	**late_totalweeks_6plus**	**late_totalweeks_7plus**
ILI Intensity Level Logit Coefficient	0.00223	0.00307	0.00401
ILI Intensity Level Marginal Effect	0.000355	0.00049	0.000638
Experimental Variables Subgroup 5	**peak_totalweeks_5plus**	**peak_totalweeks_6plus**	**peak_totalweeks_7plus**
ILI Intensity Level Logit Coefficient	-0.00367	-0.00455	-0.00575
ILI Intensity Level Marginal Effect	-0.000584	-0.000725	-0.000916
*** p < 0.05 ** p < 0.01 *** p < 0.001**			

Experimental Variables Subgroup 1	**activitylevel_8plus**	**activitylevel_9plus**	**activitylevel_10plus**
ILI Intensity Level Logit Coefficient	0.0341	0.0196	-0.0195
ILI Intensity Level Marginal Effect	0.00543	0.00312	-0.0031
Experimental Variables Subgroup 2	**totalweeks_8plus**	**totalweeks_9plus**	**totalweeks_10plus**
ILI Intensity Level Logit Coefficient	-0.00271	-0.00334	-0.00549
ILI Intensity Level Marginal Effect	-0.000433	-0.000531	-0.000874
Experimental Variables Subgroup 3	**early_totalweeks_8plus**	**early_totalweeks_9plus**	**early_totalweeks_10plus**
ILI Intensity Level Logit Coefficient	-0.00379	-0.00543	-0.00800
ILI Intensity Level Marginal Effect	-0.000604	-0.000865	-0.00127
Experimental Variables Subgroup 4	**late_totalweeks_8plus**	**late_totalweeks_9plus**	**late_totalweeks_10plus**
ILI Intensity Level Logit Coefficient	0.00356	0.00392	0.00342
ILI Intensity Level Marginal Effect	0.000568	0.000624	0.000546
Experimental Variables Subgroup 5	**peak_totalweeks_8plus**	**peak_totalweeks_9plus**	**peak_totalweeks_10plus**
ILI Intensity Level Logit Coefficient	-0.00845*	0.0824*	-0.0133**
ILI Intensity Level Marginal Effect	-0.00135*	0.0131*	-0.00212**
*** p < 0.05 ** p < 0.01 *** p < 0.001**			

APPENDIX B

H1N1 PANDEMIC AUXILIARY ANALYSES

Table B.1 – NIS Child Alternative Outcome ITS Estimation

Pandemic Variables	AME	P > z	[95%	CI]
Pre-H1N1 2009 Trend	0.0464	0.0000	0.0255	0.0673
H1N1 2009 Level	0.1502	0.0000	0.1107	0.1921
Post-H1N1 2009 Trend	-0.0583	0.0000	-0.0652	-0.0502
RSE 1 2012 Level	-0.0348	0.0000	-0.0411	-0.0289
Post-RSE 1 2012 Trend	0.0196	0.0000	0.0105	0.0287
RSE 2 2013 Level	-0.0474	0.0000	-0.0701	-0.0137
Post-RSE 2 2013 Trend	0.0181	0.0000	0.0074	0.0273
RSE 3 2017 Level	-0.0374	0.0000	-0.0453	-0.0297
Post-RSE 3 2017 Trend	0.0207	0.0000	0.0102	0.0317

Table B.2 – NIS Child Heterogeneity

Pandemic Variables	Hispanic	Caucasian	African American	Other
Pre-H1N1 2009 Trend	0.0275***	0.0581***	0.0032***	0.0294***
H1N1 2009 Level	0.0103***	0.0665***	-0.0635***	0.0334**
Post-H1N1 2009 Trend	-0.0137**	-0.0021***	-0.0397***	-0.0165***
RSE 1 2012 Level	0.0138***	0.0571**	0.0012***	0.0185***
Post-RSE 1 2012 Trend	-0.0139**	-0.0026***	-0.0455***	-0.0219***
RSE 2 2013 Level	0.0140***	0.0671***	0.0152**	0.0311**
Post-RSE 2 2013 Trend	-0.0141**	-0.0081**	-0.051**	-0.0273**
RSE 3 2017 Level	0.0142***	0.0693***	0.0091**	0.0108***
Post-RSE 3 2017 Trend	-0.0143**	-0.0031**	-0.0429***	-0.0201**
Pandemic Variables	<100% FPL	100 to 199% FPL	200 to 299% FPL	300% FPL or greater
Pre-H1N1 2009 Trend	0.0379**	0.0463***	0.0477***	0.0714***
H1N1 2009 Level	0.0152***	0.0421***	0.0364**	0.1323***
Post-H1N1 2009 Trend	-0.0252***	-0.0173***	-0.0403**	-0.0591***
RSE 1 2012 Level	0.0032***	0.0189***	0.0272***	0.0439**
Post-RSE 1 2012 Trend	-0.0292**	-0.0105***	-0.0128***	-0.0033***
RSE 2 2013 Level	0.0119***	0.0181***	0.0226**	0.0596**
Post-RSE 2 2013 Trend	-0.0381**	-0.0297***	-0.0306***	-0.0116***
RSE 3 2017 Level	0.0271***	0.0259***	0.0409***	0.0487***
Post-RSE 3 2017 Trend	-0.0481**	-0.0331***	-0.0292***	-0.0117***

APPENDIX C

LAIV POLICY AUXILIARY ANALYSES

Table C.1 – NIS Child Vaccine Specific ITS Estimations

Policy Variables	LAIV	IIV	Overall	Public	Private
Pre-LAIV 2014 Trend	0.0202***	0.0443***	0.0206***	0.0352***	0.0178***
LAIV 2014 Level	-0.0401***	-0.1331***	-0.0525***	-0.0488***	-0.3471***
Post-LAIV 2014 Trend	0.0349***	0.0251***	0.0121***	0.0259***	0.0437***
LAIV 2015 Level	0.2343***	0.0417***	0.0301***	0.1717***	0.2406***
Post-LAIV 2015 Trend	-0.0142***	-0.0198***	-0.0240***	-0.0421***	-0.0705***
LAIV 2016 Level	0.1301**	0.0502**	0.0101*	0.0197**	0.0262**
Post-LAIV 2016 Trend	-0.0629***	-0.0307**	-0.0530**	-0.0733**	-0.0622**

Table C.2 – NIS Teen Vaccine Specific ITS Estimations

Policy Variables	LAIV	IIV	Overall	Public	Private
Pre-LAIV 2014 Trend	0.0639***	0.0379***	0.0269***	0.0355***	0.0194***
LAIV 2014 Level	-0.1067***	-0.0726***	-0.0841***	-0.0902***	-0.0758***
Post-LAIV 2014 Trend	0.0298***	0.0391***	0.0717***	0.0478***	0.0594***
LAIV 2015 Level	0.0453***	0.0584***	0.0425***	0.0298***	0.0405***
Post-LAIV 2015 Trend	-0.0304***	-0.0229***	-0.0302***	-0.0233***	-0.0303***
LAIV 2016 Level	-0.0775**	-0.0471***	-0.0652***	-0.0317***	-0.0253***
Post-LAIV 2016 Trend	0.0572**	0.0397**	0.0284***	0.0152***	0.0276***

Table C.3 – NIS Child Heterogeneity

Policy Variables	Hispanic	Caucasian	African American	Other
Pre-LAIV 2014 Trend	0.0271***	0.0506***	0.0182***	0.0227***
LAIV 2014 Level	-0.0112***	-0.0025***	-0.0588***	-0.0179***
Post-LAIV 2014 Trend	0.0241***	0.0722***	0.0017***	0.0154***
LAIV 2015 Level	0.0151***	0.0662***	-0.0017***	0.0393***
Post-LAIV 2015 Trend	-0.0227***	-0.0092***	-0.0581***	-0.0263**
LAIV 2016 Level	0.0233***	0.0509***	0.0106**	0.0367***
Post-LAIV 2016 Trend	-0.0228***	-0.0051***	-0.0422***	-0.0197***
Policy Variables	<100% FPL	100 to 199% FPL	200 to 299% FPL	300% FPL or greater
Pre-LAIV 2014 Trend	0.0162**	0.0291***	0.0284***	0.0533***
LAIV 2014 Level	-0.0259***	-0.0305***	-0.0326***	-0.0186***
Post-LAIV 2014 Trend	0.0129***	0.0181***	0.0336***	0.0404***
LAIV 2015 Level	0.0101***	0.0270***	0.0644***	0.1238**
Post-LAIV 2015 Trend	-0.0311***	-0.0378***	-0.0124***	-0.0102***
LAIV 2016 Level	0.0208***	0.0295***	0.0303**	0.0477***
Post-LAIV 2016 Trend	-0.0135***	-0.0122***	-0.0274***	-0.0076***

Table C.4 – NIS Teen Heterogeneity

Policy Variables	Hispanic	Caucasian	African American	Other
Pre-LAIV 2014 Trend	0.0307***	0.0482***	0.0104***	0.0372***
LAIV 2014 Level	-0.0209***	-0.0155***	-0.0322***	-0.0195***
Post-LAIV 2014 Trend	0.0352***	0.0606***	0.0177***	0.0292***
LAIV 2015 Level	0.0110***	0.0305***	-0.0207***	0.0294***
Post-LAIV 2015 Trend	-0.0184***	-0.0071***	-0.0438***	-0.0299**
LAIV 2016 Level	-0.0598***	-0.0177***	-0.0701***	-0.0442***
Post-LAIV 2016 Trend	0.0397***	0.0633***	0.0171***	0.0304***
Policy Variables	<100% FPL	100 to 199% FPL	200 to 299% FPL	300% FPL or greater
Pre-LAIV 2014 Trend	0.0211**	0.0257***	0.0293***	0.0461***
LAIV 2014 Level	-0.0137***	-0.0121***	-0.0208***	-0.0106***
Post-LAIV 2014 Trend	0.0407***	0.0493***	0.0583***	0.0596***
LAIV 2015 Level	0.0030***	0.0286***	0.0304***	0.0342***
Post-LAIV 2015 Trend	-0.0479***	-0.0408***	-0.0238***	-0.0251***
LAIV 2016 Level	-0.0255***	-0.0261***	-0.0136***	-0.0109***
Post-LAIV 2016 Trend	0.0431***	0.0409***	0.0512***	0.0593***

Table C.5 - NIS Child and Teen Alternative Outcome ITS Estimations

	Child		Teen	
Policy Variables	**AME**	**P > z**	**AME**	**P > z**
Pre-LAIV 2014 Trend	0.0593	0.0000	0.0717	0.0000
LAIV 2014 Level	-0.0366	0.0000	-0.0649	0.0000
Post-LAIV 2014 Trend	0.0337	0.0000	0.0558	0.0000
LAIV 2015 Level	0.0482	0.0000	0.0593	0.0000
Post-LAIV 2015 Trend	-0.0478	0.0000	-0.0422	0.0000
LAIV 2016 Level	0.0273	0.0203	-0.0508	0.0001
Post-LAIV 2016 Trend	-0.0104	0.0000	0.0381	0.0000

Table C.6 - Difference in Differences (DID) Estimation Schematic

Treatment Versus Control Subgroup Designation	Pre ACIP LAIV Revocations	Post ACIP LAIV Revocations	Inter Time-Period Difference (Pre Versus Post Policy Comparison)
LAIV Eligible (Treatment)	$CIVU_{T0}$	$CIVU_{T1}$	$CIVU_{T1} - CIVU_{T0}$
LAIV Non-Eligible (Control)	$CIVU_{C0}$	$CIVU_{C1}$	$CIVU_{C1} - CIVU_{C0}$
Intra Time-Period Difference (Treatment Versus Control Comparison)	$CIVU_{T0} - CIVU_{C0}$	$CIVU_{T1} - CIVU_{C1}$	DID = $(CIVU_{T1} - CIVU_{T0}) - (CIVU_{C1} - CIVU_{C0})$