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Cost-Effectiveness Analysis of Targeted Herpes Zoster Vaccination in Adults 50-59 at Increased Cardiovascular Risk

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by

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DEDICATION

To my husband Kevin who has ALWAYS supported me in whatever I have chosen to pursue, your unwavering faith in my ability to accomplish my goals often exceeded what I believed was possible. Thank you for being my trusted and tireless proof-reader for more than three decades!

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TABLE OF CONTENTS

LIST OF ACRONYMS

AAFP	American Academy of Family Physicians
ACA	Affordable Care Act
ACIP	Advisory Committee on Immunization Practices
ACP	American College of Physicians
ACOG	American College of Obstetrics and Gynecology
ACP-ASIM	American College of Physicians – American Society of Internal Medicine
AHA	American Heart Association
AIWG	Adult Immunization Work Group
ASH	Assistant Secretary of Health
BOI	Burden of Illness
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CHD	Coronary Heart Disease
CMS	Centers for Medicare and Medicaid Services
CPSTF	Community Preventive Services Task Force
CV	Cardiovascular
CVD	Cardiovascular Disease
FDA	Food and Drug Administration
FFS	Fee-for-service
HHS	Health and Human Services
HIB	Haemophilus Influenza Type B
HIV	Human Immuno-deficiency Virus
HP 2020	Healthy People 2020
HPV	Human Papillomavirus
HS	Hemorrhagic Stroke
HZ	Herpes Zoster
HZO	Herpes Zoster Opthalmicus
IAC	Immunization Action Coalition
ICER	Incremental Cost-Effectiveness Ratio
IDSA	Infectious Disease Society of America
IS	Ischemic Stroke
IIS	Immunization Information System
IOM	Institute of Medicine
LTPS	Long-term Protection Study
MC	Monte Carlo
MI	Myocardial Infarction
MM	Markov Model

MMR	Measles, Mumps, Rubella
MMWR	Morbidity and Mortality Weekly Report
NAIIS	National Adult Influenza & Immunization Summit
NAIP	National Adult Immunization Plan
NCIRD	National Center for Immunization and Respiratory Diseases
NCQ	National Quality Forum
NHB	Net Health Benefits
NHIS	National Health Interview Survey
NHLBI	National Heart Lung Blood Institute
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NQF	National Quality Forum
ODPHP	Office of Disease Prevention and Health Promotion
PHM	Population Health Management
PHN	Post-herpetic neuralgia
PSA	Probabilistic Sensitivity Analysis
RCT	Randomized Controlled Trial
RR	Relative Risk
SCCS	Self-Controlled Case Series
SPS	Shingles Prevention Study
STPS	Short-term Persistence Study
TIA	Transient Ischemic Attack
VFC	Vaccines for Children
VZV	Varicella Zoster Virus
WTP	Willingness-to-pay
QALY	Quality of Life Years
ZEST	Zostavax® Safety and Efficacy Trial

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Over the last twenty years the incidence of herpes zoster (HZ) infection, also known as shingles, has been increasing among adults for unknown reasons. The economic burden of HZ is currently estimated at over $1 billion per year in the United States (U.S.) and is expected to increase as the susceptible adult population ages. HZ is caused by a re-activation of the varicella zoster virus (VZV), chicken pox, and more than 95% of adults living today carry the virus with a lifetime risk of 1 in 3 for developing HZ. In 2006 the FDA approved a vaccine for the prevention of HZ in adults 60 years and older and in 2011 approval was expanded to include adults age 50-59 years. Since 2006 rates of adult immunization for HZ have been modest, as of 2015 approximately two-thirds of the US population ≥ 60 are still unvaccinated and more than 94% of those ages 50-59 have not been vaccinated. There is now accumulating evidence of a significantly elevated risk of ischemic stroke (IS) within the first 12 months following infection with HZ. Every 40 seconds someone in the U.S. suffers a stroke with an estimated 795,000 strokes per year. In the U.S. stroke is a significant cause of disability with costs estimated at $33 billion per year including cost of healthcare, medication, and lost productivity. As the population in the U.S ages, the risk of both HZ infection and stroke will increase significantly thus impacting mortality, morbidity, and healthcare costs. The CDC Advisory Committee for Immunization Practices (ACIP) currently recommends routine vaccination against HZ for adults ≥ 60 but does not recommend vaccination for adults age 50-59 years and does not provided any guidance or recommendations for adults who may be at increased risk of stroke associated with

HZ infection. The current ACIP vaccination recommendations for HZ are predominately based on clinical trial efficacy data and cost-effectiveness analyses (CEAs) in adults ≥ 60. These prior analyses did not included costs associated with the recent evidence demonstrating increased risk of stroke up to one year following HZ infection.

Aims: The objectives of this study were as follows; 1) To assess the cost-effectiveness of a targeted HZ vaccination strategy for adults age 50-59 years at increased cardiovascular (CV) risk in whom vaccination is approved but not recommended; 2) To develop a white paper directed at payers, providers, and policy makers translating the findings from the analysis into appropriate population health dissemination, implementation, and adoption priority recommendations.

Methods: A decision analytic Markov Model (MM) was used to compare costs and outcomes between two vaccination strategies; usual-care (no current vaccine recommendation) and targeted vaccination in adults age 50-59 years with cardiovascular disease (CVD) in a hypothetical cohort of 100,000 adults age 50-59 years. The private payer perspective was used as it best represents this population of adults age 50-59 years who are predominately employed and covered under employer sponsored commercial insurance. The simulated cohort was assessed for incidence of IS within 12 months following HZ infection occurring within the fifth decade of life. Risk was assessed from the age at entry to the analysis, median age 55, up to age 60 using TreeAge Pro 2017 software. The cohort was then aged out to 100 years or death, whichever came first. Costs were calculated using 2016 U.S. dollars.

Findings: As it relates to aim one, compared to usual-care targeting HZ vaccination in adults age 50-59 years with prevalent CVD was cost-effective with an incremental cost-effectiveness ratio (ICER) of $55,517 per quality of life-year (QALY) gained which falls well below the standard

willingness-to-pay (WTP) threshold of $100,000 utilized in previous HZ CEAs (Le & Rothberg, 2015, 2016; Pellissier, Brisson, & Levin, 2007). The incremental cost of vaccinating the target population using a benchmark vaccination rate of 60% was $30.59 per person compared to $12.98 in the usual-care group with ICERs of $55,517 and $55,470 respectively. Moreover, when comparing the cost of universal vaccination in the entire 50-59 year old cohort cost-effectiveness was maintained with an incremental cost of $176.51 per person and an ICER of $55,523. Adopting the targeted strategy resulted in 162 fewer cases of HZ and 14 fewer strokes per 100,000 persons. Regarding aim two, following safety and efficacy, cost-effectiveness analysis are considered an essential metric in vaccine policy making and a substantial driver of vaccine adoption by policymakers, payers, and providers. Translating these favorable cost-effectiveness findings to policymakers, payers, and providers is necessary to help close the adoption curve gap in order to facilitate and inform effective and timely implementation strategies for HZ vaccination in this targeted population.

Conclusions: This study demonstrated that targeted HZ vaccination in patients age 50-59 years at increased CV risk is cost-effective and thus updating ACIP policy recommendations regarding vaccination in this population for whom the vaccine is currently FDA approved but not recommended should be considered. Furthermore, this study showed that universal vaccination in the general 50-59 year old population is cost-effective. Given the very limited data on cost-effectiveness of HZ vaccination in adults age 50-59 years, which has resulted in a lack of recommendation for this population, and recent evidence of IS risk the results of this study demonstrating cost-effectiveness of a targeted HZ vaccination strategy directly support the National Adult Immunization Plan (NAIP) to improve adult immunization uptake by providing economic evaluations which can be used to inform policymakers, payers, and providers.

SECTION I: INTRODUCTION AND THEORETICAL FRAMEWORK

Statement of Problem

Aging baby-boomers are rapidly re-shaping the United States (U.S.) age demographic. The U.S. Census Bureau reports average life expectancy has increased to 79 years, resulting from reduction in mortality at older ages (United States Census Bureau, 2017). U.S. adults are living longer but older adults are more susceptible to diseases and are prone to greater risk of associated complications. Risk of preventable diseases and associated co-morbidities in adults will continue to grow as the aging population increases. Several vaccine-preventable diseases are increasing among U.S. adults while rates of adult vaccinations continue to remain low.

In 1999 the Centers for Disease Control and Prevention (CDC) declared vaccination as the greatest public health achievement of the 20th century (Centers for Disease Control and Prevention, 1999). Tremendous progress has been made in reducing vaccine-preventable diseases among children however today the true burden of illness (BOI) from vaccine-preventable diseases is greatest among adults (Bridges et al., 2015). High rates of vaccine-preventable diseases in adults increase costs of healthcare and create additional burdens on healthcare services and delivery. Adult immunization coverage continues to be far below Healthy People 2020 (HP 2020) goals despite evidence of the effectiveness and economic benefits of vaccination (Jacob, Chattopadhyay, Hopkins, Murphy Morgan, et al., 2016; Williams et al., 2016).

Prior to the implementation of the Affordable Care Act (ACA), disease burden data in the U.S. indicated that more than 50% of adult deaths where associated with preventable disease and approximately 95% of U.S. healthcare spending is for treatment of chronic illness, including many preventable diseases, compared to 5% budgeted for health promotion and prevention (Nash, David et al., 2011). In a recent economic analysis of four adult vaccine preventable diseases, (influenza, pneumococcal disease, herpes zoster, and pertussis) the estimated annual cost of treatment for adults 50 years and older was $26.5 billion (McLaughlin, McGinnis, Tan, Mercatante, & Fortuna, 2015). In 2016, Ozawa et al. estimated vaccine-preventable disease costs (individual and societal) directly attributable to low uptake of adult immunizations at $9 billion including direct costs and lost productivity (2016).

The first comprehensive National Adult Immunization Plan (NAIP) was released in 2016 with the goal of improving adult immunization rates through public health and population health approaches in alignment with the established HP 2020 objectives (U.S. Department of Health and Human Services National Vaccine Program Office, 2016a). The NAIP established four goals to improve vaccine adoption across the lifespan (see Figure 1). The first and primary goal of the plan is to strengthen the adult immunization infrastructure and a key objective in that effort is to "generate and disseminate evidence about the health and economic impact of adult immunization, including potential diseases averted and cost-effectiveness with the use of current vaccines" (U.S. Department of Health and Human Services Vaccine Program Office, 2016, p.16). Currently there are very limited data on the economic impact of adult immunizations, and the NAIP calls out the need for this information as a "critically important element of the plan" (U.S. Department of Health and Human Services National Vaccine Program Office, 2016a).

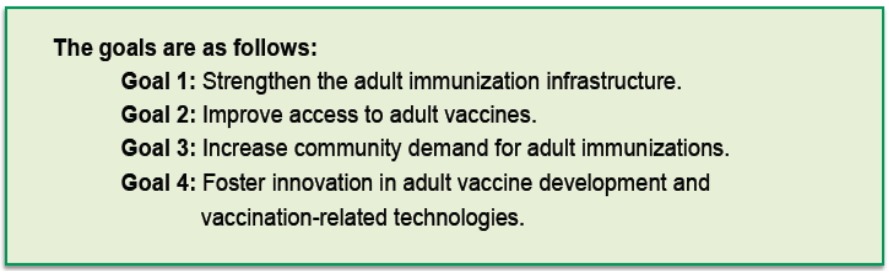

Figure 1**:** National Adult Immunization Plan Goals 2016

(U.S. Department of Health and Human Services National Vaccine Program Office, 2016a)

The Office of Disease Prevention and Health Promotion (ODPHP), a division of HHS, established the HP 2020 goals for immunization coverage and monitors progress annually based on results from the National Health Interview Survey (NHIS) conducted by the CDC. NHIS is an annualized household survey administered by the U.S. Census Bureau for CDC's National Center for Health Statistics using in person interviews. Questions related to immunization status are addressed to one randomly selected adult within each household (Williams et al., 2016). NHIS collects data on the following adult vaccines; hepatitis A, hepatitis B, human papillomavirus (HPV), herpes zoster (HZ), pneumococcal, Td, and Tdap. HP 2020 has established goals to improve rates for the following specific adult immunizations; pneumococcal, herpes zoster, and hepatitis B for healthcare personnel (U.S. Department of Health and Human Services Office of Disease Prevention and Health Promotion, 2017). Surveillance data from the 2015 NHIS concluded that adult vaccine coverage continues to remain low for most routinely recommended vaccines and many rates are still below the HP 2020 goals (Williams et al., 2017). HP 2020 recommendations serve as the national "standard benchmark" for evaluating progress in improving adult immunizations but the current measure only tracks progress on a sub-set of adult vaccinations. HP 2020 sets goals and provides clinical and community-level recommendations for interventions to improve rates(Jacob, Chattopadhyay, Hopkins, Murphy Morgan, et al.,

2016), but there are no requirements for adherence to those recommendations (the federal government has no such jurisdiction), however they serve as a guideline for other entities and organizations to establish benchmarks which can be used to monitor and rate system or physician level performance outcomes toward improving immunization rates.

In 1964, under the direction of the Department of Health and Human Services (HHS) the Advisory Committee on Immunization Practices (ACIP) was created (Walton, Orenstein, & Pickering, 2015) and for the last 50 years this body of experts has been responsible for establishing recommendations for vaccine use and monitoring their safety and effectiveness. The current ACIP recommended immunization schedule for adults 19 years and older includes routine vaccination recommendations for 13 vaccine-preventable diseases based on various age and risk criteria. Vaccination against influenza, tetanus, diphtheria and pertussis (Td/Tdap) are recommended for all persons 19 years and older (unless other risk factors preclude vaccination). HPV is routinely recommended for adult females up to age 26 and for adult males 19-21 years and for males up to age 26 with at risk conditions. HZ is routinely recommended for all adults over age 60, and two different pneumococcal vaccinations are recommended for all patients age 65 and over with supplementary recommendations for certain at risk populations. Additionally, measles, mumps, rubella, and varicella are recommended for adults who lack evidence of immunity or prior vaccination. Meningococcal, hepatitis A, hepatitis B, and Haemophilus influenza B (Hib) are also recommended in special high risk populations (Centers for Disease Control and Prevention, 2017a) (Appendix A).

Herpes Zoster (HZ)

Risk of Herpes Zoster (HZ) virus increases with age and while the epidemiology is not well understood, rates of HZ have been gradually increasing across all age groups over the last 20 years (Kenneth E Schmader & Dworkin, 2017). HZ virus, also known as shingles, is caused by a reactivation of the varicella zoster virus (VZV), commonly known as chickenpox. After initial infection with chickenpox the virus becomes dormant in the dorsal root ganglia of the central nervous system. This latency allows for potential future reactivation of the virus as HZ virus which is thought to be mediated by immunosenescence as a byproduct of aging or reduced immunity either through infection or increased stress to the immune system. HZ is an inflammatory neurological infection affecting millions of people every year and is characterized by a painful blistering rash. HZ rash develops over 5 to 7 days and can be accompanied by prodromal pain and/or tingling sensations. The itching, burning rash appears unilaterally and does not ordinarily cross the spine or midline of the abdomen, typically affecting one to three dermatomes (Kenneth E Schmader & Dworkin, 2017).

Approximately 95% of all people living today have been infected with VZV and an estimated 25-35% of those are at subsequent risk of reactivation of the virus as HZ (Warren-Gash, Breuer, Warren-Gash, & Breuer, 2017). After age 50 the risk of HZ infection increases. The overall incidence of HZ in the United States is approximately 4 cases per 1,000 annually and in people 60 years and older the rate is about 10 cases per 1,000 annually (Centers for Disease Control and Prevention, 2016a). Each year in the U.S. HZ affects approximately 1 million people and causes an estimated 96 virus-related deaths. Lifetime risk of HZ in the United States is approximately 1 in 3 and while most people will experience it only once, it is possible to have re-

activation two or three times over a lifetime after initial infection with chickenpox with long-term studies showing a 5-6% risk of recurrence (Kawai, Gebremeskel, & Acosta, 2014). Several studies report significantly higher incidence of HZ in adult women across all age groups (Johnson et al., 2015; Sundström et al., 2015), thus female gender is considered a risk factor for HZ (de Boer, Wilschut, & Postma, 2014). One in 4 people with herpes zoster are hospitalized due to complications which can range from mild to severe depending on the patient's underlying immune status and other health risks (Centers for Disease Control and Prevention, 2016c). VZV is the only known virus with the capacity to produce pathologic vascular changes associated with stroke through infection of the cerebral arteries (Nagel & Gilden, 2015). HZ is the single most common infection of the nervous system in the U.S. (Warren-Gash & Breuer, 2017).

The most common side effect of HZ infection is post herpetic neuralgia (PHN), which occurs in 10-18% of patients and is defined as prolonged pain at the site of the rash lasting at least 90 days following fading of the rash. PHN can persist for many months to years and can be debilitating. A potentially serious complication of HZ is herpes zoster opthamalmicus (HZO), which occurs when the virus infects the ophthalmic region of the trigeminal nerve (approximately 15% of patients) and can cause chronic complications, including pain and possible loss of vision (Centers for Disease Control and Prevention, 2016a). Secondary complications such as bacterial infections and transmission of the virus to other susceptible individuals can occur (although this is rare and transmission would cause the primary VZV, chickenpox, not HZ) (Kenneth E Schmader & Dworkin, 2017).

Herpes Zoster Vaccine

In June 2006 the U.S. Food and Drug Administration (FDA) approved a live attenuated vaccine for HZ (Zostavax®; Merck) for the one-time vaccination of immunocompetent adults ≥ 60 years for the prevention of HZ and expanded the approval to immunocompetent patients age 50-59 years in 2011(Centers for Disease Control and Prevention, 2011). The ACIP recommends universal HZ vaccination of all adults ≥ 60 but does not currently recommend HZ vaccination for adults age 50-59 years, despite FDA approval for this population. The ACIP has cited concerns around duration of vaccine efficacy and poor cost-effectiveness of the vaccine as the main reasons for not making a recommendation for persons 50-59 years of age (Centers for Disease Control and Prevention, 2016c). Although risk of HZ is greater in adults over age 60 there is still significant disease in younger patients. In 2015, Johnson and colleagues estimated incidence of HZ in adults age 50-59 at 6.74 per 1,000 person-years which represents an increase over previous estimates (Johnson et al., 2015). More than ten years after vaccine approval and ACIP universal recommendation for adults ≥60, rates of HZ vaccination remain low and continue to show limited improvement year over year. In 2015 HZ vaccination uptake in the universally recommended adult population of ≥ 60 finally achieved the modestly set HP 2020 goal of 30%, which is the lowest target rate for all recommended adult immunizations (see Table 1). The most recent data on HZ vaccination rates for the ACIP universal age based population reported coverage of 30.6% for adults ≥ 60 years and 34.2% for those ≥ 65 years, with the lowest rates in the 60-64 age group at 21.7% (Williams et al., 2017). The lower rate in adults 60-64 is of interest because that age group is made up of many adults who are still active in the workforce and are predominantly covered under commercial insurance compared to those over 65 where the vaccine is considered a pharmacy benefit under Medicare.

Table 1: Healthy People 2020 Adult Vaccination, 2013 Coverage and 2020 Targets

Objective IID-12: Increase the percentage of children and adults who are vaccinated annually against seasonal influenza.	2013 Percentage	2020 Target Percentage*
Adults age >18 years	39†	70
Health care personnel	62‡	90
Pregnant women	52§	No target, in development

Objective IID-13: Increase the percentage of adults who are vaccinated against pneumococcal disease.	2013 Percentage	2020 Target Percentage**
Noninstitutionalized adults age >65 years	60††	90
Noninstitutionalized high-risk adults age 18– 64 years	21‡‡	60

Healthy People 2020.[2]

† National Health Interview Survey, as reported by Healthy People 2020.[2]

‡ National Health Interview Survey, as reported by Healthy People 2020.[2]

§ Ding (2014).[12] The most recent published statistics are for the 2013–2014 influenza season; the estimate is from an Internet panel survey. The study sample did not include women without Internet access; results might not be generalizable to all pregnant women in the United States. Also, the estimate might be biased if the selection processes for entry into the Internet panel and a woman's decision to participate in this survey were related to receipt of vaccination.

** Healthy People 2020.[2]

†† National Health Interview Survey (2013).[3]

‡‡ National Health Interview Survey (2013).[3]

Objective IID-13: Increase the percentage of adults who are vaccinated against pneumococcal disease.	2013 Percentage	2020 Target Percentage**
Institutionalized adults age >18 years in long-term care or nursing homes	66§§	90

Objective IID-14: Increase the percentage of adults age >60 who are vaccinated against zoster (shingles).	2013 Percentage	2020 Target Percentage***
Adults age >60 years	24†††	30

Objective IID-15: Increase hepatitis B vaccine coverage among high-risk populations.	2013 Percentage	2020 Target Percentage‡‡‡
Health care personnel age >19 years	64§§§	90

Notes: IID = Immunization and Infectious Diseases. The objective for influenza vaccination for pregnant women is developmental, and no target has been set. Some, but not all, of the ACIP/CDC-recommended vaccines are included in the Healthy People 2020 objectives.

§§ Minimum Data Set data from 2005–2006, as reported by Healthy People 2020.[2]

*** Healthy People 2020.[2]

††† National Health Interview Survey (2013).[3]

‡‡‡ Healthy People 2020.[2]

§§§ National Health Interview Survey data from 2008, as reported by Healthy People 2020.[2]

(Adapted from "National Adult Immunization Plan" Department of Health and Human Services National Vaccine Program Office, 2016).

Significant racial and ethnic disparities for HZ vaccination persists with immunization coverage being highest among whites for all age groups (Williams et al., 2017). Data on rates of HZ immunization for those under age 60 are less reliable because the ACIP does not recommend the vaccine for this age group. The most recent data collected by the CDC using the 2014 Behavior Risk Factor Surveillance System (BRFSS) reported coverage of 5.9% among adults age 50-59 years and suggested that the lower coverage compared to other groups may be partially due to lack of an official ACIP recommendation in this population (PJ. Lu, O 'Halloran, Williams, & Harpaz, 2017). A 2013 estimate of HZ vaccination coverage among insured adults over age 50 showed approximately 1.7% of adults age 50-59 had been vaccinated (D. Zhang, Johnson, Newransky, & Acosta, 2017) and a study of Kaiser Permanente patients conducted between 2007 and 2014 found only 4.5% of patients age 50-59 had been vaccinated (Baxter et al., 2017). As stated previously, incidence of HZ has been increasing over the last 20 years for unknown reasons across all age groups. A 2017 population based burden of disease analysis from Canada reported "a significant increase in the incidence of HZ, independent of demographic shifts in the population, was found to begin in 2009/10", and was also found to be associated with increased medical cost per episode and total annual costs (Friesen, Chateau, Falk, Alessi-Severini, & Bugden, 2017).

Zostavax® was initially studied in adults ≥ 60 in the Shingles Prevention Study (SPS) and demonstrated a 51% reduced risk of HZ infection in that population. Protection against infection was greatest in patients 60-69 years of age with 64% efficacy, then declined in patients 70-79 years of age to 41%, and in patients ≥ 80 vaccine efficacy was 18% (Oxman et al., 2005). Efficacy of Zostavax® was studied in patients 50-59 years of age in the Zostavax Efficacy and Safety Trial (ZEST) which demonstrated reduced risk of developing HZ of 69.8% (Kenneth E

Schmader et al., 2012). The Short-Term Persistence Sub-study (STPS) and the Long-Term Persistence Sub-study (LTPS), both conducted in patients ≥ 60, have shown the vaccine is effective in reducing incidence of HZ, PHN, and overall BOI up to 10 years post-vaccination (Morrison et al., 2015; K. E. Schmader et al., 2012). Post licensure studies assessing the durability of the vaccine to prevent HZ infection alone (not in combination with PHN and/or BOI) have shown declining protection for Zostavax® with evidence of vaccine efficacy through 5 years after vaccination and uncertain efficacy beyond 5 years (Morrison et al., 2015; K. E. Schmader et al., 2012). A Kaiser Permanente cohort study conducted between 2007 and 2014 included patients 50 and over and reported higher vaccine efficacy during the first year after vaccination, but demonstrated decline in the second year and ongoing gradual decrease in subsequent years, reporting average efficacy of 59.5% three years after initial vaccination (Baxter et al., 2017). Limitations on long-term follow up efficacy and duration of protection of Zostavax® in adults age 50-59 years is largely due to the shorter time horizon since the vaccine was approved for this population in 2011 and the subsequent limited uptake.

Stroke Risk and Herpes Zoster

Mounting evidence of an association between HZ infection and stroke has been reported in the medical literature and is thought to be mediated through inflammatory vasculopathy resulting from VZV viral arterial infection (Nagel & Gilden, 2014, 2015; Powell, Patel, Franco-Paredes, & Lopez, 2015). The first studies to investigate the association between VZV and vascular remodeling began in 1959 and more recent epidemiologic studies from three countries in Asia and Europe have shown a 30% increased risk of stroke within one year of HZ infection establishing HZ as a significant risk factor for stroke (Gilden, Nagel, Cohrs, & Mahalingam,

2013). Nagel and Gilden suggest that the frequency of stroke after HZ is likely underestimated because VZV can reactivate without evidence of rash, therefore there may not be a HZ diagnosis (2015). VZV related vasculopathy and stroke have been reported in children but are much less common likely due to high rates of pediatric varicella vaccination (Nagel, Jones, & Wyborny, 2017).

An increase in the abundance of literature demonstrating HZ as a risk factor for stroke began appearing in 2009 predominately from cohort and case-controlled studies conducted in Taiwan, Demark, Sweden, United Kingdom (U.K.) and the U.S., each providing supporting evidence of a pronounced association between HZ and transient ischemic attack (TIA), myocardial infarction (MI), and stroke within one year of infection with HZ (Breuer, Pacou, Gauthier, & Brown, 2014; Kang, Ho, Chen, & Lin, 2009a; Langan, Minassian, Smeeth, & Thomas, 2014a; Minassian et al., 2015; Nagel, Jones, & Wyborny, 2017; Sreenivasan et al., n.d., 2013; Sundström et al., 2015; Yawn, Wollan, Nagel, & Gilden, 2016). Five meta-analyses published within the last year have reported associated relative risk (RR) of stroke within the first month after HZ with values ranging from 1.55 to 1.94, which then slowly decline, values of RR out to 12 months post virus range from 1.17 to 1.20. These studies assessed independent risk of transient ischemic attack (TIA), ischemic stroke (IS), hemorrhagic stroke (HS), and myocardial infarctions (MI) and found consistent statistical significance associated with HZ infection and IS further confirming the association reported in the individual studies. RR was highest in the time period just after HZ infection with risk gradually declining over time showing statistical significance out to one year after infection (Lian, Zhu, Tang, Yang, & Duan, 2017; Liu et al., 2016; Marra, Ruckenstein, & Richardson, 2017a; Yang et al., 2017; Zhang, Yanting; Luo, Ganfeng;Huan, Yuanwei; Yu, Qiuyan; Wang, Li; Li, 2017a).

Asserting that prior studies had not effectively accounted for confounding factors in 2017 Kim et al. conducted a propensity score-matched analysis using a Korean population database of over 570,000 people and reported confirmatory results from the previous published analyses. When adjusting for confounding this study reported a RR of stroke associated with HZ of 1.39 (95% CI 1.05-1.84) in adults 51-60; the study included additional age and CVD specific analyses (M.C. Kim et al., 2017). Prevention of HZ is possible through vaccination, suggesting that vaccinating patients at increased risk of CVD could reduce risk of stroke associated with HZ infection (Zhang, Yanting; Luo, Ganfeng;Huan, Yuanwei; Yu, Qiuyan; Wang, Li; Li, 2017b).

Stroke Risk

Although the incidence of stroke increases with age, it can strike at any time. In 2009, 34% of people hospitalized for stroke were under age 65 (Centers for Disease Control and Prevention, 2016d). There are an estimated 795,000 strokes per year in the U.S. and more than 75% of those are primary strokes. Stroke is a significant cause of disability with costs estimated at $33 billion per year including cost of healthcare, medication, and lost productivity (Centers for Disease Control and Prevention, 2016d). A stroke occurs when the blood flow to the brain is interrupted. An ischemic stroke (IS) results from an obstruction such a clot in a blood vessel leading to the brain while a hemorrhagic stroke (HS) results from a ruptured or broken blood vessel in the brain (Centers for Disease Control and Prevention, 2016). IS represents 87% of all strokes in the U.S. with HS comprising the remaining 13% (Benjamin et al., 2017).

Stroke represents a significant economic and health care delivery burden - every four minutes someone in the U.S. dies from stroke (Centers for Disease Control and Prevention, 2016d). In 2014 the CDC Division for Heart Disease and Stroke Prevention reported that the

American Heart Association (AHA) predicts direct medical costs from stroke will increase 238% between 2010 to 2030, which represents a higher predicted increase than estimated for any other CVD (including hypertension, coronary artery disease, or heart failure) (Wang et al., 2014). A significant proportion of strokes occur in adults under age 65 and estimates suggest that by 2050 about half of stroke-related costs, including treatment, rehabilitation, and lost productivity, will be incurred in this age population (Wang et al., 2014). A recent U.S. based analysis of real world third-party payer and patient out of pocket costs, including acute hospitalization and long-term follow up, within one year after IS ranged from $41,566 for patients with a disability at discharge to $26,687 for patients discharged without disability (Mu et al., 2017). Wang et al. suggest that understanding stroke risk in patients under age 65 will not only aid in development of appropriate intervention and prevention programs but subsequently reduce economic and societal burden associated with the anticipated increase in stroke incidence (Wang et al., 2014).

Herpes Zoster Vaccine Recommendations

The current ACIP universal age-based HZ vaccination recommendation for adults age ≥ 60 years does not address risk factors for patient sub-populations such as patients at increased CV risk. Universal vaccination is considered optimal from a public health approach, specifically as it relates to the benefits of herd immunity, and many adult immunizations such as pneumococcal and influenza have additional recommendations for patients with certain medical conditions (risk-based) in addition to universal (age-based) recommendations (P Bonanni, Sacco, Donato, & Capei, 2014). Cost-effectiveness analyses (CEAs) lean toward supporting targeted vaccine programs aimed at persons with the highest risk of disease because they yield the greatest return based on disease averted calculated on cost per dose administered. Universal

strategies in conjunction with targeted strategies have been shown to be most effective in reducing disease (Balicer et al., 2014; Hardt et al., 2016). Unlike influenza and pneumococcal viruses, HZ is non-communicable therefore traditional herd protection afforded by universal vaccination does not convey the same public health benefit (Centers for Disease Control and Prevention, 2016b). Prior to the emerging literature elucidating risk of stroke after HZ infection there were no evidence based risk factors on which to establish a targeted strategy for HZ vaccination leaving universal approach as the most appropriate option which was heavily reliant on cost-effectiveness data.

The economic burden of HZ is significant and has increased over time and will continue to increase as the population ages (Donatella Panatto et al., 2015). The direct cost burden from drugs, physician visits, hospitalization, and diagnostics associated with HZ are estimated at over $1 billion per year in the U.S. (Johnson et al., 2016b). Much of the published data on HZ cost-effectiveness are based on patients ≥ 60 and have demonstrated favorable results supporting the ACIP recommendation in this age group (Kawai, Preaud, Baron-Papillon, Largeron, & Acosta, 2014). Following the 2011 FDA approval of Zostavax® in persons age 50-59 years the ACIP declined to recommend the vaccine for this age group due to concerns about supply shortages and limited data on long-term protection in this population, a footnote was made that providers might chose to vaccinate patients who would have "particularly poor anticipated tolerance of HZ or post herpetic neuralgia symptoms" (Centers for Disease Control and Prevention, 2011). In a 2014 follow up review of HZ recommendations for persons age 50-59 years the ACIP again declined to expand the recommendation for this population based on unfavorable results of an unpublished CEA conducted by the CDC (Hales, C.M., Harpaz, R., Ortega-Sanchez, I., Bialek, 2014; Le & Rothberg, 2015). Under the Affordable Care Act (ACA) only ACIP recommended

vaccines are covered with no out of pocket costs, and because the vaccine is not recommended for patients age 50-59 years, those who choose to receive HZ vaccination may not receive this coverage benefit.

The ACIP has declined to recommend HZ vaccination for adults age 50-59 based on limited data on durability of protection and lack of cost-effectiveness however these decisions did not account for the recent evidence of associated stroke risk and therefore have not considered a targeted risk based approach to vaccine recommendations in this population. HZ in persons age 50-59 years represents a significant economic and population health burden including direct costs and lost productivity since most adults in this age range are still active in the workforce (Johnson et al., 2015). Both ZEST and SPS demonstrated that efficacy of Zostavax® in preventing HZ infection is greatest in younger age groups. While overall rates of HZ infection are lower in adults age 50-59 years, a recent study suggests that approximately 25% of HZ cases occurred in the 50-59 year age group and those also incurred higher incremental costs for treatment (Johnson et al., 2016b). The total direct medical costs associated with stroke are projected to almost triple between 2012 and 2030 from $71.6 billion to $184.1 billion. Finding cost-effective interventions to reduce stroke risk associated with HZ could provide significant public health benefits in population health disease burden reduction while also having a significant potential impact on the economic burdens associated with both HZ and stroke.

CEAs for HZ are highly dependent on the age of vaccination and presumptions about duration of protection (durability) of the vaccine (Kawai, Preaud, et al., 2014). The ACIP recommendations for use of Zostavax® have heavily relied on cost-effectiveness results from patient's ≥ 60. Information on duration of protection and cost-effectiveness of HZ vaccination in persons age 50-59 years are limited. While efficacy of the vaccine in adults age 50-59 years from

ZEST is estimated at nearly 70%, duration of vaccine protection was considered short term at 1.5 years (Schmader et al., 2012). Using a 2007 published Markov decision model comparing the cost-effectiveness of HZ vaccine to no vaccine in adults ≥ 60 years (Rothberg, Virapongse, & Smith, 2007), Le and Rothberg adapted the model to assess the cost-effectiveness of HZ vaccine in persons aged ≥ 50 years (2015). Without long term vaccine efficacy data available for persons age 50-59 years, the Le and Rothberg model adjusted for estimated efficacy in this population using the previously published ZEST and the LTPS (Morrison et al., 2015; Schmader et al., 2012). Although this analysis took into consideration the potentially higher vaccine efficacy in the 50-59 year old population the study concluded that vaccination did not meet generally accepted standards for cost-effectiveness, supporting the standing decision of ACIP not to recommend use in this population (Le & Rothberg, 2015).

HZ is a risk factor for stroke. Recent evidence signals significantly elevated short term risk of stroke following infection with HZ persisting for up to twelve months. Stroke is the fifth leading cause of death in the U.S. - every 40 seconds someone experiences a stroke and every four minutes one of them will die (Centers for Disease Control and Prevention, 2016d). To date there have been no studies to assess the cost-effectiveness of a targeted HZ vaccination strategy, either alone or in combination with a universal approach, in adults age 50-59 years who are at increased CV risk.

Adult immunization rates continue to remain low for most recommended vaccines specifically in contrast to other preventive service interventions. There has been much research and discussion about factors associated with low adult immunization uptake. An environmental scan employed in the development of the NAIP identified relevant barriers associated with adult immunizations and found the following as the most critical; lack of public awareness of

recommended vaccines and risk associated with vaccine preventable diseases, lack of strong provider recommendations, and limited use of evidence-based strategies (Department of Health & Services National Vaccine Program Office, 2016). In response, goals of the plan have been developed around addressing these specific barriers. Information and awareness of increased risk of stroke associated with HZ infection has not been widely or formally communicated to payers, patients, or policy makers. The evidence supporting this association has only just begun appearing in the medical literature and the gap between evidence based data appearing in the medical literature and time to clinical adoption is estimated at 17 years (Balas & Boren, 2000). Effective and timely implementation of findings from clinical research is critical to improving population health outcomes and reducing the adoption curve for evidence based practices (Evans, Snooks, Howson, & Davies, 2013). Clinical and health services research has shown that failure to translate research into practice and policy is an ongoing public health challenge (Grimshaw, Eccles, Lavis, Hill, & Squires, 2012).

Study Purpose

Given that a large proportion of strokes occur in adults under age 65 and it is projected that the cost of treating stroke in this population will account for half of all stroke related expenditures by 2050 (Wang et al., 2014), studying the potential benefit of a targeted HZ vaccination approach for adults age 50-59 years who are already at some increased risk of stroke could provide a significant contribution to identifying cost-effective interventions to reduce stroke risk in this population. The 2017 AHA Heart Disease and Stroke Statistics update reports the prevalence of CVD in adults ≥ 20 years at 36.6% and projects that by 2030, 43.9% of the U.S. population will have some form of CVD (Benjamin et al., 2017). These data only represent

those who have active diagnosed cardiovascular diseases (atherosclerosis, chronic heart disease (CHD), heart failure (HF), prior MI or stroke, etc.) and does not begin to account for the millions more Americans with one or more risk factors for CVD. The Framingham Risk Scoring criteria estimates risk of developing CVD or some component of CVD (such as coronary heart disease, stroke, peripheral vascular disease, or heart failure) over a fixed time period by assessing risk factors such as sex, age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking behavior, and diabetes status and uses these "risk scores" to recommend interventions (D 'Agostino, Pencina, Massaro, & Coady, 2013). These risk criteria could serve as the foundation of a targeted recommendation for HZ vaccination as a potential primary prevention for stroke in patients with increased CV risk factors or active disease, specifically in the 50-59 year old population for whom the vaccine is FDA approved but not currently recommended by the ACIP.

In an effort to support the NAIP goal of generating and disseminating evidence of cost-effectiveness with the use of current vaccines, the purpose of this study was to evaluate targeted HZ vaccination strategies in adults 50-59 years of age who are at increased CV risk. This study aimed to:

1. Develop an analytic model to assess the cost-effectiveness of a targeted vaccination intervention in an immunocompetent population of adults age 50-59 years, comparing two treatment strategies; usual-care vaccination, no current ACIP recommendation for adults age 50-59, versus achieving a 60% vaccination rate among a targeted population of adults at increased CV risk. This assessment considered the cost-effectiveness of HZ vaccination in reducing the risk of IS within one year of HZ infection. HZ outcomes were based on reduction of infection only and not associated morbidities of PHN and BOI.

2. Translate cost-effectiveness outcomes and related incremental cost-effectiveness ratio's (ICERs) for a target audience of three key healthcare stakeholder groups; payers, providers, and policymakers for the propose of dissemination and implementation of recommendations for reducing stroke associated with HZ and improving access and uptake of HZ vaccination in adults age 50-59 years.

Review of Theory and Frameworks

Endeavoring to advance evidence of the economic benefits of adult immunization is a cornerstone of the NAIP. Multiple CEAs have been conducting since the introduction of the vaccine for the prevention of HZ. The SPS was the primary randomized controlled clinical trial (RCT) for Zostavax® and was conducted in a cohort of immunocompetent adults over age ≥ 60 thus establishing a foundation for the predominance of cost-effectiveness analyses using this same population. A 2014 review of HZ CEAs by de Boer, Wilschut, and Postma identified the majority of these studies as having applied "traditional" decision analytic models (Cohort Models and Markov Models) and noted that the perspective most often used was that of the healthcare payer followed by the societal perspective (de Boer et al., 2014).

Cost-Effectiveness Analysis

Facilitated by ACA, healthcare delivery has been moving from a volume based fee-for-service (FFS) approach to a value based payment system accelerating significant changes in health care delivery. This shift is linked to quality improvement metrics and measures which push financial risk to the payer and provider level. Quality measures tied to performance and increased risk sharing on the part of the payers and providers is imposing greater focus on evidence-based outcomes. Healthcare decision making is now about prioritizing health

interventions in an environment of scarce and/or limited resources while assuring adherence and successful performance to meet quality metrics. Healthcare delivery systems are adopting Population Health Management (PHM) approaches (looking at patient populations tied to outcomes) to more effectively meet both performance and outcome measures. CEAs are an important influencer of informed outcome-driven healthcare decision making.

Cost-effectiveness can be defined as "the additional cost required per additional unit of health benefit produced as compared with the next most effective alternative" (J. J. Kim, 2011). As a form of economic evaluation CEAs are designed specifically to examine the difference in magnitude associated with the costs of healthcare interventions or treatments and are typically expressed as quality-adjusted life year gained (QALY), defined as costs in dollars and health benefits in units of health and incremental cost-effectiveness ratio's (ICERs), which represent the difference in cost between the interventions being considered divided by the difference in their effectiveness (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005; Owens, 1998). In the changing healthcare marketplace there is increasing focus on cost-containment and its relationship to value, as a result CEAs play a significant role in aligning cost expenditures to anticipated outcomes and are a critical consideration for healthcare decision making among policy makers and payers (Bang & Zhao, 2014).

Population Health Framework

The distinction between population health and public health is still not well appreciated even in academic settings. The most simplistic distinction between population health and public health is that population health refers to specific measurable health outcomes and public health defines the approaches used to provide health to the nation's population. For the purpose of this

analysis the perspective was based on a population health point of view keeping in mind that the measures we select to evaluate must address the health determinants which influence the outcomes we seek to impact. Kindig and Stoddard's Population Health Framework model diagrams the inter-relationships between health outcomes, patterns of health determinants, and policies and interventions at the individual and society levels (2003). This framework provided the foundational approach for the evaluation of appropriate interventions and sustainable intervention strategies used to translate the research findings into recommendations for the key stakeholders groups.

Kindig and Stoddard contend that a population health approach requires consideration of the specific allocation of resources employed to link determinants to outcomes, specifically the ability to evaluate cost-effectiveness across various intervention strategies (2003). Population health is achieved through the interaction and cooperation of multiple stakeholders such as payers, providers, and policymakers with a focus on effective knowledge transfer and dissemination among and between the various stakeholders (D. Kindig & Stoddart, 2003). The importance of the interplay between multiple stakeholders requires analysis of how the sequences of interventions rely on one another and if there is a necessary hierarchy to their adoption.

The primary objective of this study was to determine if a HZ vaccine intervention was cost-effective relative to the cost of treating stroke within the year following infection with HZ. Applying the population health framework, reduction of HZ and HZ related stroke are the outcomes to be measured and the translation of these findings is necessary to identify and address health determinants associated with vaccine adoption, from all three stakeholders

perspectives, including cost, access, risk perception, and benefits. In addition, analysis of potential policies and interventions at the individual and societal levels which can positively influence those determinants must also be evaluated and translated into recommendations.

Implementation Science

Implementation science is defined as: "research relevant to the scientific study of methods to promote the uptake of research findings into routine healthcare in clinical, organizational or policy contexts" (Eccles & Mittman, 2006). While considered a nascent field by some measures, the fundamental constructs of implementation science have been known for decades. The literature supports the consensus of the failure for timely and efficient translation of medical research findings into clinical practice and public policy (Haines, Kuruvilla, & Borchert, 2004). In 2000, Balas and Boren first reported that it takes an average of 17 years for health research to reach clinical practice, compared to newer technological innovations which take an average of four to six years (ex. iPhone/iPad) (2000).

Improving adult immunization rates will require efficient and sustainable intervention strategies. Adult immunization efforts lack the structure of routine well care visits, provider awareness, standardized policy, insurance and federal program cost coverage, and quality measures which are well established for pediatric patients. Efforts to improve rates in this population will require a multi-disciplinary approach. Applying a scientific approach to implementation is essential to bridging the gap between knowledge and practice.

There is a core foundation for implementation science under the umbrella of population health. Implementation science is interdisciplinary in nature, applying theories and knowledge from other domains such as; economics, behavior science, clinical research, public policy,

quality and performance improvement, social sciences, and marketing. As shown in Figure 2, successful and sustainable implementation approaches require multilevel, sequential intervention strategies that are interdependent (Fixsen, Naoom, Blase, Friedman, & Wallace, 2005). Translating evidenced-based research findings into practice requires a comprehensive understanding of the target population, the interventions being considered, and the structural capacity, internal and external influencers, and barriers unique to each stakeholder.

Figure 2: Multilevel Influences on Successful Implementation. From "Implementation Research: A Synthesis of the Literature", by D. L. Fixsen, S.F. Blasé, R.M. Friedman and F. Wallace, 2005, National Implementation Research Network, p. 59. Copyright 2005 by Louis de la Parte Florida Mental Health Institute Publication #231 Tampa, Florida. Used with permission.

Conceptual Model

A simulated cohort of 100,000 immunocompetent adults age 50-59 years was developed in TreeAge Pro 2017 software employing a decision tree analytic and Markov model (MM) using two vaccination strategies to assess the cost-effectiveness of targeted HZ vaccination to reduce stroke risk in adults with increased CV risk, compared to usual-care (see Figure 3). For

purposes of the model, CV risk was established using current AHA CVD prevalence data as a proxy, which only captures those with active disease, not those who are "at-risk". CV risk factors as established by the Framingham Risk Scoring criteria include; hypertension, hyperlipidemia, diabetes, age, and smoking history, whereas CVD represents those with active disease (D'Agostino et al., 2008; D 'Agostino et al., 2013).

The model compared usual care, no current ACIP recommendation for HZ vaccination in adults age 50-59 years, to a HZ targeted vaccination approach in adults age 50-59 years who are at increased CV risk with the goal of achieving a 60% vaccination rate in the targeted population. A Monte Carlo (MC) simulation of the hypothetical cohort was performed using probabilistic and deterministic parameters to estimate costs and ICERs for each treatment strategy. Costs and ICERs for each of the possible intervention strategies were then ranked by ICER and compared to standardized willingness-to-pay (WTP) thresholds to determine which interventions produce the greatest value.

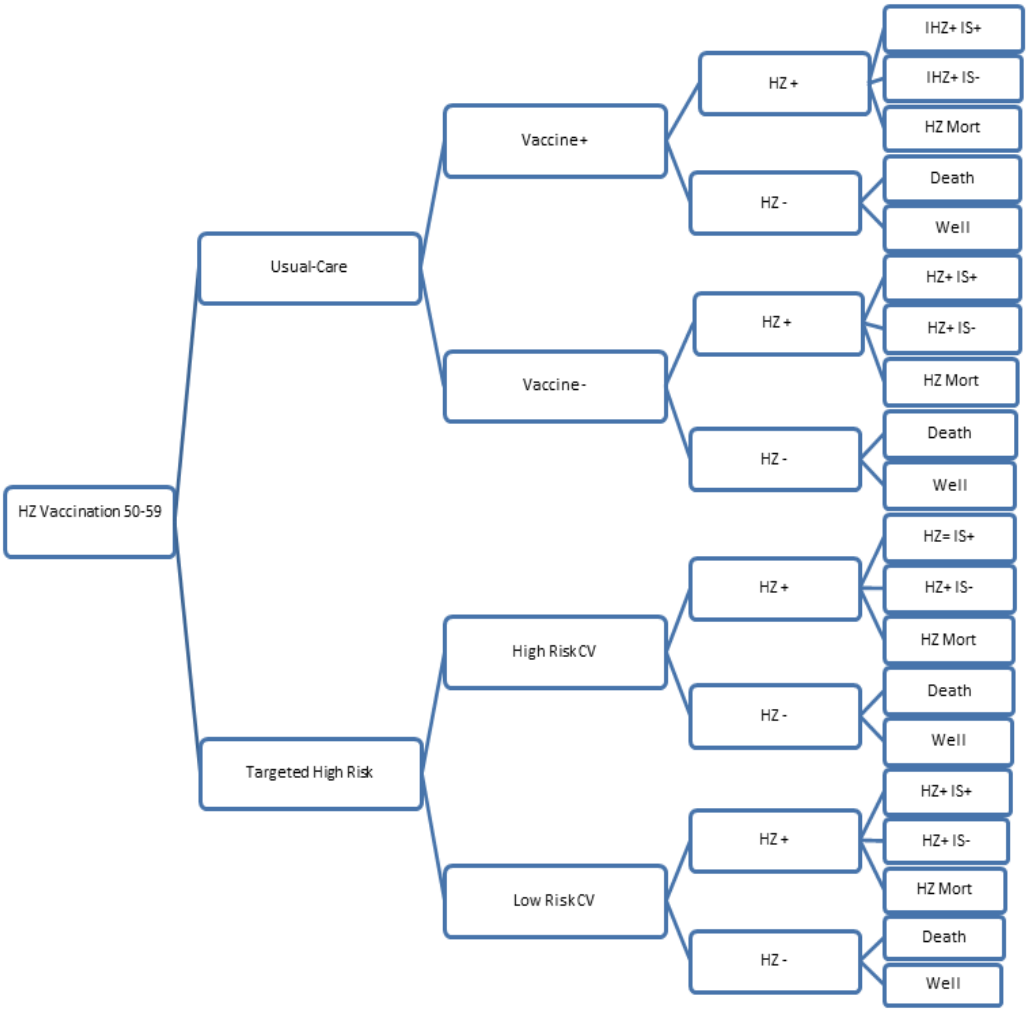

Figure 3: Example of Decision Tree

Model Parameters

Many of the parameters in this study were derived from a previously published CEA of HZ in adults age 50-59 years by Le & Rothberg permitting assessment of concordance of results (Le & Rothberg, 2015). A review of recent literature and data sources was conducted to update parameters that may have changed since 2015 in an effort to select the best and most recent

inputs for the model. Other probabilistic and base-case parameters were pulled from the literature and prior publications (Le & Rothberg, 2015; Pandya, Sy, Cho, Weinstein, & Gaziano, 2015). HZ incidence rates and healthcare utilization costs were based on the most recent data in immunocompetent adults in the U.S. (Johnson et al., 2015, 2016b). CVD prevalence and associated costs were drawn from the 2017 Heart Disease and Stroke Statistics (Benjamin et al., 2017) and direct IS costs from a payer perspective was derived from a real-world cost analysis published in 2017 (Mu et al., 2017). Background age and sex specific mortality rates were obtained using U.S. life tables for all-cause mortality (Centers for Disease Control and Prevention, 2017c).

Risk of stroke associated with HZ infection was drawn from a 2015 self-controlled case series (SCCS) analysis of a U.S. Medicare population of adults ≥ 65 years with a HZ diagnosis and IS within defined time periods using data gathered between January 2006 and December 2011 (Minassian et al., 2015). This SCCS was selected as it most closely represented the simulated cohort and was specific to a U.S. population. Because HZ infection itself is the mechanism behind the association with increased stroke risk, HZ vaccination efficacy was based on data supporting prevention of HZ infection only therefore efficacy and durability of the vaccine against PHN and BOI were not included.

Evaluating the Results

Assumptions were based on a U.S. private payer perspective. Costs were expressed in current U.S. dollars and utilities expressed as quality of life-years gained (QUALYs) and were discounted at 3% annually with ICER WTP thresholds of $50,000 and $100,000 per QUALY (Drummond et al., 2005; Gold, Marthe, R.. Siegel, Joanna, Russell, & & Weinstein, 1996).

Outcomes were synthesized to evaluate evidence-based recommendations for three important stakeholders to promulgate intervention strategies from this study. Scientific findings were translated into population health based intervention and dissemination strategies to improve decision making around appropriate vaccination of adults age 50-59 years at increased CV risk. Economic and health benefit findings were translated to the unique perspectives of three key stakeholders, payers, providers, and policymakers to aid in the development and implementation of appropriate practice and policy based intervention strategies. Private payers are increasingly relying on cost-benefit analysis for the purpose of containing healthcare costs while still delivering value based care and improving population health outcomes. In this analysis, private payers targeted costs and outcomes were calculated as per member per month (PMPM) costs associated with the intervention strategies (based on number of cases of HZ and IS avoided in the target population) providing additional information on which to assess appropriate and reasonably implemented cost-effective managed care intervention strategies aligned with PHM and quality metric outcome measures.

Provider level focus was on creating awareness for both providers and patients to help identify patients at risk and support shared decision making regarding vaccination. For policymakers, research results informed the development of suggested changes to existing immunization policies, recommendations, and quality metrics for the purpose of driving improved population health through decreasing costs and disease burden associated with stroke among a population where CVD prevalence continues to grow. Considerations included a targeted strategy for at risk groups, universal age-based strategy, and utility of combination strategies, including discussion of public health versus population health impacts of targeted strategy for a non-communicable disease. Assessment of impact on patient out of pocket cost

was considered in relation to current Affordable Care Act (ACA) coverage for all universally recommended vaccines, which currently does not include HZ vaccination in adults 50-59 years of age.

Manuscript Overview

The purpose of this study was to evaluate the cost-effectiveness from the payer perspective of a targeted HZ vaccination approach in a population of immunocompetent adults age 50-59 years with increased CV risk factors for whom the current HZ vaccine is FDA approved but not ACIP recommended. Utilizing the CEA results a white paper was developed for the purpose of informing health care intervention strategies directed at payers, providers, and policymakers. The results are presented in two manuscripts found in sections II and III.

Manuscript One (found in Section II), *Cost-Effectiveness Analysis of Targeted Herpes Zoster Vaccination in Adults 50-59 at Increased Cardiovascular Risk*

Manuscript Two- (found in Section III), *Stroke Risk Reduction through Herpes Zoster Vaccination,* a white paper translation of findings for payers, providers, and policymakers.

SECTION II: MANUSCRIPT ONE

Title Page and Journal Selection

Manuscript One Title: Cost-Effectiveness Analysis of Targeted Herpes Zoster Vaccination in Adults 50-59 at Increased Cardiovascular Risk

Primary journal selection: *Annals of Internal Medicine*

Reason for journal selection: This journal has a large readership that encompasses a broad array of health care providers and decision makers and is among the most highly cited journals in the world. This journal was selected because it publishes a variety of original research including cost-effectiveness analyses. Complete journal guidelines can be found at:

http://annals.org/aim/pages/authorsinfooriginalresearch

Secondary journal selection: *Vaccines or Stroke*

Background

Herpes zoster (HZ) affects more than 1 million adults in the U.S. each year. HZ is a risk factor for ischemic stroke (IS) based on increasing evidence of significantly elevated short term risk following HZ infection persisting for up to twelve months. Stroke is the fifth leading cause of death in the U.S. - every 40 seconds someone experiences a stroke and every four minutes one of them will die. 87% of all strokes are ischemic. HZ vaccine is approved but not recommended in adults 50-59 years of age. To date there have been no studies to assess the IS related cost-effectiveness of a targeted HZ vaccination strategy, either alone or in combination with a universal approach, in adults age 50-59 years who are at increased cardiovascular (CV) risk.

Abstract

Objective: Assess the cost-effectiveness of a targeted HZ vaccination strategy in adults age 50-59 years who are at increased cardiovascular (CV) risk for ischemic stroke (IS) versus usual-care in this population.

Design: Markov model (MM).

Data Sources: Medical Literature.

Target Population: Immunocompetent adults age 50-59 with increased CV risk.

Time Horizon: Lifetime for individuals of median age of 55 through mortality to 100 years.

Perspective: Commercial Payer Direct Costs.

Intervention: Herpes Zoster (HZ) Vaccine.

Outcome Measures: Cost-effectiveness denominated in quality-adjusted life-years (QALYs) and the Incremental cost-effectiveness ratios (ICERs).

Results of Base-Case Analysis: The incremental cost of targeted vaccination over usual-care was $30.59 per person with an ICER of $55,517 per QALY.

Results of Sensitivity Analysis: Using deterministic and sensitivity analyses all variables produced ICERs less than $56,000 per QALY. The only variables associated with increased ICERs were costs of IS resulting from HZ and cost of treating HZ.

Limitations: Rate of IS risk within one year of HZ infection was obtained using a cohort of U.S. Medicare participants aged ≥ 65 which represents an older population than the simulation model and does not represent a commercial payer population.

Conclusion: Targeted vaccination of adults 50-59 years of age at increased CV risk is cost-effective with an ICER of $55,517 per QALY, falling well within the generally accepted willingness-to-pay (WTP) threshold of $50,000 - $100,000. Moreover, these results demonstrate cost-effectiveness of a universal vaccination strategy in this population with an ICER of $55,523 per QALY. Cost of stroke associated with HZ infection is substantial and this study demonstrates that HZ vaccination intervention in adults 50-59 years of age can mitigate both the IS risk and economic burden associated with HZ infection.

Primary Funding Source: None.

Introduction

Over the last twenty years incidence of herpes zoster (HZ) infection also known as shingles, has been increasing among adults for unknown reasons (Kenneth E Schmader & Dworkin, 2017). The economic burden of HZ is currently estimated at over $1 billion per year in the United States (U.S.) and is expected to increase as the susceptible adult population increases (Johnson et al., 2016b). HZ is caused by a reactivation varicella zoster virus (VZV), chicken pox, and more than 95% of adults carry the virus with a 1 in 3 lifetime risk of developing HZ (Warren-Gash et al., 2017). Post herpetic neuralgia (PHN) is the most common side effect associated with HZ and occurs in 10-18% of patients and is defined as prolonged pain at the site of rash increasing the overall burden of illness (BOI)(Centers for Disease Control and Prevention, 2016b). HZ is a vaccine-preventable disease and in 2006 the FDA approved a live-attenuated vaccine (Zostavax ®; Merck) for the prevention of HZ in adults ≥ 60 years with an expanded approval for adults age 50-59 years in 2011. Since 2006 rates of adult immunization for HZ have been modest, as of 2015 more than two-thirds of the U.S. population ≥ 60 are still unvaccinated and more than 94% of those between age 50-59 years have not received vaccination (PJ.Lu et al., 2017; Williams et al., 2017).

Suggestion of an association between HZ and stroke was reported as early as the late 1950's (Nagel & Gilden, 2015), since then epidemiologic evidence from self-controlled case studies, population based cohort studies, systematic literature reviews, and meta-analyses have confirmed a causal relationship between HZ infection and stroke thus establishing HZ as a stroke risk factor (Breuer et al., 2014; Kang, Ho, Chen, & Lin, 2009b; Kwon et al., 2016; Langan, Minassian, Smeeth, & Thomas, 2014b; Lian et al., 2017; Liu et al., 2016; Marra, Ruckenstein, & Richardson, 2017b; Minassian et al., 2015; Nagel et al., 2017; Schink, Behr, Thone, Bricout, &

Garbe, 2016; Sreenivasan et al., 2013; Sundström et al., 2015; Yang et al., 2017; Yawn et al., 2016; Zhang, Yanting; Luo, Ganfeng;Huan, Yuanwei; Yu, Qiuyan; Wang, Li; Li, 2017b). This association is further supported by the pathologic mechanism between VZV infection and vasculopathy. VZV is the only recognized human virus that can replicate in the cerebral arteries thus producing viral arterial infection resulting in vascular inflammation and remodeling which can lead to stroke (Nagel & Gilden, 2015; Nagel et al., 2017; Powell et al., 2015; Warren-Gash & Breuer, 2017; Wu, Lin, Sung, Chou, & Yuan-Teh, 2014).

Beginning in late 2016 several meta-analyses began appearing in the medical literature, further validating evidence of significantly elevated risk of stroke, specifically ischemic stroke (IS) within 12 months following infection with HZ (Lian et al., 2017; Liu et al., 2016; Marra et al., 2017a; Yang et al., 2017; Y. Zhang et al., 2017). Currently the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommend universal HZ vaccination only for adults ≥ 60 years. Prior HZ vaccine cost-effectiveness studies, which have largely informed the ACIP recommendations, have not included assessment of the associated risk of IS.

Stroke strikes someone in the U.S. every 40 seconds with an estimated 795,000 strokes per year. Stroke is a significant cause of disability with costs estimated at $33 billion per year including cost of health care, medication, and lost productivity (Centers for Disease Control and Prevention, 2016d). As the U.S. population ages rates of HZ infection and stroke incidence will increase significantly impacting morbidity, mortality, and health care costs. The ACIP does not currently recommend vaccination for adults age 50-59 years and has not issued guidance or recommendations for adults who may be at increased risk of stroke associated with HZ infection.

Information on duration of protection and cost-effectiveness of HZ vaccination in persons age 50-59 years are limited. Efficacy of the vaccine in adults age 50-59 years is estimated at nearly 70%, based on data from the Zostavax Efficacy and Safety Trail (ZEST) however duration of vaccine protection was considered short term at 1.5 years (Kenneth E Schmader et al., 2012). Previous cost-effectiveness studies of Zostavax® in patients age 50-59 years have not demonstrated good value because they exceeded the generally accepted WTP threshold of $100,000 per QALY (Le & Rothberg, 2015). Understanding the risks, costs, and disutility associated with potential IS after HZ infection in this cohort for whom the vaccine is approved but not recommended is important for informing prevention strategies. Informing payers, providers, and policymakers is additionally important because adults age 50-59 are predominantly employed and covered under private insurance plans and would incur additional lost productivity from both HZ and IS.

Methods

A decision analytic tree and Markov Model (MM) were used to compare costs and outcomes between two HZ vaccination strategies; usual-care (no current vaccine recommendation) and targeted vaccination in adults age 50-59 years with cardiovascular disease (CVD) in a hypothetical cohort of 100,000 adults age 50-59 years. The model structure was adapted from a previously published MM which assessed the cost-effectiveness of HZ vaccination versus no vaccination in healthy immunocompetent adults age 50-59 years (Le & Rothberg, 2015). Inputs were revised as necessary to assess the benefits of a targeted vaccination approach aimed at reducing IS risk in patients 50-59 years of age with cardiovascular disease (CVD).

The private payer perspective was used as it best represents this population of adults age 50-59 years who are predominately employed and covered under employer sponsored commercial insurance. The decision analytic model stratified the two treatment strategies and the MM was employed to age the cohort to death or 100 years in order to calculate the difference in QALYs through mortality using a cycle length of one year. The simulated cohort was assessed for incidence of IS within 12 months following HZ infection occurring within the fifth decade of life. Risk was assessed from the age at entry to the analysis, median age 55, up to age 60 using TreeAge Pro 2017 software. The model assumed patients were immunocompetent and evaluated only direct costs associated with HZ infection and/or IS.

The cohort entered the model at age 50 in a "healthy" state in either the usual-care arm or the targeted increased CV risk population arm moving between health states and transition probabilities up to age 60. Both arms, usual-care and targeted at risk population were stratified as vaccinated versus non-vaccinated. Disutility for IS was assumed for a one-year period, for subsequent years stroke disutility persisted. Disutility for HZ was calculated at two months. All costs were expressed in 2016 U.S. dollars and costs and QALYs were discounted at 3% per year.

Outcomes included costs and effectiveness for each strategy. ICERs reflect the cost-effectiveness of the difference in costs between the intervention strategies divided by the difference in health benefits obtained and were then evaluated against the generally accepted WTP threshold of $50,000 to $100,000 (prior HZ CEAs used WTP of $100,000) (Le & Rothberg, 2015, 2016; Pellissier, Brisson, & Levin, 2007; Rothberg, Virapongse, & Smith, 2007; Szucs, Pfeil, Szucs, & Pfeil, 2013).

Model Inputs and Assumptions

A systematic review of the literature and data sources was performed to update any parameters that may have changed since 2015 and to identify the most current and appropriate values for the model. Data used for the model were derived from U.S. based epidemiologic and statistical data sets and medical literature data and reflect disease incidence, costs, and QALYs expected in the general U.S. population. Table 2 describes estimates used for the base-case analysis including the deterministic and probabilistic sensitivity analyses parameters used for the simulated cohort of 100,000 commercially insured adults age 50-59 years.

Epidemiologic Parameters

For reasons which are still unclear, over the last 20 years rates of HZ infection have been increasing across all age groups, even in the wake of a highly effective pediatric varicella vaccination program (Kenneth E Schmader & Dworkin, 2017). More recent epidemiologic incidence data of HZ in adults 50-59 years of age from Johnson and colleagues report a higher incidence among this population than previous studies and is consistent with data demonstrating increasing incidence of HZ across all age groups (Hales, C.M., Harpaz, R., Ortega-Sanchez, I., Bialek, 2014; Johnson et al., 2015). Estimates for vaccine coverage in adults age 50-59 years is limited due to a lack of an ACIP recommended and subsequent slow adoption in this age group. Data from the 2014 Behavioral Risk Factor Surveillance Study (BRFSS) was used to estimate vaccination rates in this population because this was one of the few resources available to obtain immunization rates in this population as data on 50-59 year olds is not included in the annual National Health Interview Survey (P.J. Lu et al., 2017). Incidence rates remained constant

Table 2: Parameters for Distributions Used in Base-Case and Sensitivity Analysis

Category	Base-Case Value	Sensitivity Analysis Range	Sensitivity Analysis PSA	Distribution	Source
HZ Incidence per 1000 person-years					
Population Aged 50 -59 years	0.00674		CI 6.66-6.82	Bernoulli	Johnson, 2015
Males Aged 50-59 years	0.00501		CI 4.92-5.11		
Females Aged 50-59 years	0.00835		CI 8.24-8.47		
MORBIDITY					
Deaths due to HZ per 100,000 cases	1.26	0.86 to 1.67		Normal	
Population Aged 50-59 years					
Stroke Mortality 2014 age adjusted death rate per 100,000	36.5				
HZ Vaccination Rates					
Population Aged 50-59 years	5.90			Beta	Lu et al, 2016
Vaccine Efficacy					
Population Aged 50-59 years	59.50%			Normal	Baxter et al, 2017
Vaccine AE's					
Local reaction	0.64	0.63 to 0.65	(7088; 4004)	Beta	Le & Rothberg, 2016
Serious reaction	0.001	0 to 0.003	(0.96; 957.48)		
CVD Prevalence					
Population Aged 40-59 years	36.60%			Normal	Benjamin, 2017
Males Aged 40-59 years	41.4%				
Females Aged 40-59 years	39.4%				
Stoke Risk within 1 year of HZ					
Population 50-59 years	12.20%			Beta	Minassian, 2015
Males Aged 50-59 years	3.54%				
Females Aged 50-59 years	8.66%				
Health Utilities					
HZ positive	0.87			Normal	Le & Rothberg, 2016
HZ positive- Stroke positive	0.65				Chan et al., 2016
Direct Medical Costs, $/case					
HZ Adults 50-59	$1614			Gamma	Johnson, 2016
IS Acute and long-term over 360 days post discharge	$29,364				Mu et al., 2017
Mortality	Background			Beta	U.S. Life Tables
Vaccine Costs (2017 US$)					
Private Sector	$212.66			Gamma	CDC Price List
Administration	$25.00				
Cost-Effectiveness					
Discount Rate	3.0%			Gamma	
Willingness to Pay (WTP)	$50,000-$100,000				

HZ = Herpes Zoster;

IS = Ischemic Stroke

throughout the analysis and no adjustments were made for potential HZ recurrence which long-term studies have reported as 5-6%. (Kawai, Gebremeskel, et al., 2014). Several studies have reported significantly higher incidence of HZ in adult women across all age groups (Johnson et al., 2015; Sundström et al., 2015), thus female gender is considered a risk factor for HZ (de Boer et al., 2014). The base-case analysis assumed equal gender distribution. The probability of death attributable to HZ for adults age 50-59 years was pulled from Le & Rothberg (2015).

IS incidence within one year of HZ infection was drawn from a 2015 self-controlled case series (SCCS) analysis of a U.S. Medicare population of adults ≥ 65 years with a HZ diagnosis and IS within defined time periods using data gathered between January 2006 and December 2011 (Minassian et al., 2015). While there has been significant literature published on the associated risk of stroke after HZ infection, this SCCS was selected as it most closely represented the population being evaluating and was specific to a U.S. population (Erskine et al., n.d.; Kang et al., 2009b; M.C. Kim et al., 2017; Langan et al., 2014b; Lian et al., 2017.; Liu et al., 2016; Marra et al., 2017a; Yang et al., 2017; Zhang, Yanting; Luo, Ganfeng;Huan, Yuanwei; Yu, Qiuyan; Wang, Li; Li, 2017b). Using this data, risk of stroke in the year following HZ was calculated at 12.20%, far below other reports of 30% or greater risk across various age populations(Gilden, Nagel, Cohrs, & Mahalingam, 2013; M.C. Kim et al., 2017). Age specific IS prevalence rates in the general population for those age 45-64 and CVD prevalence rates in the general population age 40-59 years were derived from the most current AHA heart disease and stroke statistics, specific IS and CVD prevalence data for the 50-59 year old population was not available (Benjamin et al., 2017). IS mortality was based on 2014 age adjusted death rate per 100,000.

Adults age 50-59 years have lower overall rates of HZ compared to older age groups and have a lower probability of PHN once they develop HZ (Le & Rothberg, 2015; Yawn BP., Saddier P., Wollan PC., St. Sauver JL., Kurland MJ., 2007). HZ infection is the primary risk factor for increased stroke risk associated with VZV vasculopathy (Nagel & Gilden, 2014, 2015; Nagel, Jones, & Wyborny, 2017). While prior CEAs considered direct and indirect costs associated with HZ infection as well as PHN and overall BOI, this analysis evaluated the direct private payer costs associated with HZ and efficacy of the vaccine for the prevention of HZ infection alone and did not include PHN or BOI.

Vaccine-Related Parameters

CEAs for HZ are highly dependent on the age of vaccination and presumptions about duration of protection (durability) of the vaccine (Kawai, Preaud, et al., 2014). The ACIP recommendations for use of Zostavax® have heavily relied on cost-effectiveness results in patient's ≥ 60 due to the preponderance of the data in this population. Previous cost-effectiveness studies of Zostavax® in patients age 50-59 years have not demonstrated good value based on the generally accepted WTP threshold of $100,000 per QALY due in large part to limited data on duration of efficacy in this population (Le & Rothberg, 2015). The 2015 CEA by Le and Rothberg estimated the long-term efficacy of Zostavax® in adults age 50-59 years by combining data sources from ZEST and LTPS and establishing a waning efficacy slope to project duration of protection (2015). More recent data has been cited as the preferred source for duration of efficacy for Zostavax®, specifically in the 50-59 year old cohort. Johnson, Jiang, Weiss and Graham (2017) conducted an analysis of six models of waning efficacy for the HZ vaccine and concluded that effectiveness data published by Baxter et al. (2017) should be used to predict

effectiveness and waning of the vaccine. Using this data, waning efficacy was assumed through the cohort up to age 60 regardless of the age at vaccination and was based only on reduction of HZ infection not PHN or BOI. Overall efficacy of the vaccine in this population was based on the ZEST efficacy of 69.8% (Kenneth E Schmader et al., 2012).

Stroke-Related Parameters

Meta-analyses of the associated risk stroke after HZ infection assessed independent risk of transient ischemic attack (TIA), ischemic stroke (IS), hemorrhagic stroke (HS), and myocardial infarctions (MI) and found consistent statistical significance associated with HZ infection and IS providing the basis for this analysis to focus on IS.

Quality-Adjusted Life Years (QALYs)

Following Le and Rothberg (2015), this analysis incorporated the same utilities for HZ and utilities for IS were obtained from a recent analysis which specifically evaluated utility for the 12 months following stroke (Chan et al., 2016). All utilities were age adjusted and well utilities came from the 2001 Medical Expenditure Panel Survey and the 2001 National Health Interview Survey (Hanmer, Lawrence, Anderson, Kaplan, & Fryback, 2006). Utilities range from 1.0 representing perfect health to 0 representing death. Per the manufacturer, serious adverse reactions with ZOSTAVAX® occurred at similar rates between vaccine recipients and controls and the most common reported adverse events were headache and injection-site reactions (Merck & Co., Inc. 2017). As reported adverse events associated with Zostavax® are limited with no cost specific interventions this model adopted the local and serious adverse reaction rates reported by Le and Rothberg (2015).

Costs

Costs were based on direct costs from a payer perspective and were determined using the most updated information related to HZ vaccination and disease treatment burden in adults age 50-59 years. Vaccine price was based on the private sector cost per dose published on the CDC vaccine price list and vaccine administration costs were aligned with the 2015 data presented by Le and Rothberg (Centers for Disease Control and Prevention, 2017b). Data on healthcare resource utilization and costs of HZ infection were gathered from a recent analysis by Johnson and colleagues who specifically reported data on adults age 50-59 years, and found that approximately 25% of HZ cases occur in this age group and have higher incremental than those in older age cohorts (Johnson et al., 2016b). The estimated healthcare utilization cost of $1,614 included inpatient admissions, ER visits, outpatient office visits, and other outpatient services for HZ. Johnson and colleagues further commented that "…while the ACIP does not currently recommend vaccination of adults 50-59 years of age, HZ patients in this age range have a substantial stake in the overall economic burden of HZ" (2016, p.933). The reported incremental cost was reflective of HZ infection only and does not include PHN or BOI.

A significant proportion of strokes occur in adults under age 65 and estimates suggest that by 2050 about half of stroke-related costs, including treatment, rehabilitation, and lost productivity, will be incurred in this age population (Wang et al., 2014). Most of the literature on cost analyses of stroke has been based on cost of hospitalization which typically comprises about 50% of the direct costs. The analysis by Mu et al. assessed IS stroke costs including the time period after hospitalization from the commercial payer and patient out of pocket cost perspective (2017). Cost data was selected from Mu et al. because it was IS specific, included considerations

of costs as of 2015, reflects the increased use of recombinant plasminogen activator (rt-PA), and most closely approximates the perspective (commercial payer) and time period (one year post IS) used in this analyses. Because this study population is based on claims from a large commercial database, it predominantly captured patients ≤ 65 years of age since it did not include traditional Medicare claims (Mu et al., 2017). The average age of patients discharged with disability was 64.4 years and 58.1 years for those discharged without disability. This study also examined CV comorbidities and found higher correlation between patients discharged with disability compared to those without disability. Although this study does not compart data specific to our 50-59 year old patient perspective we did find it comparable to data on IS hospitalization costs for patients 45-64 reported by Wang and colleagues in 2014. In that analysis of hospitalization only (which is estimated at approximately 50% of overall costs) costs ranged from $19,000 – $21,386 (Wang et al, 2014). In 2008 using patient-level data Luengo-Fernandez, Gray, and Rothwell reported similar stroke costs for the follow-up period of 12 months with mean costs of $28,525 and median costs of &19,635 (2009).

Sensitivity Analysis

Deterministic sensitivity analyses for all model inputs with the ranges specified in Table 2 were conducted to assess parameter uncertainties. Factors with the greatest influence on the ICER are presented using a tornado plot (see Figure 4). In order to assess the uncertainty and implications for the results for all of the input parameters simultaneously we used a MC simulation of 100,000 hypothetical adults. Iterations of the simulation make random draws for each probabilistic parameter from the underlying distributions to account for the uncertainty and variation in the model parameters calculating expected costs for a fixed set of input parameters.

Probabilistic Sensitivity Analysis (PSA) was used to determine confidence in base case analysis, strategy selection, and confirm the variance in the deterministic parameters. The analysis was based on the two defined treatment options, targeted vaccination or usual-care and used distributions rather than pre-set values to generate separate distributions each time a new value is selected.

Results

Base-Case Analysis

Compared to usual-care, targeting HZ vaccination in adults age 50-59 years with prevalent CVD was cost-effective with an increase in incremental quality-adjusted life expectancy of 0.000551 per QALY at an additional cost of $30.59 per person. The incremental cost of vaccinating the target population using a benchmark vaccination rate of 60% was $30.59 per person compared to $12.98 in the usual-care group with incremental cost-effectiveness ratios (ICERs) of $55,517 and $55,470 respectively, falling far below the generally accepted HZ vaccine WTP threshold of $100,000 used in prior CEAs. Moreover, when comparing the cost of universal vaccination in the entire 50-59 year old cohort cost-effectiveness was maintained with an incremental cost of $176.51 and an ICER of $55,523 (Table 3).

Sensitivity Analyses

The CEA results provided means and descriptive statistics for QALYs and costs for each strategy to calculate the ICER which was then compared to the generally accepted WTP thresholds. The parameters that were varied through various plausible ranges and their effects on the ICER are shown in Figure 4. All variables were assessed and variables with value of zero were excluded from the analysis. By demonstrating that the largest contribution variables, such

as the cost of vaccination, lower the ICER this data support the very conservative study approach. Stroke mortality was shown to increase the ICER if the efficacy of the vaccine declines.

Table 3: Cost-Effectiveness of Targeted HZ Vaccination in Adults 50-59 with CV Risk

Strategy	Proportion Vaccinated (%)	Costs ($) Mean	Costs ($) SD	Incremental Costs ($)	Effectiveness (QALY) Mean	Effectiveness (QALY) SD	Incremental Effectiveness	Incremental Cost Effectiveness Ratio (ICER)
No Vaccine	0.00%	$25.12			26.376759			
Usual-Care	5.90%	$38.10	6.6487	$12.98	26.376993	1.4123	0.000234	$55,470.09
Targeted	19.80%	$68.69	93.5041	$30.59	26.377544	1.4121	0.000551	$55,517.24
Universal	100.00%	$245.20		$176.51	26.380723		0.003179	$55,523.75

No Vaccine – Currently not recommended for adults 50-59
Usual-Care – Population 50-59 receiving vaccination without recommendation
Targeted (Vaccination) – Population 50-59 at CV risk using target vaccination rate of 60%
Universal (Vaccination) - Entire 50-59 age cohort
QALY – Quality-adjusted Life Year

Post hoc analysis

To contextualize these results for the payer's perspective, the number of cases of HZ and IS avoided in each treatment arm were calculated in order to quantify the disease burden avoided by adopting the targeted strategy which was superior in cost-effectiveness terms. The targeted strategy resulted in 162 fewer HZ cases per 100,000, which translates to a savings of $261,468 when then divided by 100,000 resulted in a cost of $2.61 per member per year which equates to .22 per member per month (PMPM).

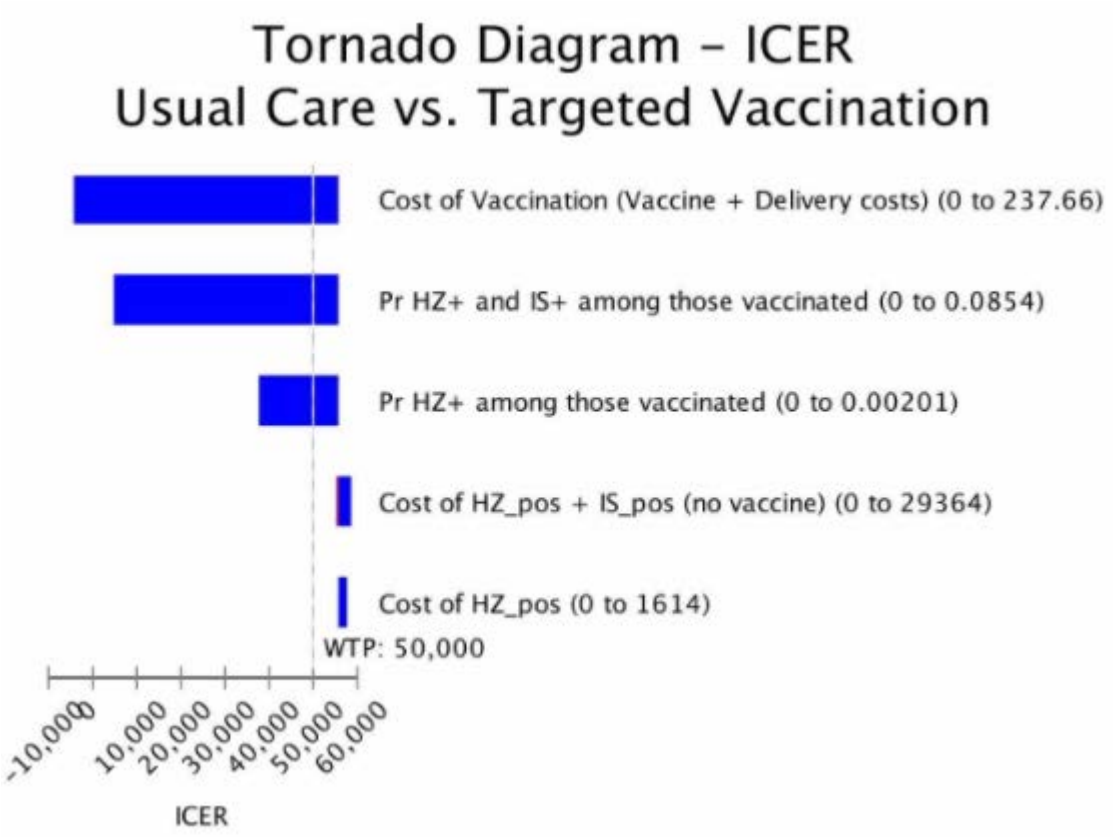

Figure 4**:** Tornado plot of the factors with the most influence on the ICER

The targeted strategy resulted in 14 fewer strokes per 100,000 which translated to savings of $ 411,096 which when divided by the 100,000 cohort equated to a cost of $4.11 per member per year and .34 PMPM. Both PMPM calculations are within reasonably expected thresholds for managed care companies to consider such an intervention strategy. These results further inform the U.S. payer perspective demonstrating this cost-effective intervention strategy and its impact on PMPM costs.

Discussion

HZ is a risk factor for stroke. Recent evidence signals significantly elevated short-term risk of IS following infection with HZ persisting for up to twelve months. Stroke is the fifth leading cause of death in the U.S. and every 40 seconds someone experiences a stroke and every four minutes one of them will die (Centers for Disease Control and Prevention, 2016). This is the first study known to assess the cost-effectiveness of targeted HZ vaccination, either alone or in combination with a universal approach in adults age 50-59 years who are at increased CV risk. This study demonstrated that targeted HZ vaccination in patients age 50-59 years at increased CV risk is cost-effective and thus should be taken under consideration by the ACIP to re-evaluate the current lack of recommendation of HZ vaccination in this population for whom the vaccine is currently FDA approved but not recommended. Furthermore, this study showed that a universal vaccination strategy in the general 50-59 year old population is cost-effective which is largely attributable to the significant cost burden associated with stroke. These results are also informative to private payer's population health management considerations for the implementation of standard protocols for adult immunizations.

The model assumed a 60% target vaccination rate in the at risk population which is twice that of the current HP 2020 benchmark for HZ vaccination in the current universal recommended population of adults ≥ 60 years. This value was selected because it mirrors the current pneumococcal vaccination HP 2020 goal for high-risk adults age18-64 years (see Table 1). This approach is supported by evidence of successful increases in pneumococcal vaccination in an at-risk populations through efforts to target that population using electronic health records and quality metrics such as hospital re-admissions (Schmaltz, Williams, Chassin, Loeb, & Wachter, 2011). The results of this CEA are also informative to the establishment of HP 2030 goals for HZ immunization which are currently being developed.

Decision analyses using simulation models to estimate cost-effectiveness of HZ vaccination are strongly represented in the literature (Le & Rothberg, 2015, 2016; Pellissier, Brisson, & Levin, 2007; Rothberg, Virapongse, & Smith, 2007) and are a useful tool to estimate cost-effectiveness without incurring the cost and time required to conduct a RCT. Previous cost-effectiveness models in both the 50-59 and the ≥ 60 year old HZ vaccination cohorts have been instrumental in informing ACIP recommendations in these populations. Given that the evidence of increased risk of IS within one year of HZ infection has only recently begun to receive broad attention in the medical literature, this study may be the first to consider cost-effectiveness of a targeted vaccination approach for a specific at-risk population of adults age 50-59 years for which currently no recommendations or risk-based guidelines exist.

The strength of these findings was confirmed by deterministic and probabilistic sensitivity analyses. Targeted vaccination of adults age 50-59 with increased CV risk resulted in an ICER under $60,000 per QALY as did universal vaccination of the entire 50-59 year age

cohort. This analysis is subject to several limitations. First, while there is now substantial literature on the HZ associated risk of IS, there was no available U.S. based specific data for IS risk after HZ representing adults 50-59 years of age using a private payer approach. The study conducted by Minassian and colleagues was selected because it most closely resembled the simulated cohort and was pre-specified to assess risk of IS related to HZ. As this study was in a Medicare population of adults ≥ 65, IS risk data was adopted from the stratified 65-69 year old population to most closely approximate the risk in our 50-59 year old cohort. Second, CVD prevalence data was from the larger 40-59 year old population since data on 50-59 year olds was not available.

There are several strengths to the study, some of which were not present in prior CEAs for the 50-59 year old group. Updated incidence, disease burden, duration of vaccine efficacy, and direct healthcare utilization costs associated with HZ specifically in the 50-59 year old population have recently been reported and were updated for this analysis (Baxter et al., 2017; Johnson et al., 2015, 2016a). Additionally, recently published third-party payer direct costs associated with IS were also incorporated into this analysis (Mu et al., 2017). CV risk was assessed using CVD prevalence data which only represents those who have active diagnosed cardiovascular diseases (atherosclerosis, chronic heart disease (CHD), heart failure (HF), prior MI or stroke, etc.) and does not begin to consider the millions more Americans with one or more risk factors for CVD. Given that the current prevalence of CVD in adults ≥20 years is estimated at 36.6% and it is estimated that by 2030, 43.9% of the U.S. population will have some form of CVD (Benjamin et al., 2017). By this measure this approach represents a very conservative estimation of the population at increased CV risk. Additionally, considering these results demonstrated favorable cost-effectiveness in the 50-59 age cohort for whom rates of HZ and IS

are lower than the ≥ 60 age cohort one could predict that increasing immunization rates in the present recommended cohort of adults ≥ 60 could provide substantial reductions in economic and disease burden associated with HZ and IS.

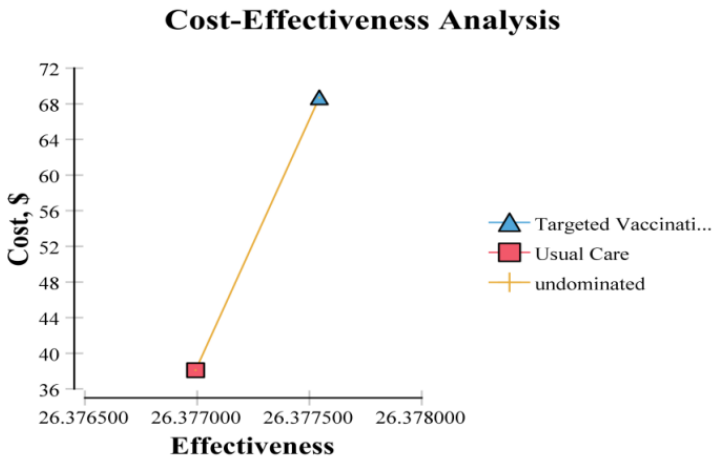

Figure 5: Cost-Effectiveness of Targeted Vaccination

In conclusion, targeted HZ vaccination in adults age 50-59 years with increased CV risk is cost effective with an ICER threshold of $55,517 far below the standard WTP applied to previous HZ vaccine CEAs. The incremental cost of vaccinating the at-risk population was $30.59 per QALY. Universal vaccination was also cost-effective at an ICER of $55,517 with an incremental QALY of $176.51 which while still cost-effective may not represent the highest value in a cost-constrained environment (see Figure 5). These findings are significant not only from a cost-effectiveness perspective but are critically necessary to inform payer, provider, and policymaker decisions aimed at improving healthcare delivery employing value based approaches focused on measureable outcomes while containing costs in order to improve overall

population health. The 2016 National Adult Immunization Plan specifically identified CEAs as a critical element of the plan because they "…help inform policymakers, health insurance plans, providers, employers, and the public about the value and importance of adult immunization and can inform decisions regarding promotion and reimbursement for adult immunization services (2016, p. 21).

SECTION III: MANUSCRIPT TWO

Title Page and Journal Selection

Manuscript Two Title: White paper – *Stroke Risk Reduction through Herpes Zoster Vaccination*

Primary journal selection: *Vaccines*

Reason for journal selection: Vaccines is the preeminent journal for researchers, clinicians, students, policymakers, and professionals interested in vaccines and vaccination. This journal was selected given its focus to inform practice and policy for the immunization public health field. Complete journal guidelines can be found at:

https://www.elsevier.com/wps/find/journaldescription.cws_home/30521?generatepdf=true

Secondary journal Selection: *American Journal of Public Health*

Executive Summary

In the United States (U.S.) adult vaccinations are highly underutilized, whereas rates of several adult vaccine-preventable diseases are increasing. Adult vaccines have been recognized as safe, effective and in most cases cost-saving if not cost-effective. Herpes zoster (HZ) is an example of one adult vaccine-preventable disease that has been increasing in incidence. A safe and effective HZ vaccine has been approved and in use for more than 10 years in the U.S. and yet only one-third of the recommended population has been vaccinated.

Evidence of an increased risk of ischemic stroke (IS) up to one year after HZ infection is accumulating in the medical literature. A significant portion of the U.S. adult population has existing cardiovascular disease (CVD), putting them at increased risk of stroke independent of HZ infection. This review evaluated the results of a cost-effectiveness analysis (CEA) of a targeted HZ vaccination approach in adults age 50-59 years with increased cardiovascular risk factors who would be eligible for preventive vaccination. This is a population for who the vaccine has been FDA approved but is not presently recommended by the Advisory Committee on Immunization Practices (ACIP). Based on these cost-effectiveness analyses (CEA) results and other findings in the literature the goal of this report is to translate this emerging science for dissemination to three key healthcare delivery and intervention stakeholder groups; payers, providers, and policymakers to guide informed decision making and coordinated adoption of effective evidence-based interventions aimed at increasing HZ vaccination among this population of at risk adults.

Introduction

Adult vaccinations are significantly underutilized despite evidence of effectiveness and economic benefits (Jacob, Chattopadhyay, Hopkins, Morgan, et al., 2016;Williams et al., 2016). Rates of several adult vaccine-preventable diseases are increasing, specifically herpes zoster (HZ). HZ, also known as shingles, affects over 1 million people in the U.S. annually with a cost of over $1 billion. Lifetime risk of HZ is about 1 in 3 and rates of HZ among all age groups have been increasing for the last 20 years for reasons that are still unclear. Epidemiological evidence of an increased risk of ischemic stroke (IS) within one year of HZ infection is mounting. A 2015 study using a U.S. Medicare database of adults ≥65 found a 2.4-fold increase in IS within the first week after HZ diagnosis followed by a gradual reduction in risk returning to baseline over the next six to twelve months (Minassian et al., 2015). HZ vaccine is FDA approved in adults 50 years and older but is currently only recommended for adults aged 60 years and above largely based on CEAs which have demonstrated support for vaccination in the over 60 population but not in the 50-59 year old age group.

Older adults are more likely to have chronic conditions and reduced overall health status and thus are more susceptible to diseases and are subsequently prone to greater risk of associated complications. Risk of preventable diseases and associated co-morbidities in adults will continue to grow as the aging population increases. The American Heart Association (AHA) projects that by 2030, 43.9% of the U.S. population will have some form of cardiovascular disease (CVD). In the U.S. stroke is the leading cause of serious long-term disability with annual costs (direct and indirect) of $33.9 billion. IS is among the leading causes of death, disability, hospitalization and healthcare expenditure in the U.S. (Mu et al., 2017).

The economic and societal burdens of HZ and IS are substantial therefore implementing cost-effective interventions such as vaccination could greatly improve population health goals and reduce costs. Effective and sustainable interventions to improve adoption and implementation of evidence based practices relies on three primary healthcare stakeholder groups; payers, providers, and policymakers. CEA of a targeted HZ vaccination approach in adults age 50-59 years with increased CVD risk has shown that such and intervention would be cost-effective. CEAs are an important component of healthcare expenditure prioritization and this new information should be rapidly disseminated for the purpose of communicating the economic and population health benefits of targeted vaccination in at risk adults.

Cost-Effectiveness Analysis Results

The purpose of cost-effectiveness analyses (CEAs) is to compare the costs and effects between two or more healthcare intervention alternatives as a means of determining if a new intervention or treatment strategy provides better health outcomes and to quantify the incremental costs associated with the additional benefits gained. Results of CEAs can be expressed in incremental-cost effectiveness ratios (ICERs) which are a dollar values assigned as a result of comparing costs between two intervention strategies divided by the difference in the quality-adjusted life years (QALYs) gained from those interventions. CEAs can also be used to calculate the number of cases of disease averted through adoption of the new intervention. The outcome measures provided from CEAs aid various healthcare decision makers in determining if new treatment or intervention alternatives should be adopted and if so, what are the costs associated with the new strategies relative to the benefits they provide. The resulting ICERs derived from CEAs are assessed against a standardized cost-effectiveness thresholds, defined as the amount of money the decision maker is willing to spend to gain one year of life, often referred to as wiliness-to-pay thresholds (WTP). Generally accepted WTP thresholds have been established for vaccine CEAs and range from $50,000 - $100,000.

CEAs can help contain healthcare costs by assisting various stakeholders in making informed decisions to assess the value associated with adoption of alternative expenditures in healthcare. Recent evidence has shown a significantly elevated risk IS within one year following infection with herpes zoster HZ. To assess the costs and benefits of an intervention strategy aimed at reducing stroke risk in adults age 50-59 years for whom the vaccine is FDA approved but not recommended, a CEA was used to evaluated the difference between two intervention strategies; usual-care (no vaccine recommendation) compared to targeting adults age 50-59 years

who are at increased cardiovascular risk with a target of achieving a 60% vaccination rate in this group. The results of the analysis demonstrated cost-effectiveness with a cost per ICER of $55,470, which is well within the generally accepted WTP threshold for vaccine interventions. This study also provided results for the number of herpes zoster and stroke cases averted through adoption of the targeted vaccination intervention strategy. Number of cases avoided can also be translated into costs incurred by insurance payers as per member per month (PMPM) costs which is another useful tool for payers to assess overall budget and health impacts of the intervention. Incremental differences in PMPM costs associated with intervention strategies can be assessed relative to the cases of HZ and IS avoided and evaluated based on the anticipated costs of implementing the vaccination intervention strategy through a population health management (PHM) approach within the payers healthcare delivery universe. In addition to demonstrating an ICER of $55, 470 for the targeted intervention strategy, the CEA calculated the PMPM cost of reducing 162 cases of HZ in the intervention versus the usual-care arm at a cost of .22 PMPM and avoidance of 14 cases of stroke at a PMPM cost of .34. Both of these PMPM costs are within reasonably expected thresholds for insurance payers to consider adoption of the intervention strategy.

These findings are significant not only from a cost-effectiveness perspective but help inform payers, providers, and policymakers decisions to improve healthcare delivery interventions focused on measureable outcomes while containing costs to improve overall population health. These results inform the basis for this report to provide recommendations for the adoption of targeted HZ vaccination in at risk adults age 50-59 years with considerations for the associated costs relative the benefits gained through reduction in the number of cases of HZ and IS avoided.

The 2016 National Adult Immunization Plan (NAIP) specifically identified CEAs as a critical element of the plan because they "…help inform policymakers, health insurance plans, providers, employers, and the public about the value and importance of adult immunization and can inform decisions regarding promotion and reimbursement for adult immunization services (2016, p. 21).

Background

Slow Adoption of Evidence-based Strategies

Dissemination and implementation of evidence-based research into practice is necessary to achieve optimal results and effectively apply research findings to improve outcomes (R. C. Brownson, Colditz, & Proctor, 2012). According to Balas and Boren it can take as long as 17 years for evidence-based research to translate into clinical practice which can result in people experiencing significant delays in being offered interventions that have been proven to improve health (2000). Translating research into practice is a complex process that involves disseminating information to appropriate stakeholders, adoption of the appropriate interventions, and successful implementation into the health care delivery setting, and then establishing sustainability of the intervention. To address complex health issues, researchers, clinicians, and healthcare decision makers need to work together and share their knowledge and expertise to increase the number of evidence-based interventions that are implemented in real-world practices. Increasing the number of interventions that translate into practice can have a direct and positive impact on the public's health by increasing access to approaches that have been demonstrated to improve health.

Adopting and implementing effective and sustainable interventions is critical to the success of improving health related outcome metrics which are increasingly being linked to pay-for-performance standards. As the U.S. continues a shift from a fee-for-service (FFS) model to a value-based payment model, increased focus on quality metrics is driving more financial risk to payers and providers. As quality measures emerge as drivers of intervention prioritization, CEAs play an important role in assisting healthcare decision makers to examine the differences in magnitude associated with the costs of various healthcare interventions and/or treatments (Drummond et al., 2005). CEAs are also an important tool for health policy decision makers. In the U.S. the Advisory Committee on Immunization Practices (ACIP) is responsible for making vaccine recommendations and as such they formally conduct and include CEAs along with other types of evidence to formulate their recommendations. With regard to vaccine policy, it has been suggested that to make cost-effectiveness analysis a more practical tool, analysts should evaluate investments across multiple diseases and interventions and include the influences of nonmonetary constraints (J. J. Kim, 2011). Assessing and implementing effective evidence based interventions has relevance for payers, providers, and policymakers. CEAs are just one of the tools which can be used to aid in informing interventions to reduce the time it takes from evidence to adoption to implementation in order to quickly and efficiently improve population health outcomes.

Herpes Zoster is a Risk Factor for Stroke

HZ infection is increasing among all age groups for unknown reasons (Kenneth E Schmader & Dworkin, 2017). Herpes Zoster Virus (HZV), also known as shingles, is caused by a reactivation of the varicella zoster virus (VZV), commonly known as chickenpox. After initial infection with chickenpox the virus hides in the central nervous system allowing for potential

future reactivation of the virus as HZV. HZ is an inflammatory neurological infection affecting approximately 1 million people every year causing an estimated 96 deaths. HZ is characterized by a painful blistering rash that develops over 5 to 7 days and can be accompanied by prodromal pain and/or tingling sensations. The itching, burning rash appears unilaterally and does not ordinarily cross the spine or midline of the abdomen, typically affecting one to three dermatomes (Kenneth E Schmader & Dworkin, 2017).

Approximately 95% of all people living today have been infected with VZV and an estimated 25-35% of those are at subsequent risk of reactivation of the virus as HZ (Warren-Gash et al., 2017). After age 50 the risk of HZ infection increases, there are presently about 42 million 50-59 year olds in the U.S. and approximately 25% of HZ cases occur in this age group (Johnson et al., 2016b). Lifetime risk of HZ in the United States is approximately 1 in 3 and while most people will have it only once it is possible to get the virus two or three times over a lifetime after initial infection with chickenpox, long-term studies show a 5-6% risk of recurrence (Kawai, Gebremeskel, et al., 2014). Several studies report significantly higher incidence of HZ in adult women across all age groups (Johnson et al., 2015; Sundström et al., 2015), thus female gender is considered a risk factor for HZ (de Boer et al., 2014). One in 4 people with herpes zoster are hospitalized due to complications which can range from mild to severe depending on the patient's underlying immune status and other health risks (Centers for Disease Control and Prevention, 2016c).

VZV is the only known virus with the capacity to produce pathologic vascular changes associated with stroke through infection of the cerebral arteries (Nagel & Gilden, 2015). HZ is the single most common infection of the nervous system in the U.S. (Warren-Gash & Breuer,

2017). There is accumulating evidence of an increased risk of stroke within one year of HZ infection (Kang, Ho, Chen, & Lin, 2009a; Langan, Minassian, Smeeth, & Thomas, 2014a; Lian, Zhu, Tang, Yang, & Duan, 2017; Liu et al., 2016; Marra, Ruckenstein, & Richardson, 2017a; Minassian et al., 2015; Yang et al., 2017; Zhang, Yanting; Luo, Ganfeng;Huan, Yuanwei; Yu, Qiuyan; Wang, Li; Li, 2017a).

Although the incidence of stroke increases with age, it can strike at any time. In 2009, 34% of people hospitalized for stroke were under age 65 (Centers for Disease Control and Prevention, 2016d). There are an estimated 795,000 strokes per year in the U.S. and more than 75% of those are primary strokes. Stroke is a significant cause of disability with costs estimated at $33 billion per year including cost of health care, medication, and lost productivity (Centers for Disease Control and Prevention, 2016d). Stroke occurs when the blood flow to the brain is interrupted, ischemic stroke (IS) results from an obstruction such a clot in a blood vessel leading to the brain while a hemorrhagic stroke (HS) results from a ruptured or broken blood vessel in the brain (Centers for Disease Control and Prevention, 2016). IS represents 87% of all strokes in the U.S. with HS comprising the remaining 13% (Benjamin et al., 2017). CVD is a significant cause of stroke and the AHA projects that by 2030, 43.9% of the U.S. population will have some form of CVD. Stroke is the leading cause of serious long-term disability with annual costs (direct and indirect) of $33.9 billion (Benjamin et al., 2017). IS is among the leading causes of death, disability, hospitalization and healthcare expenditure in the U.S. (Mu et al., 2017).

Risk of stroke associated with HZ is thought to be mediated through vasculopathy resulting from active VZV infection in the cerebral arteries. VZV is the only human virus known to infect cerebral arteries and VZV can reactivate from the dorsal root ganglia and infect cerebral

arteries without spreading to the skin (Nagel & Gilden, 2015). Nagel and Gilden suggest that the frequency of stroke after HZ is likely underestimated because VZV can reactivate without evidence of rash, therefore there may not be a HZ diagnosis (2015). Several studies have identified HZ as a risk factor for stroke and Sreenivasan and colleagues identified evidence of long-term risk of stroke in people who develop HZ before age 60 (Kang et al., 2009a; Langan et al., 2014b; Minassian et al., 2015; Sreenivasan et al., 2013).

In 2006 the FDA approved a live-attenuated vaccine (Zostavax ®; Merck) for the prevention of HZ in adults ≥ 60 years with an expanded approval for adults age 50-59 years in 2011. Zostavax® was initially studied in adults ≥ 60 in the Shingles Prevention Study (SPS) and demonstrated a 51% reduced risk of HZ infection in that population. Protection against infection was greatest in patients 60-69 years of age with 64% efficacy, then declined in patients 70-79 years of age to 41%, and in patients ≥ 80 vaccine efficacy was 18% (Oxman et al., 2005). Efficacy of Zostavax® was studied in patients 50-59 years of age in the Zostavax Efficacy and Safety Trial (ZEST) and demonstrated reduced risk of developing HZ by 69.8% (Kenneth E Schmader et al., 2012).

In 2015, HZ vaccination uptake in the universally recommended adult population of ≥ 60 finally achieved the modestly set Healthy People 2020 (HP 2020) goal of 30%, which is the lowest target rate for all recommended adult immunizations (U.S Department of Health and Human Services Office of Disease Prevention and Health Promotion, 2017; Williams et al., 2017). The most recent data on HZ vaccination among the ACIP universal age based population report rates of approximately 30.6% for ≥ 60 years and 34.2% for those ≥ 65 years, with the lowest rates in the 60-64 age group at 21.7% (Williams et al., 2017). The lower rate in adults 60-

64 is of interest because that age group is predominantly covered under commercial insurance (active in the workforce) compared to those over 65 where the vaccine is considered a pharmacy benefit under Medicare. Significant racial and ethnic disparities for HZ vaccination persists with immunization coverage being highest among whites for all age groups (Williams et al., 2017). Data on rates of HZ immunization for those under age 60 are less reliable because the ACIP does not recommend the vaccine for this age group. The most recent data collected by the CDC using the 2014 Behavior Risk Factor Surveillance System (BRFSS) reported coverage of 5.9% among adults age 50-59 years and cited that the lower coverage compared to other groups may be partially due to lack of an ACIP official recommendation (P.J. Lu et al., 2017).

CEA for HZ are highly dependent on the age of vaccination and presumptions about duration of protection (durability) of the vaccine (Kawai, Preaud, et al., 2014). The ACIP recommendations for use of Zostavax® have heavily relied on cost-effectiveness results from patient's ≥ 60. Information on duration of protection and cost-effectiveness of HZ vaccination in persons age 50-59 years are limited and studies in this population have not demonstrated cost-effectiveness based on the accepted wiliness-to-pay threshold of $50,000 - $100,000 (Le & Rothberg, 2015; Rothberg, Virapongse, & Smith, 2007). Risk of stroke associated with HZ infection has not been considered in current ACIP recommendations. ACIP does not presently provide any guidance or recommendations around HZ vaccination for adults at increased stroke risk at any age.

Increasing Cardiovascular Disease in an Aging Population

The 2017 AHA Heart Disease and Stroke Statistics update reports the prevalence of CVD in adults ≥20 years is 36.6% and project that by 2030, 43.9% of the U.S. population will have

some form of CVD (Benjamin et al., 2017). These data only represent those who have active diagnosed cardiovascular diseases (atherosclerosis, chronic heart disease (CHD), heart failure (HF), prior MI or stroke, etc.) and does not begin to consider the millions more Americans with one or more risk factors for CVD. The Framingham Risk Scoring criteria estimates risk of developing CVD or some component of CVD (such as coronary heart disease, stroke, peripheral vascular disease, or heart failure) over a fixed time period by assessing risk factors such as sex, age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking behavior, and diabetes status and uses these "risk scores" to recommend interventions (D 'Agostino et al., 2013). Stroke is the leading cause of serious long-term disability in the U.S. with annual costs of estimated at $33 billion per year including cost of health care, medication, and lost productivity. Lost productivity associated with HZ and stroke is greatest in the working population of adults under age 65 making effective interventions even more beneficial in this population.

Risk-based Targeted Vaccination Strategies

A recent CEA of a targeted HZ vaccination strategy in adults age 50-59 years that are at increased risk of ischemic stroke associated with CVD may be the first to assess the increased risk of stroke within one year of HZ infection. CEAs lean toward supporting targeted vaccine programs aimed at persons with the highest risk of disease because they yield the greatest return based on disease averted calculated on cost per dose administered. Universal strategies in conjunction with targeted strategies have been shown to be most effective in reducing disease (Balicer et al., 2014; Hardt et al., 2016). Unlike influenza and pneumococcal viruses, HZ is non-communicable therefore traditional herd protection afforded by universal vaccination does not convey the same public health benefit (Centers for Disease Control and Prevention, 2016b).

Selecting a targeted approach to HZ vaccination has several strengths. First universal vaccination strategies are expensive and hard to implement and to date have shown very modest uptake in the universal population. Second, interventions strategies can be efficiently geared to identify at risk populations who tend to have more frequent contacts with healthcare providers. Finally and perhaps most importantly a targeted HZ vaccination program in at risk adults could serve as a primary IS risk intervention, not unlike statin use, a primary prevention for those with prevalent CVD and a secondary intervention for those who have had a prior event (stroke, MI). Risk based intervention strategies targeting groups with certain co-morbidities have been proven effective in improving influenza and pneumococcal vaccine rates (Task Force on Community Preventive Services, 2005). Vaccination of risk based groups has historically been intended to identify groups or individuals who are at increased risk of disease based on their clinical co-morbidities, age, occupation, lifestyle or living conditions and for those whom the risks associated with preventable diseases could present serious complications and increased risk of death (Paolo Bonanni, 2007).

Vaccines are Safe and Effective but Underutilized

The contribution of vaccines to the reduction of infectious diseases and disease mortality is indisputable and has far reaching externalities beyond positive economic outcomes for healthcare delivery and society as a whole (Rémy, Zöllner, & Heckmann, 2015). Vaccination has been declared as the number one greatest public health advancement of the 20th century but adult vaccines are still drastically underutilized (Health and Human Services National Vaccine Advisory Committee, 2012; Centers for Disease Control and Prevention, 1999). Vaccines are often seen as a victim of their own success because as the threat of serious vaccine-preventable diseases diminish resulting from effective childhood vaccination programs individual risk

perceptions among adults decreases. The value of vaccines for adults is not merely derived from their role in prevention of disease but in long-term disease associated sequelae generating indirect impacts greater than disease prevention alone and methods to measure these impacts need to be adapted to these externalities (P Bonanni et al., 2014).

Fear of adverse outcomes or illness caused by vaccination, inconvenience (including cost), and lack of awareness of the need for vaccination are some of the reasons for under-vaccination of special populations (Doherty et al., 2016). Older adults are often unaware of the need for vaccination as a result of ineffective communication of vaccine recommendations to patients and providers or lack of specific recommendations and guidance from policymakers for at risk populations. Factors associated with vaccine uptake among older adults are; attitudes and beliefs around vaccination, strength of provider recommendations, vaccine safety and efficacy, and individual risk perception of disease susceptibility (Doherty et al., 2016).

The first comprehensive National Adult Immunization Plan (NAIP) was released in 2016 with the goal of improving adult immunization rates through public health and population health approaches in alignment with the established HP 2020 objectives (U.S. Department of Health and Human Services National Vaccine Program Office, 2016a). The plan structure is founded on four key goals, each with specific strategies and objectives to reach those goals to improve vaccine adoption across the lifespan (see Figure 6). The first and primary goal of the plan is to strengthen the adult immunization infrastructure and a key objective in that effort is to "generate and disseminate evidence about the health and economic impact of adult immunization, including potential diseases averted and cost-effectiveness with the use of current vaccines" (U.S. Department of Health and Human Services Vaccine Program Office, 2016, p.16).

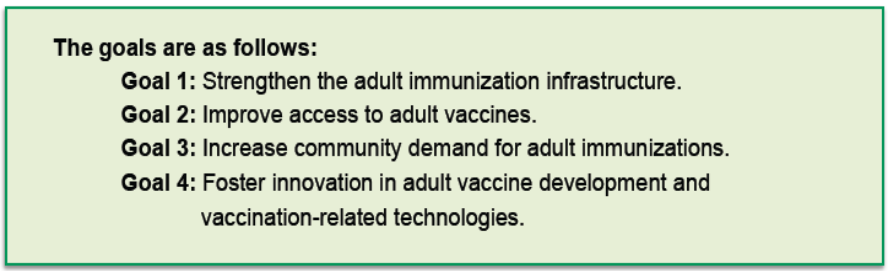

Figure 6**:** NAIP Goals

(U.S. Department of Health and Human Services National Vaccine Program Office, 2016a)

Currently there is very limited data on the economic impact of adult immunizations, the NAIP calls out the need for this information as a "critically important element of the plan" (U.S. Department of Health and Human Services National Vaccine Program Office, 2016a).

Barriers to Adult Immunization

There has been much discussion and review for decades about factors associated with low adult immunization uptake. The NAIP was developed after a comprehensive review of the current state of the research around barriers to adult immunization with specific consideration of the changing policies and practices in the healthcare delivery environment, such as the affordable care act (ACA) and pay-for-performance metrics. A formal environmental scan was conducted as part of the NAIP to review all adult immunization recommendations and reports issued between 2005 and 2015 (U.S. Department of Health and Human Services National Vaccine Program Office, 2016a). The environmental scan included a stakeholder survey to identify current perceptions of barriers to adult immunizations (Department of Health & Services National Vaccine Program Office, 2016, p. 11). The goals of the plan have been developed around addressing these specific barriers (see Figure 7). Unlike pediatric vaccinations,

administration of adult immunization is complicated by many variables including varying age ranges for delivery of adult vaccines and variables such as different recommendations by age determined by a variety of risk factors. Adults also tend to see a larger variety of care givers and many do not have a defined medical home which complicates coordination of care. Disjointed care delivery also impacts appropriate record keeping for adult immunization status. The environmental scan included surveys and feedback from a variety of stakeholders, including payers, employers, research organizations, healthcare providers, and professional associations. Successful implementation of the plan will rely on contribution, coordination, and collaboration from a wide variety of private and public entities.

Identifying and Tracking Appropriate Patients. Identifying and tracking adult immunization status impacts appropriate delivery of vaccinations. Reducing missed opportunities to immunize adults each time they see a healthcare provider can significantly improve delivery of adult immunizations (National Vaccine Advisory committee (NVAC), 2014). A key challenge is for the provider to have adequate patient immunization history at the site and time of patient care. In addition, many opportunities to vaccinate are missed because vaccination status is not routinely being evaluated at every physician visit or healthcare provider encounter (Hurley et al., 2014). Immunization Information Systems (IIS) also referred as "registries" are "confidential, computerized, population-based systems that collect and consolidate vaccination data from vaccination providers that can be used in designing and sustaining effective immunization strategies" (Frieden, Jaffe, Stephens, & Thacker, 2012, p. 1005).

Barriers to Adult Immunization

- Lack of coordination of adult immunization activities across all stakeholders, including multiple health care providers for adults
- Lack of integration of vaccines into adult medical care
- Lack or underuse of administrative systems (e.g., immunization information systems [IIS]) for documenting vaccination histories and identifying patients who are due for vaccinations in medical records
- Skepticism regarding vaccine safety and effectiveness
- Inability to pay for vaccination as a result of lack of insurance or variable coverage for recommended vaccinations across health plans
- Provider concerns about reimbursement and vaccine administration fees paid by health insurers, which discourages some providers from stocking all adult vaccines
- Lack of public knowledge regarding the adult immunization schedule and the risks and consequences of vaccine-preventable diseases; lack of awareness that adults are supposed to receive vaccines other than the influenza vaccine
- Legal barriers at the state and federal levels (e.g., restricting which providers can administer vaccines)
- Lack of and/or weak recommendations by health care providers
- Limited use of evidence-based strategies to improve vaccine uptake, such as reminder-recall and related systems
- Conflicting and inaccurate information about immunizations in mass media

Figure 7: Barriers to Adult Immunization

As of 2012, the CDC reported most all states had an IIS with the exception of the District of Columbia (DC) and New Hampshire and only two states were not collecting adult immunization data as of 2012 (Connecticut and Rhode Island) (Frieden, Jaffe, Stephens, & Thacker, 2012). IIS's have been an important technological tool to maintain patient level immunization data. A limitation for adults' inclusion in registries is that adults are just now being migrated into the systems as they receive vaccines and prior vaccination histories for adults are not captured in these registries. The adoption of IIS reporting by other health care providers such as pharmacists has greatly assisted in the ability to communicate immunization status of adults between various providers since adults are more likely to seek care from more than one provider (Frieden et al., 2012). In many cases use of IIS is a mandatory requirement for alternate providers such as pharmacists.

In 2010 the Community Preventive Services Task Force (CPSTF) recommended the use of immunization information systems on the basis of "strong evidence of effectiveness in increasing vaccination rates" (The Community Preventive Services Task Force, 2010). Specifically the report outlined 5 capabilities provided by IIS's that demonstrated effectiveness in improving immunization rates: (1) create or support effective interventions such as client reminder and recall systems, provider assessment and feedback, and provider reminders, (2) determine client vaccination status for decisions made by clinicians, health departments, and schools, (3) guide public health responses to outbreaks of vaccine-preventable disease, (4) inform assessments of vaccination coverage, missed vaccination opportunities, invalid dose administration, and disparities in vaccination coverage, and (5) facilitate vaccine management and accountability (The Community Preventive Services Task Force, 2010).

A limitation of IIS's is that they are state based systems and do not have capacity to share immunization data between states and technical limitations exist for ease of transfer of data within and between health systems and providers. In 2012 in an effort to address appropriate use of IIS's among all age groups the National Center for Immunization and Respiratory Diseases (NCIRD), a division of CDC introduced a strategic plan to facilitate that "real time, consolidated immunization data and services for all ages are available for authorized clinical, administrative, and public health users, and consumers, anytime and anywhere" (Centers for Disease Control and Prevention, 2015a). This project aims to maximize the use of health information technology through bi-directional information sharing between providers and state immunization registry databases allowing patient immunization records to cross populate between the registries and electronic health record systems. This enhanced capacity will allow for greater provider access to patient immunization status in order to more efficiently identify patients who have not received all recommended vaccinations. Interoperability between immunization registries and health care providers as well as complimentary immunization providers such as pharmacy's will greatly assist in the identification of patients in need of immunization and over time as the databases become more robust they can have great utility to identify coverage trends and provide other epidemiologic surveillance data.

Role of Vaccine Recommendations. Non-economic factors associated with barriers to adult immunization include activities facilitated within the provider's office. As noted by the NAIP survey, lack of awareness of the need for adult immunizations, lack of a strong recommendation from a health care provider, and limited application of technology to support patient identification, physician flags, and reminder recall systems are a subset of barriers in and of themselves. One could also argue that skepticism about safety and efficacy, lack of public

knowledge about adult immunizations, and the role of media influences also have a place within the purview of the health care provider environment.

Prior to the NAIP environmental scan, a multitude of studies had cited the importance of a strong provider recommendation as a key factor in improving adult immunizations rates (Hurley, Lindley, Harpaz, Stokley, & Daley, 2010; Bridges et al., 2015; Hurley et al., 2010). Strength of provider recommendation along with same day delivery of vaccination has been demonstrated as a proven strategy to improve adult immunization rates (National Vaccine Advisory committee, 2014). Factors which affect the strength of provider recommendations range from the lack of awareness on the part of the provider to a significant number of providers who do not stock routinely recommended vaccines for adults. If a physician is not stocking vaccines, they are far less likely to make recommendations or refer patients for ACIP recommended vaccines. Recent national recommendations including the 2014 National Vaccine Advisory Council (NVAC) report provides vaccine recommendation standards for all providers, including those who do and do not stock and or administer vaccines (National Vaccine Advisory committee, 2014).

Disparities Associated with Adult Immunizations. Racial and ethnic disparities continue to persist in adult immunization coverage statistics. The 2014 NHIS found that for all seven vaccines evaluated, whites generally had higher immunization rates compared to other groups and rates were generally higher among those who reported having a regular place where they received their health care services (Williams et al., 2016). The gap in racial and ethnic disparities for children has been narrowing and in aggregate significant disparities do not exist. Possible factors contributing to better coverage among racial and ethnic groups for children are increased awareness of pediatric vaccines, better coverage programs for those who are un-insured or under-

insured (vaccines for children (VFC) program), and school entry requirements (P. Lu et al., 2015). Identifying and removing barriers that specifically impact racial and ethnic minorities can help improve immunization rates. For example from 2007 to 2012 when the availability of influenza vaccination in multiple settings was increased, gaps in influenza vaccination coverage reduced slightly in non-Hispanic blacks and Asians compared to non-Hispanic whites (Lu et al., 2015, p. S423). Lu et al., recommend additional assessment of racial and ethnic disparities beyond data collected from National Health Interview Survey (NHIS) is needed (2015).

Role of Healthcare Coverage for Adult Immunizations. Lack of insurance coverage is a well-documented barrier to adult immunization coverage (Lu, O'Halloran, & Williams, 2015; Williams et al., 2016). For example in 2015, Lu, O'Halloran, and Williams reported that pneumococcal coverage for at risk adults between 18-64 years of age, for whom vaccination is routinely recommended, was 9.8% for uninsured compared to 23% for insured patients and influenza coverage rates were 14.4% versus 44.3% for uninsured versus insured (P.J. Lu et al., 2015). Coverage for all ACIP routinely recommended vaccines was included as part of the ACAs essential health benefits which requires insurers to cover services within 10 benefit categories with limited out of pocket costs or no cost sharing for certain primary prevention interventions to facilitate improved population health. With the threat of "repeal and replace" this benefit may become a casualty of the current administration's efforts to dismantle ACA.

Costs and Coverage for Adult Vaccines

Reimbursement for immunizations can be complex, even in the ACA era. The NAIP identified several barriers associated with cost of immunizations, these included patient concerns about out of pocket costs and insurance coverage as well as provider concerns about

reimbursement. The provider catch-all concern over "reimbursement" belies the many variables associated with vaccine reimbursement. Vaccines are somewhat unique in how they are delivered at the physician office level, vaccines for privately insured patients are acquired by the provider on what is often referred to as a "buy-and- bill" modality. Providers must purchase vaccines from the manufacturer or a third party distributor. Timing of when vaccines are actually paid for by the provider varies, some have delayed billing cycles with manufacturers and other vendors which allows time to get insurance reimbursements for administered vaccines, and some must pay for vaccines up front and wait for insurance reimbursement. In either scenario there are typically very large cost expenditures on the part of the physician to stock vaccines. Additionally, the more vaccines the provider stocks the more costly and challenging managing the vaccine inventory becomes. As more vaccines are added to the adult immunization schedule, the cost of providing all recommended vaccines continues to increase at the provider level. Hurley et al., identified insufficient stocking of all routinely recommended vaccines as a barrier to improving adult immunization rates (2014).

Private patient insurance coverage for the "cost" of the vaccine can vary and in many cases can be less than the cost the physician pays to purchase the vaccine, known as "acquisition cost". There are variable reasons for this, one can be price increases from the manufacturer which take time to get re-adjusted by the insurance provider or it may be an issue of contract negotiation between providers and payers. Providers consistently reference their overall cost of vaccines as a barrier (Bridges et al., 2015; Hurley et al., 2014). Providers have to manage the cost of the actual administration of vaccines. These "indirect costs" can include; the durable goods costs associated with administering vaccines (alcohol prep wipes, band aids, gloves etc.), personnel costs for ordering vaccines and providing adequate storage and handling (quality

control), storage costs, insurance against inventory loss, cost from wastage, non- payment and shrinkage (product lost to theft, or administrative or vendor errors), and lost opportunity costs (cost associated with maintaining a vaccine inventory) (American Academy of Pediatrics, 2012).

In most provider's offices vaccines are administered by a nurse or a medical assistant, rarely are vaccines ever administered by the physician. Most vaccine reimbursement arrangements have a provision to cover the cost of administration, however the standard reimbursement rate has not increased substantially over time and is typically far below the actual "real" cost associated with administration (athenahealth, 2011). Vaccines must be stored at specific temperatures and those temperatures must be monitored daily to ensure vaccine potency. Most vaccines must be refrigerated and some like varicella and herpes zoster vaccines must be kept frozen. All vaccines must be kept separate from food and other non-vaccine items so typically this requires a separate refrigerator and freezer (freezers must meet stringent temperature control requirements so a refrigerator/freezer combo is often unacceptable for this purpose) (Centers for Disease Control and Prevention, 2017d). All of these account for real economic and administrative costs for providers.

Role of Alternate Providers in Delivering Adult Vaccinations

The role of community pharmacists in the delivery of adult immunizations has increased dramatically as more adult vaccines are approved and recommended for use. Since the early 1990's pharmacists authority to administer vaccines has been steadily increasing. Currently 46 states (including the District of Columbia and Puerto Rico) allow pharmacists to administer vaccinations. Authority varies by state as to whether or not pharmacists are permitted to administer immunizations without a prescription and which vaccines can be administered in the

pharmacy setting (American Pharmacists Association, 2015). Pharmacists are also actively participating in the use of state IISs partly due to the fact that in many states registry reporting was mandated as part of the legislation allowing vaccine administration authority. A challenge still remains for effective delivery of immunizations in the pharmacy setting due to the requirement for the pharmacy to be considered an "in-network" provider to process commercial insurance claims for patients. Efforts to close this gap are under way but there is still a long way to go to facilitate commercial insurance coverage in the pharmacy setting.

Population Health versus Public Health

The distinction between public health and population health is not well understood, even among academics. Moving away from fee-for-service toward value based healthcare delivery provider and payers are facing increasing focus on cost-containment while also attempting to achieve measureable improvement in health related outcomes. Understanding how a population health approach differs from a public health approach is particularly informative to the intervention strategies we select and how we go about adopting and implementing them effectively and sustainably.

The ACA has been a catalyst in moving the U.S. health care system from a public health approach to a population health approach and much of the evolution in health care policy reform is owed to Donald Berwick and the IHI for putting forth the Triple Aim, establishing focus and emphasis on improving the patient experience, reducing the cost of care, and perhaps most importantly focusing on improving the health of populations (D. Kindig & Isham, 2014). In 2008 Berwick addressed the need to improve U.S. healthcare delivery, stating "the remaining barriers to integrated care are not technical; they are political" (Berwick, Nolan, & Whittington, 2008).

The Triple Aim demonstrated how to put population health into action and established a framework for population health management.

Population health can be defined as health outcomes and their distribution in the population, and outcomes are achieved by patterns of healthcare determinants over the life course which are produced by policies and interventions at the individual and population levels (D. A. Kindig, 2007b, p. 141). Immunizations are recommended by a governing body (ACIP) and in some cases they are required (healthcare workers, school entry) so they can serve as a perfect example of where a healthcare intervention policy is directed at the individual but whose benefits of the outcome on the individual also accrue to the population (through herd immunity and reduced cost of treating disease), demonstrating a population health impact.

Prior to the implementation of the ACA, more than 50% of adult deaths where associated with preventable diseases and approximately 95% of U.S. healthcare spending was for the treatment of chronic illness, including many preventable diseases, compared to 5% budgeted for health promotion and prevention (Nash, David et al., 2011, p. 7-8). Nash et al., suggest that presented with this data most policy makers, regulators, and politicians recognize the need for preventive care (Nash, David et al., 2011, p. 8). However, the challenge has been actually getting policymakers, payers, and providers to prioritize and effectively implement preventive care strategies like adult immunizations. There are real challenges in how each of these three key stakeholders would go about putting prevention at the forefront of healthcare delivery and cost-effectiveness analyses are just one of the tools which can be employed to inform their decision making.

Without the tools and information to evaluate, measure, and translate outcomes from evidence-based public health interventions we are limited in our capacity to use that information to improve policies that drive improvements in population health. To emphasis the important role policymaking plays in improving health outcomes, Brownson, Chriqui, and Stamatakis cited the 1999 review of the 10 great public health achievements of the 20th century, of which immunizations was number one, and they note that each of those important public health advancements was influenced by a policy change such as seat belt laws or regulations governing permissible workplace exposures (2009).

Vaccine Quality Measures

Implementation of influenza and pneumococcal vaccination performance measures among high-risk individuals have proven effective in improving vaccination rates both in hospital and ambulatory settings (Jha, Wright, & Perlin, 2007; Pennant et al., 2015; Schmaltz, Williams, Chassin, Loeb, & Wachter, 2011). Adult vaccination quality measures could not only improve population health through improved patient outcomes but also reduce costs to the U.S. healthcare system. There are currently two national projects underway which could establish quality metrics to drive improved delivery of adult immunizations (Appleby, Hodin, Satcher, Schaffner, & Perfetto, 2016). The Medicare Access and CHIP Reauthorization Act (MACRA) of 2015, is part of the CMS payment reform aimed at shifting toward a volume based payment system which will require 90% of Medicare fee-for-service payments to be linked to quality by 2019, pushing financial risk to the provider level (Centers for Medicare and Medicaid Services, 2017). This program is designed to incentivize providers to drive quality of care while reaching positive health outcomes and thus provides an appropriate foundation to establish adult

immunization measures. Also, America's Health Insurance Plans (AHIP) and its member plans are collaborating with the Centers for Medicare and Medicaid Services (CMS), the National Quality Forum (NCF), national physician organizations, employers, and consumers on the Core Quality Measures Collaborative project to promote consensus on core performance measures (Appleby et al., 2016). As part of this collaborative, CMS has posted 7 proposed core measures which will go through a public notice and comment rule-making process before implementation (Centers for Medicare & Medicaid Services, 2017). It is particularly noteworthy that the currently proposed measures include pediatric vaccinations but make no mention of adult immunizations (comment periods have not yet opened).

Recommendations/Solutions

This analysis has outlined the challenges, barriers, and benefits associated with adoption of evidence-based effective and sustainable interventions to improve adult vaccine delivery specifically for HZ which has been FDA approved but not ACIP recommended for adults age 50-59 years. Based on recent evidence of significantly increased risk of IS within one year of HZ infection, across all age groups, and cost-effectiveness data supporting targeted HZ vaccination in adults age 50-59 years who are at increased CV risk, the most important place to begin putting forth recommendations and solutions to close the adult immunization gap is to successfully translate these findings from research into practice for payers, providers (and patients), and policymakers.

Focus must be maintained on identifying measurable outcomes and prioritization of intervention efforts which yield the greatest population health impact. The following recommendations are suggestions to assist payers, providers, and policymakers to evaluate

various actions, practice, and policy changes which have been shown to influence adult vaccine adoption and delivery. Many of these interventions cannot be effectively implemented without the coordination and collaboration between the various stakeholder groups.

Stakeholder Specific Recommendations

Payers

- Evaluate cost-effectiveness data in support of targeted vaccination in the at risk population paying particular attention to the attribution of stroke risk with rising population prevalence of CVD, specifically in those under age 65 with increased comorbidities and in those with CV risk factors.
- Conduct budget impact analyses evaluating per member per month (PMPM) costs of targeting at risk patients for HZ vaccination to establish intervention strategies. Which can be accomplished through;
    - Utilization of electronic health record patient identification flags.
    - Education to providers and patients about the increased risk of IS after HZ.
    - Utilize provider education venues and other established communication routes to inform and educate providers about increased risk of IS after HZ infection.
    - Generate patient directed information via electronic patient portals or print communications targeting at risk patients.
- Select appropriate cost-effective intervention strategies and create dissemination frameworks to support sustainable efficient implementation of those interventions.
- Collaborate with other stakeholders to evaluate opportunities to develop and link quality metrics to improvement of adult immunizations.
- Adopt a population health management perspective to prevention interventions.
- Establish in-network status for Pharmacies to allow them reimbursement for vaccine delivery.

Providers

- Participate in grand-rounds, CME and other educational opportunities to learn more about the HZ IS risk association to better evaluate individual patient's risks.
- Proactively communicate risk of IS after HZ to appropriate patients and back it up with a strong vaccination recommendation.
- Utilize electronic health record systems to integrate vaccination into routine workflow.
- Institute standing orders for HZ vaccination in at risk patients.
- Add HZ vaccination status to routine patient questionnaires at each visit.
- Incorporate evaluation of HZ vaccination status in conjunction with annual influenza vaccine strategies.
- Routinely educate patients about the risks of vaccine preventable diseases and the benefits of vaccination.
- Be prepared to provide same day vaccination or provide a referral to an alternate provider.

Policymakers

- Support continued ACA coverage of routine vaccinations with no out of pocket costs.
    - Support funding mechanism for the uninsured
- Evaluate the evidence of increased IS risk associated with HZ and consider possible policy changes which could impact improvement of HZ vaccine uptake.
- Collaborate with other stakeholder groups to include adult immunizations as a core metric in the Core Quality Measures Collaborative performance measures which are presently under development and do not address adult immunizations.

- Roles for Health and Human Services (HHS) and Centers for Disease Control and Prevention (CDC);
    - ACIP:
        - Evaluate adding a risk-based recommendation for this population giving specific consideration to ACA coverage which does not extend to vaccinations that are not explicitly recommended by ACIP such as HZ in adults age 50-59.
        - Review CEA data on targeted vaccination in at risk adults and consider updating vaccine and stroke risk resources to reflect this associated risk.
    - Generate education of HZ associated IS risk through PSAs and social media.
    - Evaluate opportunities to communicate the increased risk of IS through other vaccine specific education and patient engagement campaigns.
    - Update Pink book and Vaccine General Recommendations to reflect this data.
    - Establish and promote effective immunization information systems with inter-operability between providers, payers, and other vaccine delivery entities such as pharmacies.
    - Establish Healthy People HP 2030 guidelines including recommendations for HZ in at risk populations with benchmarks appropriately aligned to achieving population health goals to reduce adult vaccine preventable diseases.
- NCQA, CMS, AHRQ, NQF; support adoption of quality metrics to improve adult immunizations such as;
    - Include evaluation of adult immunization in Medicare star ratings.

    - Health effectiveness data and information set (HEDIS) measures for adult immunizations
    - Implementation of hospital based discharge metrics for age appropriate patients similar to those proved successful with pneumococcal immunization.
- National Quality Forum (NQF); promote information of increased stroke risk with HZ and support adoption of performance measures to improve adult vaccine delivery.
- National Adult Immunization Plan (NAIP); update plan to include HZ increased stroke risk information and cost-effectiveness of targeted vaccination in at risk patients.
- NHLBI (National Heart Lung and Blood Institute)
    - Update stoke guidelines to include information on risk of IS and HZ.
    - Provide education and direction to providers on how to identify and recommend HZ vaccination in appropriate patients.
- Medical society and vaccine advocacy groups endorsements, recommendations, and education. Examples include;
    - Immunization Action Coalition; develop educational resources and communicate risk of HZ and IS.
    - American College Physicians (ACP); update adult immunize resources to communicate risk of HZ and IS.
    - National Foundation for Infectious Diseases (NFID); Update resources and develop educational programs to inform members of associated risk of HZ and IS and encourage efforts to identify, promote, and deliver HZ immunizations to at risk populations.

Discussion

Healthcare systems are under increasing strain to provide high quality care while maintaining healthcare costs. Establishing stakeholder awareness of the elevated risk of IS associated with HZ infection and the cost-effectiveness of a targeted intervention strategy is an important step in promoting primary prevention through vaccination of at risk adults.

Many government agencies, organizations, and interest groups have established recommendations for addressing the gaps in adult immunizations and an effective population health management approach requires that we recall the fundamental difference between public health and population heath, which is a focus on measurable outcomes and the factors that influence them. Once selected, those measurable outcomes must be disseminated and implemented through efficient and sustainable intervention strategies requiring an in depth understanding of the determinants of implementation. The adoption and implementation of intervention strategies such as HZ vaccine recommendations for at risk populations and inclusion of adult immunizations in quality metrics are necessary to support efforts to promote primary prevention strategies, reduce healthcare costs, and improve population health.

SECTION IV: CONCLUSIONS AND RECOMMENDATIONS

Study Implications

Epidemiologic evidence of increased stroke risk after HZ infection and the cost-effectiveness of a targeted vaccination approach have been analyzed in the context of the various drivers and barriers to adult immunization adoption. Using a population health framework focused on measurable outcomes, these variables have been translated to provide intervention recommendations which can be achieved through changes in policy and practice.

The volume of new research findings can exceed capacity to effectively evaluate their utility in a timely and cost-effective manner. Closing the gap between evidenced-based research and practice requires effective and sustainable dissemination and implementation intervention strategies. Translational researchers seek to identify the most beneficial and cost-effective evidenced-based strategies to improve population health. Tools like CEAs using simulated cohorts are a good way assess the various values associated with multiple intervention options in order to most efficiently identify those strategies that are likely to have the greatest likelihood of adoption by payers, providers, and policymakers.

Study Strengths and Limitations

This analysis is subject to several limitations. First, while there is now substantial literature on the HZ associated risk of IS, there was no available U.S. based specific data for IS risk after HZ representing adults 50-59 years of age using a private payer approach. The study

conducted by Minassian and colleagues was selected because it most closely resembled the simulated cohort and was pre-specified to assess risk of IS related to HZ. As this study was in a Medicare population of adults ≥ 65, IS risk data was adopted from the stratified 65-69 year old population to most closely approximate the risk in the simulated 50-59 year old cohort. Second, the CVD prevalence data was pulled from the larger 40-59 year old population since data on 50-59 year olds is not available. However this analysis has several strengths, some of which were not represented in prior CEAs for the 50-59 year old group. Updated incidence, disease burden, duration of vaccine efficacy, and direct healthcare utilization costs associated with HZ specifically in the 50-59 year old population have recently been reported and were updated for this analysis (Baxter et al., 2017; Johnson et al., 2015, 2016a). Additionally, recently published third-party payer direct costs associated with IS were also incorporated into this analysis (Mu et al., 2017). CV risk was assessed using CVD prevalence data which only represents those who have active diagnosed cardiovascular diseases (atherosclerosis, chronic heart disease (CHD), heart failure (HF), prior MI or stroke, etc.) and does not begin to consider the millions more Americans with one or more risk factors for CVD. This point is significant given that the current prevalence of CVD in adults ≥ 20 years is estimated 36.6% and it is projected that by 2030, 43.9% of the U.S. population will have some form of CVD (Benjamin et al., 2017). By these measures this CEA represents a very conservative estimation of the population at increased CV risk. Furthermore, bearing in mind that these results demonstrated favorable cost-effectiveness in the 50-59 age cohort for whom rates of HZ and IS are lower than the ≥ 60 age cohort one could predict that increasing immunization rates in the present recommended cohort of adults ≥ 60 could provide substantial reductions in economic and disease burden associated with HZ and IS.

While this model provided the number of cases of both HZ and IS avoided in the targeted vaccination group based on a theoretical cohort, it was unable to specifically translate those results into reductions among the general U.S. population based on current HZ and IS incidence data. Future studies may benefit from adapting the results from the model cohort into real-word incidence reduction for the benefit of payer and policy decision makers, providing the capacity to consider interventions directly related to the potential impact on the real-world patient populations they serve.

Selecting a targeted approach to HZ vaccination has several strengths. First universal vaccination strategies are expensive and can be hard to implement and to date have shown very modest uptake in the universal population. Second, interventions strategies can be efficiently geared to identify at risk populations who tend to have more frequent contacts with healthcare providers which is further facilitated by the increased use of electronic health records. Finally and perhaps most importantly a targeted HZ vaccination program in at risk adults could serve as a primary IS risk intervention, not unlike statin use, a primary prevention for those with prevalent CVD and a secondary intervention for those who have had a prior event (stroke, MI). Risk based intervention strategies targeting groups with certain co-morbidities have been proven effective in improving influenza and pneumococcal vaccine rates (Task Force on Community Preventive Services, 2005). Vaccination of risk based groups has historically been intended to identify groups or individuals who are at increased risk of disease based on their clinical co-morbidities, age, occupation, lifestyle or living conditions and for those whom the risks associated with preventable diseases could present serious complications and increased risk of death (Paolo Bonanni, 2007).

Implications for Public and Population Health

A common public health point of view of universal age-based vaccination strategies is that they are more feasible and less resource intensive. This may be true for vaccine interventions which provide additional societal benefits through herd protection. However, HZ is non-communicable therefore; traditional thinking about benefits of vaccinating this population must be adapted to consider the individual risk from a population health perspective. HZ presents an interesting consideration in the realm of vaccination strategies which have always emphasized the benefits of herd protection. Because HZ arises from a virus that is already inside you and it is not communicable there are two significant strategies to be considered. First, primary prevention of VZV (chickenpox) can be obtained with pediatric and adolescent vaccination, over time this should reduce the susceptible adult population, so this approach fits into traditional thinking for public health interventions. Second, there is now an effective vaccine intervention to reduce risk of HZ in those who have already had chickenpox however unlike the public health approach to facilitate herd protection where the benefits accrue to the larger population HZ is non-communicable so the benefits of vaccination translate at the individual and population health levels. Specifically with the new information of increased risk of stroke in an aging U.S. population with increasing rates of CVD, implementing effective strategies that provide the benefits of primary prevention for HZ infection and potentially stroke, vaccination could also serve as a secondary CV intervention strategy for reducing additional stroke risk in those already at risk. This population health approach accrues benefits at both the individual and societal levels. By reducing stroke risk and improving disease related outcomes at the individual level the benefits of reduced disease and healthcare utilization translate to the population, thus promoting population health.

The most significant population health related outcome from this analysis is the need to establish greater awareness of the IS stroke risk associated with HZ infection and as such generate greater focus on improving strategies to reduce that risk through effective vaccination of all CVD risk groups. There are multiple factors which determine population health; healthcare behaviors, genetics, socio-economics, and when it comes to population health policy the actors for this range of factors is spread across the public and private sectors (government at all levels, employers, healthcare organizations, school boards, community organizations). There is no one actor or agent accountable and responsible for such broad population health outcomes as mortality, morbidity and disparities making intervention strategies difficult to translate across these varied stakeholders (D. A. Kindig, 2014). The National Adult Immunization Plan (NAIP) has the lofty goal of improving adult immunization rates through public health and population health approaches in alignment with the established Healthy People 2020 objectives (U.S. Department of Health and Human Services National Vaccine Program Office, 2016a). Success of the NAIP relies on multifaceted, multi-stakeholder, public-private partnerships to achieve its goal of improving adult immunization uptake and delivery.

The Role of Theory and Frameworks

Translating the results of this study by applying the population health framework required evaluation of the role of health determinants and policy interventions (at the individual and societal levels) as they related to the health outcomes this research was attempting to address. The outcome measure was to evaluate if targeting HZ vaccination in at risk adults could be cost effective and determining cost-effectiveness included evaluation of how much HZ infection and HZ infection related strokes would be avoided in the vaccinated versus unvaccinated cohorts. Once this data is gathered it is not enough just to report out those findings, they must be

considered in the context of health determinants and policy interventions that would influence meaningful change in practice to facilitate increased adoption of vaccination. As noted, achieving population health improvements requires the collaboration between multiple partners which was the purpose of the relationship between the recommendations and solutions provided in the white paper addressed three different stakeholder groups.

The population health framework approach is closely inter-related to implementation and dissemination models in that they are both seeking to improve adoption of evidence-based practices and reduce the time to adoption which improves overall population health. The recommendations and solutions for payers, providers and policymakers in the white paper were developed with the understanding of the need for a collaborative approach among the various stakeholders and how interventions are interdependent, for example without ACIP recommendation ACA coverage is not guaranteed, therefore ACIP recommendations must be implemented prior to expecting improvement in cost-related barriers to patient and provider level adoption. Understanding the roles various health determinants and policies play in influencing outcomes is necessary to developing recommendations for interventions which must then be effectively implemented and disseminated in order to achieve overall population health improvements. There is no one approach that works, it must be a thoughtfully considered collaboration with an understanding of implementation barriers and need for hierarchical intervention approaches in order to be sustainable and successful.

Impact of this research is perhaps greatest for the cardiovascular world. Given that a large proportion of strokes occur in adults under age 65 and projections are that the cost of treating stroke in this population will account for half of all stroke related expenditures by 2050, understanding stroke risk and cost-effective intervention strategies such as targeted HZ

vaccination in at risk adults can not only aid in development of appropriate intervention and prevention programs but subsequently reduce economic and societal burden associated with the anticipated increase in stroke incidence (Wang et al., 2014). Introducing a cost-effective, evidence-based primary prevention strategy to reduce stroke risk in a population with escalating CVD prevalence resents an excellent example of the application of translating research into practice in order to improve population health.

Implications for Commercial Payers

With the introduction of the triple-aim and changes in the marketplace driven by ACA and the shift from volume to value, healthcare decision making power is now largely consolidated at the payer level. Focus on population health management (PHM) at the payer level requires informed decision making to guide the prioritization of multiple competing priorities. Efforts to communicate and promote the economic and health benefits of primary prevention strategies must be aligned to the perspective of the payer and demonstrate measurable outcomes relative to cost. Decision analytic models like the one employed in this HZ target vaccination CEA can be employed to inform managed care decision makers of the potential effects of costs relative to outcomes associated with the vaccination intervention strategy (Graham et al., 2016). Simulated decision analytic models provide a timely and cost-effective approach to evaluating multiple intervention approaches by providing insight to the number of cases of disease averted by the intervention and quantify how those interventions affect per member per month (PMPM) cost to the payer.

In this CEA of targeted HZ vaccination of at risk adults age 50-59 years the number of cases of HZ and IS avoided in each treatment arm were calculated in order to quantify the

disease burden avoided when the targeted strategy was adopted which was superior in cost-effectiveness terms. The targeted strategy resulted in 162 fewer HZ cases per 100,000, which translated to savings of $261,468 when then divided by 100,000 resulted in a cost of $2.61 per member per year which equates to .22 per member per month (PMPM). The targeted strategy resulted in 14 fewer strokes per 100,000 which translated to savings of $ 411,096 which when divided by the 100,000 cohort equated to a cost of $4.11 per member per year and .34 PMPM. Both PMPM calculations are within reasonably expected thresholds for managed care companies to consider such an intervention strategy. Translating these results in the form of budget impact analyses demonstrating the cost-effectiveness of this intervention strategy and its impact on PMPM costs can facilitate rapid decision making and support more timely adoption of evidence based intervention strategies. Expanded use of analytic models to demonstrate the value and benefits of adult immunization interventions through cost-effectiveness and budget impact analyses should be considered as they can play a significant role in aligning cost expenditures to anticipated outcomes and are a critical consideration for healthcare decision making among policymakers and payers (Bang & Zhao, 2014).

Vaccination is generally believed to provide important public health benefits that also translate into positive economic outcomes which can significantly reduce the costs of treating disease (Rémy et al., 2015). Vaccination has also made significant contributions to the sustainability of healthcare systems by reducing the burden of infectious diseases and the resource use associated with them (Largeron, Lévy, Wasem, & Bresse, 2015).

Implications for Policy

The adult immunization barriers identified in this analysis could be addressed through various policy approaches, some at the "big P" policy level such as formal laws, rules and regulations implemented by elected officials and some could be addressed through "small p" policies such as organizational guidelines, agency or system level decisions and social norms that guide behavior like education (Ross Brownson, Chriqui, & Stamatakis, 2009). The translation of these study findings into recommendations for each of the three key stakeholder groups includes both "big P" policies such as ACIP recommendations and "small p" policies such as patient recall and reminder interventions at the provider level. However, they are interdependent on each other, a change in recommendation by the ACIP is not sufficient unless "small p" policies changes are adopted to assure the practical compliance with "big P" policies. The policy making process is multifaceted and policies must not only be "technically sound, but also politically and administratively feasible" (Ross Brownson et al., 2009, P. 1578). Kindig states that one of the most critical issues facing us today is finding political and ideological common ground for improving population health (D. A. Kindig, 2015a). This is particularly important when successful adoption of intervention strategies relies on collaboration between multiple stakeholders.

The National Quality Forum report on addressing performance measure gaps in adult immunizations tells us that quality metrics have to measure what matters most and our measures must be prioritized to strategically target those aspects of care that will promote the health outcomes we want to achieve. One of the challenges regarding measures for adult immunizations is that there is no one standardized measure utilized across the population health spectrum. CMS

Core Measures, HEDIS, Healthy People 2020 all establish performance measures for reaching adult immunization goals but the outcome goals are not unified nor are the metrics used to measure them. Additionally there is no hierarchy within these measures to assess them by level of importance or how achieving success in one area can facilitate success in another area of measure. There is no standardization across healthcare delivery segments (providers, hospitals, and payers) for adoption and implementation of quality metrics so it is difficult to optimize alignment of goals between these sectors.

Informed by CEAs, the inclusion of appropriate adult immunization performance measures could serve to directly and indirectly improve other heath measures through the benefits of primary prevention, thus providing a significant population health benefit. Efforts such as the NAIP are helpful to improve awareness of adult vaccination for primary prevention and the plan specifically identifies adult vaccine CEAs as an unmet need in the ongoing efforts to inform decision making among payers, providers and policymakers.

There are three areas where timely translation of these CEA results should be evaluated in the context of policy implications: First, the ACIP should evaluate this data and consider adopting risk based HZ vaccination recommendations or guidance for at risk adults. Second, the current Core Quality Measures Collaborative should evaluate this data to inform decision making around adoption of adult immunization metrics (which to date has not been considered). And finally the HP 2030 benchmarks are currently under development and they too should evaluate this information to inform achievable goals that are sufficient to promote population health.

Implications for Research

While it is very encouraging that this analysis using Zostavax® demonstrated cost-effectiveness not only for the targeted strategy but for the universal approach as well but perhaps even more encouraging is the recent approval and ACIP recommendation of a second HZ vaccine, Shingrix manufactured by GlaxoSmithKline for adults 50 years and over. Due to superior efficacy and anticipated longer duration of protection compared to Zostavax® the ACIP voted preferentially recommend the new vaccine for primary vaccination as well as re-vaccination in patients who previously received Zostavax® (Lowes, 2017). In terms of research implications this new vaccine is a game changer in the context of cost-effectiveness analyses. While the new vaccine is a two dose series, efficacy in the younger age cohort is almost 100% out to four years of demonstrated effectiveness. Comparing those variables to the base case values used in this CEA, it is highly probable that the CE of Shingrix in an at-risk population would outperform the results in this analysis.

Opportunities for timely evaluation of multiple parameters using this new vaccine are wide open and the current targeted CEA provides a strong foundation to develop additional simulation models to facilitate comparisons between the two vaccines and various intervention strategies and their respective cost-effectiveness. There are several parameters that would be of value to further investigate which were not included in the current analysis, one of which was gender differences in the incidence of HZ infection. The current CEA assumed equal gender distribution in both groups but the epidemiologic data report significantly higher rates of HZ in females, establishing female gender as an independent risk factor (Gilden, Nagel, Cohrs, & Mahalingam, 2013).

Conclusions

Every year in the U.S. there are approximately 200 vaccine-preventable deaths in children compared to 70,000 vaccine preventable deaths in adults, translating to a 350 fold difference. With the aging U.S. population the number of adults ill or dying of vaccine preventable diseases will continue to grow (Paolo Bonanni et al., 2017). Achieving high adult immunization coverage necessary to provided improved population health and health outcomes can only be reached through coordinated stakeholder engagement and universal support of vaccine policies and adoption of evidence-based intervention strategies.

This CEA assessing a targeted HZ vaccination strategy in adults age 59-59 years at increased CV risk increased total health expenditures in the target population by $30.59 per person, compared with $12.98 for the usual-care population. Additionally the incremental expenditure for a universal vaccination approach was considered cost-effective at $176.51 although this cost may not represent an acceptable intervention strategy relative to the value provided. The incremental cost to extend life by 1 QALY ranged from $55,470 - $55,523.00 for usual-care to universal coverage with vaccination being cost-effective in the target population at $55,517.24 per QALY which falls far below the established WTP threshold employed in prior HZ CEA.

The overall societal value of vaccination is often not captured in traditional health-economic measures of vaccine cost-effectiveness, socioethical contributions such as effects on health equity, sustaining the public good of herd immunity, and social integration of minority groups are often neglected in cost-effectiveness analysis (Luyten & Beutels, 2016). The value of preventing disease is hard to measure and even harder to promote in a way so that people can

appreciate the benefits of something they have never had to experience. This is perhaps what is most unique and challenging about efforts to communicate the benefits of vaccines to all appropriate stakeholders and decision makers. Schwartz and Mahmoud state in their 2016 publication "When not all that counts can be counted; Economic evaluations and the value of vaccination", that a better articulation of the value of vaccination could offer the potential for greater government attention and enthusiasm for vaccination programs (Schwartz & Mahmoud, 2016).

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Warren-Gash, C., Breuer, J., Warren-Gash, C., & Breuer, J. (2017). Herpes Zoster and Vascular Risk Abbreviations AIS Acute ischaemic stroke CI Confidence interval CPRD Clinical Practice Research Datalink EHR Electronic health record HR Hazard ratio HZ Herpes zoster HZO Herpes zoster ophthalmicus IR Incidence ratio IRR Incidence rate ratio MI Myocardial infarction PVD Peripheral vascular disease SAH Subarachnoid haemorrhage SVV Simian varicella virus THIN The Health Improvement Network TIA Transient ischaemic attack VZV Varicella zoster virus. Springer International Publishing Switzerland. http://doi.org/10.1007/978-3-319-44348-5_8

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APPENDICES

APPENDIX A: LITERATURE REVIEW

Herpes Zoster Epidemiology

Herpes zoster virus (HZV), also known as shingles is caused by a reactivation of the varicella zoster virus (VZV), commonly known as chickenpox. Rates of herpes zoster (HZ) infection are continuing to increase across all age groups despite the introduction of effective pediatric and adolescent vaccination programs for VZV (chickenpox) (Centers for Disease Control and Prevention, 2016c). Risk of HZ infection increases with age and those who have compromised or suppressed immune systems are at greater risk of infection and subsequent complications (Centers for Disease Control and Prevention, 2016a). HZ virus is an inflammatory neurological infection affecting millions of people every year and is characterized by a painful blistering rash. After initial infection with chickenpox, the virus becomes dormant in the dorsal root ganglia of the central nervous system. This latency allows for potential reactivation of the virus as HZ, which is thought to be brought on by advancing age or reduced immunity either through infection or increased stress to the immune system. Approximately 95% of all people living today have been infected with VZV and an estimated 25-35% of those are at subsequent risk of reactivation of the virus as HZ (Warren-Gash et al., 2017).

The HZ rash develops over 5 to 7 days and can be accompanied by prodromal pain and/or tingling sensations. The itching, burning rash appears unilaterally and does not ordinarily cross the spine or midline of the abdomen, typically affecting one to three dermatomes. The

annual rate of HZ in the U.S. is approximately 4 cases per 1,000 population which translates to about 1 million cases annually with a lifetime risk of developing HZ of 1 in 3 (Centers for Disease Control and Prevention, 2016c). While most people will have HZ only once, it is possible to experience the virus two or three times over a lifetime after initial infection with chickenpox. Long term studies show a 5-6% risk of recurrence (Kawai, Gebremeskel, et al., 2014). Risk of HZ increases with age and in people ≥ 60 the rate is about 10 cases per 1,000 annually (Centers for Disease Control and Prevention, 2016a). In 2015, Johnson and colleagues estimated rates of HZ in adults age 50-59 at 6.74 per 1,000 person-years (Johnson et al., 2015). Several studies report significantly higher rates of HZ in adult women across all age groups (Johnson et al., 2015; Sundström et al., 2015).

The most common side effect of HZ infection is post herpetic neuralgia (PHN), which occurs in 10-18% of patients and is defined as prolonged pain at the site of the rash lasting at least 90 days following fading of the rash. PHN can persist for many months to years and can be debilitating. A potentially serious complication of HZ is Herpes zoster opthamalmicus (HZO), which occurs when the virus infects the ophthalmic region of the trigeminal nerve (approximately 15% of patients) and can cause chronic complications, including pain and possible loss of vision (Centers for Disease Control and Prevention, 2016a). Secondary complications such as bacterial infections and transmission of the virus to other susceptible individuals can occur (although this is rare and transmission would cause the primary VZV, chickenpox, not HZ) (Kenneth E Schmader & Dworkin, 2017). Complications from HZ can range from mild to severe depending on the patient's underlying immune status and other health risks. Hospitalizations occur in 1-4% of those infected with HZ with an estimated 96 HZ- related deaths each year in the U.S. (Centers for Disease Control and Prevention, 2016c).

Herpes Zoster Vaccine

Currently Zostavax® (Merck) is the only vaccine available for the prevention of HZ virus. Zostavax® was initially studied in adults ≥ 60 in the Shingles Prevention Study (SPS) and demonstrated a 51% reduced risk of HZ infection in that population. Protection against infection was greatest in patients 60 - 69 years of age with 64% efficacy, then declined in patients 70 - 79 years of age to 41% , and in patients ≥80 vaccine efficacy was 18% (Oxman et al., 2005). Efficacy of Zostavax® was studied in patients 50-59 years of age in the Zostavax® Efficacy and Safety Trial (ZEST) and demonstrated reduced risk of developing HZ by 69.8% (Kenneth E Schmader et al., 2012). The Short-Term Persistence Sub-study (STPS) and the Long-Term Persistence Sub-study (LTPS), both conducted in patients ≥ 60, have shown the vaccine is effective in reducing incidence of HZ, PHN, and overall burden of illness (BOI) up to 10 years post- vaccination (Morrison et al., 2015; K. E. Schmader et al., 2012). Post licensure studies assessing the durability of the vaccine to prevent HZ infection alone, not in combination with PHN and overall BOI), have shown declining protection for Zostavax® with evidence of vaccine efficacy through 5 years after vaccination and uncertain efficacy beyond 5 years (Morrison et al., 2015; K. E. Schmader et al., 2012).

Stroke Epidemiology

Stroke is the 5th leading cause of death in the U.S., independent of other cardiovascular (CV) diseases, resulting in more than 133,000 deaths per year (American Heart Association & American Stroke Association, 2017). Although the incidence of stroke increases with age, it can strike at any time. In 2009, 34% of people hospitalized for stroke were under age 65 (Centers for Disease Control and Prevention, 2016d). There are an estimated 795,000 strokes per year in the

U.S. and more than 75% of those are primary strokes. Stroke is the leading cause of serious long-term disability and the economic impact of stroke is estimated at $33 billion per year including cost of health care, medication, and lost productivity (American Heart Association & American Stroke Association, 2017; Centers for Disease Control and Prevention, 2016d).

A stroke occurs when the blood flow to the brain is interrupted. An ischemic stroke (IS) results from an obstruction such a clot in a blood vessel leading to the brain while a hemorrhagic stroke (HS) results from a ruptured or broken blood vessel in the brain (Centers for Disease Control and Prevention, 2016). An estimated 87% of all strokes are ischemic (Mu et al., 2017). Rates of ischemic stroke have declined significantly in adults ≥ 60 between 2000 and 2010 while rates in adults 45-59 have remained essentially unchanged (Benjamin et al., 2017). Women have a higher lifetime risk of stroke although age-specific incidence rates are lower than men in younger and middle age groups but increase with advancing age. The prevalence of stroke survival among women is expected to increase as the population ages (Benjamin et al., 2017).

Stroke Risk Factors

The National Heart Lung and Blood Institute (NHLBI) identifies primary coronary heart disease (CHD) risk factors as; hyperlipidemia, hypertension, diabetes and pre-diabetes, obesity, smoking, lack of physical activity, unhealthy diet, stress, age, gender, and family history (National Heart Association, 2016). Age, gender, and a family history of CHD are the only risk factors considered outside the control of the individual. Atherosclerosis, plaque buildup in the arteries leading to CHD, is thought to be caused by hyperlipidemia, hypertension, and cigarette smoking along with any prior coronary event such as heart attack or stroke are also risk factors for a coronary event.

Cardiovascular disease (CVD) includes numerous conditions affecting the heart and blood vessels including, CHD, acute myocardial infarction (AMI), atherosclerosis, and stroke (American Heart Association, 2017). In the U.S. approximately 92.1 million adults have some form of CVD or residual stroke sequelae. CVD accounts for 1 out of every 3 deaths in the U.S. each year, and claims more lives than all forms of cancer and chronic lower respiratory diseases with combined costs of more than $316 billion a year (direct and indirect costs). Stroke can cause long-term disability with approximately half of all stroke survivors suffering moderate to severe disability with cost of care estimated at $18.8 billion per year (American Heart Association & American Stroke Association, 2017). Lost productivity and premature mortality are estimated at an additional $15.5 billion (Frieden, Jaffe, Stephens, & Thacker, 2012). Diabetes increases risk of stroke incidence for all age groups however, ischemic stroke patients with diabetes tend to be younger, are more likely to be black, have hypertension, hyperlipidemia, and prior history of myocardial infarction (MI) than non-diabetics (Benjamin et al., 2017).

HZ and Stroke Epidemiology

Evidence that HZ is a trigger for vascular events among certain populations is growing (Warren-Gash & Breuer, 2017) and may have first been described as early as 1896 (Nagel & Gilden, 2015). VZV is thought to be the only human virus that can replicate in cerebral arteries which can lead to productive infection causing vasculopathy and increased risk of ischemic and hemorrhagic stroke (Gilden, Nagel, Cohrs, & Mahalingam, 2013). The first studies to further investigate the association between VZV and vascular remodeling began in 1959 and more recent epidemiologic studies from three countries in Asia and Europe have established HZ as a significant risk factor for stroke (Nagel & Gilden, 2015). Nagel and Gilden suggest that the

frequency of stroke after HZ is likely underestimated because VZV can reactivate without evidence of rash, therefore there may not be HZ diagnosis (2015). The abundance of literature demonstrating HZ as a risk factor for stroke began appearing in 2009 predominately from cohort and case-controlled studies conducted in Taiwan, Demark, Sweden, United Kingdom (U.K.) and the U.S., each providing supporting evidence of a pronounced association between HZ and TIA's, MI's, and stroke within one year of infection with HZ (Breuer, Pacou, Gauthier, & Brown, 2014; Kang et al., 2009; Langan, Minassian, Smeeth, & Thomas, 2014; Nagel, Jones, & Wyborny, 2017; Sundström et al., 2015; Yawn, Wollan, Nagel, & Gilden, 2016). Recently meta-analyses of these prior studies have been published further confirming the temporal association reported in the individual studies reporting relative risks for first month post virus ranging from 1.55 to 1.94, and from 1.17 to 1.20 for 12 months post virus (Kang et al., 2009a; Lian et al., 2017; Liu et al., 2016; Marra et al., 2017a; Yang et al., 2017; Zhang, Yanting; Luo, Ganfeng;Huan, Yuanwei; Yu, Qiuyan; Wang, Li; Li, 2017b). Asserting that prior studies had not effectively accounted for confounding factors, Kim et al. (M.-C. Kim et al., 2017) conducted a propensity score-matched analysis using a Korean population database of over 570,000 people and reported confirmatory results from the previous analyses (2017). When adjusting for confounding this study reported a RR of stroke associated with HZ of 1.39 with a 95% confidence interval of 1.05-1.84 in adults 51-60, the study included additional age specific and CVD specific analyses (M.C. Kim et al., 2017).

Adult Immunization

Vaccination has been hailed as the most important public health advancement of the 20th century (Centers for Disease Control and Prevention, 1999). Vaccines for rabies, typhoid, cholera, and plague were developed before 1900 but had not been widely used. The period from

1900 to 1999 saw the most dramatic increase in not only the development of vaccines but also their widespread use (Centers for Disease Control and Prevention, 1999). Between 1900 and 1999 there were 17 vaccines developed and approved for use and as a result, it was during this period that we witnessed the eradication of smallpox. In addition, there was a 99-100% decline in the number of cases of diphtheria, pertussis, tetanus, paralytic poliomyelitis, measles, mumps, rubella (including congenital rubella syndrome), and haemophilus influenza type b (HIB) (Centers for Disease Control and Prevention, 1999). Early emphasis on pediatric vaccination significantly reduced disease burden in children, and perhaps that is why today the true BOI from vaccine preventable diseases is greater among adults than for children (Bridges et al., 2015).

Biologically adults are at greater risk of acquiring vaccine preventable diseases due to overall reduction in the effectiveness of the immune system as we age, known as immunosenescence, which also reduces the robustness of vaccine immunologic response in adults (Gruver, Hudson, & Sempowski, 2007). The CDC reports that each year influenza causes more than 200,000 hospitalizations and between 3,000-49,000 deaths the majority of those (more than 75%) affected are adults, in addition there are approximately 900,000 cases of pneumococcal pneumonia each year with up to 400,000 hospitalizations and 19,000 deaths (Centers for Disease Control and Prevention, 2016e). Lu et al., reports that in 2012 there were approximately 3,300 patient deaths from invasive pneumococcal disease, 95% of these cases were in adults (P. Lu et al., 2015). Several vaccine preventable diseases are increasing in incidence among adults. In 2012 of the reported 41,880 cases of pertussis (whooping cough), 9,000 were in adults, additionally there are about 1 million cases of herpes zoster reported each year (America's Health Insurance Plans, 2015). High rates of disease in adults, also increases

cost of health care and creates additional burdens on healthcare services and delivery. In a recent analysis of the economic cost of four adult vaccine preventable diseases (influenza, pneumococcal disease, herpes zoster, and pertussis) the estimated annual cost of treating these diseases in adults 50 years and older is approximately $26.5 billion (McLaughlin et al., 2015).

Immunization Recommendations

The Advisory Committee on Immunization Practices (ACIP) was established in 1964, under the direction of the Department of Health and Human Services (HHS) (Walton et al., 2015). For the last 50 years this body of experts has been responsible for establishing recommendations for vaccine use and monitoring their safety and effectiveness. In 1984 the first attempt at developing formal recommendations for adult immunizations was undertaken by the ACIP and the American College of Physicians (ACP) (Walton, Orenstein, & Pickering, 2015). This initial "Guide for Adult Immunization" highlighted the use of four adult vaccines, tetanus and diphtheria, influenza, pneumococcal, (at least one dose of each vaccine for all patients but at differing ages) and hepatitis B (for at risk individuals) (Centers for Disease Control and Prevention, 1984). At this same time, the childhood immunization schedule recommended the use of vaccines to prevent seven infectious diseases; diphtheria, measles, mumps, pertussis, poliomyelitis, rubella and tetanus (Eickhoff, 1985). The 1984 recommendation guide also included discussions on the success of pediatric vaccination and notable emphasis was placed on the underutilization of adult vaccines. Furthermore, there was additional guidance provided around the need to educate physicians and students about the importance of adult immunizations using a variety of medical education venues, including grand rounds, medical conferences, and consultation conversations (Eickhoff, 1985). Eight years later in February of 2002 the first ACIP schedule of routinely recommended adult immunizations for adults 19 years and older was

approved (Centers for Disease Control and Prevention, 2002). The schedule was established based on existing published recommendations from the ACIP, the American Academy of Family Physicians (AAFP), the American College of Obstetricians and Gynecologists (ACOG), the American College of Physicians – American Society of Internal Medicine (ACP-ASIM), and the Infectious Disease Society of America (IDSA) (Centers for Disease Control and Prevention, 2002). These new recommendations included the four vaccines previously recommended in the guide published in 1984, and added hepatitis A (for at risk persons), measles, mumps, rubella (MMR) (1 dose for those who had no documented history of vaccination and 2 doses for those with risk factors), varicella (for susceptible people), and meningococcal (for persons with specific indications). This schedule also included a separate table which specified recommended immunizations based on certain medical conditions, including pregnancy, diabetes, and human immunodeficiency syndrome (HIV), among others (Centers for Disease Control and Prevention, 1999a). When the approved schedule was printed in the Morbidity and Mortality Weekly Report (MMWR) in October of 2002 it also included recommendations for providers (family physicians, gynecologists, internists, and others) to assess vaccination opportunities during office visits and promoted the use of standing orders, patient reminder recalls, and provider reminder systems to decrease missed opportunities to assess vaccination status and administer appropriate vaccinations (Centers for Disease Control and Prevention, 2002, p. 905-906). Fifteen years later, these same recommendations to reduce missed opportunities continue to be a focal point in improving adult immunization rates.

The current 2017 ACIP recommended immunization schedule for adults 19 years and older includes routine recommendation for eight vaccines based on various age requirements. Vaccination against Influenza, Tetanus, diphtheria, pertussis (Td/Tdap), and varicella are

recommended for all persons 19 years and older (unless other risk factors preclude vaccination). Human papillomavirus vaccination is routinely recommended for adult females up to age 26 and for adult males 19-21 years and for males up to age 26 with at risk conditions. Herpes zoster is routinely recommended for all adults over age 60, and two different pneumococcal vaccinations are recommended for all patients age 65 and over (Centers for Disease Control and Prevention, 2017a).

Efforts to Improve Adult Immunizations

The Office of Disease Prevention and Health Promotion (ODPHP), a division of HHS, establishes the Healthy People 2020 (HP 2020) goals for immunization coverage and monitors progress annually based on results from the National Health Interview Survey (NHIS) conducted by the CDC. NHIS is an annualized household survey administered by the U.S. Census Bureau for CDC's National Center for Health Statistics using in person interviews. Questions related to immunization status are addressed to one randomly selected adult within each household (Williams et al., 2016). NHIS collects data on the following adult vaccines; hepatitis A, hepatitis B, human papillomavirus, herpes zoster, pneumococcal, Td, and Tdap. HP 2020 has established goals to improve rates for the following specific adult immunizations; pneumococcal, herpes zoster, and hepatitis B for health care personnel (U.S Department of Health and Human Services Office of Disease Prevention and Health Promotion, 2017). The most recent surveillance data from the 2015 NHIS concluded that adult vaccine coverage continues to remain low for most routinely recommended vaccines and current rates all fall below the HP 2020 goals (Williams et al., 2017).

Between 1990 and 2010 multiple reports and recommendations were aimed at improving adult immunizations from a variety of agencies including; the National Vaccine Advisory Committee (NVAC), the Institute of Medicine (IOM), the Trust for America's Health, and the Infectious Disease Society of America (IDSA), all aimed at improving adult immunizations, all with little to no impact or improvement (HHS National Vaccine Advisory Committee, 2012). Escalating focus on improving adult immunization rates began with the NVAC formation of the Adult Immunization Working Group (AIWG) in 2008. This group issued a report in 2009 outlining recommendations to improve adult immunizations (HHS National Vaccine Advisory Committee, 2012). In response to the report, the Assistant Secretary for Health (ASH) directed NVAC "to develop recommendations for establishing a comprehensive, sustainable, national adult immunization program that will lead to vaccine preventable disease reduction by improving adult immunization levels" (HHS National Vaccine Advisory Committee, 2012, p. 1). A series of reports, recommendations, and workgroups soon followed. In 2010, HHS released the National Vaccine Plan (NVP) which outlined goals for improving vaccination for all people between 2010 and 2020 (U.S. Department of Health and Human Services National Vaccine Program Office, 2010).

The National Vaccine Program Office (NVPO), a division of HHS is responsible for coordinating activities among various federal agencies with a range of responsibilities related to vaccines and immunizations (U.S. Department of Health and Human Services National Vaccine Program Office, 2017). It is the responsibility of NVPO to coordinate the activities and collaboration among these agencies in order to execute the strategies and goals outlined in the NVP. The NVPO is responsible for staffing NVAC, which was established in 1987 and is charged with oversight for recommendations for vaccine research and development, availability

and adequate supply, and direction for the prevention of vaccine adverse events. NVAC also makes recommendations to the ASH who also serves as Director of the NVPO on vaccine program related objectives (U.S. Department of Health and Human Services National Vaccine Program Office, 2017) Although all of these agencies have a role in making recommendations, setting priorities, and establishing goals and objectives for achieving improved prevention of vaccine preventable diseases through immunization, they lack any regulatory authority to require or mandate compliance with any of the recommendations set forth in the NVP.

Even after the release of the NVP in 2010, rates for adult immunization uptake continue to lag far behind rates which would be needed to achieve herd protection and far behind goals established by HP 2020. Herd protection, or "community immunity" is achieved when a sufficient number of people in a population are immune to a communicable disease, either from immunization or prior disease exposure, such that the disease can not be easily spread from person to person (US Department of Health and Human Services National Institutes of Health National Institute of Allergy and Infectious Diseases, 2010). In follow up to the 2009 AIWG report and at the request of the ASH, in 2012 NVAC issued updated recommendations for adult immunizations. The report titled "A Pathway to Leadership for Adult Immunization: Recommendations of the National Vaccine Advisory Committee" identified nine categories of barriers to adult immunization and developed specific recommendations to address them. The report also identified additional adult immunization gaps and addressed those by developing five categories of recommended actions; (1) general infrastructure needs, (2) expanded access, (3) provider or system based interventions, (4) increasing community demand for vaccines and (5) research needs. (HHS National Vaccine Advisory Committee, 2012 p.1). Shortly thereafter, by 2014 there was a need to update the recommendations again as a result of significant changes in

the adult immunization environment including outcomes and learnings from the 2009 H1N1 influenza pandemic and healthcare changes driven by the Affordable Care Act (ACA) of 2010 (National Vaccine Advisory Committee, 2014).

National Adult Immunization Plan

Another stimulus driving increased focus on adult vaccinations was the establishment of an annual National Adult and Influenza Immunization Summit (NAIIS). Previously an annual summit on influenza had been convened but in 2012, adult immunizations were added. NAIIS is a public private partnership of over 700 partner organizations, including NVPO, focused on improving adult immunizations. NVPO co-chairs the summit with in collaboration with the CDC and the Immunization Action Coalition (IAC) which is a private non-profit 501(c)(3) corporation (The National Adult and Influenza Immunization Summit, 2016.). The momentum gained from the creation of the summit and the engagement of the multitude of summit partners along with the NVPO's 2010 NVP and the publication of the updated NVAC recommendations in 2014, helped drive the development of a National Adult Immunization Plan (NAIP). Developed by the NVPO and released in early 2016, this plan is "intended to facilitate coordinated action by federal and nonfederal partners to protect public health and achieve optimal prevention of infectious diseases and their consequences through vaccination of adults" (U.S Department of Health and Human Services The National Vaccine Program Office, 2016, p. i).

The ASH serves as the director of the NVPO and as such will also lead the implementation of the NAIP. The plan structure is founded on four key goals, each with specific strategies and objectives to reach those goals. The timeframe for the NAIP is aligned with the 2020 targets for the existing national plans addressing vaccines, like Healthy People 2020 and

the NVP. Some of the goals can be standalone projects but others may be dependent upon the success of other goals as a stepping stone to success. The goals are:

1. Strengthen the adult immunization infrastructure.
2. Improve access to adult vaccines.
3. Increase community demand for adult immunizations.
4. Foster innovation in adult vaccine development and vaccination-related technologies

(U.S. Department of Health and Human Services Vaccine Program Office, 2016b, p.i).

The plan was developed after a comprehensive review of the current state of the research around barriers to adult immunization and consideration of the changing policies and practices in the healthcare delivery environment, such as ACA. These four goals share common themes with the five categories of recommendations that came out of the 2012 NVAC recommendations (HHS National Vaccine Advisory Committee, 2012). A formal environmental scan was conducted to review all adult immunization recommendations and reports issued between 2005 and 2015, many of which we have addressed here (U.S. Department of Health and Human Services National Vaccine Program Office, 2016a). The environmental scan also included stakeholder surveys and feedback. These stakeholders included various groups of partners like payers, employers, research organizations, healthcare providers, and professional associations. Focus groups were convened and subject matter experts were interviewed. Successful implementation of the plan will rely on contribution, coordination, and collaboration from a wide variety of private and public entities.

The NAIP had included indicators and performance measures which will be tracked against goals established and outlined in the plan (Department of Health & Services National Vaccine Program Office, 2016). Because many national indicators are already in place, such as

the HP 2020 goals, care was given to aligning goals within NAIP to existing national plans (if existing immunization goals were identified in other national plans, they were not changed) (Department of Health & Services National Vaccine Program Office, 2016). Measuring progress is a great step forward, however given that there are no specific incentives or disincentives for patients, providers, and NAIP partners ensuring improvement will be largely dependent upon the successful collaboration of the public private partnership groups like the NAIIS, and IAC (Department of Health & Services National Vaccine Program Office, 2016).

Adult Immunization Barriers

There are many reasons attributed to low vaccination rates among adults. Adult vaccines have not benefited from the robust infrastructure for delivery that exists for pediatric vaccinations. Pediatric vaccine delivery has many benefits including, routine patient visits (especially for infants), long standing vaccine financing programs beginning with federal funding for polio vaccination in 1955 (Centers for Disease Control and Prevention, 1999) and the Vaccines for Children (VFC) program which was created by the Omnibus Budget Reconciliation Act of 1993 and implemented in 1994 (Centers for Disease Control and Prevention, 2014). There is also greater public awareness of the needs and benefits of pediatric vaccination as well as state level policy requirements for many pediatric vaccinations to be completed prior to school entry (Cole & Swendiman, 2014).

The NAIP environmental scan included a stakeholder survey to identify current perceptions of barriers to adult immunizations (Department of Health & Services National Vaccine Program Office, 2016). Goals of the plan have been developed around addressing these specific barriers. Unlike pediatric vaccinations, administration of adult immunization is

complicated by many variables including varying age ranges for delivery of adult vaccines and variables such as different recommendations by age determined by a variety of risk factors. Adults also see a larger variety of care givers and many do not have a defined medical home which complicates coordination of care. Disjointed care delivery also impacts appropriate record keeping for adult immunization status.

Identifying and tracking adult immunization status impacts appropriate delivery of vaccinations. Reducing missed opportunities to immunize adults each time they see a healthcare provider can significantly improve delivery of adult immunizations (National Vaccine Advisory committee, 2014). A key challenge is for the provider to have adequate patient immunization history at the site and time of patient care. In addition, many opportunities to vaccinate are missed because vaccination status is not routinely being evaluated at every physician visit or healthcare provider encounters (Hurley et al., 2014). Immunization Information Systems (IIS) also referred as "registries" are "confidential, computerized, population-based systems that collect and consolidate vaccination data from vaccination providers that can be used in designing and sustaining effective immunization strategies" (Frieden, Jaffe, Stephens, & Thacker, 2012, p. 1005). As of 2012 the CDC reported most all states had an IIS with the exception of the District of Columbia (DC) and New Hampshire and only two states were not collecting adult immunization data as of 2012 (Connecticut and Rhode Island) (Frieden, Jaffe, Stephens, & Thacker, 2012, p. 1005, pp.4). IIS's have been an important technological tool to maintain patient level immunization data. A limitation for adults' inclusion in registries is that adults are just now migrated into the systems as they receive vaccines and prior vaccination histories for adults are not captured in the registries. The adoption of IIS reporting by other healthcare providers such as pharmacists has greatly assisted in the ability to communicate immunization

status of adults between various providers since adults are more likely to seek care from more than one provider (Frieden et al., 2012, p.1006, pp.3). In many cases use of IIS is a mandatory requirement for alternate providers.

In 2010 the Community Preventive Services Task Force recommended the use of immunization information systems on the basis of "strong evidence of effectiveness in increasing vaccination rates" (The Community Preventive Services Task Force, 2010). Specifically the report outlined 5 capabilities provided by IIS's that demonstrated effectiveness in improving immunization rates: (1) create or support effective interventions such as client reminder and recall systems, provider assessment and feedback, and provider reminders, (2) determine client vaccination status for decisions made by clinicians, health departments, and schools, (3) guide public health responses to outbreaks of vaccine-preventable disease, (4) inform assessments of vaccination coverage, missed vaccination opportunities, invalid dose administration, and disparities in vaccination coverage, and (5) facilitate vaccine management and accountability (The Community Preventive Services Task Force, 2010).

An outstanding limitation of IIS's is the fact that they are state based systems and do not have the capacity to share immunization data between states and technical limitations exist for ease of transfer of IIS data within and between health systems and providers. In 2012 in an effort to address appropriate use of IIS's among all age groups the National Center for Immunization and Respiratory Diseases (NCIRD), a division of CDC introduced a strategic plan to facilitate that *"real time, consolidated immunization data and services for all ages are available for authorized clinical, administrative, and public health users, and consumers, anytime and anywhere*" (Centers for Disease Control and Prevention, 2015a). This project aims to maximize the use of health information technology through bi-directional information sharing between

providers and state immunization registry databases allowing patient immunization records to cross populate between the registries and electronic health record systems. This enhanced capacity will allow for greater provider access to patient immunization status in order to more efficiently identify patients who have not received all recommended vaccinations. Interoperability between immunization registries and healthcare providers as well as complimentary immunization providers such as pharmacy's will greatly assist in the identification of patients in need of immunization and over time as the databases become more robust they can have great utility to identify coverage trends and provide other epidemiologic surveillance data. The inability for information to be shared between states has been a notable limitation, particularly in areas where people live close to state borders and may get care in more than one state. Presently there are some pilot programs being undertaken to test cross state capacities but due to multiple technical variability's it is not likely that this problem will be resolved any time soon (Centers for Disease Control and Prevention, 2015b).

Non- economic factors associated with barriers to adult immunization include activities facilitated within the provider's office. As noted by the NAIP survey, lack of awareness of the need for adult immunizations, lack of a strong recommendation from a healthcare provider, and limited application of technology to support patient identification, physician flags, and reminder recall systems are a subset of barriers in and of themselves. One could also argue that skepticism about safety and efficacy, lack of public knowledge about adult immunizations, and the role of media influences also have a place within the purview of the healthcare provider environment.

Prior to the NAIP environmental scan, a multitude of studies had cited the importance of a strong provider recommendation as a key factor in improving adult immunizations rates (Hurley, Lindley, Harpaz, Stokley, & Daley, 2010; Bridges et al., 2015; Hurley et al., 2010).

Strength of provider recommendation along with same day delivery of vaccination has been demonstrated as a proven strategy to improve adult immunization rates (National Vaccine Advisory committee, 2014). Factors which affect the strength of provider recommendations range from the lack of awareness on the part of the provider to a significant number of providers who do not stock routinely recommended vaccines for adults. If a physician is not stocking vaccines, they are far less like to make recommendations or refer patients for ACIP recommended vaccines. Recent national recommendations including the 2014 NVAC report provides vaccine recommendation standards for all providers, including those who do and do not stock and or administer vaccines (National Vaccine Advisory Committee, 2014).

Racial and ethnic disparities continue to persist in adult immunization coverage statistics. The 2015 NHIS found that whites adults generally had higher immunization rates compared to other groups and rates were generally higher among those who reported having a regular place where they received their healthcare services (Williams et al., 2017). The gap in racial and ethnic disparities for children has been narrowing and in aggregate significant disparities do not exist, possible factors contributing to better coverage among racial and ethnic groups for children are increased awareness of pediatric vaccines, better coverage programs for those who are un-insured or under-insured (VFC program), and school entry requirements (P. Lu et al., 2015). Identifying and removing barriers that specifically impact racial and ethnic minorities can help improve immunization rates. For example from 2007 to 2012 when the availability of influenza vaccination in multiple settings was increased, gaps in influenza vaccination coverage reduced slightly in non-Hispanic blacks and Asians compared to non-Hispanic whites (Lu et al., 2015, p. S423). Lu et al., recommend additional assessment of racial and ethnic disparities beyond data collected from NHIS is needed.

Lack of insurance coverage is a well-documented barrier to adult immunization coverage (Lu, O'Halloran, & Williams, 2015; Williams et al., 2016). For example in 2015, Lu, O'Halloran, and Williams reported that pneumococcal coverage for at risk adults between 18-64 years of age, for whom vaccination is routinely recommended, was 9.8% for uninsured compared to 23% for insured patients and influenza coverage rates were 14.4% versus 44.3% for uninsured versus insured (P.-J. Lu et al., 2015). In the post ACA era, understanding why such a large percentage of the population still does not have health insurance coverage for vaccination, which is covered at no out of pocket cost needs to be better understood. In addition immunization rates even among the insured are still exceptionally low. The ACA requirement for coverage of preventive care services including vaccinations was placed into effect starting with the first plan year after September of 2010, and allowed for "grandfathered" plans (determined as plan that was in effect as of March 2010) to be exempt unless changes were made to any portion of the plan (Koh & Sebelius, 2010; Rosenbaum, 2011). As of 2014, approximately 26% of those with employer provided health insurance were still in "grandfathered" plans (The Henry J. Kaiser Family Foundation, 2014). Data from the most recent report from the Census Bureau and the U.S. Department of Commerce on health insurance coverage, shows that the rate of those uninsured decreased by 2.9% between 2013 and 2014 and that 66% of the population had private insurance comparted to 36.5% with some form of government insurance coverage (Smith & Medalia, 2015). Between 2013 and 2014 health insurance coverage among those 19 to 64 years of age increased 4.2% (Smith & Medalia, 2015 p.8). Due to eligibility for Medicare, rates of insurance coverage for individuals over age 65 vary very little from year to year (Smith & Medalia, 2015, p. 7-8). Coverage for those under public plans such as Medicare and Medicaid has experienced less direct benefits from the ACA. Provision for immunization coverage under

Medicare and Medicaid vary and moreover while Medicare immunization coverage and benefit design is established at the federal level, coverage for immunizations under Medicaid is determined at the state level (Rosenbaum et al., 2003).

U.S. Vaccine Policy

Authority for mandating vaccines resides within States rights. Under the Public Health Service Act, HHS has the authority to "prevent the introduction, transmission, or spread of communicable diseases from foreign countries to the states or from state to state" (Cole & Swendiman, 2014, p.1). This includes authority to establish quarantine and isolation in order to halt the spread of communicable diseases however this does not include authority to mandate routine vaccination within states. Currently the only mandatory vaccination laws in the United States are those established for childhood school entry. As a result of measles outbreaks in schools in the 1960's and 1970's (measles virus can be aerosolized and therefore easily transmitted in the air where it can remain for up to 2 hours)(Centers for Disease Control and Prevention, 2017) adoption of school entry requirements were established to reduce transmission of measles and subsequently other communicable diseases among children (Cole & Swendiman, 2014). In the decades following mandatory school entry immunization requirements have been expanded to include a variety of immunizations for diseases which are highly communicable like measles and some which are not such as HPV. Currently all states, including the District of Columbia have laws requiring immunizations for school entry however states vary widely with regard to what vaccines are required and at what age they must be received (Cole & Swendiman, 2014). With regard to states mandating adult immunizations, a handful of states have requirements for immunization of healthcare workers for certain highly communicable diseases such as measles, mumps, rubella, and influenza, and some states require hepatitis B and

meningococcal vaccination for college students but these requirements often have very liberal "opt-out" provisions (Cole & Swendiman, 2014). Federal compulsory vaccinations have been established by the Secretary of HHS for immigrants of all ages entering the United States and these generally include all vaccines routinely recommended by the ACIP, with the exception of human papillomavirus and herpes zoster vaccination (Cole & Swendiman, 2014).

Immunizations and the Affordable Care Act (ACA)

The ACA of 2010 has the potential to be the most significant driver of improving adult immunization rates seen to date. One of the major goals of ACA is to increase health insurance and subsequently access to care for virtually all Americans. In addition to increasing access to care the ACA also requires coverage of certain preventive health services under the ten essential health benefits provision of the act, including all ACIP routinely recommended vaccines which must be covered with no out of pocket costs and no deductible (The Henry J. Kaiser Family Foundation, 2014). Challenges with delivery of adult immunizations have long been centered on issues of payment coverage. Without a federally subsidized program like the VFC program there was not a mechanism to provide coverage for adult immunizations to those who lacked private insurance and there were no requirements (or incentives) for private insurance payers to cover routine adult vaccinations. ACA was a huge game changer for immunization coverage at a population level however the Kaiser Family Foundation reports that public awareness of the preventive service requirement is very low, as of 2014 less than half the population (43%) was aware of the no out of pocket cost provision (The Henry J. Kaiser Family Foundation, 2014). The requirement for preventive services coverage through ACA applies to all private insurance plans, with the exception of plans that met a "grandfathered" status (Henry J. Kaiser Family Foundation, 2015).

While the ACA significantly improved access to vaccines for millions of patients by removing the financial barrier of patient out of pocket costs, the behemoth legislation contained no provision for or discussion of financial barriers at the provider level regarding stocking and inventory management and cost of administering vaccines (Department of Health & Services National Vaccine Program Office, 2016, p. 24). In an acknowledgement of the significance of the financial barriers associated with providers acquiring, stocking, and administering vaccines, the NAIP includes a specific objective dedicated to this topic (Department of Health & Services National Vaccine Program Office, 2016, p. 24). Goal 2 of the NAIP is to "Improve Access to Adult Vaccines", and there are four objectives for this goal and objective 2.2 is to "Assess and improve understanding of providers' financial barriers to delivering vaccinations, including stocking and administering vaccines (Department of Health & Services National Vaccine Program Office, 2016, p. 24).

Population Health

Nash, Reifsnyder, Fabius, and Pracilio define the primary components of the population health as; integrated health promotion and chronic illness disease management in the context of determinants of health (Nash, David, Reifsnyder, Fabius, & Pracilio, Valerie, 2011, p.7.). The term "population health" has recently been popularized as a staple in the healthcare lexicon, and it has been widely associated with and even attributed to the "Triple Aim", established by Donald Berwick and others at the Institute of Healthcare Improvement (IHI) in 2007 (Institute for Healthcare Improvement (IHI), 2016). In 2003 Kindig and Stoddart published a comprehensive articulation of the term "population health" (D. Kindig & Stoddart, 2003). In their article titled "What is Population Health?" published in the *American Journal of Public Health* in 2003, Kindig and Stoddart asserted that population health was a relatively new term

which had not yet been precisely defined and therefore proposed their own definition as; "the health outcomes of a group of individuals, including the distribution of such outcomes within the group," and they further argued "that the field of population health includes health outcomes, patterns of health determinants, and policies and interventions that link these two" (2003, p. 380). In the time since that publication there has been much discussion and debate about how to define population health and how it is different than public health. In 2007 questions still remained as to whether population health was a concept of health or a field of study of health determinants and if population health and public health were the same or different (Kindig, 2007, p. 139). There are a vast number of definitions of public health. Here are just two examples selected from well-respected U.S. national health organizations; the CDC and the IOM:

> Public health is the science of protecting and improving the health of families and communities through promotion of healthy lifestyles, research for disease and injury prevention and detection and control of infectious diseases. Overall, public health is concerned with protecting the health of entire populations. These populations can be as small as a local neighborhood, or as big as an entire country or region of the world (CDC Foundation, n.d.).

> "What we as a society do collectively to assure the conditions in which people can be healthy" (IOM, 1988:1). Although government bears special legal responsibility, this and similar definitions extend to more than just the activities of government, broadly referring to the efforts, science, art, and approaches used by all sectors of society (public, private, and civil society) to assure, maintain, protect, promote and improve the health of the people (IOM, 1988; Last, 1995; Petersen and Lupton, 1996; Acheson, 1998; ASPH,

1999;Kass, 2001; Turnock, 2001)." (*The Future of the Public's Health in the 21st Century*, 2003).

As you can see from the 2003 IOM definition, many researchers and academicians have weighed in on defining public health. Both of these definitions are well aligned with traditional thinking around the role of public health however they both fail to addresses quantifiable metrics and activities which can assess outcomes which can then be used to achieve the goal of "protecting and improving the health families and communities". Kindig suggests that distinguishing the difference between public health and population health essentially comes down to the more specific intention of population health which is to focus on the measurement of healthcare outcomes (2007, p. 143). I agree with this view and furthermore I would submit that not intentionally and thoughtfully measuring the results of our health improvement efforts so we can most efficiently deploy our resources to achieve the most optimal health improvements is contradictory to any definition of public health.

In Kindig' s 2007 article on population health terminology, his stated goal is to provide a "concise compilation of terms and concepts useful to public and private policy makers, students and scholars from other fields" (2007, p.140). In this paper he provides updated comprehensive definitions of population health terms which provide additional granularity to the distinction between public health and population health.

***Population health*:** (1) A conceptual framework for thinking about why some populations are healthier than others, as well as the policy development, research agenda, and resource allocation that flow from it (Young 1998). (2) The health outcomes of a group of individuals, including the distribution of such outcomes within the group

(Kindig and Stoddart 2003). (3) The health of a population as measured by health status indicators and is influenced by social, economic, and physical environments; personal health practices; individual capacity and coping skills; human biology; early childhood development; and health services (Dunn and Hayes 1999), (Kindig, 2007, p. 145).

Public health: (1) Activities that a society undertakes to assure the conditions in which people can be healthy. These include organized community efforts to prevent, identify, and counter threats to the health of the public (Turnock 2004). (2) What we do as a society collectively to assure conditions in which people can be healthy (IOM 1988) (Kindig, 2007, p. 146).

In these updated more comprehensive definitions the major distinction between them continues to be the population health emphasis on health outcomes, indicators (for individuals and groups), distribution of outcomes, and the influencers that drive those outcomes, whereas the public health definition continues to emphasize the role of "assuring" a societal approach to engaging in activities related to health. I most prefer the population health definition by Dunn and Hayes as it provides for the recognition and inclusion of a variety of "determinants" which can then be measured and evaluated in order to identify the most effective interventions to advance the population health continuum (Dunn & Hayes, 1999).

In 2015 Kindig authored a Health Affairs blog in which he posted that the term population health required additional evolution due to its close association with the Triple Aim and its wide use by health organizations to describe patient clinical outcomes both of which in his view have created conflicting understandings of the term (2015). Kindig argued that there is now a need for multiple definitions, primarily to address new terms which are used to "describe

activities limited to clinical populations and a narrower set of health outcome determinants" (2015). Because "population health" has become a rather generic term, straying from his intended purpose which was to establish greater focus on the role of non-clinical factors such as education and economics, Kindig proposes the use of the term "population health management (PHM)" or "population medicine", to be used when referring to patient populations and then the original term "population health" could be used to represent geographic populations. Other suggestions included replacing the term population health with "total population health" (D. A. Kindig, 2015b). Ultimately the IOM roundtable on Population Health Improvement elected to maintain the term "population health" while acknowledging its intended objective to align with geographical outcomes and not clinical populations. Kindig acknowledges that to some this discussion may appear to be just semantics (2015) but my own research has lead me to agree with the need to more clearly define the terms. There are too many concepts now being included in "population health" terminology and the critical intended distinction in adopting the term population health, as put forth by Kindig and Stoddard (2003), was to focus on outcomes and how determinants (specifically economic and social) factored into those outcomes.

The most simplistic distinction between population health and public health is that population health refers to specific measurable health outcomes and population health defines more of the approaches we use to provide health to the nation's population.

Appendix B: 2017 Adult Immunization Schedule

Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017

In February 2017, the *Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017* became effective, as recommended by the Advisory Committee on Immunization Practices (ACIP) and approved by the Centers for Disease Control and Prevention (CDC). The 2017 adult immunization schedule was also reviewed and approved by the following professional medical organizations:

- American College of Physicians (www.acponline.org)
- American Academy of Family Physicians (www.aafp.org)
- American College of Obstetricians and Gynecologists (www.acog.org)
- American College of Nurse-Midwives (www.midwife.org)

CDC announced the availability of the 2017 adult immunization schedule at www.cdc.gov/vaccines/schedules/hcp/index.html in the *Morbidity and Mortality Weekly Report* (*MMWR*).[1] The schedule is published in its entirety in the *Annals of Internal Medicine*.[2]

The adult immunization schedule describes the age groups and medical conditions and other indications for which licensed vaccines are recommended. The 2017 adult immunization schedule consists of:

- Figure 1. Recommended immunization schedule for adults by age group
- Figure 2. Recommended immunization schedule for adults by medical condition and other indications
- Footnotes that accompany each vaccine containing important general information and considerations for special populations
- Table. Contraindications and precautions for vaccines routinely recommended for adults

Consider the following information when reviewing the adult immunization schedule:

- The figures in the adult immunization schedule should be read with the footnotes that contain important general information and information about vaccination of special populations.
- When indicated, administer recommended vaccines to adults whose vaccination history is incomplete or unknown.
- Increased interval between doses of a multi-dose vaccine does not diminish vaccine effectiveness; therefore, it is not necessary to restart the vaccine series or add doses to the series because of an extended interval between doses.
- Adults with immunocompromising conditions should generally avoid live vaccines, e.g., measles, mumps, and rubella vaccine. Inactivated vaccines, e.g., pneumococcal or inactivated influenza vaccines, are generally acceptable.
- Combination vaccines may be used when any component of the combination is indicated and when the other components of the combination vaccine are not contraindicated.
- The use of trade names in the adult immunization schedule is for identification purposes only and does not imply endorsement by the ACIP or CDC.

Details on vaccines recommended for adults and complete ACIP statements are available at www.cdc.gov/vaccines/hcp/acip-recs/index.html. Additional CDC resources include:

- A summary of information on vaccination recommendations, vaccination of persons with immunodeficiencies, preventing and managing adverse reactions, vaccination contraindications and precautions, and other information can be found in *General Recommendations on Immunization* at www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm.
- Vaccine Information Statements that explain benefits and risks of vaccines are available at www.cdc.gov/vaccines/hcp/vis/index.html.
- Information and resources regarding vaccination of pregnant women are available at www.cdc.gov/vaccines/adults/rec-vac/pregnant.html.
- Information on travel vaccine requirements and recommendations is available at wwwnc.cdc.gov/travel/destinations/list.
- *CDC Vaccine Schedules App* for clinicians and other immunization service providers to download is available at www.cdc.gov/vaccines/schedules/hcp/schedule-app.html.
- *Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger* is available at www.cdc.gov/vaccines/schedules/hcp/index.html.

Report suspected cases of reportable vaccine-preventable diseases to the local or state health department.

Report all clinically significant post-vaccination reactions to the Vaccine Adverse Event Reporting System at www.vaers.hhs.gov or by telephone, 800-822-7967. All vaccines included in the 2017 adult immunization schedule except herpes zoster and 23-valent pneumococcal polysaccharide vaccines are covered by the Vaccine Injury Compensation Program. Information on how to file a vaccine injury claim is available at www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382.

Submit questions and comments regarding the 2017 adult immunization schedule to CDC through www.cdc.gov/cdc-info or by telephone, 800-CDC-INFO (800-232-4636), in English and Spanish, 8:00am–8:00pm ET, Monday–Friday, excluding holidays.

The following acronyms are used for vaccines recommended for adults:

HepA	hepatitis A vaccine
HepA-HepB	hepatitis A and hepatitis B vaccines
HepB	hepatitis B vaccine
Hib	*Haemophilus influenzae* type b conjugate vaccine
HPV vaccine	human papillomavirus vaccine
HZV	herpes zoster vaccine
IIV	inactivated influenza vaccine
LAIV	live attenuated influenza vaccine
MenACWY	serogroups A, C, W, and Y meningococcal conjugate vaccine
MenB	serogroup B meningococcal vaccine
MMR	measles, mumps, and rubella vaccine
MPSV4	serogroups A, C, W, and Y meningococcal polysaccharide vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
RIV	recombinant influenza vaccine
Td	tetanus and diphtheria toxoids
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
VAR	varicella vaccine

[1] MMWR Morb Mortal Wkly Rep. 2017;66(5). Available at www.cdc.gov/mmwr/volumes/66/wr/mm6605e2.htm?s_cid=mm6605e2_w.
[2] Ann Intern Med. 2017;166:209-218. Available at annals.org/aim/article/doi/10.7326/M16-2936.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Figures 1 and 2 should be read with the footnotes that contain important general information and considerations for special populations.

Figure 1. Recommended immunization schedule for adults aged 19 years or older by age group, United States, 2017

Vaccine	19–21 years	22–26 years	27–59 years	60–64 years	≥ 65 years
Influenza[1]	1 dose annually				
Td/Tdap[2]	Substitute Tdap for Td once, then Td booster every 10 yrs				
MMR[3]	1 or 2 doses depending on indication				
VAR[4]	2 doses				
HZV[5]				1 dose	
HPV–Female[6]	3 doses				
HPV–Male[6]	3 doses				
PCV13[7]	1 dose				
PPSV23[7]	1 or 2 doses depending on indication				1 dose
HepA[8]	2 or 3 doses depending on vaccine				
HepB[9]	3 doses				
MenACWY or MPSV4[10]	1 or more doses depending on indication				
MenB[10]	2 or 3 doses depending on vaccine				
Hib[11]	1 or 3 doses depending on indication				

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended for adults with additional medical conditions or other indications

No recommendation

Figure 2. Recommended immunization schedule for adults aged 19 years or older by medical condition and other indications, United States, 2017

Vaccine	Pregnancy[1-6,9]	Immuno-compromised (excluding HIV infection)[3-7,11]	HIV infection CD4+ count (cells/μL)[3-7,9-11]		Asplenia, persistent complement deficiencies[7,10,11]	Kidney failure, end-stage renal disease, on hemodialysis[7,9]	Heart or lung disease, chronic alcoholism[7]	Chronic liver disease[7-9]	Diabetes[7,9]	Healthcare personnel[3,4,9]	Men who have sex with men[6,8,9]
			< 200	≥ 200							
Influenza[1]	1 dose annually										
Td/Tdap[2]	1 dose Tdap each pregnancy	Substitute Tdap for Td once, then Td booster every 10 yrs									
MMR[3]	contraindicated			1 or 2 doses depending on indication							
VAR[4]	contraindicated			2 doses							
HZV[5]	contraindicated			1 dose							
HPV–Female[6]		3 doses through age 26 yrs									
HPV–Male[6]		3 doses through age 26 yrs		3 doses through age 21 yrs							3 doses through age 26 yrs
PCV13[7]		1 dose									
PPSV23[7]		1, 2, or 3 doses depending on indication									
HepA[8]	2 or 3 doses depending on vaccine										
HepB[8]	3 doses										
MenACWY or MPSV4[10]	1 or more doses depending on indication										
MenB[10]	2 or 3 doses depending on vaccine										
Hib[11]	3 doses post-HSCT recipients only	1 dose									

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended for adults with additional medical conditions or other indications

Contraindicated

No recommendation

Footnotes. Recommended immunization schedule for adults aged 19 years or older, United States, 2017

1. Influenza vaccination

General information

- All persons aged 6 months or older who do not have a contraindication should receive annual influenza vaccination with an age-appropriate formulation of inactivated influenza vaccine (IIV) or recombinant influenza vaccine (RIV).
- In addition to standard-dose IIV, available options for adults in specific age groups include: high-dose or adjuvanted IIV for adults aged 65 years or older, intradermal IIV for adults aged 18 through 64 years, and RIV for adults aged 18 years or older.
- Notes: Live attenuated influenza vaccine (LAIV) should not be used during the 2016–2017 influenza season. A list of currently available influenza vaccines is available at www.cdc.gov/flu/protect/vaccine/vaccines.htm.

Special populations

- Adults with a history of egg allergy who have only hives after exposure to egg should receive age-appropriate IIV or RIV.
- Adults with a history of egg allergy other than hives, e.g., angioedema, respiratory distress, lightheadedness, or recurrent emesis, or who required epinephrine or another emergency medical intervention, may receive age-appropriate IIV or RIV. The selected vaccine should be administered in an inpatient or outpatient medical setting and under the supervision of a healthcare provider who is able to recognize and manage severe allergic conditions.
- Pregnant women and women who might become pregnant in the upcoming influenza season should receive IIV.

2. Tetanus, diphtheria, and acellular pertussis vaccination

General information

- Adults who have not received tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap) or for whom pertussis vaccination status is unknown should receive 1 dose of Tdap followed by a tetanus and diphtheria toxoids (Td) booster every 10 years. Tdap should be administered regardless of when a tetanus or diphtheria toxoid-containing vaccine was last received.
- Adults with an unknown or incomplete history of a 3-dose primary series with tetanus and diphtheria toxoid-containing vaccines should complete the primary series that includes 1 dose of Tdap. Unvaccinated adults should receive the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second dose.
- Notes: Information on the use of Td or Tdap as tetanus prophylaxis in wound management is available at www.cdc.gov/mmwr/preview/mmwrhtml/rr5517a1.htm.

Special populations

- Pregnant women should receive 1 dose of Tdap during each pregnancy, preferably during the early part of gestational weeks 27–36, regardless of prior history of receiving Tdap.

3. Measles, mumps, and rubella vaccination

General information

- Adults born in 1957 or later without acceptable evidence of immunity to measles, mumps, or rubella (defined below) should receive 1 dose of measles, mumps, and rubella vaccine (MMR) unless they have a medical contraindication to the vaccine, e.g., pregnancy or severe immunodeficiency.
- Notes: Acceptable evidence of immunity to measles, mumps, or rubella in adults is: born before 1957, documentation of receipt of MMR, or laboratory evidence of immunity or disease. Documentation of healthcare provider-diagnosed disease without laboratory confirmation is not acceptable evidence of immunity.

Special populations

- Pregnant women who do not have evidence of immunity to rubella should receive 1 dose of MMR upon completion or termination of pregnancy and before discharge from the healthcare facility; non-pregnant women of childbearing age without evidence of rubella immunity should receive 1 dose of MMR.
- Adults with primary or acquired immunodeficiency including malignant conditions affecting the bone marrow or lymphatic system, systemic immunosuppressive therapy, or cellular immunodeficiency should not receive MMR.
- Adults with human immunodeficiency virus (HIV) infection and CD4+ T-lymphocyte count ≥200 cells/μl for at least 6 months who do not have evidence of measles, mumps, or rubella immunity should receive 2 doses of MMR at least 28 days apart. Adults with HIV infection and CD4+ T-lymphocyte count <200 cells/μl should not receive MMR.
- Adults who work in healthcare facilities should receive 2 doses of MMR at least 28 days apart; healthcare personnel born before 1957 who are unvaccinated or lack laboratory evidence of measles, mumps, or rubella immunity, or laboratory confirmation of disease should be considered for vaccination with 2 doses of MMR at least 28 days apart for measles or mumps, or 1 dose of MMR for rubella.
- Adults who are students in postsecondary educational institutions or plan to travel internationally should receive 2 doses of MMR at least 28 days apart.
- Adults who received inactivated (killed) measles vaccine or measles vaccine of unknown type during years 1963–1967 should be revaccinated with 1 or 2 doses of MMR.
- Adults who were vaccinated before 1979 with either inactivated mumps vaccine or mumps vaccine of unknown type who are at high risk for mumps infection, e.g., work in a healthcare facility, should be considered for revaccination with 2 doses of MMR at least 28 days apart.

4. Varicella vaccination

General information

- Adults without evidence of immunity to varicella (defined below) should receive 2 doses of single-antigen varicella vaccine (VAR) 4–8 weeks apart, or a second dose if they have received only 1 dose.
- Persons without evidence of immunity for whom VAR should be emphasized are: adults who have close contact with persons at high risk for serious complications, e.g., healthcare personnel and household contacts of immunocompromised persons; adults who live or work in an environment in which transmission of varicella zoster virus is likely, e.g., teachers, childcare workers, and residents and staff in institutional settings; adults who live or work in environments in which varicella transmission has been reported, e.g., college students, residents and staff members of correctional institutions, and military personnel; non-pregnant women of childbearing age; adolescents and adults living in households with children; and international travelers.
- Notes: Evidence of immunity to varicella in adults is: U.S.-born before 1980 (for pregnant women and healthcare personnel, U.S.-born before 1980 is not considered evidence of immunity); documentation of 2 doses of VAR at least 4 weeks apart; history of varicella or herpes zoster diagnosis or verification of varicella or herpes zoster disease by a healthcare provider; or laboratory evidence of immunity or disease.

Special populations

- Pregnant women should be assessed for evidence of varicella immunity. Pregnant women who do not have evidence of immunity should receive the first dose of VAR upon completion or termination of pregnancy and before discharge from the healthcare facility, and the second dose 4–8 weeks after the first dose.
- Healthcare institutions should assess and ensure that all healthcare personnel have evidence of immunity to varicella.
- Adults with malignant conditions, including those that affect the bone marrow or lymphatic system or who receive systemic immunosuppressive therapy, should not receive VAR.
- Adults with human immunodeficiency virus (HIV) infection and CD4+ T-lymphocyte count ≥200 cells/μl may receive 2 doses of VAR 3 months apart. Adults with HIV infection and CD4+ T-lymphocyte count <200 cells/μl should not receive VAR.

5. Herpes zoster vaccination

General information

- Adults aged 60 years or older should receive 1 dose of herpes zoster vaccine (HZV), regardless of whether they had a prior episode of herpes zoster.

Special populations

- Adults aged 60 years or older with chronic medical conditions may receive HZV unless they have a medical contraindication, e.g., pregnancy or severe immunodeficiency.
- Adults with malignant conditions, including those that affect the bone marrow or lymphatic system or who receive systemic immunosuppressive therapy, should not receive HZV.
- Adults with human immunodeficiency virus (HIV) infection and CD4+ T-lymphocyte count <200 cells/μl should not receive HZV.

6. Human papillomavirus vaccination

General information

- Adult females through age 26 years and adult males through age 21 years who have not received any human papillomavirus (HPV) vaccine should receive a 3-dose series of HPV vaccine at 0, 1-2, and 6 months. Males aged 22 through 26 years may be vaccinated with a 3-dose series of HPV vaccine at 0, 1–2, and 6 months.
- Adult females through age 26 years and adult males through age 21 years (and males aged 22 through 26 years who may receive HPV vaccination) who initiated the HPV vaccination series before age 15 years and received 2 doses at least 5 months apart are considered adequately vaccinated and do not need an additional dose of HPV vaccine.
- Adult females through age 26 years and adult males through age 21 years (and males aged 22 through 26 years who may receive HPV vaccination) who initiated the HPV vaccination series before age 15 years and received only 1 dose, or 2 doses less than 5 months apart, are not considered adequately vaccinated and should receive 1 additional dose of HPV vaccine.
- Notes: HPV vaccination is routinely recommended for children at age 11 or 12 years. For adults who had initiated but did not complete the HPV vaccination series, consider their age at first HPV vaccination (described above) and other factors (described below) to determine if they have been adequately vaccinated.

Special populations

- Men who have sex with men through age 26 years who have not received any HPV vaccine should receive a 3-dose series of HPV vaccine at 0, 1-2, and 6 months.
- Adult females and males through age 26 years with immunocompromising conditions (described below), including those with human immunodeficiency virus (HIV) infection, should receive a 3-dose series of HPV vaccine at 0, 1–2, and 6 months.
- Pregnant women are not recommended to receive HPV vaccine, although there is no evidence that the vaccine poses harm. If a woman is found to be pregnant after initiating the HPV vaccination series, delay the remaining doses until after the pregnancy. No other intervention is needed. Pregnancy testing is not needed before administering HPV vaccine.
- Notes: Immunocompromising conditions for which a 3-dose series of HPV vaccine is indicated are primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, e.g., B-lymphocyte antibody deficiencies, complete or partial T-lymphocyte defects, HIV infection, malignant neoplasm, transplantation, autoimmune disease, and immunosuppressive therapy.

APPENDIX C: PERMISSION TO USE MULTILEVEL INFLUENCES on SUCCESSFUL IMPLEMENTATION FIGURE

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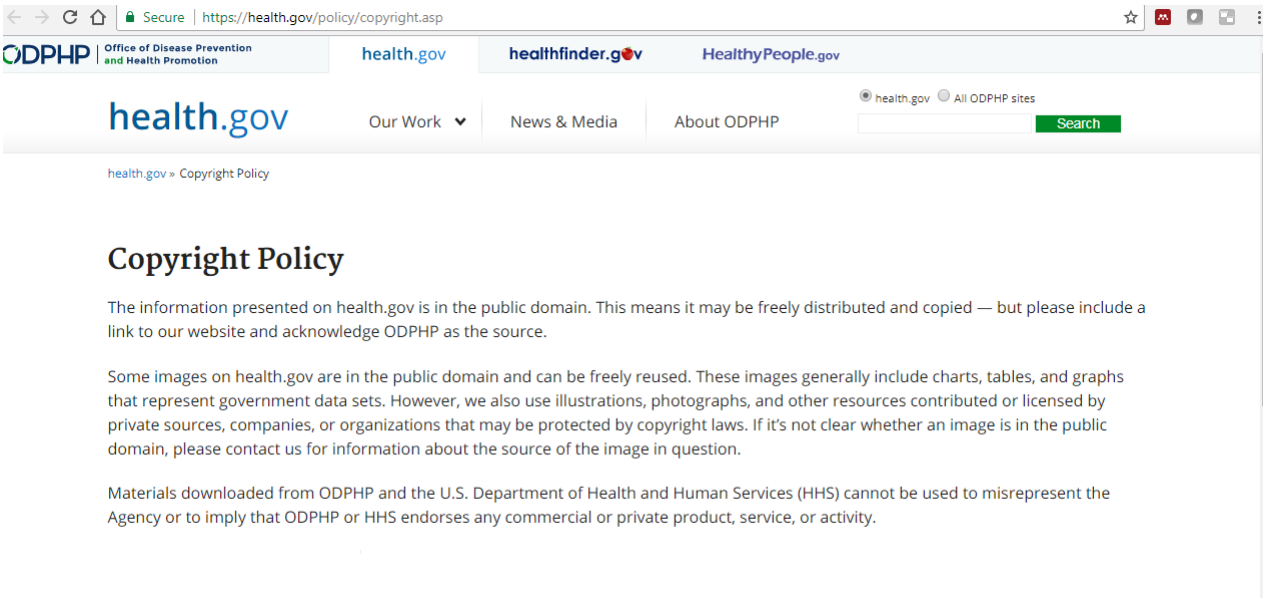
APPENDIX D: PERMISSION TO USE NATIONAL ADULT IMMUNIZATION PLAN FIGURES AND TABLES



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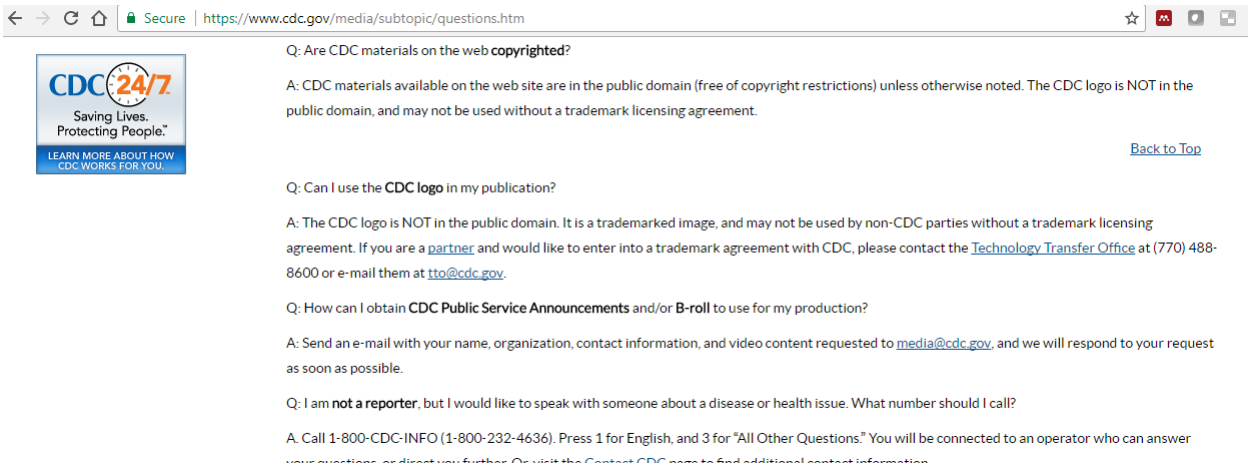

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