CHARACTERIZATION OF CURRENT AND FUTURE VACCINATION CHALLENGES IN THE UNITED STATES: INFLUENZA AND THE POLICY IMPLICATIONS OF VACCINOMICS

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A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland

May 2020

Abstract

Background: Vaccine concerns are common. Influenza vaccine coverage is poor despite high safety and moderate effectiveness. Vaccinomics aims to improve influenza and other vaccines' safety and effectiveness by applying genomics to vaccine development and use. We characterized vaccine confidence, influenza vaccination prevalence, and public values through a qualitative-quantitative mixed-methods study.

Methods: Community meetings (N=94; themes identified based on Grounded Theory) informed a subsequent online panel survey (N=1,925). Vaccine hesitancy, vaccination, sociodemographic factors, personal health history, and vaccinomics were cross-tabulated. Bivariate and multivariable log binomial and Poisson regression models identified associations with influenza vaccination and vaccinomics opposition, respectively.

Results: In-person participants supported vaccinomics' potential for increased personalization, but worried about inequitable implementation. The survey population was 50.6% female, 61.8% White, non-Hispanic, 62.9% had a child<18 years old, 47.1% had a ≤high school education, and 19.7% perceived vaccine reaction experience. Most respondents had ≥1 vaccine concern, and belief that children receive too many vaccines was common (51.1%). Most (75.8%) respondents expected vaccinomics to increase their vaccine confidence. In multivariable models, ≥college education versus ≤high school and complementary/alternative medicine (CAM) use versus nonuse were associated with vaccination. High versus low vaccine hesitancy was associated with lower vaccination prevalence. Vaccinomics support was associated with serious reaction experience, low vaccine hesitancy (in all but parents of young children), and higher education, income, and trust in public health authorities. Opposition to vaccinomics was associated with low trust in public health and perceived reaction experience. Discussing vaccinomics and adverse events following immunization did not impact vaccine safety perceptions.

Discussion: Vaccine concerns, CAM use, and perceived vaccine reactions were common. Influenza vaccination coverage was associated with CAM use and ≥college education. Most respondents expected vaccinomics to improve their vaccine confidence. Low trust in public health authorities and experience with serious reactions were associated with vaccinomics opposition. Increased awareness of federal vaccine safety oversight might improve confidence.

Conclusion: Federal agencies should 1) tailor influenza interventions by education-level, 2) collaborate with complementary/alternative medicine providers, 3) research strategies to reach disadvantaged populations, 4) allocate funding for vaccinomics-related research, and 5) implement policies to bolster public trust.

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Acknowledgements

My whole-hearted thanks go to my advisor, Dan Salmon, for convincing me to apply to the PhD program a year earlier than I promised Amber D'Souza, my former supervisor, that I would and never wavering in his belief (or at least not letting me perceive any doubt) that this day would come. Dan absolutely exceeded my expectations of an advisor. My classmates often remind me not to take for granted that Dan and I get along well, as this has made the PhD process particularly enjoyable. I am ever so grateful to have had his ear when I needed to problem-solve and his support when I was struggling to make progress. He has been a tremendous resource, motivator, and inspiration. I look forward to collaborating with Dan in the years to come.

Thank you to Amber D'Souza in the Department of Epidemiology for hiring me to work with her on studies of oral human papillomavirus incidence and persistence after I completed my master's degree. Through this experience, I realized I wanted and needed a PhD. I am very grateful to her for this, and for supporting my PhD application.

Thank you to my Thesis Advisory Committee (TAC) members for their thoughtful contributions; my dissertation is stronger and more focused for having followed their suggestions. Maria Merritt, Larry Moulton, and Rupali Limaye were my TAC members. Maria provided insightful suggestions about how to make the survey Pretest methodologically stronger and served on my departmental, schoolwide, and thesis oral exam committees. Rupali patiently guided me through my first qualitative data analysis and drafting the results. She also served on my departmental oral exam committee. While driving on a long, flat stretch of road back to Maryland from Canada, Larry advised me by phone about the sample size calculations for my thesis research proposal. He also served on my departmental oral exam committee and was the PhD Program Director for most of my time at JHSPH. I am grateful for Larry, Rupali, and

Maria's dedication to helping me through this process, for reminding me that they believed in me, and providing levity along the way.

Thank you to the additional faculty who served on my schoolwide oral exam committees: Kate Clegg Smith, Stéphane Helleringer, and Joanne Katz (alternate) and my thesis defense oral exam committee: John McGready (schoolwide oral and defense committees), Meghan Moran (chair), Andy Ruff (alternate) and Saiffudin Ahmed (alternate). Dr. Ahmed was especially helpful in answering my numerous questions about how to weight survey data to the U.S. population.

Thank you to the faculty and staff of the International Health Department for their time and being friendly faces who made me smile, especially when I was my most sleep deprived and disheveled. Peter Winch, Caitlin Kennedy, Alain Labrique, Joanne Katz, Victoria Chou, Yvonne Tam, Sassan Noazin, Cristina Salazar, Audrey Lindhal, Tiana Burrell, Madeleine Blunt, Tina Proveaux, Kristina Povazanova, and Karen Charron. Karen led the GDEC Seminar with Yvonne Tam while I served as the TA from 2018-2019 and was instrumental in helping me realize that I enjoy teaching. Her generosity in teaching me pedagogy was an unexpected, and useful outcome, of the Department's TA requirement.

Thank you to my JHSPH classmates, especially those who collaborated with me on group projects, read drafts of my thesis research proposal, attended my mock oral exam, and advised me during this grueling process. Thank you to Hyunju Kim, Laura Beres, Jessica Atwell, Wangeci Kagucia, Ashley Sheffel, Mellisa Roskosky, Mark Jones, Pierre Muhoza, Taylor Holroyd, Andrea Carcelen, Elizabeth Hazel, Jessica Schue, and Anastasia Lombrou, Juan Sanchez, and Francesca Schiaffino Salazar. Thank you to the students who were enormously helpful in testing the survey and managing the resulting data, especially Madeleine Blunt who was instrumental in my being able to defend today.

Outside of school, I am part of two wonderful sailing programs, the Downtown Sailing Center (DSC) and Baltimore City Yacht Association (BCYA). The teamwork involved in sailboat racing has been a perfect antidote and respite from the individual-level work required to earn my PhD. I am grateful beyond words for my sailing friends and family's support. Special thanks to my DSC and BCYA teams, Short Sheeters and Dark Crystal, and competitors. My sailing friends helped me reach this defense as much as my academic supporters. Sailing is the best part about living in Baltimore and I am grateful for my sailing friends' support and guidance on and off the water.

Thank you to my non-sailing friends across the world, especially those at the London School of Hygiene and Tropical Medicine who helped me believe I was PhD-material, and to the friends I made while living in the Boston metropolitan area, New Orleans, and Baltimore. Thank you to my dear friends, Jess Cohen, Deanna Chan, Jen Thibault, and Alex Mazares, who are my personal cheerleaders. Special thanks to my first and oldest friends in Baltimore: Meghan Hoffmann, Jordan Bradshaw, and Ashly Hunt who always make me laugh, and are the first to celebrate my accomplishments.

Thank you to my mom, dad, and stepmom for listening when I was frustrated, visiting me in Baltimore, and serving as my personal cheering squad. They proofread my dissertation proposal, my CV, and parts of this dissertation, though they said the content was a little dense. Thank you to my sisters and extended family for your love and support, visits, hugs and kisses. I could not do this without you and I would not want to.

My father and my Grandpa Gerber encouraged me to get a PhD years before I found the idea even remotely palatable. When I told my Grandpa I was applying to masters programs, he asked why I was not applying for the highest degree in my field. I snootily replied I did not need a PhD and I did not want one. He persisted, but temporarily lost the argument. Grandpa lived

long enough to see me start, but not finish, the PhD program. At our last visit, he told his physical therapist he had "no doubt, no doubt whatsoever" that I would finish my PhD. Again, he was right.

Grandma Gerber continues to support me and enjoys regular updates on my dissertation, frequently asking to read excerpts. She showed a four-minute-long animation about vaccinomics, produced for our study participants, to her friends using her iPad. I admire her for having earned two master's degrees, the second after having three children, and appreciate her genuine interest in my research.

Thank you to Grandma and Grandpa Gerrish for their warmth, love, and support. A picture of my late grandfather waterskiing reminds me of the value of perseverance. My grandfather failed to get up waterskiing at age 79. A year later, he got up. Afterward, he described doing "deep knee bends" for months to build up the strength to waterski again. Grandpa's determination and bull-headed dedication to his goal are the same attributes that helped me get to where I am now. In Grandpa's absence, Grandma Gerrish serves as my guiding light to do what is right and rejuvenates me with hugs, blueberry pancakes, and smiles whenever I visit her.

And thank you, reader, for your attention to this work. The PhD process has taken longer and been a lot harder than I anticipated. Thank you for reading the results of my efforts, of which I am most proud.

With love, I dedicate this dissertation to my family for their enthusiastic support and affection that has propelled me to this defense.

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List of terms and abbreviations

ACIP	Advisory Committee on Immunization Practices
ACS	American Community Survey
AE	Adverse Event
aP	Acellular Pertussis Containing Vaccine
CAM	Complementary/Alternative Medicine
CDC	Centers for Disease Control and Prevention
CHIP	Children's Health Insurance Program
CITI	Collaborative Institutional Training Initiative
CMS	Centers for Medicare and Medicaid Services
COVID-19	Coronavirus Disease 2019
CPS	Current Population Survey
HHS	Department of Health and Human Services
DOD	Department of Defense
DTaP	Diphtheria, Tetanus, and acellular Pertussis vaccine
ELSI	Ethical, Legal, and Social Implications
EMA	European Medicines Agency
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GINA	Genetic Information Non-Discrimination Act

HBsAg+	Hepatitis B Surface Antigen positive
HepA	Hepatitis A Vaccine
HepB	Hepatitis B Vaccine
HHS	Department of Health and Human Services
Hib	*Haemophilus Influenzae* Type b
HPV	Human Papillomavirus
IDSA EIN	Infectious Disease Society of America Emerging Infections Network
IIV	Inactivated Influenza Vaccine
IOM	Institute of Medicine
IPV	Inactivated Polio Vaccine
IRB	Institutional Review Board
LAIV	Live Attenuated Inactivated Influenza Vaccine
LDTs	Laboratory Device Testing
MenACWY-D	Meningococcal Conjugate Vaccine: Contains Strains ACWY
MenACWY-CRM	Meningococcal Conjugate Vaccine: Contains Strains ACWY
MenB-FHbp	Meningococcal Conjugate Vaccine: Contains Strain B
MERS	Middle Eastern Respiratory Syndrome
MMR	Measles, Mumps and Rubella vaccine
NHANES	National Health and Nutrition Examination Survey

NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
NIS	National Immunization Survey
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OR	Odds Ratio
PACV	Parent Attitudes about Childhood Vaccines survey
PCV13	Pneumococcal Conjugate Vaccine: Contains 13 strains
PI	Principal Investigator
PR	Prevalence Ratio
RR	Risk Ratio
RV1	Rotarix® Rotavirus Vaccine
RV5	RotaTeq® Rotavirus Vaccine
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event
SARS	Sudden Acute Respiratory Syndrome
Tdap	Tetanus, Diphtheria and acellular Pertussis Booster Vaccine
U.S.	United States
VAERS	Vaccine Adverse Events Reporting System
VAR	Varicella Vaccine

VE	Vaccine Effectiveness
VICP	Vaccine Injury Compensation Program
VSD	Vaccine Safety Datalink
VZV	Varicella Zoster Virus
WHO	World Health Organization
wP	Whole-cell Pertussis Containing Vaccine
ZVL	Zoster Vaccine Live
95% CI	95% Confidence Interval

Chapter 1. Introduction

Vaccine delay or refusal – despite the availability of vaccines and vaccination services – contributed to worldwide measles outbreaks in 2019 and could be a barrier or facilitator to implementing a new vaccination paradigm based on genomics, called vaccinomics.(1-3) We have a real challenge before us: how to convince people to accept new vaccines and a new model governing who gets which vaccines and at what dose, when most are concerned about the vaccines used now.(3-6) Influenza vaccines are mistrusted by many due to annual changes in their formulation, making them seem new and less trustworthy than other vacccines, like tetanus-containing vaccines.(4, 6-13) Vaccinomics, a new field based on genomics, is expected to lead to new vaccine products and changes to vaccine schedules.(3, 14-17)

Vaccinomics and adversomics are emerging fields that aim to use genomics to improve vaccine development and use, and apply this knowledge to the study of adverse events following immunization, with the goal of making vaccines even safer and more effective than they are now.(3, 14-17) For simplicity, both fields will be referred to as "vaccinomics" here. Vaccinomics may decrease vaccine hesitancy through improved safety and personalization of vaccine scedules. Despite its potential, vaccinomics may stoke public skepticism due to privacy concerns around genomic data.(3, 14-17) The direction of association remains unknown. The ethical, legal, and social implications (ELSI), or more broadly termed, policy implications, of vaccinomics may include:

- Vaccine prioritization based on genetics/genomics
- Societal benefits
- Reduced agency
- Confidence in primary care providers, government, and public health authorities, and vaccines

- Increased stigma and/or discrimination
- Reduced privacy and genomics, in general
- Privacy issues related to genetic testing and genomics, in general
- Other advantages/disadvantages of vaccinomics

Vaccinomics-related policy issues are not carefully explored in the peer-reviewed literature nor is vaccine hesitancy around influenza vaccines for children or adults. We signal out influenza vaccines since they are recommended for everyone 6 months and older and have variable effectiveness from year-to-year, due to antigenic drift and shift in the viruses' genomes, the recipient's health, age, and biological sex.(18-24) Influenza vaccines have relatively poor uptake compared with other vaccines, in part due to vaccine hesitancy and misinformation,(13, 25) and are prime targets for improvement through vaccinomics.(23)

Though vaccinomics implementation is 10-15 years away, now is the time to explore vaccinomics' policy implications, so that this information can guide federal funding priorities, research, and implementation of vaccinomics within existing immunization programs. This project aimed to elucidate the public's opinions and values around vaccinomics, vaccine hesitancy, and influenza vaccines by conducting community meetings and a survey demographically representative of the U.S. We planned to present the results in March 2020 to a group of vaccine stakeholders representing public health authorities (Centers for Disease Control and Prevention [CDC], National Institutes of Health [NIH], and Food and Drug Administration [FDA]), pharmaceutical companies, high-impact NGOs, and academics. Due to COVID-19, this meeting was delayed, as many of the invited vaccine stakeholders are involved in the pandemic response. Once the pandemic is under control, we hope to share our results with vaccine stakeholders and that they will incorporate the public's values into their decision-making processes regarding public funding for research, public health programs, and policies around vaccinomics. Our original goal was to inform implementation of vaccinomics, though we also hope

lessons learned will be extended to the introduction of other novel vaccines and prioritization paradigms, as may be needed to allocate limited supplies of future COVID-19 vaccines.

Chapter 2. Literature Review and Study Background

2.1 Impact of Vaccines: Effectiveness and Safety

The standards for vaccine safety and effectiveness are high, because vaccines are given to large numbers of healthy individuals, including vulnerable populations such as children and pregnant women. Prior to vaccination, healthcare providers and scientists cannot usually predict who will be exposed to infectious pathogens, and thus directly benefit from vaccination. Given the near universal use of many vaccines, a small increase in risk for an adverse reaction can impact a large number of people. Safety standards are especially high for vaccines required for school entry, as parental autonomy is limited.(7, 8) Most people who get vaccinated are protected from the pathogen of interest. While local minor reactions are relatively common, serious adverse events (SAEs) are exceedingly rare.(26) Because of the limited size and duration of clinical trials, rare and delayed associations cannot be detected until vaccines are administered population-wide.(26) Due to stringent inclusion/exclusion criteria for clinical trials, subpopulations are often excluded or underrepresented due to their small size.(27) Therefore, safety and efficacy cannot be evaluated for these subgroups. For example, the first *Haemophilus influenzae* type b (Hib) vaccine did not induce an adequate immune response in Native Alaskan and American populations, but this was only discovered post-licensure.(27) Post-licensure monitoring and evaluation are essential to detect rare events in individuals and subpopulations.(26) Overall, most people react well, obtaining the desired immune response and having limited adverse reactions due to the immune system's over-response to immunization, known as reactogenicity or reactogenic events. Safety and effectiveness vary by type of vaccine, the age of the vaccinated individual (the vaccinee), and circulating pathogens. The effectiveness and safety of all vaccines currently recommended by the Advisory Committee on Immunization Practices (ACIP) for use in the U.S. are shown in **Table 1**.

The terms Adverse Event Following Immunization (AEFI), adverse reaction, and serious adverse event (SAE) represent a hierarchy of labels used to describe the severity of and degree of causal association with vaccination. The WHO acknowledges that the public has become increasingly concerned with vaccine safety as the visual burden of vaccine-preventable disease has decreased.(28) It is essential to promptly investigate these events to show the public that these concerns are taken seriously and to uncover possible vaccine adverse reactions.(28) AEFIs are events following immunization which have not yet been determined to be causally associated with vaccination.(29) Adverse reactions/events and SAEs are distinguished by their causal association with vaccination.(26) The safety and effectiveness of vaccines recommended by the ACIP are described in **Table 1.**

2.2 Public Health Benefits of Vaccination

Vaccinations have drastically reduced morbidity and mortality from infectious disease, leading to the control of over 14 vaccine-preventable infections and the eradication of smallpox in 1980 (last case detected in 1977). Eradication is the permanent reduction of disease incidence due to a specific organism to 0 as the result of deliberate control efforts, such that further interventions are no longer needed.(30) Poliovirus type 2 was also eradicated in 2015 and type 3 was eradicated in 2019.(31) While polioviruses types 1 remains an eradication target,(32) incidence of all three virus types declined >99% since the pre-vaccination era.(33) Infectious disease control, unlike eradication, requires continuous interventions to reduce morbidity and mortality, without which the disease would resurge to pre-intervention levels.(30) Many infectious diseases have also been regionally controlled through vaccinations, including: diphtheria, tetanus, yellow fever, pertussis, *Haemophilus influenzae* type b disease, measles, mumps, rubella, typhoid, rabies, rotavirus, and HepB.(33)

Although vaccines have made a big difference thus far, new innovations are needed to combat emerging viruses, like COVID-19, and more familiar viruses that are not yet vaccine-preventable, like HIV

and hepatitis C.(34) There is also considerable room for improvement to existing influenza vaccines, which require annual vaccination and have suboptimal effectiveness.(35)

2.3 Role of Infection and Genetics in Vaccine Response

Genetic variances in the adaptive and somatic immune systems contribute to individual-level differences in clinical outcomes. The adaptive immune system, the focus of vaccinations, is based on antigen-specific T and B lymphocytes,(36) which correspond to the humoral and cellular immune systems, respectively.(37) The immune system can be temporarily or permanently suppressed due to genetics, infections, and chronic health conditions, increasing susceptibility to infection. Approximately 300 single-gene errors are known to cause immunosuppression. Although these genetic variations are rare, there is population-level evidence that the severity of infection and likelihood of death are genetically linked.(36) For example, being homozygous for the sickle-cell trait increases the risk of infection; however, being a heterozygous carrier is protective against severe forms of malaria.(36) Similarly, genetic polymorphisms are linked with progression of hepatitis C and HIV.(36) Single polymorphisms, like the cause of sickle-cell disease, are common among genetically-linked diseases of childhood. In adults, complex gene associations are more commonly linked with disease.(36)

Although genomic links have not yet been identified, it is highly likely that genomics predispose some individuals to be more contagious than others. These “super spreaders” likely shed more infectious material and perhaps shed longer than others. Genomics may one day explain why Typhoid Mary(38) and less infamous individuals infected the majority of cases in outbreaks of Middle East Respiratory Syndrome coronavirus (MERS), Sudden Acute Respiratory Syndrome (SARS), and Ebola.(39)

Genomics clearly play a role in infectious disease outcomes and are now known to influence vaccine response as well. Host factors like age, sex, and race interact with non-host factors like the number of vaccine doses administered, amount and quality of antigen in the vaccine, and route of

administration to influence individual-level vaccine response both in terms of vaccine effectiveness (VE) and vaccine safety.(15)

2.4 Safety Profile of Vaccines Routinely Recommended in the United States

Vaccines routinely recommended in the U.S. are extremely safe. Reactogenic events, such as swelling at the injection site, fever, or rash, are relatively common post-vaccination and usually resolve within a few days (**Table 1**). SAEs are rare. Five to 15 percent of children who receive the live attenuated measles, mumps, and rubella (MMR) vaccine have mild fever seven to 12 days post-vaccination, lasting one to two days, and/or rash seven to 10 days post-vaccination, lasting seven to 12 days.(40) On average, 3.3 seizures occur per every 100,000 doses given to children, usually following the first MMR dose.(41) However, febrile seizures have not been associated with long-term sequelae. Other common reactions include transient arthralgia (joint pain) in <1% children. Rare events include parotitis (inflammation of the parotid gland), lymphadenopathy (inflammation of the lymph nodes), and encephalopathy (brain swelling). Even rarer, measles inclusion body encephalitis and immune thrombocytopenia purpura (low blood platelet count causes bruising/bleeding in 1/30,000 doses) may occur.(18) The Institute of Medicine (IOM) concluded that there is a causal relationship between MMR and anaphylaxis (1-2/million dose).(42) Despite the occasional occurrences of SAEs, MMR continues to be used because it is safe for most children and two doses are highly effective in controlling measles.(18)

The inactivated influenza vaccines (IIV) for children and adults are also very safe. Local adverse reactions (soreness, erythema and induration at the injection site) lasting less than two days and systemic reactions (fever, chills, malaise, and myalgia) are common in children.(18, 43) Systemic symptoms are reported in less than 30% of children.(18) These symptoms often begin within 6-12 hours of vaccination and resolve within a few hours. IIV is similarly safe in adults: in clinical trials, 14-16% of vaccinees reported myalgia within one week of receiving the unadjuvanted IIV and 31-39% reported

myalgia following adjuvanted IIV. Rates were higher after receiving the 2009 H1N1 vaccine compared to seasonal vaccines.(18)

One SAE rarely associated with influenza infection and vaccination is Guillain-Barré Syndrome (GBS).(18) GBS is an ascending paralysis that may necessitate hospitalization and rarely causes death. The association between influenza vaccination and GBS was first detected when a pandemic was expected in 1976-1977 due to a novel circulating "swine flu" and a widespread vaccination campaign was undertaken. Post-licensure surveillance detected one person developed GBS per every 100,000 vaccinated, above the baseline rate of 10-20 cases per million adults.(19) The vaccine was subsequently removed from the market. During the 2009-2010 H1N1 pandemic, vaccinated adults had 2.35 (95% CI: 1.42, 4.01) times greater risk of GBS than unvaccinated adults, resulting in about 1.6 excess cases of GBS per million vaccinated persons.(44) In other years, seasonal influenza vaccines have been associated one case per one million vaccinated.(19) What caused GBS rates to be so high remains unknown. What is known, is that the risk of GBS increases with age, and a recent systematic review indicates children are not at increased risk of GBS. No other vaccines currently used in the U.S. are known to cause GBS.(18) Summaries of the safety profiles for vaccines recommended for routine use in the U.S. are shown in **Table 1.**

2.5 Vaccine Effectiveness

Nearly all vaccines routinely recommended have >80% effectiveness at preventing clinical disease when individuals are vaccinated with the ACIP-recommended number of doses **(Table 1).** Influenza vaccine effectiveness is typically lower, and some vaccines induce immunity that wanes over time. Influenza vaccine effectiveness (VE) varies depending on the match between circulating viruses and the viruses contained within the vaccine, the recipient's health, age, and biological sex.(18, 22-24) Additionally, influenza VE varies by the outcome of interest in reported studies. Reduced hospitalization is a simpler, yet more imprecise, measure of influenza vaccine effectiveness compared to the gold

standard, laboratory-confirmed illness by reverse transcriptase-polymerase chain reaction (RT-PCR).(45) It is difficult to measure influenza VE in clinical trials because of the unpredictability of influenza circulation. Among the few observational studies using RT-PCR-confirmed influenza in children enrolled from pediatric intensive care units versus clinic-based controls, estimates ranged from 37% (95% CI: 25, 68) for A(H3N2) to 82% (95% CI: 23, 96) during the 2010-2011 and 2011-2012 seasons.(35) Meta-analyses of observational data from adults ≥60 years showed VE against RT-PCR confirmed influenza to be 52% (95% CI: 41, 61) during epidemics and 58% (95% CI**:** 30, 70%) during regional outbreaks when the vaccine strains matched circulating viruses and even lower when there was a mismatch.(35) VE at one point in time does not fully represent whether a vaccine is protective. The duration of vaccine protection is also essential. Two diseases for which VE is very high, mumps and pertussis, are resurging, and this is in part due to waning immunity.(43-48)

2.6 Waning Immunity

Waning immunity to vaccination can be an important issue. As time since vaccination increases, immunity against the vaccine-specific pathogen wanes. This leads to a growing pool of susceptible individuals. If this pool reaches a critical threshold, a sustained outbreak of vaccine preventable disease may occur.(3) Two vaccine-preventable diseases for which this has recently occurred are mumps and pertussis.(43-48)

2.7 Mumps Vaccine

Mumps is caused by a virus transmitted via saliva droplets; individuals are infectious approximately one week before symptoms occur and 5-14 days after symptom onset.(46) The incubation period is 16-18 days. Prior to a vaccine being available, most children worldwide contracted mumps by age 15 years and mumps was the leading cause of encephalitis and sudden onset deafness. It is characterized by swelling around one or both ears and one or both testes in males.(46)

Children in the U.S. and many other countries are vaccinated against measles, mumps, and rubella (MMR) simultaneously using a live viral vaccine.(46) Unlike measles, waning immunity to mumps has led to outbreaks in previously vaccinated populations, mainly ages 18-25 years old. Outbreaks of measles, on the contrary, have mostly been among pockets of unvaccinated individuals. The older ages of the mumps cases and high mumps VE (one dose: 77%; two doses: 85%) indicated these cases were in part due to waning immunity, not primary vaccine failure.(46)

Other factors may work synergistically with waning immunity to cause outbreaks, otherwise they would occur continually as cohorts age and time since initial vaccination increases.(46) Theoretical causes of mumps outbreaks include differences in memory-B cell production in vaccinees following subcutaneous injection versus production in those naturally infected via nasal or buccal droplet exposure. Antigenic differences between naturally circulating viruses and the viral vaccine strain have been hypothesized to contribute to waning immunity and outbreaks. The fact that mumps has been controlled for decades in countries that continually use the same vaccine, when the naturally circulating viruses have likely shifted, indicates antigenic differences are not the primary cause of mumps outbreaks in vaccinees.(46) Mathematical models further indicated that incomplete vaccine protection due to antigenic shifts did not drive recent mumps outbreaks.(47) If antigenic changes in circulating viruses were responsible, more mumps cases would be expected among young children than have been observed.(48)

Instead, the duration and intensity of close contact, coupled with waning immunity, were implicated in causing recent outbreaks. Prolonged, close contact was associated with mumps outbreaks at religious schools in two U.S. states and may explain why mumps outbreaks frequently occur in college dormitories.(46) Mathematical models indicated that waning immunity and decreased exposure to circulating mumps viruses primarily caused adolescents to be at greatest risk of mumps in the 1980's and for adults to be at the greatest risk now.(48) Receiving mumps vaccine (any dose) is estimated to

confer 27.4 (95% CI 16.7, 51.1) years of immunity. However, 25% of the population is estimated to lose immunity within 7.9 (95% CI 4.7, 14.7) years of vaccination. Additional doses, administered to as a one-time dose to 18-year-olds and/or repeated booster doses administered to adults every 10-20 years, may be needed to prevent future outbreaks.(48)

2.8 Pertussis Vaccine

Like mumps, pertussis (whooping cough) is a disease that was nearly universal in childhood prior to the advent of an effective vaccine.(49) Pertussis is common among all age groups, but is most serious among infants. The incubation period for pertussis is often 7-10 days (range 4-21 days) and appears like an upper respiratory infection. Quickly, the intermittent cough progresses to become nearly constant and spasmatic, lasting 2-6 weeks or longer. Pertussis is characterized by the "whoop" infected individuals often make as they inhale air. However, not all individuals develop the "whoop," and it is uncommon in infants. In a study of 2,592 individuals ages 6 days to 41 years old from whom the causative agent, *B. pertussis*, had been isolated, unvaccinated individuals most often presented with a spasmodic cough (90.2%), whooping (78.9%), and post-cough vomiting (53.3%). Pertussis is caused by a bacterium and should be treated with antibiotics. This is especially important to prevent death in infants.(49)

Routine immunization programs in North America, Europe, and parts of Asia and Latin America exclusively use acellular pertussis (aP) rather than the original, whole cell pertussis (wP) vaccines.(49) The acellular vaccines were developed to reduce local and systemic reactions, making them safer than whole cell vaccines. The impact of acellular vaccines is hampered by waning immunity. This problem is exacerbated by the fact that most individuals are no longer naturally exposed to *B. pertussis*, which would otherwise boost their immune systems, leaving those vaccinated with aP more susceptible to clinical disease.(49)

The epidemiology of pertussis has changed since the introduction of aP vaccines.(50) Pertussis is now reported most frequently in infants, who are too young to receive three DTaP doses.(51) Infections in adolescents and adults frequently occur in individuals who have been vaccinated, naturally infected, or both.(50) This may be due to waning immunity, better awareness and diagnosis of pertussis in older age groups(51), and clustering of individuals with non-medical vaccine exemptions to school immunization requirements.(52, 53) In 2010, California had an outbreak of 9,120 reported pertussis cases. In the preceding 10 years, the rate of nonmedical vaccine exemptions for school attendance tripled within the state. Those with vaccine exemptions clustered; up to 84% of students within a single school had nonmedical exemptions.(52) Using geospatial analysis methods, Census Tracts with a cluster of nonmedical exemptions were found to be 2.5 times as likely as Census Tracts without exemption clusters to also have a pertussis cluster (OR 2.47 95% 2.22, 2.75).(52) A similar study was conducted using nonmedical exemption data for kindergarteners for the 2011-2012 and 2012-2013 academic years and reported pertussis cases during the same time periods in Oregon, Arizona, Utah, Washington, and New Jersey.(53) In this study, there was strong evidence of nonmedical exemption clustering (RR 2.80, $p<0.0001$ for having an exemption within versus outside a cluster).(53) Simultaneously, 31 out of 134 (23%) counties studied had pertussis clusters that included adolescents 10-14 years old.(53) These data suggest clustering of nonmedical exemptions is contributing pertussis outbreaks in addition to waning immunity.(53)

2.9 Vaccine Confidence and Hesitancy

The Strategic Advisory Group of Experts (SAGE) on Immunization at the WHO defines vaccine hesitancy as delaying or refusing available vaccines.(1) This definition does not encompass the totality of vaccine hesitancy, which also includes vaccine acceptance for oneself or one's child despite having concerns about vaccine safety, effectiveness, or ingredients.(7, 8) The WHO's definition does not

account for vaccine delay or refusal due to parents' competing priorities. If adults need to choose between taking their child to get vaccinated or spending that time earning wages to support their family, they may delay or refuse vaccines for financial reasons rather than hesitancy. Current methods of measuring vaccine hesitancy do not make this distinction, nor do they account for parental concerns that are masked by compliance with school vaccination requirements.(7, 8)

Vaccine hesitancy is a global problem, designated by the WHO as one of the top 10 threats to global health in 2019.(54) It is difficult to quantify where vaccine hesitancy is highest since disparate methods were used in a survey of 67 countries and many African and Asian countries were excluded.(55) The number of measles cases in recent years indicates vaccine hesitancy is high and MMR coverage is low in many countries.(56) In 2019, the UK, Albania, Greece, and the Czech Republic lost their certification from WHO for having eliminated measles.(57) In 2018, the Ukraine had the highest number of reported cases – 53,218 – followed by Madagascar, which had the highest percent increase over the prior year.(5) Only 50% of Ukrainians agree that vaccines are effective, a misconception common in Eastern European countries outside the European Union.(5) Many miles away in Samoa, there were 77 reported measles deaths in 2019,(58) reflecting safety concerns after two infants died when nurses reconstituted the vaccine with muscle relaxants rather than sterile water.(59) Whereas the crisis in Samoa stems from a medical error, in developed settings, a discredited theory(60) continues to have ramifications as 10% of U.S. adults reported in 2019 that vaccines cause autism.(6) Misinformation spread via Political Action Committees and the media propagates vaccine concerns.(61)

Vaccine hesitancy in other countries is linked to outbreaks in the U.S.(62) In 2019, 1,282 measles cases were reported in 31 U.S. states(63) As of October 1, 2019, 64% of 81 imported cases occurred among unvaccinated U.S. residents returning from international travel.(62) An outbreak in New York was linked to travel to Israel,(64) which simultaneously had high levels of measles circulation.(65) In the

U.S., 89% of cases were unvaccinated and 10% were unknown to be vaccinated with a measles containing vaccine.(62) Ten percent of cases required hospitalization.(62)

Though this was a nationwide outbreak, 73% of cases were reported in New York where two outbreaks occurred among ultra-orthodox Jewish communities.(62, 63) Vaccine misinformation targeting ultra-orthodox Jews, formatted to look like something that would be found in a doctor's office, circulated in New York since 2014 or earlier.(66, 67) This misinformation likely contributed to New York's outbreaks.(66) The pamphlet is available online.(67)

Many people worry about vaccine safety in general and are particularly worried about influenza vaccines due to annual changes in the formulation.(4, 6-13) Despite a lack of epidemiological evidence, individuals commonly worry that they or their children may be at increased risk of diseases with genetic risks factors (i.e. autoimmune disorders) or that children's immune systems could be overloaded by receiving too many vaccines at once.(61, 68, 69) Individuals who refuse or delay vaccines due to their concerns often cluster in geographic and social groups, contributing to vaccine preventable disease outbreaks.(52, 62, 70)

The most recent data on vaccine hesitancy come from a 2019 Gallup poll of American adults.(6) The proportion of Americans who said it was "extremely or very important" that parents vaccinate their children fell 10% from 94% in 2001 to 84% in 2015, but remained constant at 84% from 2015 to 2019. Overall, 86% indicated vaccines were not more dangerous than the diseases they prevent. Ten percent believed that vaccines cause autism, but 46% were unsure and only 45% were sure they do not. Older age, higher education, identifying as a Democrat, and not having children aged under 18 years were associated with higher belief in the value of parents vaccinating their children, that vaccines are not more dangerous than the diseases they prevent, and belief that vaccines do not cause autism.(6)

The results of the 2010 HealthStyles Survey, published in *Health Affairs*, are the most recent vaccine confidence data among parents published in the peer-reviewed literature.(4) The prevalence of parental vaccine concerns was reported amongst a sample of 376 parents who intended to vaccinate their <6-year-old child with some or all recommended vaccines.(4) In this sample, 77% of parents had at least one vaccine concern. Parents were most concerned about it being painful for their child to get so many vaccines at once (38%), the child getting too many vaccines in one doctor's visit (36%), children getting too many vaccines in the first two years of life (34%), vaccines may cause fevers (32%), and vaccines may cause learning disabilities, such as autism (30%). Concerns also included the ingredients in vaccines being unsafe (26%), vaccines not being tested enough for safety (17%), vaccines may cause chronic disease (16%), vaccines are for diseases children are unlikely to get (11%), vaccine shortages causing children not to be vaccinated on time (9%), and the diseases prevented by vaccines are not serious (8%).(4)

Vaccine hesitancy may also be due to increased fear of vaccine reactions compared to less visible vaccine preventable diseases, the temporal association between onset of disorders like autism, allergies, and autoimmune diseases and the timing of when children receive many vaccines and increase in the number of vaccines given to children over the last 25 years.(7, 8) Parents may prefer the risks associated with forgoing vaccination for their children (risks of omission) to the risks of deliberate vaccination (risks of commission), meaning the risks of opting out of vaccination (disease) outweigh the risks of complying with vaccination. Voluntary vaccine refusal may be preferred to mandatory vaccination for school attendance. Refusing to comply with vaccine requirements may give parents the sense that they are in control, rather than the school or healthcare system. The risks of SAEs from vaccination may seem less predictable than the seemingly lower risk of an unvaccinated child contracting a well-controlled disease. Vaccines made once very visible diseases, like polio, exotic. Many parents are more fearful of visible and familiar disorders, like autism, than vaccine preventable

infections. Some parents prefer natural products and infection to man-made products, like vaccines.(7, 8)

Vaccine delay and refusal were measured on the national-level by the CDC-sponsored National Immunization Survey (NIS). From 2003-2009, the proportion of parents who delayed vaccines nearly doubled (21.8% to 39.8%).(7, 8) The 2009 NIS found that 40.8% (95% CI: 38.2%, 41.4%) of parents reported delaying or refusing any vaccines for their children ages 24-35 months-old.(71) In 2012, a separate survey conducted by the National Center for Immunization and Respiratory Diseases at the CDC found that 3.4% (95% CI: 2.6%, 4.5%) of parents with children 6-23 months reported refusing all vaccines for their child.(72) Among these vaccine refusers, 31.4% (95% CI: 19.1%, 45.9%) listed "vaccine side effects" as their top concern.(72) In a separate study, medical record abstraction from eight managed care organizations that are part of the Vaccine Safety Datalink (VSD) indicated 3% (95% CI: 11.9%, 14.2%) of children were under-vaccinated due to parental vaccine hesitancy.(7, 8) Some children are vaccinated on time by age 36 months; however, they are vaccinated on an alternate schedule, receiving a maximum of two vaccines at a time. The proportion of such children increased from 0.7% in 2002-2005 to 2.3% in 2011-2012.(7, 8)

Vaccine refusal is often measured by the prevalence of nonmedical vaccine exemptions (religious and/or personal belief) to school immunization requirements.(73) Each state requires children to obtain vaccines before entering kindergarten; however, the ease of obtaining nonmedical exemptions varies by state.(7, 8) The simplicity in obtaining nonmedical exemptions (incidence rate ratio: 1.53; 95% CI: 1.10, 2.14) and whether states permit personal belief exemptions (incidence rate ratio: 1.48; 95% CI: 1.03, 2.13) are associated with the incidence of pertussis, after adjusting for demographic factors.(73) States report the prevalence of exemptions to the CDC for national surveillance purposes; however, local level surveillance is critically important to identify clustering of vaccine exemptions and prevent potential outbreaks like what occurred in Northern California in 2010.(7, 8, 52)

Vaccine hesitancy is negatively impacting the proportion of children who are fully vaccinated on time and jeopardizing "herd immunity," or community protection. Over 90% vaccine coverage is needed for mumps and >95% for measles vaccines to afford community-wide protection.(7, 8) Not all vaccinated individuals will have an adequate immune response, therefore these numbers reflect the bare minimum levels of vaccine coverage needed to protect the public. As these data show, waning vaccine confidence and immunity to certain vaccines, combined with clustering of unvaccinated individuals, are contributing to vaccine preventable disease outbreaks and threatening public health.(7, 8, 52)

In summary, with some variability between vaccines, most people have a sufficient immunological response to protect them from disease and do not experience serious adverse reactions. Some people under respond to vaccination, and are thus insufficiently protected. Others have an immune system that over-responds, leading to adverse reactions **(Figure 1)**. Differences in how individuals respond to particular vaccines may be due to previous or concurrent illness,(36) other environmental factors,(52) nutrition,(74) and genomics.(74, 75)

2.10 Defining Vaccinomics

Gregory A. Poland et al. coined the term "vaccinomics" to signify a departure from the "Isolate–Inactivate–Inject" paradigm that reigned from when the first vaccines were administered to humans by Edward Jenner in 1798 until the late 1900s.(3) Vaccinomics is an emerging field that has the potential to improve vaccine development and use through the science and study of genomics and vaccines, and application of that knowledge to construct new vaccine candidates and personalization of vaccine schedules.(3) Vaccinomics aims to make vaccines safer and more effective, targeting vaccine use and optimizing the prevention of disease and adverse reactions.(17)

"Adversomics" refers to the application of immunogenetics (at the individual-level) and immunogenomics (at the population level) to the study of adverse events.(15) Adverse events due to genetics or genomics may be preventable.(15) There are many related terms, such as proteomics, which refers to studying how pathogens grow, and immunomics, used to identify vaccine candidates most likely to be elicit an adequate immune response in humans.(17) For simplicity, these concepts will collectively be referred to as "vaccinomics" henceforth.

Improved understanding of genetic factors that influence vaccine response may lead to the development of safer and more effective vaccines and more individualized, or subgroup specific vaccine schedules.(17) Although the present vaccination system does not account for genetic predispositions, vaccines are safe and effective for most individuals **(Table 1).**(15)

2.11 Research and Development for New Vaccines and Adjuvants

The lower limit of effectiveness for each vaccine provides the baseline above which vaccinomics could be even more effective. Highly effective vaccines, like MMR and Hib (**Table 1**), have little room for improvement. On the contrary, influenza vaccines have relatively low and varied effectiveness depending on the match between the vaccine strain and circulating influenza viruses.(43) Influenza vaccines are prime targets for vaccinomics research because they are relatively ineffective compared to other vaccines.

Influenza vaccines have notoriously low effectiveness, despite being made since the 1930's.(35) Influenza vaccine effectiveness varies annually due to frequent point mutations in the viruses' hemagglutinin (HA) and neuraminidase (NA) surface antigens (antigenic drift), abrupt changes in the viruses in response to a decreasing pool of susceptible individuals (antigenic shift), and reassortment with other influenza viruses in mammals (emergence of new viruses). These three types of changes necessitate the creation of new vaccines semiannually worldwide, and annually for use within the U.S.(35)

Historically, each influenza vaccine virus is grown in a chicken's egg, which is a slow process.(35) However, some vaccines are now grown in mammalian cells(35) and others are made with recombinant technology.(20) Monovalent vaccine viruses are inactivated, purified, and combined to form multivalent IIV.(35) It takes five to six months and international collaboration to develop a new supply of influenza vaccines each year.(76)

It takes approximately 9 months to produce the nation's influenza vaccine supply, therefore U.S. U.S. officials must decide which virus strains to include in influenza vaccines more than six months before influenza season begins,.(35) These decisions are based on the WHO's surveillance of antigenic drift and shift and ultimate recommendations. Sometimes officials make inaccurate predictions, leading to mismatches between influenza vaccines and circulating viruses. When this occurs, influenza vaccine effectiveness is particularly low. This was the case for the 2017-2018 influenza season, which resulted in very low vaccine effectiveness (25% VE against the dominant A [H3N2]). VE was higher for subgroups of the population, reducing the risk of medically-attended influenza among children by 41%. Despite the mismatch, the influenza vaccine had a substantial public health benefit for a small portion of the population.(77)

Pandemic preparedness is especially challenged by the ever-changing influenza viruses and the long vaccine production process. To be adequately protected against a novel virus, each individual may require a higher vaccine dose, multiple doses, or an adjuvanted vaccine compared to what would be used during a regular seasonal influenza outbreak.(35) Requiring multiple doses would further strain limited vaccine resources. Although unadjuvanted vaccines were used in the U.S. in 2009 when a novel H1N1 virus emerged, adjuvanted vaccines were used in Europe.(78) Adding an adjuvant allowed for a lower amount of viral material to be included per dose, helping to stretch the limited vaccine supply (U.S.: 15 µg HA; Europe: 3.75 or 7.5 µg HA).(78) Clinical trials in the U.S., indicated a single dose of H1N1 vaccine would induce antibody titers high enough to reduce the risk of illness in 95–98% of healthy

adults by 50%; however, two doses were deemed necessary to induce protection in 90–100% of children.(78)

Vaccinomics could help with seasonal and pandemic preparedness in many ways. Perhaps a genetic factor will be identified that is associated with immunity to all influenza viruses. Suppose 20% of the population carries this trait, and would be immune to all influenza viruses if vaccinated. Given that there are over 325 million people in the U.S.,(79) there would likely be public health benefits, and it may even be cost-effective, to create and distribute a vaccine that would make 20% of the population immune to all influenza viruses. At minimum, the vaccine could protect the health of 20% of the population. At best, it could help thwart circulation of influenza community-wide.

Vaccinomics could play a role in improving the effectiveness of influenza and other vaccines by helping to identify more promising vaccine and adjuvant candidates earlier in clinical trials, minimizing the chances that subgroups under respond to vaccines once licensed and used population-wide.(27) For example, the original Hib vaccine was ineffective in Alaskan and Native American populations post licensure. Vaccinomics could help identify potential subgroups of nonresponders earlier in the research and development process so that resources can be redirected towards vaccine candidates that will more likely be immunogenic (stimulate an immune response) for their target audiences.(27) Furthermore, vaccinomics could leverage genomic differences to identify vaccine candidates expected to be immunogenic and safe for specific subpopulations, under the expectation that these vaccines would only be given to people with the relevant genetic traits.(27) This would be a more tailored vaccination strategy than is currently used. Clinical trials measure how well vaccines work on average, regardless of genomics. The ACIP makes its recommendations for the general population based on clinical trial results.(27)

In addition to developing new vaccines against influenza and other hypervariable viruses (ex. HIV, Hepatitis C),(80) vaccinomics may make vaccines safer by developing novel adjuvants.(17) Adjuvants are often included in subunit vaccines, which are generally safer than whole organism and live attenuated vaccines but less immunogenic.(17) Vaccinomics could lead to safer adjuvants that bolster the vaccine recipient's immune response while minimizing reactogenic responses compared to current adjuvants.(17) New adjuvants could also lead to the development of vaccines against diseases that are not yet vaccine-preventable, like HIV, Alzheimer's Disease, and most forms of cancer.(17) Furthermore, new adjuvants may also lead to more immunogenic vaccines for populations with reduced immune reactions, like the elderly, and those whose immune systems are overly compromised, such as those with or undergoing cancer treatment.(17)

Identifying appropriate vaccine candidates earlier would also minimize the likelihood that clinical trial participants are exposed to unnecessary risks and speed up the vaccine development process.(17) A universal influenza vaccine that eliminates the need for annual vaccine production could be enormously helpful for both seasonal and pandemic preparedness.(81) These innovations could ultimately lead to a more cost-effective vaccine development pipeline, with fiscal benefits to bulk vaccine purchasers like the federally-funded Vaccines for Children Program (VFC) and to individuals paying out of pocket or through their health insurance provider.

2.12 Ascertaining if Adverse Events Following Immunization (AEFIs) are Vaccine Reactions

Vaccinomics could be used to analyze AEFIs and determine whether these events are causally associated with vaccination. In analyzing reported AEFIs, vaccinomics may help to uncover genetic susceptibilities to adverse events (AEs). For example, epidemiological evidence from studies in several northern European countries showed a strong association between the AS03 adjuvanted pandemic H1N1 2009-2010 vaccine (Pandemrix™) and narcolepsy in children, adolescents, and adults under 40 years old.(75) Data from five countries indicated the increased risk of narcolepsy in vaccinated

individuals was 4-13 times greater for children and adolescents and 2-4 times greater for adults.(75) Narcolepsy diagnoses also increased in China following the 2009-2010 influenza season, yet the AS03 adjuvanted vaccine was not used. Diagnoses later returned to pre-2009 levels.(75) This indicated there may be an association between the H1N1 antigen and risk of narcolepsy, in addition to the Pandemrix™ vaccine. This hypothesis is consistent with prior evidence that streptococcal infections are also associated with narcolepsy onset. In Canada, the same AS03 adjuvant included in Pandemrix™ was used in a different H1N1 vaccine, Arepanrix™, administered to 57% of Quebec's population during the 2009-2010 season yet, only two cases of narcolepsy were reported among 17 million individuals over 6 months old, providing no evidence of increased incidence.(75) The AS03 adjuvant itself may not induce narcolepsy, rather it may enhance the Pandemrix™ antigen as a trigger.(75)

A genetic allele may be needed for Pandemrix™ and H1N1 infection to trigger narcolepsy. Regardless of ethnicity, 88–95% of narcolepsy patients with cataplexy are DQB1*06:02 positive; however, the association is weaker among those without cataplexy.(75) The prevalence of this genotype is 25-30% in Northern Europe, where narcolepsy cases sharply increased following Pandemrix™ vaccination, and 25% in China where narcolepsy diagnoses increased following the influenza season in 2009-2010 but Pandemrix™ was not used.(75) In comparison, the prevalence of the DQB1*06:02 positivity is 12% in Japan where narcolepsy prevalence is highest worldwide (160 per 100,000).(75) Taken together, epidemiologic and laboratory data indicate the DQ0602 heterodimer may be a necessary, but insufficient cause of narcolepsy, which requires an environmental trigger like H1N1 infection or vaccination with Pandemrix™ to induce an immune-mediated process that causes narcolepsy.(75) Due to an inability to reproduce their results, De la Herrán-Arita et al. retracted their article, supporting the role of auto-reactive T-cells in the immune-mediation process, weakening the evidence base for this hypothesis.(82, 83) As scientific understanding of what causes narcolepsy and other AEFIs progresses, if the risks of vaccination outweigh the risks of being unvaccinated, individuals

with DQB1*06:02 and other genotypes may be advised to abstain from getting certain vaccines. The ACIP may eventually amend vaccine schedules to reflect genetic predispositions to vaccine adverse reactions, which would be a more targeted vaccination strategy than is currently in place.

2.13 Targeting Vaccine Use

Vaccinomics can be used to prevent AEs through pre-vaccination screening once the etiology of these events is understood.(81) This includes identifying genetic markers of adverse reactions, such as gender or racial factors, and creating targeted vaccination schedules for subgroups of the population.(17) Once the mechanisms for AEs are identified, individuals could be pre-screened, told their increased risk,(84) and advised not to get or prohibited from getting the vaccine if the risks outweigh the benefits for this genetic subpopulation. For example, specific haplotypes of the IL 1, IL 18, and IL4 genes have been associated with increased risk of fever following smallpox vaccination, and may be responsible for an increased risk of fever following MMR or other vaccinations.(15) If these associations are determined to be causal, pre-vaccination screening could significantly decrease the occurrence of fever and febrile seizures in children.(15) This screening could theoretically be added to standard practice screening done on newborns now(85) or at a primary care provider's office for older children.

It is also hypothesized that genetics play a role in susceptibility to GBS. Genes involved in the immune system may lead to the production of antibodies that recognize the proteins on individuals' own nerves, leading to nerve damage.(86) A gene that encodes for a proinflammatory cytokine, tumor necrosis factor (TNF), is associated with multiple aspects of cell function and may be associated with GBS. TNF is also associated with autoimmune disease, insulin resistance, and cancer.(86) If genetic linkages are identified between specific genes and GBS, this provides a potential target for pre-vaccination screening and recommendations regarding who should and should not get influenza vaccines and/or other vaccines that may increase their risk of an adverse event.(15)

Pre-vaccination screening may help medical providers and public health officials use limited vaccine supplies on those who are most likely to have the desired immunogenic response. Vaccinomics has been applied to study genetic factors affecting immunity, and found that host factors may be more pertinent to immune response to measles vaccination than to mumps or rubella vaccination.(17) Pre-vaccination screening could identify individuals most likely to respond to the measles component of MMR, and the vaccine could be targeted towards those most likely to have the desired immune response. Perhaps another version of MMR or an additional measles booster would be recommended for those who do not sufficiently respond to a single dose. Although the costs and logistics of pre-vaccination genetic screening are infeasible today, this might be a cost-effective strategy in the future, as it may conserve vaccine antigen by preventing wastage on non-responders. Ten to fifteen years from now, primary care doctors may already have individuals' genetic information on file and could easily implement this approach. Individuals may have access to their own genetic information through direct to consumer testing. Pre-vaccination screening may help us implement vaccinomics, reduce adverse reactions, and prevent vaccines from being wasted on non-responders.

2.14 Vaccine Compensation

If vaccine-related adverse reactions decrease due to improved vaccine safety through vaccinomics, there may be fewer individuals injured and filing for compensation through the National Vaccine Injury Compensation Program (VICP). The VICP was established in 1986 to compensate individuals who believe that they were injured by a covered vaccine and who file the necessary paperwork.(87) Covered vaccines are limited to those recommended by the ACIP for routine use in children; however, adults may be eligible for compensation for injuries believed to have resulted from childhood immunization. A $0.75 excise tax is levied per disease prevented by all vaccines routinely recommended for children by the ACIP. Vaccines like IIV are taxed $0.75 for preventing one disease

(influenza) whereas DTaP is taxed $2.25 because it prevents diphtheria, tetanus, and pertussis. Income from these excise taxes are used by the VICP to compensate individuals of all ages.(87)

Parents, legal guardians, and legal representatives may file petitions on behalf of children, disabled adults, and deceased individuals.(87) After filing a petition, the U.S. Department of Health and Human Services (HHS) reviews the petition and makes a preliminary recommendation whether there is medical evidence of an injury. The U.S. Department of Justice reviews the report and adds a legal analysis of the case based on the Vaccine Injury Compensation Table. Injuries that meet specifications in the table (ex. anaphylaxis or anaphylactic shock onset within four hours of vaccination) are assumed to be caused by the vaccine.(88) In this case, compensation is dispensed based on the table. If not, petitioners must present their case before the U.S. Court of Federal Claims (the Court), which appoints a special master to decide the case. This decision may follow a hearing during which both parties may submit evidence. If damages are deemed appropriate, the amount to be paid is determined by the special master and may include the petitioner's legal fees. Damages awarded by the Court are paid by HHS. The Court's decisions may be appealed in Civil Court.(87)

During the VICP's 29 year-long history, 6,085 petitions have been compensated, costing $3.9 billion.(89) From 2006-2016 3,723 petitions to the Court were compensated out of 5,492 petitions filed. Approximately one individual was compensated per every million vaccine doses distributed. During the same ten year-long period, influenza vaccinees received more than nine times as many compensations compared to all other vaccines (1st influenza: 2,482; 2nd Tdap: 314; 3rd: DTaP-HepB-IPV: 140).(89)

These numbers reflect that over half of all claims were financially compensated; however, this does not provide evidence of a causal association between vaccines and adverse events. A substantial proportion of cases are compensated for reasons of risk mitigation and a substantial proportion of funds have been used to pay for petitioner attorney and expert witnesses who are paid regardless of the

outcome of the case. The VICP has an obligation to pay claims based on the Vaccine Injury Compensation Table and settle claims that go to The Court relatively quickly. Claimants need to provide plausible evidence of an association between their adverse event and the preceding vaccination; however, the correlation does not mean there is a causal relationship. Independent of vaccination, individuals have a chance greater than zero of GBS. This chance is approximately doubled within 6 weeks of influenza vaccination according to the results of meta-analyses.(44) When a case of GBS is reported to the VICP, the background rate of disease is not considered, as it is not incorporated into the Vaccine Injury Compensation Table used as the basis for payments.(88) The VICP is likely making payments for claims that are in fact not vaccine-induced.(89) Vaccinomics could be used to determine if cases of GBS and other adverse events are actually caused by vaccines, improve vaccine safety, reduce federal government payments through the VICP, and hopefully improve the public's confidence in vaccines.

2.15 ELSI and Infectious Disease

ELSI refers to ethical, legal, and social implications (ELSI). The ELSI Research Program was established in 1989 as part of the Human Genome Project, which was led by the National Advisory Council for Human Genome Research (NACHGR).(90) The program was elevated to an NIH Institute in 1997 and renamed the National Human Genome Research Institute (NHGRI). It funds research and training opportunities related to the ELSI of 1) genetic and genomic research, 2) genetic and genomic healthcare, and 3) broad legal, policy, and societal issues.(90) This project is funded under the Institute's third research domain as it relates to genetic and genomic technological advances, research, and use of these technologies in clinical and non-clinical settings.(90)

This project is the first infectious disease focused grant funded by the NHGRI ELSI program. Recently, the NIH announced $18.9 million will be awarded through the NHGRI, National Cancer Institute, and the National Institute on Minority Health and Health Disparities to fund research focused

on using genomic sequencing in clinical care. Research sites will aim for 60% of participants to be enrolled from diverse and underserved areas,(91) supporting NHGRI's investment in exploring the heterogeneity of genomics and its impact on healthcare. As the association between vaccinomics and cancer prevention evolves, in the form the HPV and Hepatitis B vaccines, the biological basis of vaccinomics may become an increasingly important and funded domain.

2.16 How the Public Can Inform Policy Implications of Vaccinomics

2.16.1 Funding

What the public thinks about the policy implications of vaccinomics is critically important and should be considered by public health stakeholders, including 1) public health authorities (CDC, FDA, NIH, etc.) allocating taxpayers' money to vaccinomics and other research priorities and 2) public health and medical professionals charged with implementing vaccinomics. Whether or not vaccinomics is successful depends upon these stakeholders and the public at large accepting vaccinomics as a safe and effective alternative to traditional vaccination strategies. Vaccinations are also largely funded through tax-payer dollars. Federal funds are allocated to the Vaccines for Children Program (VFC), which buys ACIP-recommended vaccines in bulk and distributes them free of charge to healthcare providers for children who are uninsured, under-insured, or Native American. Children who could not otherwise afford to be vaccinated are vaccinated through this program.(92) The vaccine itself if free-of-charge; however, a vaccine administration fee is billed to Medicaid or the child's parent/legal guardian if the child is not a Medicaid recipient. The federal government funds vaccinations through additional programs as well. CMS funds state-based administration of Medicaid and the Children's Health Insurance Program (CHIP) and covers influenza vaccinations, among others.(92, 93) Medicare covers under-utilized adult vaccinations, including pneumococcal, influenza, and HepB.(92) Because of the vast amount of public funding for vaccinations, the role of public opinion in vaccine acceptance and refusal,(94) and an inherent belief that what the public thinks should influence public policies, the Johns

Hopkins Research Team convened a meeting with public health stakeholders to discuss areas where public values around policy implication of vaccinomics issues could impact vaccinomics-related decision-making.

2.16.2 Parent Study

The Vaccinomics Project (PI: Daniel Salmon) is the basis for this dissertation and it is one of three pilot projects embedded within the Center for Bridging Infectious Diseases, Genomics and Society (BRIDGES). Supported by the National Human Genome Research Institute (NHGRI), BRIDGES is the first Center for Excellence designed to explore the ELSI of genomics and infectious disease (Co-PIs: Gail Geller and Jeffrey Kahn; RM1HG009038). The vaccinomics project highlights the role of genomics in the public health context. The Center's other two pilot projects highlight the role of genomics in the research context (focusing on HIV and HCV) and the clinical context (focusing on the management of high-consequence infections in the hospital setting).

At the start of this grant in April 2017, we held a meeting with academic vaccinologists and Federal agencies involved in vaccines, including representatives from the National Institutes of Health, Food and Drug Administration, Centers for Disease Control and Prevention, and Health Resources and Services Administration (National Vaccine Injury Compensation Program). We facilitated a discussion about what policy issues might emerge throughout the lifecycle of vaccinomics, and where public input would be useful, even though vaccinomics may not be implemented in the U.S. for 10-15 years. Discussions with vaccine stakeholders led us to identify the following policy issues that would benefit from public input:

- Who gets access to (possibly) personalized vaccines (and at what cost) for public health benefit?
- Should prioritization of vaccinomics research be placed on rare, serious, adverse reactions or common, mild adverse reactions? Should subpopulation differences in vaccine response

and contagiousness ("more contagious" and "more susceptible" populations) be used instead?

- Does the personalization of vaccines increase confidence in their safety and effectiveness, including vaccine scheduling and dosing? Why?
- Should funding for vaccinomics be prioritized over existing federal priorities?

Stakeholders encouraged the Research Team to assess the public's values, assess public perceptions of the vaccine risks and. benefits for adults versus children, and the acceptability of a biorepository or biobank that could potentially be associated with the Vaccine Adverse Event Reporting System (VAERS) or the Infectious Disease Society of America's Emerging Infections Network (IDSA EIN). VAERS is a passive reporting system into which providers are legally required to report certain types of adverse events. Vaccine manufacturers must report all AEFIs and the public can report AEFIs as well.(95) IDSA EIN is a network of over 1,100 infectious disease specialists that gathers clinical and epidemiological data on emerging infectious diseases and works collaboratively with the CDC and other investigators.(96) When AEFIs occur, individuals could be asked for consent to have their biological samples stored in a biobank linked to VAERS and the IDSA EIN. As samples accumulate, there would be a growing evidence base to assess potential relationships between vaccines, adverse events, and genomics.

Stakeholders expected the public would have important contributions regarding the equity of including minority populations in vaccinomics research. For example, minority populations could be oversampled in research studies to increase the likelihood that, if there are adverse events in these groups, they are detected early. However, this may be interpreted as subjecting minority groups to more of the risks of vaccinomics research than is proportional to their population size, and therefore unfair.

Based on these discussions, the Research Team concluded that the public's opinions needed to be further explored through qualitative research prior to conducting a quantitative survey. We aimed to elucidate the policy implications of vaccinomics, and to characterize vaccine hesitancy and influenza vaccine uptake, which we expected may change in response to vaccinomics in the future.

2.16.3 Policy Implications of Vaccinomics and Adversomics

Although there is a breadth of published literature about "omics" in general and "omics" of infectious disease, very few articles specifically discuss the ELSI or policy implications of vaccinomics. Articles that discuss vaccine preventable infections and public policy have a broad focus, and are not specific to vaccinomics. An article coauthored by many members of this Research Team discusses the policy implications of prioritizing subgroups for treatment based on genomics, such as the policy implications of prioritizing individuals at high risk for developing active tuberculosis or chronic hepatitis B for curative and therapeutic treatment, respectively.(97) In this article, Geller et al. discuss some issues specific to vaccinomics, such as potentially using genetic information to identify high-risk subgroups for vaccine development, and using genetic information to decide who is prioritized for vaccination during a vaccine shortage.(97) However, it is the ELSI of infectious disease at large, not specific to vaccines, that is the article's focus. Articles that discuss issues directly related to vaccinomics, such as the potential uses of Big Data in studying AEFIs(98) and systems immunology;(99) do not specifically explore policy issues. Other vaccinomics-related articles mention ELSI issues, typically in the introduction or discussion section, or focus on governance and legality.(100) Data on public attitudes and values around vaccinomics are absent from the published literature. Understanding public attitudes and values is very important when developing research priorities, policies, and ultimately incorporating technology into healthcare and public health practice. Vaccinomics-related themes explored through this dissertation include:

- **Genetically-based Vaccine Prioritization**
    - Is it acceptable to the public and if so, how high of a funding priority, to use federal funds to prioritize targets of vaccine development that will only help subgroups of the population? What does the public think about using genomics to prioritize subgroups of people for vaccines, such as telling non-responders they are ineligible for vaccines or telling super spreaders (those at increased likelihood of infecting others)(38) that they should or are mandated to get a vaccine? What if vaccines were prioritized by something phenotypically visible and can be accurately determined by self-report, like race or biological sex? The result of these recommendations may be increasingly complex vaccine schedules. What does the public think about that?
- **The Ethical Repercussions of Vaccinomics**
    - Is there a moral obligation to take steps that may help protect others if one knows they are a super spreader? Genetic research may identify traits that indicate someone is more likely to be a super spreader. Super spreaders may have a moral obligation to stay home when ill to prevent spreading their infection, or to avoid certain careers, like working with immunosuppressed individuals, to avoid infecting others while harboring an asymptomatic infection. Employers may be faced with ethical and legal dilemmas, as it is illegal to discriminate based on genetics according to the only piece of federal legislation prohibiting genetic discrimination, the Genetic Information Nondiscrimination Act (GINA), yet they have an obligation to protect others in the workplace.(101) This conundrum will be especially pronounced within the healthcare industry, in which employers and employees will be obliged to protect patients as well.
- **Societal Benefits**
    - Is the public willing to share their genetics through a biobank for the greater good? Do they think that the reduced risk of adverse reactions and potential to decrease the spread of vaccine preventable disease is worth the risks to privacy and other potential hazards of vaccinomics?

- **Reduced Agency**
    - If genetic testing results show an individual is less likely than others to have an immunogenic response, does that person have the right to receive the vaccine anyway? Is that person's health insurer (private or public) obligated to pay for that vaccine? If someone is recommended not to get a vaccine because genetic testing shows an increased risk of an adverse reaction, can they get it anyway? If they get the vaccine against advisement and have an adverse reaction, is their health insurer required to pay for treatment?
- **Confidence in Primary Care Providers, Government, Public Health Authorities, Pharmaceutical Companies, and Vaccines**
    - Individuals with lower confidence in these groups and vaccines may be less supportive of vaccinomics, genetic testing, and currently available vaccines. They may have concerns about their health care provider sharing their genetic information with others, including their insurance company and public health authorities. On the contrary, individuals with lower confidence in these groups and vaccines may be more supportive of vaccinomics because of vaccinomics' potential for improved safety and effectiveness and targeted vaccine use. Vaccinomics' more individualized approach may be especially appealing to those who are hesitant about current vaccines.
    - Trust in pharmaceutical companies, public health authorities, government, and newer versus older vaccines may also be associated with influenza vaccine uptake by children and adults now. Understanding vaccine confidence and behavior now could inform our understanding of vaccinomics in the future.
- **Stigma and/or Discrimination**
    - If vaccinomics were based on a gene that is predominantly associated with one race, this could impact racism. If someone is identified as a super spreader, this may make them a target of

harassment and discrimination. Fear of stigma and discrimination may prevent some individuals from undergoing the genetic testing needed to implement vaccinomics.

- **Other Advantages/Disadvantages of Vaccinomics**
  - Researching, funding, and developing vaccinomics: will Congress provide vaccinomics sufficient funding to make tangible progress if they perceive public support to be high? Will Federal agencies (NIH, CDC) prioritize vaccinomics within their discretion of existing funding? Will the public trust vaccinomics if its products are developed by for-profit companies rather than government agencies or academic researchers?
  - Post-licensure surveillance regarding vaccine safety and effectiveness: will Congress adequately fund post-licensure research to detect and investigate safety and effectiveness issues? Will the public trust this system to detect adverse events? Do members of the public trust public health authorities will take appropriate actions for their protection if safety signals are detected?
- **Genetic Testing and Genomics in General**
  - Individuals may be concerned about whether a nonprofit or government agency holds the patent to the test and is profiting from its use. Individuals may also be concerned about the privacy of the results – are the results retained by them alone or their healthcare provider? Will the results be reported to their health insurer or shared with a third-party operating a genetic database used for surveillance of AEFIs or other purposes? How will the individuals' privacy be protected?
  - Will individuals have the right to refuse genetic testing or keep the results private, even if this hampers the public health impact of vaccinomics? Will providers be forced to stock "old" vaccines for patients who refuse genetic testing and "new" vaccines for those on board with vaccinomics?
- **Personal Privacy and Genomics in General**
  - What short and long-term privacy protections are there for people who agree to genetic testing and participate in vaccinomics? Will doctors share patient information with health insurers or

government-run vaccine surveillance systems? Who will own individuals' genetic information? Will individuals have privacy concerns regarding genetic databases due to recent news reports of genealogy databases being used for criminal investigations?(102)

2.17 Discordance in the Scientific Community

Vaccinomics remains contentious in the scientific community due to concerns about cost effectiveness, regulation, and the feasibility of implementing more complicated vaccine schedules. Cost effectiveness may be hampered by vaccinomics, as it will be difficult to encourage researchers and manufacturers to develop vaccines for small subgroups of the population.(103) Furthermore, there may be significant costs associated with research and development of vaccinomics screening tests, used for vaccine prioritization.(103) In 1967, there were 26 vaccine manufacturers;(103) five vaccine manufacturers represented 79% of the market share in 2012. Consolidation of the market could lead to price increases; however, vaccinomics provides an opportunity for market expansion.(104)

Individuals at the CDC, medical providers, and the public may believe that complicating vaccine schedules will not be worth the added burden. The CDC has found that complexity and ambiguity in vaccine schedules does not work well. In 1988, the ACIP recommended hepatitis B vaccination (HepB) within 12 hours of birth to infants born to hepatitis B surface antigen-positive (HBsAg+) mothers as a means of preventing mother-to-child transmission.(105) Despite the ACIP's initial recommendations, hepatis B incidence remained high. Recommendations have been expanded and simplified several times since then, including calling for universal HepB vaccination at birth,(105) vaccination of 11-12 year-olds to prevent infection from high-risk behaviors in adulthood, recommending hospitals adopt standing orders to vaccinate all infants before discharge to perinatal transmission(106) and more.(107-109)

There are concerns that vaccinomics could make vaccine schedules overly complicated and difficult for providers to implement, like the previous HepB recommendations. However, these concerns

are based on the assumption that providers will be making vaccination decisions in the future in the same manner as they do now. The growing complexity of the vaccine schedule may lead to a technological approach beyond a one-page schedule that could incorporate vaccinomics. Providers may only need to input a few details about each patient, and an algorithm will dictate the appropriate vaccine schedule. Although vaccinomics may complicate vaccine schedules, other innovations and benefits may offset this complexity.

Stakeholders may believe that talking about current vaccine safety issues relative to current vaccines and the potential of vaccinomics could scare the public and limit vaccinomics' potential. However, this strategy is counterintuitive and belies current medical practice. Pediatricians are encouraged to start conversations with vaccine hesitant parents in advance of when children become vaccine eligible.(110) In 2006 and 2013, pediatricians reported in a survey conducted by the American Academy of Pediatrics that they were able to convince approximately 30% of parents to vaccinate their children after initial refusal.(110) Similarly, in a cross-sectional study conducted at pediatric offices in Washington state, parents of children ≥6 months were more likely to accept influenza vaccination for their child if the provider used presumptive language (ex. "we're going to vaccinate your child today") rather than a participatory approach (ex. "how do you feel about vaccinating your child today;" 94% versus 28%, $p<0.001$). Pediatricians who continued to push vaccination after parents expressed hesitance were also more successful in getting children vaccinated versus ending the discussion (80% versus 13%, $p<0.05$).(110) These data suggest that discussing vaccines with hesitant parents may increase vaccine acceptance, rather than have detrimental effects.

While vaccines are regulated by the Food and Drug Administration (FDA) and recommendations for vaccine use are made by the CDC, regulation of the laboratory tests needed to implement vaccinomics may be an area of bureaucratic contention. Laboratory tests are currently overseen by the FDA, CMS, and CDC depending on the contents and purpose of the test.(103) Tests that include all

necessary components and are sold directly to consumers and laboratories are deemed “medical devices” and regulated by FDA.(103) Other tests, such as those developed by laboratories for their own use, are “medical services” regulated by CMS and CDC.(103) Joly et al. expect that vaccinomics tests would be designated Class II, which is how the FDA classified pharmacogenomic tests in 2005.(103) These tests are not inherently dangerous; however, the results may be associated with psychological or social distress. Erroneous test results due to poor sensitivity or specificity could carry significant consequences in the age of vaccinomics, such as someone getting the incorrect vaccine type or dose. Tests need to be regulated to prevent these kinds of errors. FDA previously argued that by not enforcing regulation of laboratory device testing (LDTs) in the past, it encouraged innovation.(103) This policy was implemented in June 2010, and could make it more difficult to sell vaccinomics-related tests.(103) The LDT-centered regulatory approach encourages development of novel tests, which may or may not be relevant for vaccinomics or other clinical purposes.(103) CMS and CDC may be able to pressure FDA to regulate LDTs needed for vaccinomics more closely, and have leverage to do so given how much public funding is currently spent on vaccines and would likely be spent on vaccinomics.

Angst and discordance about vaccinomics likely stem from an inability to look at how vaccines and laboratory tests are administered and regulated at present and to imagine how different the world may be in the future. This is understandable. But it is not a scientific reason to discount the potential of vaccinomics. This project explored the policy implications of vaccinomics and characterized the association between influenza vaccines, which are new each year, and vaccine hesitancy to help stakeholders prepare for a future in which vaccinomics is a reality.

2.18 Tables for Chapter 2

Table 1. ACIP Recommended Vaccines for Children, Adolescents, and Adults

Vaccine	Age and Dose(s)	Effectiveness	Safety
Children and Adolescents			
Hepatitis B (HepB)(20)	3 doses at 2, 4, and 12-15 months if PedvaxHIB used. Otherwise, 4 dose series at 2, 4, 6, and 12-15 months.(20)	>95% develop immunity in response to the vaccine series and VE against clinical disease is estimated at 95-100%.(18)	There is no link between the vaccine and chronic hepatitis B.(18) Anaphylaxis (allergic reaction) occurs in 1-2 persons/million doses administered.(26)
Rotavirus (RV) Rotarix (2-doses); RotaTeq®: (3 doses)(20)	Rotarix: 2-dose series at 2 and 4 months. RotaTeq®: 3-dose series at 2, 4, and 6 months.(20)	In clinical trials, VE against any rotavirus gastroenteritis was estimated to be 74-87% and it was estimated to be 85-98% against severe disease.(18) Post-licensure data from the U.S. Vaccine Safety Datalink (VSD) analyses associates the vaccine with an 18-20% decrease in seizure-related emergency department visits and hospitalizations.(111, 112) Rotavirus vaccines are estimated to prevent 53,000 hospitalizations and 170,000 emergency department visits among 4.5 million babies in the U.S. per year.(113)	A previous rotavirus vaccine, RotaShield, was associated with intussusception.(111, 112) Post-licensure studies in the U.S. indicate a small increased risk of intussusception from both currently licensed rotavirus vaccines (1-5 cases/100,000 infants vaccinated with 1 or 2 doses).(111, 112)

Table 1, Continued			
Vaccine	**Age and Dose(s)(114)**	**Effectiveness**	**Safety**
Children and Adolescents			
Diphtheria, tetanus, & acellular pertussis (DTaP if <7 years) (20)	5-dose series: 2, 4, 6, 15 to 18 months-old; and 4 to 6 years old.(20) Does 4 may be given beginning at 12 months old. If dose 4 is given early when the child is 12 months old and ≥4 months after dose 3, it may be counted.(20, 114)	VE against clinical disease: diphtheria 95%; tetanus 100%; acellular pertussis 84% (within 3 years vaccination).(18) Immunity from acellular pertussis vaccines wanes rapidly over time and is contributing to outbreaks in adolescents and adults, who can subsequently infect infants.(49, 50) Immunity to tetanus wanes slower and requires booster shots with every pregnancy.(18, 50, 115) Infants born to vaccinated women have 50-100% of their mother's pertussis antibody levels.(18)	20-40% infants: pain, redness, and swelling after first 3 doses; 3-5% fever >101°F.(18) Severe systemic reactions occur in <1 per 10,000 doses: fever >105°F, febrile seizures, persistent crying >3 hours and hypotonic hypo responsive episodes.(18) Anaphylaxis in 1-2/million doses administered.(26) Adolescents should be vaccinated while seated, out of view of others getting vaccinated, and observed for 15 minutes afterward due to the risk of syncope.(18)
***Haemophilus influenzae* type (Hib) (20)**	3-dose series: 2, 4, and 12-15 months (PedavaxHIB®).(20) 4-dose series: 2, 4, 6, and 12–15 months (ActHIB®, HIberix®, or the DTaP-Hib-IPV combination vaccine, Pentacel®).(18, 20)	VE against clinical disease 95-100% (18, 116)	5-30% get minor reactions lasting 1-2 days (i.e. pain, redness, swelling).(18) Systemic reactions, like fever, are infrequent. Serious adverse events are rare.(18) A review of data from 1990-2013 provided no evidence of a causal effect Hib vaccines on transverse myelitis (inflammation on both sides of spinal cord), thrombocytopenia (low blood platelet count), anaphylaxis, and Guillain-Barré syndrome (GBS).(117)
Pneumococcal conjugate (PCV13 and PPSV23) (20)	Children 2 to 5-years old: 4-dose series of PCV13: 2, 4, 6, and 12–15 months.(20) Children 6 to 18 years old: series of PPSV23:1 dose ≥8 weeks after a prior PCV13 dose.(20)	>90% VE pneumococcal disease; reduces nasopharyngeal carriage and risk of transmission to others.(18)	5-49% have mild local reactions (pain, redness and swelling).(18) 8% have severe local adverse reactions (ex. arm tenderness impairs movement). Local adverse reactions are commonest after the fourth dose. In clinical trials, 24-35% had fever >100.4°F within 7 days of vaccination; <1% had high fever. May cause increased risk of febrile seizures when administered with influenza vaccines. Febrile seizures, have no long-term consequences.(18)

Table 1, Continued			
Vaccine	**Age and Dose(s)(114)**	**Effectiveness**	**Safety**
Children and Adolescents			
Inactivated poliovirus (IPV) (20)	4-dose series at ages 2, 4, 6–18 months, and 4–6 years. Administer the final dose on or after the 4th birthday and at least 6 months after the previous dose.(20)	Serological immunity against all 3 poliovirus serotypes is developed in ≥90% after 2 doses and ≥99% after 3 doses.(18) Vaccine-induced immunity is long-term (exact duration unknown).(18)	Local redness and pain at injection site occur occasionally.(18) Anaphylaxis in 1-2 persons/million doses administered.(26)
Inactivated Influenza (IIV), Recombinant Inactivated Vaccine, or Live Attenuated Inactivated Influenza (LAIV) Multiple trivalent and quadrivalent vaccines are licensed in the U.S.(18) Most are IIV; there is 1 trivalent recombinant vaccine and 1 quadrivalent recombinant vaccine also licensed. One LAIV vaccine, FluMist® has been recommended since 2018-2019, but was not recommended in the two previous influenza seasons.(18)	IIV: Children 6 months–8 years: 1 dose.(20) LAIV: 1 dose if >2 years of age, not pregnant, and without immunosuppression and other health conditions.(20) Both vaccines: Children 6 months to 8-years old get 2 doses separated by at least 4 weeks if they did not receive ≥2 doses prior to July 1, 2018.(20)	VE varies depending on the match between circulating viruses and vaccine viruses, the recipient's health, age, and biological sex.(18, 22-24) Immunity wanes during the 6 months post-vaccination.(18) Among the few observational studies using RT-PCR-confirmed influenza in children as the outcome, VE ranges from 37% (95% CI: 25, 68) for A(H3N2) to 82% (95% CI: 23, 96) in studies of children in pediatric Intensive Care Units versus clinic-based controls during the 2010-11 and 2011-12 seasons. LAIV had higher VE than for IIV in multiple studies and meta-analyses.(118) Despite low VE, vaccination decreases risk of infection, severe illness, hospitalization, death, and transmission to others.(18)	IIV: Local adverse reactions (soreness, erythema and induration at the injection site) lasting ≤2 days and systemic adverse reactions (fever, chills, malaise, and myalgia) are common.(18) Systemic symptoms usually begin within 6–12 hours of vaccination, lasting a few hours. <30% of children reported systemic symptoms after getting IIV. Allergic reactions, likely to a vaccine component, occur rarely. (18) LAIV: Increased risk of runny nose, congestion, and fever compared to IIV. SAEs reported through VAERS (passive surveillance system; indicates non-causal association) in children 2-4 years old were highest in 2007-08, including neurologic (29.2%) and respiratory events (22.4%).(119) Neither IIV or LAIV cause influenza. Influenza vaccines are associated with 1-3 excess cases of Guillain-Barré Syndrome (GBS).(18) Anaphylaxis in 1-2 persons/million doses administered.(26)

Table 1, Continued			
Vaccine	**Age and Dose(s)(114)**	**Effectiveness**	**Safety**
Children and Adolescents			
Measles, mumps, rubella (MMR) (20)	2-dose series at 12–15 months and 4–6 years and at least 4 weeks apart.(20) MMR and Varicella (V) vaccines should be given separately for the first doses due to the increased risk of febrile seizures in toddlers. The combined MMRV vaccine is preferred for the second dose (maximum age of administration is 12 years old).(18, 20)	1 dose: 93% VE against measles, 77% against mumps, and 97% VE against rubella.(18, 46) 2 doses: increases measles VE to 97% (immunizes those not covered by 1st dose); mumps VE 66% to 85%, waning over time.(18)	Mild fever lasting 1 to 2 days in 5 to 15% of vaccinees and rash lasting 7-12 days in 5% of vaccinees occurs after the 1st dose.(18) The risk of febrile seizure increased 2 to 3 times in toddlers who received MMRV versus MMR and varicella vaccines separately. The risk of febrile seizure was 4 times greater in toddlers who received MMRV versus MMR alone. The increased risk of febrile seizure is only for the 1st dose, not 2nd.(18) Rare adverse reactions include joint pain (<1% children), parotitis (inflammation of the parotid gland), lymphadenopathy (inflammation of the lymph nodes), and encephalopathy (brain swelling). Very rarely, measles inclusion body encephalitis and immune thrombocytopenia purpura (low blood platelet count causes bruising/bleeding count in 1/30,000 doses).(18, 41) Anaphylaxis in 1-2 persons/million doses and febrile seizures in 3.3 persons/100,000 doses administered.(26)
Varicella (VAR)(20)	2-dose series: 12 to15 months and 4 to6 years (2nd dose at least 4 weeks after 1st dose).(20) Use separate varicella vaccine for dose 1, combination MMRV for dose 2 due to risk of febrile seizures.(18) MMRV is only for children 12 years old and younger.(20)	1 dose: VE 76% to 94% against clinical or laboratory-confirmed disease; VE 78-100% against severe disease.(18) 2 doses: VE 94% against clinical diseases; 98% against moderate or severe disease. Effectiveness wanes over time.(18)	Mild reactions (pain, swelling) reported by 21 to25% of children +/- 3 days of vaccination. Rash occurs in 1 to4% and fever in 4-7% within 7 to21 days of vaccination.(18) There is an increased risk of in febrile seizures following the 1st dose. There is a risk of transmitting varicella to immunocompromised individuals if a post-vaccination rash is visible.(18) Anaphylaxis in 1-2 persons/million doses administered.(26)

Table 1, Continued			
Vaccine	**Age and Dose(s)(114)**	**Effectiveness**	**Safety**
Children and Adolescents			
Hepatitis A (HepA) Havrix® (contains preservative) and Vaqta® (no preservative)(18)	2 doses, separated by 6 to18 months, between the 1st and 2nd birthdays.(20) Havrix®: give 2 doses 6 to 12 months apart. Vaqta®: give 2 doses 6 to 18 months apart.(20)	1 dose: >97% children and adolescents immune within 1 month.(18) 2 doses: 96 to100% immune. In clinical trials, vaccine efficacy was 94% for Havrix® and 100% for Vaqta®.(18)	20 to50% get local adverse reactions (pain, redness, and swelling); <10% get systematic reactions (fatigue, malaise, and low-grade fever). Rare cases of anaphylaxis occur.(18)
Meningococcal MenACWY-D >9 months MenACWY-CRM ≥2 months) These are both quadrivalent vaccines.(20)	Recommended 1st dose at 11 to 12 years old; 2nd dose at 16 years old.(20)	MenACWY-CRM is highly immunogenic in children, beginning at age 2 months.(120) After 2 doses given at 12 and 18 months, 100% had protective titers against Men groups C, W, and Y and 84% had protective titers against Men A.(120)	MenACWY-CRM: local adverse reactions at the injection site (20%) and erythema (14%); syncope (fainting) (9%).(20) MenACWY-D: fever (17%), headache (16%), injection site erythema (15%), dizziness (13.4%) and syncope (10%). Adolescents should be vaccinated while sitting and be observed for 15 minutes due to risk of syncope (fainting). SAEs are rare for both vaccines.(20) Anaphylaxis 1-2/million doses administered.(26)

Table 1, Continued			
Vaccine	**Age and Dose(s)**	**Effectiveness**	**Safety**
Children and Adolescents			
Tetanus, diphtheria, & acellular pertussis (Tdap: >7 years)(20)	Adolescents 11 to12 years of age: 1 dose.(20) Pregnant adolescents: 1 dose during each pregnancy (gestational weeks 27–36 preferred).(20)	Antibody response in adults is similar to how infants respond to DTaP (see DTaP above).(18)	21-66% of adults receiving Tdap have local reactions and 1.4% have a fever >100.4°F and may also induce febrile seizures.(18) Occasional reports of mild systemic adverse reactions (headache or drowsiness).(18) Anaphylaxis in 1-2/million doses administered.(26)
Human papillomavirus (HPV) Bivalent: Cervarix® Quadrivalent: Gardasil-4® Ninevalent (only vaccine currently used in the U.S.): Gardasil 9®(18)	Recommended for 11 to 12 year-olds; licensed for 9 year-olds.(20). For 9 to 14-year-olds: 2-dose series at 0 and 6-12 months. If ≥15 years old at series initiation, 3-doses are required: 0, 1-2 months, and 6 months(20)	2 dose series: >97.9% antibody response against all vaccine strains.(18) 3-dose series: 93-97% efficacy against cervical intraepithelial neoplasia, depending on the vaccine.(18) Quadrivalent vaccine only: efficacy against genital warts 99% for females and 88% for males. 2 doses is noninferior to 3 doses.(18) The nine-valent vaccine is noninferior to the quadrivalent vaccine.(18)	Adolescents should be seated out of view of other vaccinees and observed for 15 minutes after vaccination due to syncope reports.(18) 20-90% report mild local adverse reactions (ex. pain, swelling) at the injection site.(18, 121) Anaphylaxis reported in 1-2/million doses administered.(26)

Table 1, Continued			
Vaccine	**Age and Dose(s)**	**Effectiveness**	**Safety**
Adults			
Inactivated Influenza Vaccine (IIV), Recombinant Influenza Vaccine, or Live Attenuated Inactivated Vaccine (LAIV) (20, 21)	1 dose annually; IIV, any age. LAIV recommended only if 18-49 years and not pregnant or immunocompromised.(21)	Although age may influence VE, a pooled analysis of U.S. Flu VE Network data over 5 influenza seasons published in *Vaccine* showed comparable VE across age groups.(122) Metanalysis of observational data from adults ≥60 years old showed VE against RT-PCR confirmed influenza to be: 52% (95% CI: 41, 61) during epidemics when the circulating viruses matched those in the vaccine and 58% (95% CI: 30, 70) and 36% (95% CI: 22, 48) when there was a mismatch.(19)	IIV: 14-16% of adults reported myalgia within 1 week of receiving unadjuvanted IIV; 31-39% reported myalgia following adjuvanted IIV. Rates were higher after receiving the 2009 H1N1 vaccine.(18) LAIV: runny nose and congestion are more common than with IIV.(119) Reports of GBS and cardiovascular events were more frequent among Department of Defense versus civilian populations.(119) Simultaneous administration of influenza vaccines with PCV increases the risk of febrile seizures in infants, which do not have long-term effects.(18) The increased risk of GBS is 1-3 excess cases/1 million persons vaccinated.(18)
Tetanus, diphtheria, and pertussis (Tdap) or tetanus-diphtheria (Td) (20, 21)	1 dose Tdap, then Td booster every 10 years. Only need 1 dose of Tdap in lifetime. EXCEPTION: 1 dose Tdap with each pregnancy to protect infant.(21)	Same as for adolescents receiving Tdap (see Tdap above)	Same as for adolescents receiving Tdap (see Tdap above)

Table 1, Continued			
Vaccine	**Age and Dose(s)**	**Effectiveness**	**Safety**
Adults			
MMR	1 dose needed if no evidence of immunity (infected or born before 1957). Pregnant women get 1 dose post-delivery before leaving healthcare facility (contraindicated during pregnancy).(21)	Same as for children (see MMR above).	Same as for children (see MMR above).
HPV	3 doses if series initiated at age 15-years old or later.(21) Routinely recommended up to age 26 years old for females and 22 years old for males. Males may be vaccinated up to 26 years old depending on the clinician's judgement.(21)	Same as for adolescents (see HPV above).	Same as for adolescents (see HPV above).
Varicella (VAR)	Adults without evidence of natural immunity/previous vaccination only: 2 doses 4–8 weeks apart if previously received no varicella-containing vaccine(21)	Same as for children (see Varicella above)	Same as for children (see Varicella above)

Vaccine	Age and Dose(s)(114)	Effectiveness	Safety
Adults			
Zoster (Shingles) Inactivated Recombinant Adjuvanted Subunit Zoster Vaccine (RVZ): Shingrix® Live Attenuated Zoster Vaccine (ZVL): Zostavax®)(21, 123)	Adults ≥50 years old: 2 doses 2-6 months apart.(21) Adults ≥60 years old: 2 doses (RZV preferred) 2-6 months apart or 1 dose zoster live vaccine (ZVL)(18, 21)	Efficacy decreases with increasing age.(18) RZV efficacy: 50-59 years old: 96.6%, 60-69 years old: 97.4%, 70-79 years old: 91.3%, and 91.4% ≥80 years old. RZV protection ≥85% 4 years post-vaccination; ZVL efficacy 50-59 years old: 70%, 60-69 years old: 64%, 70-79 years old: 41%, and ≥80-year-old: 18%. VE<35% 6 years post-vaccination. Effectiveness in Medicare participants ≥65 years: 33% within 3 years and 19% within 4 years post-vaccination.(18)	Local adverse reactions at the Injection site were common (RZV 81.5% versus Placebo 11.9%; ZVL 48.3% versus Placebo 16.6%).(18) RZV: most reactions were mild/moderate (median duration 1-3 days); 17% had reactions that impaired with everyday activities vs 3% on placebo. ZVL: headaches slightly higher but no increase in fever versus placebo; most reactions were mild and lasted ≤4 days. Those with herpes zoster infection or are pregnant or breastfeeding are cautioned from getting the vaccine.(18)

Notes:

1) Recommendations listed above exclude the acceptable ranges for catch-up immunization, ranges for high-risk groups, and recommendations for non-high groups depending on specific clinicians' decisions. Contraindications and precautions are also excluded from the above summary.

2) Anaphylaxis is a very rare allergic reaction. According to the IOM, there is convincing data supporting a causal relationship between MMR, influenza, HepB, DTaP, and meningococcal vaccines and anaphylaxis. The IOM accepts the evidence of a causal association with the HPV vaccine. There is insufficient evidence supporting a causal association with HepA.(42)

2.19 Figures for Chapter 2

Figure 1. Distribution of Vaccine Response

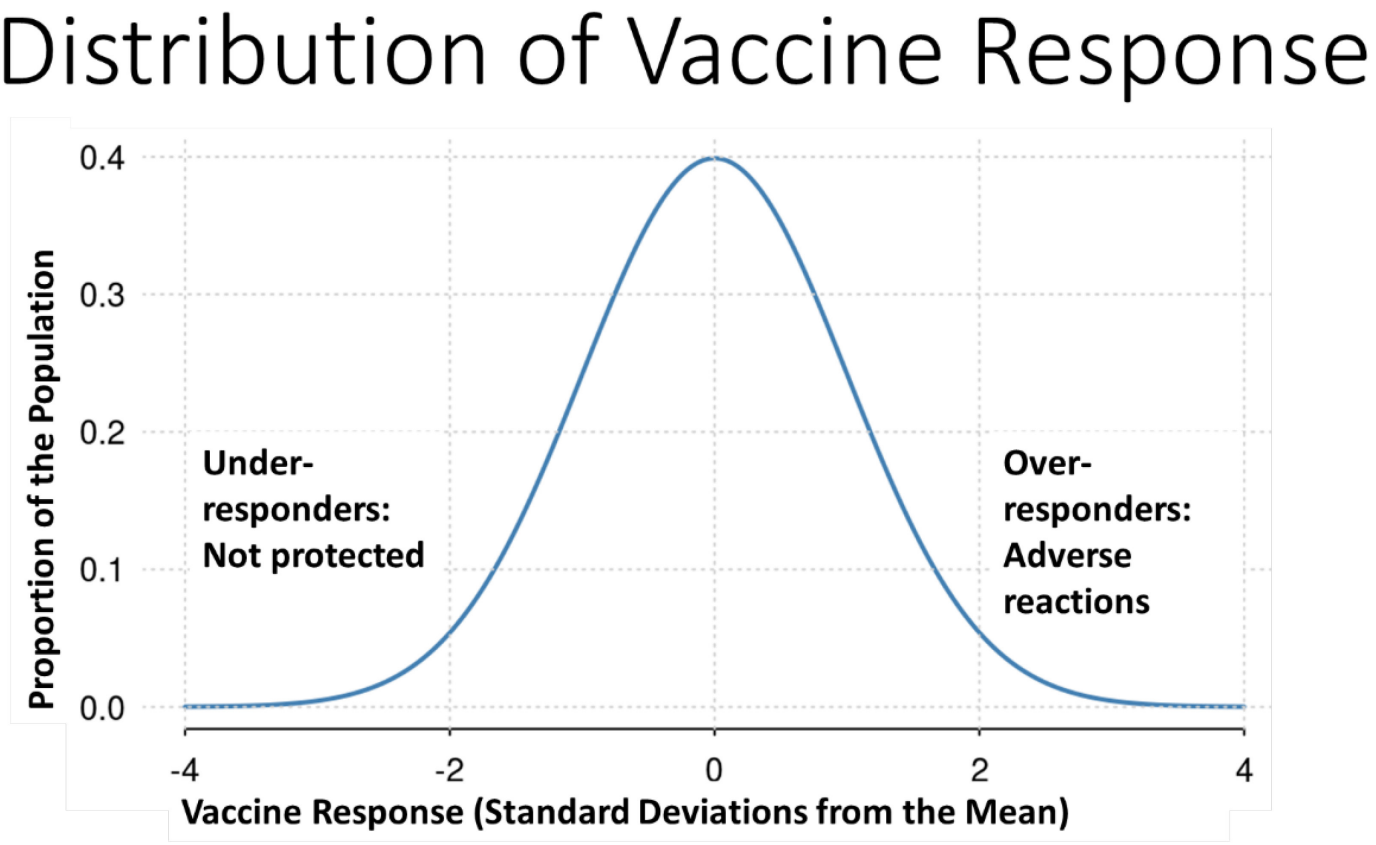


Figure 1 adapted from a Normal Distribution Graph.(124)

Chapter 3. Methods

3.1 A Priori Hypotheses

Based on prior research and the Research Team's experience, we hypothesized a priori that individuals' views on the policy implications of vaccinomics would vary based on specific criteria, including age, level of education, income, race/ethnicity, region, and being a parent of a young child as these factors are associated with vaccine hesitancy.(125) High vaccine hesitancy was also hypothesized to be associated with views on the policy implications of vaccinomics, as both inherently involve some level of questioning vaccine science and policies. This questioning may be driven by skepticism in the credibility of the information presented, a belief in one's right to autonomy, and other factors. Those with low vaccine hesitancy are more likely to accept vaccines due to fear of the disease, a desire to do as other's they respect do, or coercion.(27) Regardless of the underlying motivation, respondents with low and high vaccine hesitancy were expected to have divergent, unique, and diverse views on the policy implications of vaccinomics.

3.2 Specific Aims

1. To identify and analyze the policy implications of vaccinomics through community meetings with members of the public in Boulder, CO and Baltimore, MD.
2. To create a survey tool for measuring policy implications of vaccinomics and related attitudes and beliefs.
3. To characterize vaccine hesitancy and influenza vaccine uptake among a sample of U.S. adults, representative of the U.S. demographic profile.

The following hypothesis will be tested for Aim 3:

H10: Younger age, higher education, living in the northeast and west regions (versus south and Midwest), and higher vaccine hesitancy are not associated influenza vaccination

4. To characterize public values about the policy implications of vaccinomics among a sample of U.S. adults, representative of the U.S. demographic profile

The following hypotheses will be tested for Aim 4:

H10: Younger age, higher education, and living in the northeast and west regions (versus south and Midwest) are not associated with values related to vaccinomics.

H20: Parents are do not have different values related to vaccinomics than nonparents.

H30: Vaccine hesitant individuals do not have different values related to vaccinomics than non-hesitant individuals.

3.3 Overall Study Methods

Community meetings in Boulder and Baltimore were held in March and April 2018*.* We used a sequential qualitative-quantitative mixed methods study design. The goal of the formative work was to identify constructs and themes about the policy implications of vaccinomics **(Aim 1)** to be further explored in a survey representative of the U.S. demographic profile **(Aims 2-4).** These meetings informed the creation of de novo survey items about vaccinomics and increased the likelihood that the survey had high content validity, covering the full range of applicable domains, asking pertinent questions, and providing appropriate response options **(Aim 2).** We expected this study design to provide high-quality data to answer questions about the characterization of vaccine hesitancy and prevalence of influenza vaccination, which may inform vaccinomics implementation **(Aim 3).** This design was also selected to measure the prevalence of vaccinomics-related concerns, and if these concerns varied by sociodemographic factors and vaccine hesitancy status, and to explore public values around government funding for vaccinomics compared to existing federal priorities **(Aim 4).** The data collected through this study provided meaningful insights to answer **Aims 1-4.**

3.4 Study Population and Procedures

3.4.1 Aim 1 Methods

3.4.1.1 Sampling Strategy: Aim 1 - Community Meetings

To capture the breadth of possible outcome-related views and experiences individuals may have, purposive sampling was used in recruiting community meeting participants. This strategy increased the likelihood that an adequate number of individuals were from these key groups and that all possible content domains were represented. Purposive sampling aided in making sure that the variety of comments heard have enough variability and depth to adequately understand each construct or theme that emerges from the data. This increased the content validity of the qualitative results and informed subsequent quantitative work.

Recruitment purposively targeted parents of young children, as they make frequent decisions about whether to vaccinate their children on-time or not. Since Boulder, CO has a high prevalence of children with school vaccine exemptions, we hoped to enroll vaccine hesitant individuals indirectly, by focusing on parents of young children in this metropolitan area.(126) Recruitment was broadly conducted in a high income and education setting (Boulder)(126) and a low-income, primarily African American setting (Baltimore). Opinions from these key groups and other members of the public aided researchers in understanding the diversity of views held on vaccinomics.(127)

In Boulder, recruitment was conducted by two Colorado-based research staff who visited local libraries and schools to engage potential participants, post and distribute fliers, and advertise the meetings on social media. These efforts targeted young parents. A professor at the University of Colorado Boulder also promoted the meeting to his students. Students were of interest as they represent a highly educated and young demographic.

In Baltimore, the Project Manager and a doctoral student recruited for the one-day meeting. The Project Manager focused on enrolling parents of young children from local schools. The doctoral student posted the event on local radio station's community calendars and contacted these stations for on-air promotions. The host of a Saturday morning radio program for children provided an on-air promotion. Fliers were distributed to community organizations and to the staff at a local gym to recruit low-income individuals. In all cities, participants were 18 years or older. Parenthood was not a requirement for inclusion as it is not a requirement for vaccine hesitancy.

All participants completed a short demographics questionnaire in advance of the group discussion. Individuals received a $50 Visa gift card for attending the meeting and parents were eligible to receive an additional $30 childcare subsidy. Recruitment and community meetings were conducted in English.

Sample size calculations in qualitative work are often driven by the principle of saturation. Glaser and Strauss (1999) proposed researchers conduct ongoing analyses. When the addition of one more observation fails to add new information to the results, the sample has reached saturation, or the maximum size needed.(128) Malterud et al. suggested information power be used to determine sample size. Having broad study aims, as the community meetings did, requires larger samples.(128) Purposively sampling participants, so that they have specific relations to the study aims increases the information power and decreases the sample size needed. Recruitment for this study was purposive, so this decreased sample size requirements related to random recruitment.

Community meeting sample size requirements were relatively increased because the meetings were not theory-based.(128) Information power and sample size requirements also depend on the quality of discussion between the participants and facilitators.(128) Community meetings discussions were led by trained facilitators and followed the Facilitator's Guide **(Appendix 1)**. This strategy aimed to

keep discussions on-point, further increasing the information power of the sample.(128) Although Malterud et al.'s model was developed for individual interviews, not groups as were used here,(128) focus group work often relies on purposive sampling, as done here. Purposive sampling also increases the information power and decreases sample size requirements.

The number of enrolled participants and discussion groups was based on the investigators' professional judgement and budgetary constraints.(129) We assumed participants were unfamiliar with vaccinomics before the community meetings, and that their comments about vaccinomics would be based on the information we provided. This limited the breadth of their comments, leading to rapid saturation. This contrasts with asking participants about something with which they are familiar, such as antibiotic resistance, for which most people could be expected to have familiarity through personal experience, conversations with healthcare providers, the media, or others in their social network. In this case, participants would have a broader array of opinions, necessitating a larger sample size to reach saturation.(129)

In Boulder, two meetings were held on consecutive days. Two small group discussions were held each day, and each discussion was facilitated by a professional facilitator. In Baltimore, four small discussion groups were held on a single day. Groups discussions were led by a professional facilitator, the PI, the Project Manager, and a doctoral student, all trained in qualitative methods. In total, 8 focus groups were conducted in three cities to provide enough information power to answer Aim 1.

3.4.1.2 Tools for Data Collection: Community Meetings

Suggestions provided at the previously held stakeholder's meeting (January 2017) were incorporated into how vaccinomics was communicated. Stakeholders' suggestions and emergent themes from that meeting were incorporated into the Community Meeting Facilitator and Recorder's Guide, (**Appendix 1**) used as the basis for discussion. For simplicity, adversomics, a subarea focused on

genomics and adverse events (AEs),(15) was explained as being synonymous with vaccinomics. Vaccinomics was introduced via a four-minute-long animation that explained the risk of a SAE is about one in one million. This number was based on the excess risk of GBS from influenza vaccination.(18) The animation noted this risk could be reduced to be closer to zero in one million with vaccinomics, and may be viewed here: <https://vimeo.com/bonnemaison/review/259404584/ae6fbf93fa>.

A preventative medicine physician and vaccine expert, who was experienced working at the FDA, multiple pharmaceutical companies, and JHSPH, answered participants' questions for approximately 10 minutes. Participants were randomly divided into groups of 10-15 people for nested discussion groups.

Group discussions were led according to the Facilitators and Recorders' Guide, developed by the Research Team **(Appendix 1**). Participants were presented with a hypothetical situation and told "imagine this winter there's a disease outbreak that is spreading easily and quickly." Participants were told the disease is a serious and potentially fatal vaccine-preventable disease. Next, the facilitator said, "vaccinomics will let you prioritize giving the vaccine to 'super spreaders' and those most at risk for serious consequences first." Prompts were used to elicit participants' opinions, understand how they felt about genetics being used to identify super spreaders (extra contagious individuals), prioritizing super spreaders for vaccination, and if vaccinomics changed their confidence in vaccine safety and effectiveness.

In a second hypothetical situation, participants were told a new contagious disease emerged, and the preventative vaccine was expected to be safe for nearly everyone. About one in one million were expected to have a serious reaction to the vaccine, causing permanent paralysis or death (mimicking GBS). Vaccinomics could use genetic markers to identify who was at increased risk for this adverse reaction, reducing the risk of paralysis and death closer to zero in one million. Participants'

views were elicited with similar prompts to the first scenario, and also asked whether vaccinomics altered their trust in government to respond to the outbreak.

Data from Hypothetical 1 were used as evidence of community meeting participants' support for vaccinomics compared to other vaccine-related options the U.S. government currently funds. Hypothetical 2 data were used to assess support for vaccine-related research and development compared to cancer (including cancer-preventing vaccines), diabetes, and cardiovascular disease.

Participants rated their confidence in vaccine safety before and after the group discussion. They also wrote an explanation for their ratings. Handwritten comments were categorized, and emergent themes were deduced using methods influenced by Grounded Theory.(130) The discussion group results and pre-post comparisons of vaccine confidence indicated whether discussing vaccines and vaccinomics changed individuals' views about vaccine safety and effectiveness. Policymakers have informally conveyed to the Research Team they fear discussing vaccine safety could encourage vaccine hesitancy. These data may assuage these concerns.

3.4.1.3 Community Meetings: Ethical Review

This project was determined to be nonhuman subjects research by the Johns Hopkins Institutional Review Board.

3.4.1.4 Community Meetings: Data Analysis

Transcriptions from the audio recordings from the small group discussions (n=7 in total as 1 group recording failed) were iteratively coded and sub-coded using inductive reasoning, influenced by Grounded Theory.(130) Qualitative analyses were conducted using Atals.ti 8® for Windows.(131) Quantitative sociodemographic, vaccine confidence, and funding data were explored in Stata®, version 16 and Microsoft Office.(132) **These analyses met the goals of Aim 1: to elucidate and characterize the**

policy implications of vaccinomics and set the groundwork for Aim 2: to create novel survey items about the policy implications for vaccinomics.

3.4.2 Aim 2 Methods

3.4.3 Aim 2: Survey Pretest Recruitment

To ensure survey question and answer choices were appropriate and the survey flow made sense to respondents, a pretest and cognitive interviews were conducted. Respondents (N=131) ≥18 years old living in the United States who previously volunteered for the Qualtrics online panel completed the survey in exchange for $3-$4 in rewards points.(133) Respondents' names, email addresses, and phone numbers were collected to facilitate scheduling follow-up phone calls, and were subsequently destroyed. Individuals who did not provide consent did not see the survey items and were redirected to a thank you message.

Respondents took the online survey and completed their follow-up phone call within one to two weeks of initial contact with the study team. Cognitive interviews were conducted with a convenience sample of 20 adults among 131 who took the pretest version of the survey. After a 20-30-minute-long phone call, interviewees were sent a $20 electronic Amazon gift card. The survey was revised prior official launch through the Qualtrics online panel.(133)

3.4.4 Aims 3 and 4: National Survey

3.4.4.1 Survey Recruitment

National Survey enrollment occurred in December 2019 and January 2020 (N=1,925 enrolled) through Qualtrics online panel.(133) The National Survey included quotas based on the U.S. Census,(134) American Community Survey(135) and Current Population Survey(136) so that respondents would reflect the sociodemographic distribution of the US. Due to difficulty enrolling

individuals with minority race/ethnicity, in the lowest income, age, and education brackets, quotas were ignored for the last 400 individuals enrolled.

3.4.4.2 Pretest and National Survey Content

Survey questions covered the ages of participants' youngest children, their beliefs about vaccines and vaccine schedules during public health emergencies, trust in public health agencies and pharmaceutical companies, their personal health, sociodemographic information, and what they thought of vaccinomics. A four-minute-long animation about vaccinomics, previously shown to community meeting participants, was embedded in the survey.

In the pretest, vaccine hesitancy was measured using select items from the PACV and PACV Short Scale.(137, 138) In the nationwide survey, the PACV items were only administered to parents of children under 11 years old. Though the PACV has been demonstrated to have high content validity, it was designed for parents of young children.(137-139) In the National Survey, two sets of items were adapted from The Vaccination Confidence Scale(140) for parents of teenagers and other adults. This scale was originally designed for online administration to parents of teenagers.(140) Twenty trust items were developed through a literature review.(141) Ten of these items were asked in the pretest, all 20 were included in the nationwide survey. Approximately 20 items were removed and others were streamlined to shorten response time and enhance comprehension. One item was added to measure concerns around the security of genetic test results, based on a pretest interviewee's feedback.

3.4.4.3 Pretest and National Survey: Ethical Review

This work was determined to be exempt by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

3.5 Aim 3: Vaccine Hesitancy and Influenza Vaccination – Survey Data Analysis

Using survey estimation procedures and Taylor-linearized variance estimates,(141) univariate and bivariable analyses were conducted to characterize the associations between sociodemographic factors and vaccine hesitancy and vaccination status, respectively. Bivariable and multivariable Poisson models for survey data estimated prevalence ratios for influenza vaccination in 2018-2019 and 2019-2020. Analyses were separately conducted among parents of young children, parents of teenagers, and parents without minor children, in accordance with how we measured vaccine hesitancy. Poisson models, without an offset, were used due to the failure of log binomial models to converge.(142)

3.6 Aim 4: Policy Implications of Vaccinomics – Survey Data Analysis

Using survey estimation procedures and Taylor-linearized variance estimates,(141) univariate and bivariable analyses were conducted to characterize the associations between vaccinomics-related policy issues and sociodemographic factors, parent status, vaccine hesitancy status, trust in public health authorities and experience with or knowing someone who had a serious vaccine reaction. Respondents were instructed, "serious reactions include permanent disability, hospitalization, life-threatening illness, or death." In stratified analyses, differences between groups ≥10% were identified as having potential policy implications.

Post-hoc analyses characterized individuals who opposed vaccine prioritization, including 1) those who thought they would be angry if not prioritized during a shortage and 2) those who believed vaccination was an individual's choice. Log binomial regression was used to estimate prevalence ratios for the association between sociodemographic factors, parent status, trust, and vaccine hesitancy with expected opposition to vaccine prioritization.

3.7 Aims 3 and 4 Common Analysis Methods

Taylor-linearized variance estimates were used for survey data.(142) P-values were estimated with two-sided general tests of association, excluding. P-values were estimated excluding "prefer not to answer" or "don't know" responses constituting <10% of the sample size. These observations were included in estimates of proportions, which were reported in table footnotes.

In bivariable regression, factors associated with the outcome at $p<0.1$ were included in a saturated multivariable model. Backwards stepwise regression was used to identify parsimonious models with $p \leq 0.5$. Due to a change ≥10% in the remaining parameter estimates when education was removed from one Aim 3 model, education was included in all multivariable models as a potential confounder, regardless of its p-value. A change ≥10% was not evident for other variables included in models for Aims 3 or 4. When there were 3 times as many respondents in one group compared to the other, this study had 96.9% power to detect a difference of 10% between two groups when the proportion in the reference group was 0.5. Stata®, Version 16, was used for all analyses.(132)

These analyses support Aim 3 and 4, to characterize vaccine hesitancy and influenza vaccine uptake (Aim 3) and evaluate whether attitudes and beliefs about the policy implications of vaccinomics vary by vaccine hesitancy status and sociodemographic characteristics among adults, representative of the U.S. demographic profile (Aim 4).

3.8 Tables for Chapter 3

Table 2. Community Meeting Sample Size

	Baltimore	Boulder	Total
N Individuals to Recruit	50	120	170
N Groups	4	4	8

Chapter 4. Vaccine hesitancy and influenza vaccine uptake: results of a cross sectional survey among U.S. adults

4.1 Abstract

Background: Vaccine coverage is lower for influenza than for other vaccines, varying by age, race/ethnicity, and U.S. state. Vaccine safety concerns are common, despite a lack of epidemiological evidence. We characterized vaccine hesitancy and identified associations with influenza vaccination among U.S. adults.

Methods: Respondents ≥18 years old opted-in to an online survey (N=1,925). We measured sociodemographic characteristics, vaccine confidence, influenza vaccination history (2018-2019 and 2019-2020), trust in pharmaceutical companies and public health authorities, and perceived vaccine reaction history. Variables hypothesized to be associated with vaccine hesitancy and influenza vaccination were cross-tabulated. Bivariable and multivariable prevalence ratios were estimated using survey estimation procedures and Poisson regression. Backwards stepwise regression identified parsimonious models ($p<0.05$).

Results: The weighted study population was 50.6% female, 61.8% White, non-Hispanic, 62.9% had a child <18 years old, and 47.1% had a high school education or less. High vaccine hesitancy prevalence was 45.4% among parents of young children, 27.6% among parents of teenagers, and 37.7% among other adults. Across age groups, higher education and use of complementary/alternative medicine (CAM) were associated with higher vaccination prevalence in multivariable models. High vaccine hesitancy was associated with lower vaccination (excluding parents of young children).

Discussion: We identified common vaccine misconceptions and vaccine hesitancy. CAM use and higher education were consistently associated with vaccination across age groups. CAM use may mediate the income-vaccination association**.** Vaccine hesitancy differed by age, and may have influenced results. Awareness of federal vaccine safety oversight was low. Results are subject to selection and social

desirability biases, though quotas were used to enroll a sample representative of sociodemographic distribution of the U.S.

Conclusions: Age and education-level appropriate, targeted communications are needed. Future research should investigate how to reach sociodemographic minorities, less likely to use CAM or be vaccinated, and whether raising public awareness of federal vaccine safety oversight improves confidence.

4.2 Background

Influenza is a serious, life-threatening illness, often misperceived as "just a cold," and influenza vaccines are unnecessary, ineffective, and unsafe.(4, 6-13, 143-146) The Centers for Disease Control and Prevention estimated influenza caused 35.5 million illnesses, 16.5 million medical visits, 490,600 hospitalizations, and 34,200 deaths in 2018-2019.(147) Multiple vaccines are licensed, including inactivated influenza vaccines (IIV) and live attenuated influenza vaccines (LAIV). All are very safe with moderate effectiveness, though effectiveness and coverage are lower than other vaccines.(18, 19, 118) Influenza vaccines uniquely require annual administration and are recommended for everyone ≥6 months old.(20, 21) VE estimates for RT-PCR confirmed influenza were estimated to be 25% (95% CI 10%, 37%) among children 6 months to 8 years old and 25% (95%CI 10%, 37%) among adults 18-49 years old.(77) Estimates were lower among other age groups. There is an opportunity to improve coverage, which was 62.6% for children and 45.3% for adults in 2018-2019.(20, 21, 25) Despite these challenges, influenza vaccines were estimated to avert 2.3 million illnesses, 58,000 hospitalizations, and 3,500 deaths in 2018-2019.(148)

Vaccine coverage in the U.S. varies by race/ethnicity, state, age, and education.(12, 25) In 2018-2019, coverage was 73.4%, among children 6 months-4-years old, 63.6% among 5-12-year-olds and 52.2% among 13-17-year-olds.(25) Among children, coverage ranged from 46.0% (Wyoming) to 81.1% (Massachusetts) by state and from 60.9% (White only, non-Hispanic) to 58.5% (American Indian/Alaska

Native) by race/ethnicity. Coverage was lower among adults: 68.1% among ≥65-year-olds, 47.3% among 50-64-year-olds, and 34.9% among 18-49-year-olds. Adult coverage ranged from 33.9% (Nevada) to 56.3% (Rhode Island) by state and from 48.7% (White only, non-Hispanic) to 37.1% (Hispanic) by race/ethnicity. Vaccination prevalence increases with education level.(12) One study associated CAM use with reduced influenza vaccination, and other studies with reduced childhood immunization.(141, 149, 150)

Influenza vaccines are very safe and cannot cause influenza.(18) Local adverse reactions (soreness, erythema and induration at the injection site) lasting less than two days and systemic reactions (fever, chills, malaise, and myalgia) are common.(18) These symptoms often begin within 6-12 hours of vaccination and resolve within a few hours. There is an increased risk of runny nose, congestion, and fever from LAIV compared to IIV. Serious, life threatening reactions like anaphylaxis (1-2 cases per million doses administered)(26) and Guillain-Barré Syndrome (1-3 cases per 1,000,000 doses administered) are very rare.(18)

Vaccine hesitancy is the delay or refusal of vaccines, despite their availability.(1) In 2019, the World Health Organization designated vaccine hesitancy one of the top 10 threats to global health.(2) Despite a lack of epidemiological evidence, many people worry about vaccine safety in general, especially for children. The anti-vaccine movement spreads misinformation via Political Action Committees and the media, sewing doubt in vaccine safety.(61)

Like many childhood vaccines, infleunza vaccines are mistrusted by some due to concerns about side effects and mistrust of pharmaceutical companies, public health authorities, and the media.(4, 6-9, 12, 13, 143-146) Influenza vaccine hesitancy may be different than for other vaccines, particularly routine childhood vaccines, as they require annual vaccination and have lower vaccine effectiveness than other routinely used vaccines.(12, 13, 143-146, 151) In a survey demographically representative of the U.S., 41.6% of respondents ≥19 years old believed influenza vaccines could cause "bad side effects or

adverse reactions," 22.6% worried the vaccine could "cause the disease," and 26.5% that the "ingredients in the vaccine are bad for me."(152) School vaccine requiements for other vaccines indicate necessity, and a lack of them for influenza, combined with individuals' personal experience recovering from influenza (or what was thought to be influenza) in the past, perpetuates the misperception that vaccination is unnecessary.(13)

Vaccine attitudes, beliefs, and uptake vary by age, race, and level of education.(12, 152) Compared to 50-64-year-olds, 19-49-year-olds are less likely to believe influenza vaccines are safe (82.7% versus 89.5%), effective (68.3% versus 74.1%), or know they are recommended for adults (91.5% versus 95.6%).(152) Among respondents with less than a high school education, being African American and Hispanic were associated with more negative influenza vaccine beliefs; however, these disparities dissipated with increasing education.(12)

Multiple measures of vaccine hesitancy exist. Vaccine hesitancy has most frequently been measured with the Parent Attitudes About Childhood Vaccines PACV, designed to measure attitudes and beliefs regarding several vaccines routinely recommended for young children.(137, 138) The Vaccine Confidence Scale was created to measure vaccine hesitancy in parents of teenagers.(140) Vaccine hesitancy in general, or influenza-specific, may be associated with influenza vaccine refusal.(153)

We aimed to characterize vaccine hesitancy and identify attitudes, beliefs and behaviors associated with influenza vaccine acceptance among a sample of U.S. adults, representative of the U.S. demographic profile.

4.3 Methods

Recruitment and Consent

Respondents were enrolled through a Qualtrics panel (N=1,925) were out of approximately 10 million panel participants, using a double opt-in process.(133) All consented to answer survey items

between January 22 and February 11, 2020. Quotas were based on the Current Population Survey,(154) American Community Survey,(135) and 2010 Census(134) so that respondents reflected the sociodemographic profile of the U.S. Quotas were ignored when enrolling the last 400 (approximate) of 1,925 respondents, due to challenges enrolling individuals with minority race/ethnicity, in the lowest income, age, and education brackets, and from the Midwest and West.

Survey Content

Sociodemographic items were adapted from national surveys and the Census.(134, 135, 154) Other items covered vaccine confidence, influenza vaccination history, personal health, and trust in pharmaceutical companies and public health authorities.

Measures of vaccine hesitancy were based on whether the person had a child and that child's age, using previously developed and validated scales.(137, 138, 140) Modified PACV items were administered to parents of children ≤10 years old.(137, 138) Vaccine confidence was measured among parents of teenagers and adults without minor children using separate items adapted from The Vaccination Confidence Scale.(140). Parents of children <18 years old were prompted to think about vaccines other than influenza and adults without minor children were prompted to think about influenza when responding.

Respondents with children <18 years old reported whether their child received the influenza vaccine in 2018-2019 and 2019-2020. Adults without minor children reported their vaccination status for the same years.

Serious vaccine reactions were measured with the question: "Have you or anyone you know ever had a serious reaction to a vaccine? Serious reactions include permanent disability, hospitalization, life-threatening illness, or death?" CAM use was captured by: "Have you or members of your family (spouse/partner or children) used the services of a chiropractor, acupuncturist, or other complementary/alternative medicine provider in the last five years?" Twenty items on trust in public

health authorities ("trust" henceforth) were developed based on a literature review.(141) Most items used a 4-point Likert Scale. Four NHANES items were included to assess the comparability of the sample to the U.S. in terms of health behaviors.

Data Analyses

To facilitate making inferences about the U.S. population, data were weighted to the 2010 Census by region, race, and Hispanic ethnicity.(134) The distribution of the weights was visualized using histograms and the adequacy of weighting was evaluated by comparing the weighted data to the 2010 Census and 2015-2016 NHANES.(155) Variables measured on a 4-point Likert Scale were dichotomized (strongly agree/agree versus strongly disagree/disagree) for stratified analyses.

Vaccine hesitancy data were converted to a score (range 0 to 100) using a linear transformation. The distributions of the transformed data were visualized with histograms. Since the median in one of the three groups equaled zero, preventing dichotomization at that point, scores were dichotomized at the weighted mean (low versus high hesitancy) for each group (parents of children ≤10 years old, parents of teenagers 11-17 years old, and adults without minor children).

Using survey estimation procedures and Taylor-linearized variance estimates,(142) univariate and bivariable tabulations characterized associations between three outcomes: vaccine hesitancy and influenza vaccination status for each of the 2018-2019 and 2019-2020 seasons, with sociodemographic factors, parent status, use of CAM, perceived serious reaction experience ("serious reaction" henceforth), and trust in pharmaceutical companies and public health authorities.

We tested the hypothesis that younger age, higher education, and living in the Northeast and West (versus Midwest), and higher vaccine hesitancy were not with associated influenza vaccination.(125) Experience with serious reactions, trust in pharmaceutical companies and public health authorities, use of CAM, awareness of vaccine resources, and sociodemographic factors were

cross tabulated against vaccine hesitancy and influenza vaccination status (2018-2019 and 2019-2020) by the three age groups in which vaccine hesitancy was measured.

Associations with influenza vaccination in 2018-2019 and 2019-2020 were explored using Poisson regression for survey data. Excluding knowledge of vaccine resources, like the Vaccine Adverse Events Reporting System (VAERS), and types of CAM, factors listed in **Table 3** associated with vaccination at $p<0.1$ in bivariable regression were included in saturated multivariable models, by age group. Parsimonious models were identified using backwards stepwise regression, retaining variables associated with the outcome at $p\leq0.05$. Due to a change in estimate ≥10% in one model, education was included in all multivariable models as a potential confounder, regardless of its p-value. This large a change was not evident for other variables, so they were not forced into multivariable models. "Prefer not to answer" responses for income and education and "don't know" for vaccination status were excluded from multivariable models in which these variables were included.

Trust in public health authorities (low versus high) was derived from a linear score of 14 items, dichotomized at the mean, explained elsewhere.(156) When the proportion in the reference group was 0.5 and there were 3 times as many respondents in one group compared to the other, this study had 96.9% power to detect a difference of 10% between two groups. P-values were estimated using two-sided general tests of association. Analyses were conducted using Stata®, Version 16.(132) Weighted results are reported below.

Ethical Review

This survey was ruled "exempt" by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

4.4 Results

Sociodemographic Characteristics of the Study Population

The weighted study population was 50.6% female, 61.8% White, non-Hispanic; 36.0% 18-34-year-olds, 62.9% had a child <18 years old, 44.7% had a household annual income ≤$49,999, and 47.1% had a high school education or less. Most respondents had some science training through high school (55.7%), college (32.7%), graduate/continuing education (15.8%), and on the job training (13.7%), though 7.7% had none of these types of training. Respondents represented a broad geographic distribution of the U.S. (Midwest: 22.2%, Northeast: 18.1%, South: 36.9%, West: 22.6%). CAM users constituted 40.0% of respondents **(Table 1).**

Vaccine Attitudes, Beliefs and Hesitancy:

Parents of Young Children

Many respondents strongly agreed/agreed with positive statements regarding vaccine attitudes; however, over half indicated children receive too many vaccines. Agreement with "Children get more vaccines than are good for them," (51.1%) and "It is better for children to get fewer vaccines at the same time (61.1%) was high. A lower proportion (38.7%) agreed "It is better for my child to develop immunity by getting sick than by getting a vaccine." Agreement with positive vaccine statements was higher: "I trust the information I receive from doctors about vaccines" (85.7%), "I can openly discuss my questions about vaccines with my child's doctor" (90.5%), and "The Centers for Disease Control and Prevention (CDC) and professional medical associations' recommended vaccine schedule is a good fit for my child" (87.9%). Most parents (69.9%) expressed ≥1 negative attitudes/beliefs **(Table 2).**

The distribution of vaccine hesitancy was right-skewed **(Figure 1).** The proportion with high hesitancy differed by education level (≤high school: 54.6% versus graduate degree: 27.8%) and household income level (≤$49,999: 52.4% versus ≥$150,000: 36.0%). Mistrust of pharmaceutical

companies was common among those with high hesitancy (62.3%) compared to low hesitancy (39.4%). A lower proportion of those with high (40.1%) trust in public health authorities had high hesitancy versus low trust (59.9%). There were no differences in vaccine hesitancy by perceived history of serious reactions or CAM use **(Table 3).**

Teenagers

Most (>85%) parents of teenagers (n=515) strongly agreed/agreed with positive statements about vaccine attitudes and beliefs. Respondents strongly agreed/agreed that "Vaccines are necessary to protect the health of teenagers" (90.9%), "Vaccines do a good job of preventing the diseases they are intended to prevent" (90.1%), "If I do not vaccinate my child, he/she may get a disease such as pertussis or human papillomavirus (HPV) and cause other people to get sick" (85.1%), "The Centers for Disease Control and Prevention (CDC) and professional medical associations' recommended vaccine schedule is a good fit for my child" (89.9%), "I trust the information I receive from doctors about vaccines" (87.8%), and "I can openly discuss my questions about vaccines with my doctor" (91.1%). Some parents of teenagers (29.4%) expressed ≥1 negative attitude/belief **(Table 2).**

High hesitancy varied by education level (≤high school: 32.9% versus graduate degree: 17.6%) and household income (≤$49,999: 33.4% versus ≥$150,000: 18.4%). Black, non-Hispanics had a higher prevalence of high hesitancy (41.6%) than White, non-Hispanics (23.0%). Older respondents (≥55-year-olds: 17.8%) were less likely to have high hesitancy than younger respondents (18-35-year-olds: 33.7%; 35-54-year-olds: 30.8%). High hesitancy was most common in the Midwest (53.6%) and least common in the Northeast (38.7%). Perceived serious reaction experience was 35.1% among those with high hesitancy, compared to 25.4% among those without reaction experience. Among those who mistrusted pharmaceutical companies, 33.8% had low and 61.2% had high hesitancy. A lower proportion of those with high (15.0%) trust in public health authorities had high hesitancy versus low trust (85.0%). There were no differences in hesitancy by CAM use **(Table 3).**

Adults

The majority of adults without minor children (n=686) strongly agreed/agreed with positive statements about vaccine attitudes and beliefs, indicating low levels of vaccine hesitancy. Most (82.9%) of respondents strongly agreed/agreed that "Vaccines are necessary to protect the health of adults." Agreement with "Vaccines do a good job in preventing the diseases they are intended to prevent" was 83.6% and "I trust the information I receive from doctors about vaccines" was 82.1%. Agreement was lower regarding respondents' risk of influenza infection: 74.9% strongly agreed/agreed that "If I do not get vaccinated, I may get influenza or the flu and cause other people to get sick." Most adults without minor children (77.8%) expressed ≥1 negative attitude/belief **(Table 2).**

The prevalence of high hesitancy varied by age group (18-34-year-olds: 47.5% versus ≥55-year-olds: 30.5%) and education level (≤high school: 59.2% versus graduate degree: 86.5%). High hesitancy was more prevalent among those with lower (≤$49,999: 40.7%) than higher household income (≥$150,000: 22.0%). Those with high hesitancy were more likely to mistrust than trust pharmaceutical companies (67.6% versus 26.2%). High hesitancy was least prevalent among Black, non-Hispanics (33.6%) and White, non-Hispanics (36.8%) compared to other races (41.7%). A lower proportion of those with high (26.3%) trust in public health authorities had high hesitancy versus low trust (73.7%). Perceived history of serious reactions and CAM use were unassociated with vaccine hesitancy **(Table 4).**

Demographic and Attitudinal Associations with Vaccine Uptake

Young children

Respondents reported 71.5% of young children were vaccinated against influenza in 2018-2019 and 82.9% in 2019-2020. In 2018-2019, vaccination was associated with graduate education (86.6%) compared to ≤high school (68.4%) and having an income ≥$150,000 (81.5%) compared to (≤$49,999: 67.9%). Most respondents who reported a history of serious reactions were vaccinated (83.8%), as were

those without this experience (63.8%). CAM users were mostly vaccinated as well (80.3%). Among those who mistrusted pharmaceutical companies, 44.5% had low and 55.5% had high hesitancy. The majority of participants (76.7%) with high versus low (23.3%) trust in public health authorities vaccinated their child against influenza in 2018-2019. In 2019-2020, the same variables were associated with vaccination, except for household income **(Table 3).**

In bivariable regression, the prevalence of vaccination in 2018-2019 marginally varied by household income level when ≤$49,999 was the baseline. Perceived serious reactions were associated with a slightly lower prevalence of vaccination, compared to no reactions (PR: 0.97; 95% CI: 0.96, 0.99). Vaccination prevalence in 2019-2020 increased with education level (graduate degree versus ≤high school PR: 1.11; 95% CI: 1.03, 1.19), and among those with perceived serious reactions versus without (PR: 1.08; 95% CI: 1.01, 1.15). Trust in pharmaceutical companies versus mistrust (PR: 1.22 95% CI: 1.11, 1.35), and CAM use versus nonuse (PR: 1.15; 95% CI: 1.07, 1.24) were also associated with higher vaccination prevalence **(Table 5).**

In multivariable analysis, vaccination in 2018-2019 was highest among those with graduate education versus ≤high school (PR: 1.20; 95% CI: 1.07, 1.34), with versus without perceived vaccine reactions (PR: 1.14; 95% CI: 1.04, 1.26), and CAM use versus nonuse (PR: 1.18; 95% CI: 1.07, 1.32). In 2019-2020, higher education (graduate versus ≤high school degree PR: 1.03**;** 95% CI: 0.96, 1.11), CAM use versus nonuse (PR: 1.14; 95% CI: 1.07, 1.23), and trust versus mistrust of pharmaceutical companies (PR: 1.24; 95% CI: 1.13, 1.38) were associated with higher vaccination prevalence **(Table 5).**

Teenagers

Respondents indicated 70.5% of teenagers were vaccinated in 2018-2019 and 75.9% in 2019-2020. Vaccination prevalence was higher among respondents with graduate degrees (88.1%)) versus ≤high school (66.9%) and an income of ≥$150,000 (83.4%) versus ≤$49,999 (63.7%). Vaccination was higher in the Northeast (79.3%) than the Midwest (63.5%). Most CAM users were vaccinated (77.8%).

Among respondents with vaccinated teenagers, 75.1% trusted and 58.4% mistrusted pharmaceutical companies. In 2019-2020, the same variables were associated with vaccination. There was no association between vaccination and history of serious reactions or trust in public health authorities **(**p<0.1; **Table 3).**

In bivariable regression, vaccination in 2018-2019 was lower among those with high versus low vaccine hesitancy (PR: 0.75; 95% CI: 0.64, 0.88) and older age (≥55 versus 18-34-year-olds PR: 0.85; 95% CI: 0.72, 1.01). Vaccination prevalence was increased among respondents with higher income ($150,000 versus ≤$49,999: PR 1.31; 95% CI 1.13, 1.51) and higher education (graduate versus ≤high school degree: PR: 1.32; 95% CI: 1.15, 1.51). Respondents from the Northeast (PR: 1.25; 95% CI: 1.05, 1.49) and South (PR: 1.22; 95% CI: 1.02, 1.45) had higher vaccination prevalence than those from the Midwest. CAM users had higher vaccination prevalence than nonusers (PR: 1.17; 95% CI: 1.05, 1.32). Trust in pharmaceutical companies and perceived serious reaction experience were unassociated with vaccination **(Table 6).**

In bivariable regression, vaccination prevalence in 2019-2020 was lower among those with high versus low vaccine hesitancy (PR: 0.72; 95% CI: 0.62, 0.84). Prevalence was higher among those with graduate degrees versus ≤high school (PR: 1.29; 95% CI: 1.15, 1.45), higher household income (≥$150,0000 versus ≤$49,999 PR: 1.30, 95% CI: 1.16, 1.47), and living outside the Midwest (Northeast: PR 1.19; 95% CI 1.01, 1.40; South: PR 1.19; 95% CI 1.01, 1.39). CAM users had higher vaccination prevalence compared to nonusers (PR: 1.17; 95% CI: 1.06, 1.29). High trust in public health authorities was associated with higher vaccination prevalence (PR: 1.15, 95% CI: 1.04, 1.28), but having a perceived serious reaction was not **(Table 6).**

In multivariable regression 2018-2019 vaccination prevalence was lower among teenagers whose parents had high vaccine hesitancy (PR: 0.81; 95% CI: 0.77, 0.95). Compared to respondents 18-34 years old, older parental age was associated with lower vaccination prevalence (≥55-year-olds PR

0.80; 95% CI: 0.68, 0.94). Higher prevalence was associated with graduate versus ≤high school education (PR: 1.29; 95% CI: 1.12, 1.48) and living in the Northeast (PR: 1.19; 95% CI: 1.00, 1.41) or South versus the Midwest (PR: 1.21; 95% CI: 1.02, 1.44). Trust in pharmaceutical companies, versus mistrust, was associated with higher vaccination prevalence (PR: 1.20; 95% CI: 1.01, 1.42). In 2019-2020, vaccination was reduced among teenagers whose parents had high vaccine hesitancy (PR: 0.79; 95% CI: 0.68, 0.91). Graduate education was associated with increased vaccination compared to ≤high school (PR: 1.20; 95% CI: 1.06, 1.35). Trust versus mistrust of pharmaceutical companies (PR: 1.23; 9% CI: 1.05, 1.43) and CAM use versus nonuse (PR: 1.14; 95% CI: 1.03, 1.25) were associated with higher vaccination prevalence **(Table 6).**

Adults

Over half of respondents (56.4%) reported getting the influenza vaccine in 2018-2019 and 65.0% did in 2019-2020. Vaccination was highest among those aged ≥55 (63.3% and 35-54 (60.7%) compared to 18-34-year-olds (46.8%) in 2018-2019. Black, non-Hispanics had higher vaccination prevalence (76.2%) compared to White, non-Hispanics (57.2%) and other races (54.0%). Respondents with graduate degrees (86.4%) were more likely to be vaccinated than those with a ≤high school education (50.5%). Having an income ≥$150,000 was associated with higher vaccination prevalence compared to ≤$49,999 (73.0% versus 53.2%). Vaccinated respondents were more likely to trust (67.7%) pharmaceutical companies than mistrust them (31.3%). Most (64.4%) CAM users were vaccinated. In 2019-2020, the same variables were associated with vaccination, except for age and race/ethnicity with vaccination **(Table 4).**

In bivariable regression, high vaccine hesitancy (PR 0.40; 95% CI 0.33, 0.49) reduced vaccination prevalence, compared to low hesitancy in 2018-2019. Prevalence increased with age (≥55- versus 18-34-year-olds: PR 1.35; 95% CI 1.15, 1.59), education level (compared to ≤high school, ≤college degree: PR 1.39; 95% CI 1.21, 1.59; graduate degree: PR 1.71; 95% CI 1.46, 2.01). White, non-Hispanics had higher

prevalence than other races/ethnicities (PR: 1.33; 95% CI: 1.11, 1.60), and higher household income (≥$150,000 versus $49,999 PR 1.37; 95% CI 1.11, 1.70) were associated with vaccination. Compared to mistrust, trust in pharmaceutical companies (PR: 2.16; 95% CI: 1.73, 2.70) was associated with higher vaccination prevalence, as was high versus low trust in public health authorities (PR: 1.38; 95% CI: 1.20, 1.60), and CAM use versus nonuse (PR: 1.16; 95% CI: 1.01, 1.33). In 2019-2020, the same variables were associated with vaccination, with the addition of high versus low trust in public health authorities (PR: 1.23; 95% CI: 1.09, 1.38) and the exception of race/ethnicity. Perceived experience with vaccine reactions was unassociated with vaccination in both years **(Table 7).**

In multivariable regression, the prevalence of vaccination in 2018-2019 was half as high among those with high versus low vaccine hesitancy, controlling for other variables in the model (PR: 0.47; 95% CI: 0.38, 0.58). Higher education was associated with increased vaccination prevalence compared to ≤high school (≤college: PR 1.22; 95% CI 1.08, 1.37; graduate degree: PR 1.56; 95% CI 1.33, 1.84). In 2018-2019, trust versus mistrust of pharmaceutical companies (PR: 1.61; 95% CI: 1.29, 2.02) and CAM use versus nonuse (PR: 1.12; 95% CI: 1.00, 1.27) were associated with higher vaccination prevalence. In 2019-2020, those with high versus low vaccine hesitancy had a lower prevalence of vaccination (PR: 0.38; 95% CI: 0.31, 0.45). High versus low trust in public health authorities was associated with lower vaccination prevalence (PR: 0.91; 95% CI: 0.83, 1.00), as was older age. Compared to 18-34-year-olds (35-54-year-olds: PR 0.76; 95% CI 0.63, 0.92; ≥55-year-olds: PR 0.78; 95% CI 0.71, 0.85). Higher education, compared to ≤high school, was associated with increased vaccination prevalence (≤college degree: PR 1.14; 95% CI 1.02, 1.27; graduate degree: PR 1.40; 95% CI 1.21, 1.62; **Table 7).**

4.5 Discussion

The majority of respondents had favorable vaccine attitudes and beliefs. However, misconceptions and vaccine hesitancy were common. Respondents with a high school education or less had reduced vaccination prevalence compared to those with more education. Access to accurate

vaccine safety and effectiveness information was associated with higher uptake.(13) In this study, more than half of parents of young children indicated children are given too many vaccines. Vaccine hesitancy was associated with lower vaccination prevalence among most respondents. In bivariable analysis, younger age was associated with higher vaccination prevalence of children. Among those without minor children, older age was associated with vaccination of oneself. National-level data, not stratified by parent status, indicated younger people have less positive influenza vaccine attitudes and beliefs than older people.(152) Communication campaigns to dispel misinformation should target individuals with a high school education or less, and be stratified by age when promoting influenza vaccines for adults and children.(12, 151, 152) Prior research suggests stratification by race/ethnicity may be needed as well.(151)

Most respondents had one or more vaccine concerns, comparable to a prior study that reported 77% of parents of children aged ≤6 years old had at least one concern. In that study, 36% of parents worried "My child is getting too many vaccines in one doctor's visit."(4) A higher proportion (61%) of parents of children ≤10 years old indicated "It is better for children to get fewer vaccines at the same time." We used different wording and included parents of slightly older children than the prior study. Since national-level vaccine hesitancy data have not been published in the peer-reviewed literature since 2011, it is unclear whether the observed differences are due to changes over time, selection bias, or differences in measurement.

We hypothesized that vaccine hesitancy for vaccines other than influenza would be associated with influenza vaccine uptake among children <18 years old and that influenza-specific vaccine hesitancy would be associated with influenza vaccination among adults. Two studies support this hypothesis, finding vaccine hesitancy, in general and specific to influenza vaccines, was associated with influenza vaccination among adults and children.(144, 157) We measured vaccine hesitancy with the PACV(137, 138) among parents of young children and with the Vaccine Confidence Scale(140) among parents of

teenagers and adults without minor children. Vaccine hesitancy was only associated with vaccination among those who received the modified Vaccine Confidence Scale in this study.(140) The PACV asks parents to think about vaccines other than influenza when answering.(137, 138) To avoid overburdening respondents, we did not ask these questions a second time about influenza vaccines. The Vaccine Confidence Scale, as adapted here, may be a better predictor of influenza vaccination than the PACV scale.(140)

Several studies indicate CAM use is associated with vaccine refusal and delay of childhood vaccines. (141, 144, 149, 158) One study found influenza vaccination was lower among CAM users, the opposite of our finding.(159) CAM has become increasingly popular.(160) Using these services may now be associated with proactive health behavior. According to the National Health Interview Survey, use was 11.6% children and 32.2% among adults in 2012.(161, 162) CAM use is highest among adults 18-44 years old.(162) Non-Hispanic, White women and children most frequently use CAM.(160) The normalization of CAM, especially among non-Hispanic whites, and shift in the anti-vaccine movement's focus to "informed decision-making" from its past focus on protecting the body from unnatural products, may explain why CAM use was associated with increased influenza vaccine prevalence here.(163)

The proportion of respondents who indicated familiarity with the Vaccine Adverse Events Reporting System (VAERS) and the Vaccine Injury Compensation Program (VICP) was similar to the proportion who reported having heard of the fictitious National Vaccine Safety Hotline.(95, 164) This indicates social desirability bias.(165) The true proportion of adults familiar with the VICP and VAERS is likely lower than reported.

Prior reported associations between CAM use and reduced vaccination prevalence could be confounded by mistrust of government, education, income, and race/ethnicity due to their joint association with vaccine hesitancy.(7, 8, 125, 141, 144, 156, 158, 166) We controlled for

sociodemographic variables in saturated multivariable models, and found that income and CAM were independently associated with influenza vaccination. Other studies may indeed be confounded, or it may be that CAM is a mediator of the income-race/ethnicity-vaccination relationship. Income and race/ethnicity were unassociated with vaccination in multivariable models that included CAM, and CAM was statistically significant in all models. This suggests the total effect of income and race/ethnicity may be mediated through CAM. We studied any use of CAM, which respondents may have interpreted more broadly than the examples given in the survey.

Associations between vaccination and sociodemographic factors were stronger in 2018-2019 compared to 2019-2020. In 2019-2020, the outcome included "planning to get vaccinated," as the survey was fielded in January and February 2020, during what is typically the middle of influenza season. Uncertainty around future behavior may have caused effects to attenuate, though most associations remained consistent over time.

Trust in public health authorities was unassociated with vaccination most regression models. The lack of association with trust in public health authorities contradicts a separate analysis of these data; however, we analyzed young children separately from teenagers for consistency with how vaccine hesitancy was measured, and the other study combined these groups for increased power.(156)

Strengths and Limitations

The 15-item PACV and 5-item PACV Short Scale were developed to screen parents of young children in medical offices.(137, 138) The Vaccine Confidence Scale was originally administered online with a 10-point Likert scale, rather than the 4-point scale used here.(140) These scales have been demonstrated to have internal validity,(138, 139) but our adapted items may have had problems with external validity. However, these adapted items may have higher validity than de novo items. Though this was not a probability-based sample and the probabilities of selection and nonresponse were unavailable, poststratification weights were used to facilitate making inferences about the U.S.

population.(167) Weighted results were comparable to the 2010 Census and 2015-2016 NHANES (data not shown).(134, 167) Variance estimates are inflated by weighting, compared to what they would be using a simple random sample.(167) Despite this, strong statistical associations resulted. The 10 states with the lowest influenza vaccine coverage are in the West and South.(25) In this survey, parents of teenagers from Southern states reported high vaccination prevalence. This may reflect selection bias, as enrollment quotas by region were not met and this was an opt-in survey. Associations with vaccine prevalence may change over time if trust in vaccines, pharmaceutical companies, and public health authorities change in response to current events. Cross-sectional surveys are inherently limited by collecting data at one point in time. Self-reported responses are subject to social desirability bias, which was evident in the VAERS and VICP familiarity reports, and may have affected influenza vaccination history. Responses were anonymized and survey items used neutral language to minimize bias.(165)

Public Health Implications

We identified influenza vaccine attitudes and beliefs that do not favor vaccination and subpopulations that can be targeted. Individuals with a high school education or less had lower vaccination prevalence, and national-level data indicates younger adults, have less positive vaccine perceptions compared to older age groups.(152) Adults with little education and young age should be targeted with education-level appropriate, individualized communications. CAM nonusers had lower vaccine prevalence, and are likely to be racial/ethnic minorities and have lower socioeconomic status than CAM users.(158) How to reach those most likely to refuse the influenza vaccine and what kinds of information will resonate with them require further research.

Awareness of VAERS and the VICP is likely lower than respondents indicated. Public health authorities should invest in making the public aware of these resources, and the Vaccine Safety Datalink, as knowing the government invests in vaccine safety oversight may boost confidence.

4.6 Conclusions

Public health authorities should invest in improving vaccine attitudes, beliefs, and coverage, so that influenza vaccination prevalence is brought on par with other vaccines. These efforts need to target populations with a high school education or less and younger age.(152) More research is needed into how to improve coverage among disadvantaged populations, which are less likely to use CAM, and whether vaccination support varies by CAM discipline used.

Funding

This study was supported by grant number RM1HG009038 from the National Human Genome Research Institute (JEG, AS, MB, JB, JK, GG, DAS). The funder was not involved in the design, implementation, analysis, interpretation, or reporting of this study.

4.7 Tables for Chapter 4

Table 1. Sociodemographic distribution of the study population

	Unweighted N=1,925 (%)	Weighted %		Unweighted N=1,925 (%)	Weighted %
			Child <18 years old[7]		
Gender[1]			Yes	1,239 (64.4)	62.9
Male	934 (48.5)	48.6	No	686 (35.6)	37.1
Female	976 (50.7)	50.6	**Youngest child's age (years)[8]**		
Race/ethnicity[2]			≤5	323 (22.6)	22.2
White, Non-Hispanic	1,136 (59.0)	61.8	6-10	401 (28.0)	27.7
Black, Non-Hispanic	230 (11.9)	11.4	7-11	515 (36.0)	35.9
Other	559 (29.0)	26.8	≥18	181 (12.6)	13.3
Respondent's age (years)[3]			**Vaccine hesitancy: parents of children ≤10 years old[5]**		
18-34	691 (36.0)	36.0	Low	396 (54.7)	54.6
35-54	661 (34.4)	33.4	High	328 (45.3)	45.4
≥55	569 (29.6)	30.6	**Vaccine hesitancy: parents of children 11- 17 years old[6]**		
Highest level of education[4]			Low	376 (73.0)	72.4
≤High school degree	893 (46.4)	47.1	High	139 (27.0)	27.6
≤College degree	728 (37.8)	37.4	**Vaccine hesitancy: other adults[6]**		
Graduate degree	277 (14.4)	14.0	Low	424 (61.8)	62.3
Household annual income[5]			High	262 (38.2)	37.7
$0-$49,999	855 (44.4)	44.7	**Science courses and training**		
$50,000-$99,999	508 (26.4)	26.7	High school	1,059 (55.0)	55.7
$100,000-$149,999	236 (12.3)	11.9	College	634 (32.9)	32.7
≥$150,000	290 (15.1)	14.8	Graduate/continuing education	315 (16.4)	15.8
Region[6]			Work/training	267 (13.9)	13.7
Midwest	397 (20.6)	22.2	None of the above	149 (7.7)	7.7
Northeast	510 (26.5)	18.1	**Complementary/Alternative medicine[7]**		
South	664 (34.5)	36.9	No	1,082 (56.2)	56.3
West	35 (18.2)	22.6	Yes	773 (40.2)	40.0

[1]gender: n=15 “trans/prefer not to answer” [2]race/ethnicity: n=0 missing; [3]respondent's age: n=4 missing; [4]respondent's education, n=27 missing, n=27 “prefer not to answer”; [5]household annual income: n=36 missing, n=36 “prefer not to answer”; [6]region: n=3 missing, n=3 “Puerto Rico/prefer not to answer”; [7]child<18 years old: "no" includes n=481 nonparents, n=12 "prefer not to answer, and n=181 child ≥18 years old; [8]age of youngest child: n=12 “prefer not to answer”; [9]vaccine hesitancy among parents of children≤10 years old estimated using a composite score from items adapted from Opel et al.(137, 138), unweighted n=724; weighted n=705.73; [10]vaccine hesitancy among parents of children 11-17 years old estimated using a composite score from items adapted from Gilkey et al.(140), unweighted n=515; weighted n=507.03; [11]vaccine hesitancy among other adults measured based on Gilkey et al.(140), [7]complementary/alternative medicine: n=70 "don't know; "unweighted n=686; weighted n= 715.12

Table 2. Bivariable analysis of overall vaccine hesitancy score components, by age group

Vaccine hesitancy components	Unweighted N (%) Yes	No	Don't know	Weighted % Yes	No	Don't know
Parents of Children≤10 Years Old						
Have you ever delayed having your child get a vaccine (not including the flu vaccine) for reasons other than illness or allergy?	189 (26.1)	529 (73.1)	6 (0.8)	26.0	73.2	0.8
Have you ever decided not to have your child get a vaccine (not including seasonal flu vaccine) for reasons other than illness or allergy?	139 (19.2)	571 (78.9)	14 (2.0)	18.7	79.3	2.0

	Unweighted N (%) Not at all Hesitant	Not too Hesitant	Somewhat Hesitant	Very Hesitant	Total	Weighted % Very/ Somewhat Hesitant	Very/ Somewhat Hesitant
Overall, how hesitant about childhood vaccines are you?[1]	147 (28.9)	131 (25.7)	146 (28.7)	79 (15.5)	509	44.2	44

	Unweighted N (%) Strongly Disagree	Disagree	Agree	Strongly Agree	Total	Unweighted % Strongly Agree/Agree	Weighted (%) Strongly Agree/Agree
I trust the information I receive from doctors about vaccines.[2]	41 (5.7)	42 (5.8)	265 (36.6)	356 (49.2)	724	85.8	85.7
I can openly discuss my questions about vaccines with my child's doctor.[3]	23 (3.2)	31 (4.3)	256 (35.4)	400 (55.2)	724	90.6	90.5
Children get more vaccines than are good for them.	87 (17.1)	158 (31.0)	182 (35.8)	82 (16.1)	509	51.9	51.1
It is better for my child to develop immunity by getting sick than by getting a vaccine.	130 (25.5)	180 (35.4)	140 (27.5)	59 (11.6)	509	39.1	38.7
It is better for children to get fewer vaccines at the same time.	57 (11.2)	139 (27.3)	230 (45.2)	83 (16.3)	509	61.5	61.1
The Centers for Disease Control and Prevention (CDC) and professional medical associations' recommended vaccine schedule is a good fit for my child.	38 (5.2)	50 (6.9)	388 (53.6)	248 (34.3)	724	87.8	87.9

Table 2. Continued	Unweighted N (%)					Unweighted %	Weighted (%)
Parents of Teenagers	**Strongly Disagree**	**Disagree**	**Agree**	**Strongly Agree**	**Total**	**Strongly Agree/Agree**	**Strongly Agree/Agree**
Vaccines are necessary to protect the health of teenagers	17 (3.3)	27 (5.2)	237 (46.0)	234(45.4)	515	91.5	90.9
Vaccines do a good job of preventing the diseases they are intended to prevent	14 (2.7)	33 (6.4)	227 (44.1)	241 (46.8)	515	90.9	90.1
If I do not vaccinate my child, he/she may get a disease such as pertussis or human papillomavirus (HPV) and cause other people to get sick	37 (7.2)	38 (7.4)	208 (40.4)	232 (45.0)	515	85.4	85.1
The Centers for Disease Control and Prevention (CDC) and professional medical associations' recommended vaccine schedule is a good fit for my child.	25 (4.9)	27(5.2)	238 (46.2)	225 (43.7)	515	89.9	89.9
I trust the information I receive from doctors about vaccines.[4]	22 (4.3)	21 (4.7)	164 (31.8)	290 (56.3)	515	88.2	87.8
I can openly discuss my questions about vaccines with my doctor.[5]	11 (2.1)	18 (3.5)	152 (29.5)	319 (61.9)	515	91.5	91.1
Adults without Minor Children							
Vaccines are necessary to protect the health of adults.	30 (4.4)	88 (12.8)	340 (49.6)	228 (33.3)	686	82.8	82.9
Vaccines do a good job in preventing the diseases they are intended to prevent	30 (4.4)	84 (12.2)	369 (53.8)	203 (29.6)	686	83.4	83.6
If I do not get vaccinated, I may get influenza or the flu and cause other people to get sick.	64 (9.3)	110 (16.0)	292 (42.6)	220 (32.1)	686	74.6	74.9
I trust the information I receive from doctors about vaccines[6]	42 (6.1)	50 (7.3)	266 (38.8)	295 (43.0)	686	81.8	82.1

[1]6 selected "Don't Know";[2] 20 selected "Don't Know"; [3]14 selected "Don't Know";[4] 15 selected "Don't Know"; [5] 15 selected "Don't Know"; [6] 33 selected "Don't know"; ≥1 concern: 69.9% parents of young children, 29.4% parents of teenagers, and 77.8% adults without minor children.

Table 3. Influenza vaccine update by vaccine hesitancy status, history of a serious vaccine reaction, and sociodemographic factors among adults with children <18 years old

	Parents of Young Children[1]									Parents of Teenagers[2]								
	Vaccine Hesitancy			Influenza Vaccination 2018-2019[3]			Influenza Vaccination 2019-2020[4]			Vaccine Hesitancy			Influenza Vaccination 2018-2019[5]			Influenza Vaccination 2019-2020[6]		
	Low	High	P-value	No	Yes	P-value	No	Yes	P-value	Low	High	P-value	No	Yes	P-value	No	Yes	P-value
Overall study population	54.6	45.4	N/A	27.1	71.5	N/A	15.6	82.9	N/A	72.4	27.6	N/A	28.1	70.5	N/A	22.5	75.9	N/A
History of serious vaccine reaction																		
No/ don't know	74.9	77.3	0.46	31.2	68.8	<0.01	17.5	82.5	0.05	74.6	25.4	0.04	28.8	71.2	0.77	22.6	77.4	
Yes	25.1	22.7		16.2	83.8		10.9	89.1		64.9	35.1		27.4	72.6		23.6	76.4	0.82
Region[7]																		
Midwest	46.4	53.6		28.0	72.0		16.1	83.9		73.0	27.0		36.5	63.5		32.0	68.0	
Northeast	61.3	38.7		22.0	78.0		14.7	85.3		79.7	20.3		20.6	79.4		19.0	81.0	
South	56.1	43.9		29.0	71.0		17.7	82.3		72.0	28.0		22.7	77.3		19.4	80.6	
West	52.0	48.0	0.09	28.9	71.1	0.46	13.8	86.2	0.71	64.9	35.1	0.12	38.4	61.6	<0.01	24.2	75.8	0.08
Age (years)																		
18-34	43.7	56.3		30.1	69.9		13.6	86.4		66.3	33.7		20.9	79.1		16.7	83.3	
35-54	65.8	34.2		24.9	75.1		18.7	81.3		69.2	30.8		28.6	71.4		23.9	76.1	
≥55	66.8	33.2	<0.01	24.3	75.7	0.31	16.3	83.7	0.24	82.2	17.8	<0.01	32.7	67.3	0.20	24.4	75.6	0.39
Race/ethnicity																		
White, Non-Hispanic	60.9	39.1		26.8	73.2		17.8	82.2		77.0	23.0		30.5	69.5		25.0	75.0	
Black, Non-Hispanic	56.9	43.1		30.1	69.9		18.3	81.7		58.4	41.6		27.1	72.9		18.0	82.0	
Other	44.1	55.9	<0.01	27.1	72.9	0.77	12.0	88.0	0.16	66.5	33.5	<0.01	23.7	76.3	0.36	19.1	80.9	0.29

Table 3, Continued	Parents of Young Children[1]									Parents of Teenagers[2]								
				Influenza Vaccination									Influenza Vaccination					
	Vaccine Hesitancy			2018-2019[3]			2019-2020[4]			Vaccine Hesitancy			2018-2019[5]			2019-2020[6]		
	Low	High	P-value	No	Yes	P-value	No	Yes	P-value	Low	High	P-value	No	Yes	P-value	No	Yes	P-value
Education[8]																		
≤High school degree	45.4	54.6		31.6	68.4		16.0	84.0		67.1	32.9		33.1	66.9		28.5	71.5	
≤College degree	56.1	43.9		29.7	70.3		19.1	80.9		72.0	28.0		31.5	68.5		24.5	75.5	
Graduate degree	72.2	27.8	<0.01	13.4	86.6	<0.01	7.1	92.9	0.01	82.4	17.6	0.03	11.9	88.1	<0.01	7.7	92.3	<0.01
Household annual income[9]																		
$0-$49,999	47.6	52.4		32.1	67.9		17.9	82.1		66.6	33.4		36.3	63.7		31.7	68.3	
$50,000-$99,999	54.2	45.8		29.6	70.4		16.3	83.7		75.2	24.8		26.5	73.5		20.8	79.2	
$100,000-$149,999	63.2	36.8		23.3	76.7		12.0	88.0		71.6	28.4		25.2	74.8		19.2	80.7	
≥$150,000	64.0	36.0	<0.01	18.5	81.5	0.08	13.7	86.3	0.49	81.6	18.4	0.05	16.6	83.4	<0.01	10.9	89.1	<0.01
I trust pharmaceutical companies to make very safe and effective vaccines.																		
Strongly disagree/disagree	33.7	62.3		44.5	55.5		27.9	72.1		33.8	61.2		41.6	58.4		38.0	62.0	
Strongly agree/agree	60.6	39.4	<0.01	21.4	78.6	<0.01	11.7	88.3	<0.01	81.8	18.2	<0.01	24.9	75.1	<0.01	18.7	81.3	<0.01

Table 3, Continued	Parents of Young Children[1]									Parents of Teenagers[2]								
	Vaccine Hesitancy			Influenza Vaccination 2018-2019[3]			Influenza Vaccination 2019-2020[4]			Vaccine Hesitancy			Influenza Vaccination 2018-2019[5]			Influenza Vaccination 2019-2020[6]		
	Low	High	P-value	No	Yes	P-value	No	Yes	P-value	Low	High	P-value	No	Yes	P-value	No	Yes	P-value
Trust in public health authorities																		
Low	50.2	49.8		30.7	69.3		18.5	81.5		54.8	45.2		32.3	67.7		29.1	70.9	
High	59.9	40.1	0.01	23.3	76.7	0.03	13.0	87.0	0.05	85.0	15.0	<0.01	25.8	74.2	0.13	18.4	81.6	<0.01
Have you heard of the following resources before? Select all that apply.																		
Vaccines Injury Compensation Program (VICP)	55.2	44.8	0.83	16.5	83.5	<0.01	9.1	90.9	<0.01	73.9	26.1	0.70	10.3	89.7	<0.01	6.9	93.1	<0.01
Vaccines Adverse Events Reporting Systems (VAERS)	63.5	36.5	<0.01	15.7	84.3	<0.01	8.7	91.3	<0.01	73.5	26.5	0.77	13.1	86.9	<0.01	9.8	90.2	<0.01
National Vaccine Safety Hotline (NVSH)	65.2	36.8	<0.01	21.0	79.0	0.02	11.9	88.1	0.09	76.1	23.9	0.28	20.0	80.0	0.02	14.1	85.9	<0.01
Not aware of VICP, VAERS, or NVSH	49.8	50.2	0.01	35.0	65.0	<0.01	22.3	77.7	<0.01	73.2	26.8	0.62	35.5	64.5	<0.01	29.7	70.3	<0.01

Table 3, Continued	Influenza Vaccination																	
	Vaccine Hesitancy			2018-2019[3]			2019-2020[4]			Vaccine Hesitancy			2018-2019[3]			2019-2020[4]		
	Low	High	P-value	No	Yes	P-value	No	Yes	P-value	Low	High	P-value	No	Yes	P-value	No	Yes	P-value
Have you or members of your family (spouse/partner or children) used the services of a chiropractor, acupuncturist, or other complementary/ alternative medicine provider in the last five years?[10]																		
Yes	55.6	44.4	0.84	19.7	80.3	<0.01	10.3	89.7	<0.01	72.2	27.8	0.99	22.2	77.8	0.03	16.1	83.9	0.01
Types of complementary/ alternative medicine used:[10]																		
Acupuncture	56.5	43.5	0.80	24.1	75.9	0.01	6.3	93.7	0.07	70.4	29.6	0.66	13.1	86.9	0.02	11.5	88.5	0.15
Biofeedback or hypnosis	58.6	41.4	0.69	12.6	87.4	0.06	0.0	100	0.02	88.6	11.4	0.06	5.1	94.9	0.05	5.1	94.9	0.16
Chiropractic	53.5	46.5	0.36	8.1	91.9	0.12	13.4	86.6	0.03	74.3	25.7	0.27	27.1	72.9	<0.01	20.6	79.4	<0.01
Essential oils	50.2	49.8	0.12	22.5	77.5	0.85	10.5	89.5	0.96	68.9	31.1	0.45	20.7	79.3	0.72	15.2	84.8	0.80
Folk remedies	58.5	41.5	0.67	18.1	81.9	0.78	8.0	92.0	0.56	74.7	25.3	0.72	5.4	94.6	0.01	7.6	92.4	0.13
Herbal remedies	59.5	40.5	0.29	15.6	84.4	0.17	6.9	93.1	0.17	79	21	0.15	12.9	87.1	0.04	13.8	86.2	0.55

Table 3, Continued	Influenza Vaccination									Influenza Vaccination								
	Vaccine Hesitancy			2018-2019[3]			2019-2020[4]			Vaccine Hesitancy			2018-2019[3]			2019-2020[4]		
	Low	High	P-value	No	Yes	P-value	No	Yes	P-value	Low	High	P-value	No	Yes	P-value	No	Yes	P-value
High-dose megavitamins	61.3	38.7	0.44	14.7	85.3	0.39	8.2	91.8	0.63	77.4	22.6	0.50	7.3	92.7	0.04	10.5	89.5	0.38
Homeopathy	55.8	44.2	0.97	14.7	85.3	0.26	10.1	89.9	0.93	83.2	16.8	0.20	7.6	92.4	0.07	7.6	92.4	0.23
Energy healing	60.4	39.6	0.53	14.7	85.3	0.42	10.2	89.8	0.96	91.5	8.5	0.03	5.0	95.0	0.05	0.0	100	0.01
Spiritual healing	42.6	57.4	0.05	24.2	75.8	0.40	14.2	85.8	0.37	84.1	15.9	0.21	0.0	100	<0.01	0.0	100	0.02

[1]For parents of young children: unweighted n = 724, weighted n=705.73; [2]For parents of teenagers: unweighted n = 515, weighted n = 507.03; [3]2018-2019 among parents of young children: 10 = “don’t know”,[4]2019-2020 among parents of young children; 11 = “don’t know”; [5]2018-209 among parents of teenagers: 7 = “don’t know”, [6]2019-2020 among parents of teenagers; 8 = “don’t know [8]For education level; 2 = "prefer not to answer," ≤college degree includes some college, Associate's or Bachelor's degree; [9]For household annual income: 3=prefer not to answer; CAM: 21="don't know";[10]Multiple responses allowed; may not sum to 100%; proportions estimated among those who indicated they or their families used complementary/alternative medicine For parents of young children: 24 = “don’t know” & 21="don't know among parents of teenagers. Taylor-linearized variance estimation used and p-values estimated with two-sided general tests of association

Table 4. Associations between vaccine attitudes, demographics, and influenza vaccination in 2018-2020: stratified proportions among adults without children <18 years old

	Weighted %								
				Influenza Vaccination					
	Vaccine Hesitancy			2018-2019[3]			2019-2020[4]		
	Low	High	P-value	No	Yes	P-value	No	Yes	P-value[8]
Overall study population	62.3	37.7	N/A	41.6	56.4	N/A	35.0	65.0	N/A
History of serious vaccine reaction[1]									
No/ don't know	63.8	36.2		41.4	58.6	0.16	34.1	65.9	
Yes	51.7	48.3	0.16	49.4	50.6		41.2	58.8	0.20
Region[2]									
Midwest	62.3	37.7		40.9	59.1		33.7	66.3	
Northeast	58.7	41.3		41	59		37.8	62.2	
South	62.5	37.5		44.4	55.6		37.8	62.2	
West	63.5	36.5	0.89	42.7	57.3	0.89	31.1	68.9	0.50
Age (years)									
18-34	52.5	47.5		53.2	46.8		39.3	60.7	
35-54	57.9	42.1		39.3	60.7		38.5	61.5	
≥55	69.5	30.5	<0.01	36.7	63.3	<0.01	32.0	68.0	0.17
Race/ethnicity									
White, Non-Hispanic	63.2	36.8		42.8	57.2		36.2	63.8	
Black, Non-Hispanic	66.4	33.6		23.8	76.2		25.5	74.5	
Other	58.3	41.7	0.04	46.0	54.0	0.04	33.3	66.7	0.36

Table 4, Continued	Vaccine Hesitancy			Flu Vaccination 2018-2019[6]			Flu Vaccination 2019-2020[7]		
	Low	High	P-value	Unvaccinated	Vaccinated	P-value	Unvaccinated	Plan to be/ am Vaccinated	P-value[8]
Education[3]									
≤High school degree	40.8	59.2		49.5	50.5		40.8	59.2	
≤College degree	24.6	75.4		30.0	70.0		24.6	75.4	
Graduate degree	13.5	86.5	<0.01	13.6	86.4	<0.01	13.5	86.5	<0.01
Household annual income[4]									
$0-$49,999	59.3	40.7		46.8	53.2		39.9	60.1	
$50,000-$99,999	63.4	36.6		38.5	61.5		29.5	70.5	
$100,000-$149,999	73.7	26.3		36.2	63.8		22.9	77.1	
≥$150,000	78.0	22.0	0.03	27.0	73.0	0.03	28.4	71.6	0.02
I trust pharmaceutical companies to make very safe and effective vaccines.									
Strongly disagree/disagree	32.4	67.6		68.7	31.3		60.8	39.2	
Strongly agree/agree	73.8	26.2	<0.01	32.3	67.7	<0.01	25.2	74.8	<0.01
Trust in public health authorities									
Low	48.1	51.9	<0.01	52.7	47.3		42.3	57.7	
High	73.7	26.3		34.5	65.5	<0.01	29.3	70.7	<0.01

Table 4, Continued	Vaccine Hesitancy			2018-2019[6]			2019-2020[7]		
	Low	High	P-value	Unvaccinated	Vaccinated	P-value	Unvaccinated	Vaccinated	P-value[8]
Have you heard of the following resources before? Select all that apply.									
Vaccines Injury Compensation Program (VICP)	62.0	38.0	0.95	35.9	64.1	0.25	25.6	74.4	0.08
Vaccines Adverse Events Reporting Systems (VAERS)	60.8	39.2	0.77	38.6	61.4	0.48	31.6	68.4	0.51
National Vaccine Safety Hotline (NVSH)	65.4	34.6	0.52	41.5	58.5	0.85	25.9	74.1	0.06
Not aware of VICP, VAERS, or NVSH	61.6	38.4	0.49	43.1	56.9	0.52	37.8	62.2	<0.01
Have you or members of your family (spouse/partner or children) used the services of a chiropractor, acupuncturist, or other complementary/ alternative medicine provider in the last five years?[5]									
Yes	62.7	37.3	0.72	35.6	64.4	0.04	29.5	70.5	0.06
Types used;									
Acupuncture	70.6	29.4	0.99	35.7	64.3	0.99	31.7	68.3	0.71
Biofeedback or hypnosis	59.7	40.3	0.91	33.7	66.3	0.91	21.9	78.1	0.62
Chiropractic	68.6	31.4	0.73	34.8	65.2	0.73	27.9	72.1	0.46
Essential oils	54.7	45.3	0.52	40.4	59.6	0.52	29.0	71.0	0.93
Folk remedies	91.7	8.3	0.02	7.2	92.8	0.02	7.2	92.8	0.06
Herbal remedies	55.2	44.8	0.85	37.4	62.6	0.85	31.1	68.9	0.87
High-dose megavitamins	70.7	29.3	0.28	19.6	80.4	0.28	19.6	80.4	0.48
Homeopathy	38.2	61.8	0.22	51.8	48.2	0.22	32.9	67.1	0.79
Energy healing	46.0	54.0	0.60	28.1	71.9	0.61	16.9	83.1	0.34

Spiritual healing	36.2	63.8	0.85	37.9	62.1	0.85	45.0	55.0	0.18

[1]serious vaccine reaction: 44 ="don't know"; [2]region: 2 = "Puerto Rico"; [3]educationl: 10 = "prefer not to answer," ≤college degree includes some college, Associate's or Bachelor's degree; [4]household annual income: 18 = "prefer not to answer"; [5]complementary/alternative medicine: 29 = "don't know"; 2.5% all respondents = missing; multiple responses allowed; may not sum to 100%;[6]2018-2019 season: 13 = missing; [7]2019-2020 season: 65.0% vaccinated includes 10.0% planning to get vaccinated, [8]Taylor-linearized variance estimation used and p-values estimated with two-sided general tests of association

Table 5. Associations between vaccine attitudes and demographics and influenza vaccination in 2018-2020: regression analyses among parents of young children (≤10 years old)

	2018-2019[3]				2019-2020[4]			
	Bivariable		Multivariable[6]		Bivariable		Multivariable[6]	
	PR[5] (95% CI)	P-value	PR[5] (95% CI)	P-value	PR[5] (95% CI)	P-value	PR[5] (95% CI)	P-value
Vaccine hesitancy								
Low	Ref				Ref			
High	1.02 (0.99, 1.04)	0.19	N/A	N/A	0.95 (0.89, 1.01)	0.11	N/A	N/A
Trust pharmaceutical companies								
Strongly disagree/disagree	Ref				Ref		Ref	
Strongly agree/agree	0.98 (0.95, 1.02)	0.41	N/A	N/A	1.22 (1.11, 1.35)	<0.01	1.25 (1.13, 1.38)	<0.01
Respondent's age								
18-34	Ref				Ref			
35-54	0.99 (0.97, 1.01)	0.18	N/A	N/A	0.94 (0.88, 1.01)	0.10	N/A	N/A
≥55	1.03 (0.96, 1.11)	0.38	N/A	N/A	0..97 (0.86, 1.10)	0.68	N/A	N/A
Education[1]								
≤High school degree	Ref		Ref		Ref		Ref	
≤College degree	0.99 (0.96, 1.02)	0.47	1.03 (0.92, 1.16)	0.57	0.97 (0.89, 1.04)	0.38	0.94 (0.87, 1.01)	0.10
Graduate degree	0.99 (0.96, 1.03)	0.70	1.20 (1.07, 1.34)	<0.01	1.11 (1.03, 1.19)	<0.01	1.03 (0.96, 1.11)	0.38
Race/ethnicity								
White, not Hispanic	Ref				Ref			
Black, not Hispanic	0.98 (0.96, 1.01)	0.16	N/A	N/A	1.08 (0.77, 1.52)	0.65	N/A	N/A
Other	0.99 (0.96, 1.02)	0.41	N/A	N/A	0.77 (0.56, 1.04)	0.09	N/A	N/A

Table 5. Continued	2018-2019[3]				2019-2020[4]			
	Bivariable		Multivariable[6]		Bivariable		Multivariable[6]	
	PR[5] (95% CI)	P-value	PR[5] (95% CI)	P-value	PR[5] (95% CI)	P-value	PR[5] (95% CI)	P-value
Household annual income[2]								
≤$49,999	Ref				Ref			
$50,000-$99,999	1.01 (0.97, 1.04)	0.72	N/A	N/A	1.02 (0.94, 1.11)	0.64	N/A	N/A
$100,000-$149,999	0.98 (0.96, 1.00)	0.05	N/A	N/A	1.07 (0.98, 1.18)	0.15	N/A	N/A
≥$150,000	1.00 (0.96, 1.03)	0.86	N/A	N/A	1.05 (0.96, 1.15)	0.26	N/A	N/A
Region								
Midwest	Ref				Ref			
Northeast	0.98 (0.94, 1.03)	0.43	N/A	N/A	1.01 (0.92, 1.12)	0.78	N/A	N/A
South	0.98 (0.94 1.02)	0.28	N/A	N/A	0.98 (0.89, 1.08)	0.71	N/A	N/A
West	0.99 (0.94, 1.03)	0.56	N/A	N/A	1.03 (0.93, 1.15)	0.59	N/A	N/A
Trust in public health authorities								
Low	Ref				Ref			
High	0.99 (0.97, 1.02)	0.65	N/A	N/A	1.07 (1.00, 1.14)	0.05	N/A	N/A
Experience with a serious vaccine reaction								
No/Don't know	Ref		Ref		Ref			
Yes	0.97 (0.96, 0.99)	<0.01	1.14 (1.04, 1.26)	<0.01	1.08 (1.01, 1.15)	0.03	N/A	N/A
Personal/family use of complementary/alternative medicine								
No	Ref		Ref		Ref		Ref	
Yes	0.98 (0.96, 1.00)	0.10	1.18 (1.07, 1.32)	<0.01	1.15 (1.07, 1.24)	<0.01	1.14 (1.07, 1.23)	<0.01

[1]respondent's education, n=3 "prefer not to answer," ≤college degree includes some college, Associate's or Bachelor's degree; [2]household annual income: n=4 "prefer not to answer"; [3]2018-2019 Vaccine Status n=14 missing [Multivariable unweighted n= 662; weighted n= 690.79] ; [4]2019-2020 Vaccine Status n=17 missing [Bivariable unweighted n= 669, weighted n= 697.29 & Multivariable unweighted n= 642; weighted n = 669.59] [5]Prevalence Ratio (PR) and 95% Confidence Interval (95% CI) estimated using log binomial regression for survey data and the difficult option to facilitate model convergence. Taylor-linearized variance estimation used and p-values

estimated with two-sided general tests of association. Bivariable full population Unweighted N=672 weighted n=701.03; Values labeled “N/A” were excluded from the parsimonious multivariable model because they were nonsignificant (p>0.05) in the saturated multivariable model

Table 6. Associations between vaccine attitudes and demographics and influenza vaccination in 2018-2020: regression analyses among parents of teenagers (11-17 years old)

	2018-2019[4]				2019-2020			
	Bivariable PR[5] (95% CI)	P-value	Multivariable[6] PR[5] (95% CI)	P-value	Bivariable PR[5] (95% CI)	P-value	Multivariable[6] PR[5] (95% CI)	P-value
Vaccine hesitancy								
Low	Ref		Ref		Ref		Ref	
High	0.75 (0.64, 0.88)	<0.01	0.81 (0.77, 0.95)	<0.01	0.72 (0.62, 0.84)	<0.01	0.79 (0.68, 0.91)	<0.01
Trust pharmaceutical companies								
Strongly disagree/disagree	Ref		Ref		Ref		Ref	
Strongly agree/agree	1.29 (1.08, 1.53)	<0.01	1.20 (1.01, 1.42)	0.03	1.31 (1.12, 1.54)	<0.01	1.23 (1.05, 1.43)	0.01
Respondent's age								
18-34	Ref				Ref			
35-54	0.90 (0.78, 1.04)	0.15	0.86 (0.74, 0.99)	0.03	0.91 (0.81, 1.03)	0.15	N/A	N/A
≥55	0.85 (0.72, 1.01)	0.06	0.80 (0.68, 0.94)	<0.01	0.91 (0.79, 1.04)	0.18	N/A	N/A
Education[1]								
≤High school degree	Ref		Ref		Ref		Ref	
≤College degree	1.02 (0.89, 1.18)	0.74	1.00 (0.88, 1.16)	0.92	1.06 (0.93,1.20)	0.39	1.02 (0.90, 1.15)	0.75
Graduate degree	1.32 (1.15, 1.51)	<0.01	1.29 (1.12, 1.48)	<0.01	1.29 (1.15 1.45)	<0.01	1.20 (1.06 1.35)	<0.01

	2018-2019[4]				2019-2020			
	Bivariable PR[5] (95% CI)	P-value	Multivariable[6] PR[5] (95% CI)	P-value	Bivariable PR[5] (95% CI)	P-value	Multivariable[6] PR[5] (95% CI)	P-value
Race/ethnicity								
White, not Hispanic	Ref				Ref			
Black, not Hispanic	1.05 (0.87, 1.26)	0.61	N/A	N/A	1.09 (0.94, 1.27)	0.23	N/A	N/A
Other	1.10 (0.97, 1.24)	0.14	N/A	N/A	1.08 (0.97, 1.20)	0.17	N/A	N/A
Region								
Midwest	Ref		Ref		Ref			
Northeast	1.25 (1.05, 1.49)	0.01	1.19 (1.00, 1.41)	0.05	1.19 (1.01, 1.40)	0.03	N/A	N/A
South	1.22 (1.02, 1.45)	0.03	1.21 (1.02, 1.44)	0.03	1.19 (1.01, 1.39)	0.04	N/A	N/A
West	0.97 (0.77, 1.22)	0.79	0.98 (0.78, 1.22)	0.85	1.11 (0.93, 1.34)	0.25	N/A	N/A
Household annual income[2]								
≤$49,999	Ref				Ref			
$50,000-$99,999	1.15 (0.99, 1.35)	0.07	N/A	N/A	1.16 (1.01, 1.33)	0.03	N/A	N/A
$100,000-$149,999	1.18 (0.99, 1.40)	0.07	N/A	N/A	1.18 (1.01, 1.38)	0.03	N/A	N/A
≥$150,000	1.31 (1.13, 1.51)	<0.01	N/A	N/A	1.30 (1.16, 1.47)	<0.01	N/A	N/A
Trust in public health authorities								
Low	Ref				Ref			
High	1.10 (0.97, 1.24)	0.13	N/A	N/A	1.15 (1.04, 1.28)	<0.01	N/A	N/A
Experience with a serious vaccine reaction								
No/Don't know	Ref				Ref			
Yes	1.02 (0.89, 1.16)	0.77	N/A	N/A	0.99 (0.88 1.11)	0.15	N/A	N/A
Personal/family use of complementary/alternative medicine								
No	Ref				Ref		Ref	
Yes	1.17 (1.05, 1.32)	<0.01	N/A	N/A	1.17 (1.06, 1.29)	<0.01	1.14 (1.03, 1.25)	<0.01

[1]respondent's education, n=3 "prefer not to answer," ≤college degree includes some college, Associate's or Bachelor's degree; [2]household annual income: n=4 "prefer not to answer"; [3]2018-2019 Vaccine Status n=14 missing [Multivariable unweighted n= 662; weighted n= 690.79] ; [4]2019-2020 Vaccine Status n=17 missing [Bivariable unweighted n= 669, weighted n= 697.29 & Multivariable unweighted n=

642; weighted n = 669.59] [5]Prevalence Ratio (PR) and 95% Confidence Interval (95% CI) estimated using log binomial regression for survey data and the difficult option to facilitate model convergence. Taylor-linearized variance estimation used and p-values estimated with two-sided general tests of association. Bivariable full population Unweighted N=672 weighted n=701.03; [6]Values labeled "N/A" were excluded from the parsimonious multivariable model because they were nonsignificant (p>0.05) in the saturated multivariable model

Table 7. Associations between vaccine attitudes, demographics, and influenza vaccination in 2018-2020: regression analyses among adults without minor children

	2018-2019[3]				2019-2020[4]			
	Bivariable		Multivariable[6]		Bivariable		Multivariable[6]	
	PR[5] (95% CI)	P-value	PR[5] (95% CI)	P-value	PR[5] (95% CI)	P-value	PR[5] (95% CI)	P-value
Vaccine hesitancy								
Low	Ref		Ref		Ref		Ref	
High	0.40 (0.33, 0.49)	<0.01	0.47 (0.38, 0.58)	<0.01	0.42 (0.35, 0.50)	<0.01	0.38 (0.32, 0.45)	<0.01
Trust pharmaceutical companies								
Strongly disagree/disagree	Ref		Ref		Ref			
Strongly agree/agree	0.98 (0.95, 1.02)	0.41	1.61 (1.29, 2.02)	<0.01	1.91 (1.58, 2.31)	<0.01	N/A	N/A
Respondent's age								
18-34	Ref				Ref		Ref	
35-54	1.30 (1.02, 1.64)	0.03	N/A	N/A	1.01 (0.82, 1.26)	0.91	0.79 (0.66, 0.95)	0.01
≥55	1.35 (1.15, 1.59)	<0.01	N/A	N/A	1.12 (0.99, 1.27)	0.08	0.83 (0.75, 0.93)	<0.01
Education[1]								
≤High school degree	Ref		Ref		Ref		Ref	
≤College degree	1.39 (1.21, 1.59)	<0.01	1.22 (1.08, 1.37)	<0.01	1.27 (1.13, 1.43)	<0.01	1.13 (1.02, 1.26)	0.02
Graduate degree	1.71 (1.46, 2.01)	<0.01	1.56 (1.33, 1.84)	<0.01	1.46 (1.25, 1.70)	<0.01	1.38 (1.19, 1.60)	<0.01
Race/ethnicity								
White, not Hispanic	Ref				Ref			
Black, not Hispanic	1.33 (1.11, 1.60)	<0.01	N/A	N/A	1.17 (0.96, 1.42)	0.12	N/A	N/A
Other	0.94 (0.80, 1.12)	0.50	N/A	N/A	1.04 (0.91, 1.19)	0.52	N/A	N/A
Household annual income[2]								
≤$49,999	Ref				Ref			
$50,000-$99,999	1.16 (0.99, 1.35)	0.06	N/A	N/A	1.17 (1.03, 1.33)	0.01	N/A	N/A
$100,000-$149,999	1.20 (0.96, 1.50)	0.11	N/A	N/A	1.28 (1.09, 1.51)	<0.01	N/A	N/A
≥$150,000	1.37 (1.11, 1.70)	<0.01	N/A	N/A	1.19 (0.96, 1.48)	0.11	N/A	N/A

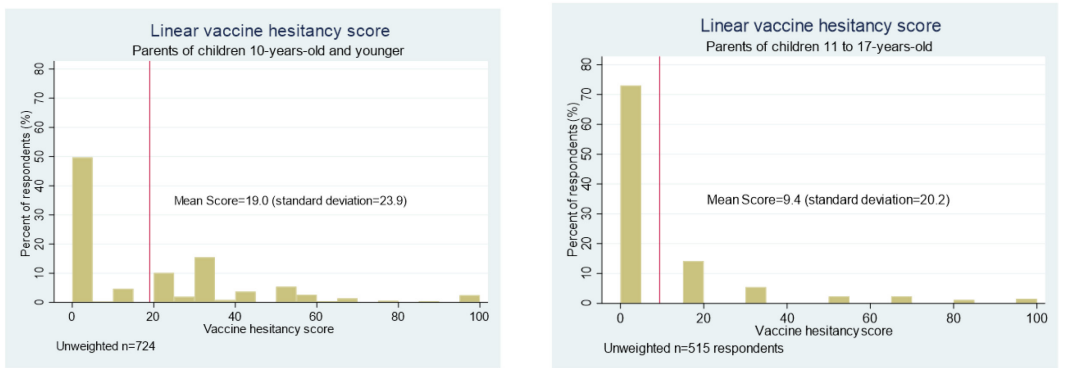
Table 7, Continued	2018-2019[3]				2019-2020[4]			
	Bivariable PR[5] (95% CI)	P-value	Multivariable[6] PR[5] (95% CI)	P-value	Bivariable PR[5] (95% CI)	P-value	Multivariable[6] PR[5] (95% CI)	P-value
Region								
Midwest	Ref				Ref			
Northeast	1.00 (0.83, 1.20)	0.99	N/A	N/A	0.94 (0.79, 1.11)	0.46	N/A	N/A
South	0.94 (0.80, 1.12)	0.49	N/A	N/A	0..94 (0.81, 1.09)	0.39	N/A	N/A
West	0.97 (0.80, 1.18)	0.75	N/A	N/A	1.04 (0.89,1.22)	0.63	N/A	N/A
Trust in public health authorities								
Low	Ref				Ref		Ref	
High	1.38 (1.20, 1.60)	<0.01	N/A	N/A	1.23 (1.09, 1.38)	<0.01	0.91 (0.83, 1.00)	0.05
Experience with a serious vaccine reaction								
No/Don't know	Ref				Ref			
Yes	0.86 (0.69, 1.08)	0.19	N/A	N/A	0.89 (0.74, 1.07)	0.23	N/A	N/A
Personal/family use of complementary/alternative medicine								
No	Ref				Ref			
Yes	1.16 (1.01, 1.33)	0.03	1.12 (1.00, 1.27)	0.05	1.12 (1.00, 1.26)	0.05	N/A	N/A

[1]respondent's education, n=3 "prefer not to answer," ≤college includes some college, Associate's or Bachelor's Degree;; [2]household annual income: n=4 "prefer not to answer"; [3]2018-2019 Vaccine Status n=14 missing [Multivariable unweighted n= 662; weighted n= 690.79] ; [4]2019-2020 Vaccine Status n=17 missing [Bivariable unweighted n= 669, weighted n= 697.29 & Multivariable unweighted n= 642; weighted n = 669.59] [5]Prevalence Ratio (PR) and 95% Confidence Interval (95% CI) estimated using log binomial regression for survey data and the difficult option to facilitate model convergence. Taylor-linearized variance estimation used and p-values estimated with two-sided general tests of association. Bivariable full population Unweighted N=672 weighted n=701.03; Values labeled "N/A" were excluded from the parsimonious multivariable model because they were nonsignificant (p>0.05) in the saturated multivariable model

4.8 Figures for Chapter 4

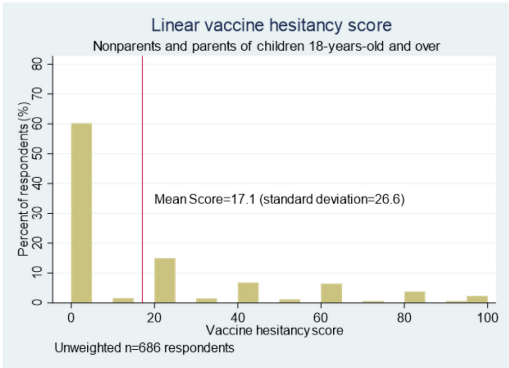
Figure 1. Distribution of Vaccine Hesitancy by Age Group

The values of variables from the various vaccine hesitancy scales used were summed and transformed to a score ranging from 0 to 100. These scores were dichotomized at the mean rather than the median because the median equaled 0 in one group.



A. Vaccine hesitancy among parents of young children (≤10-years-old)

B. Vaccine hesitancy among parents of teenagers (11-17-years-old)



C. Vaccine hesitancy among parents without minor children

Chapter 5. Policy implications of vaccinomics in the United States: community members' perspectives

5.1 Abstract

Objectives: Vaccinomics may use genomics to improve vaccine safety and effectiveness. The policy implications of vaccinomics are known. We aimed to elucidate public values around vaccinomics.

Methods: Adults ≥18 years old were recruited through community organizations and schools, and randomly assigned to one of eight nested discussion groups held in Boulder, CO and Baltimore, MD in 2018. Preceding learning about vaccinomics through animation and following these discussions, participants rated their confidence in vaccine safety and effectiveness. Participants allocated funding to vaccinomics versus federal vaccine (safety and efficacy studies, new vaccines, free vaccines for children) and chronic disease (cancer, heart disease, and diabetes) priorities.

Results: Participants broadly supported vaccinomics. Emergent themes included concerns about reduced privacy/confidentiality, increased stigma/discrimination based on genetic information, and reduced agency from genetically-based vaccine prioritization. Participants supported vaccinomics' potential for increased personalization, but said policies would be needed to support equitable implementation. While some participants favored prioritizing others over themselves during a vaccine shortage, many wanted to retain their agency to make vaccination decisions. Some participants worried health insurance companies would discriminate against them based on genetic information discovered through vaccinomics. Participants recalled historical cases of African Americans' rights and medical research ethics being violated. Many participants worried inequitable implementation of vaccinomics would further marginalize

vulnerable populations. Discussing vaccinomics did not appear to impact perceptions of vaccine safety and effectiveness. Federal funding for vaccinomics was broadly supported.

Conclusion: Participants supported vaccinomics' potential for increased personalization, noting policy safeguards are needed to facilitate equitable implementation and protect privacy. Despite some concerns, participants hoped vaccinomics would improve vaccine safety and effectiveness. Vaccine confidence was unaltered by discussing vaccinomics and serious adverse reactions. Policies that address public values around privacy and confidentiality of genetic information and support vaccinomics being implemented equitably, in terms of benefits and harms, are needed.

5.2 Introduction

Vaccinomics is an emerging field that has the potential to improve vaccine development and use. Vaccinomics is the application of advances in immunology and genomics to the study of vaccine response and development of vaccine candidates.(3) While vaccinomics could influence how vaccines are designed and used, “adversomics” is the application of vaccinomics to the study of adverse events following immunization (AEFI) and reducing vaccine reactions.(3) There are many examples of genomic differences such as biological sex, race, and specific genetic loci being associated with immune response and vaccine adverse reactions.(24, 168-177) The science of vaccinomics is nascent, such that its potential has not been fully elucidated and will not be realized in the near future. Ethical, legal, and social implications, or more broadly termed, policy issues, will arise from vaccinomics. We have an opportunity to consider these issues now, before the science becomes fully available. Early understanding of public values, views, and preferences can inform vaccinomics policy and the development of vaccinomics. The public could be influential in how future research and development is conducted on new vaccines, clinical trials, licensure, recommendations for use, injury compensation and communications.

Vaccinomics may impact vaccine hesitancy, either positively or negatively. In 2019, the World Health Organization designated vaccine hesitancy one of the top 10 threats to global health.(2) Serious vaccine reactions, like Guillain-Barre Syndrome (GBS), are very rare.(18, 44) The excess risk of GBS due to influenza vaccination is estimated to be 1 to 3 cases of GBS per 1 million persons vaccinated, which pales in comparison to the vaccine benefit.(44) Despite the rarity of serious reactions, many people are concerned vaccine safety.(4, 6-12) Individuals with vaccine safety concerns often believe they or their children may be at increased risk of autoimmune diseases, asthma, and multiple sclerosis, all of which have genetic risk factors.(68, 69) Some parents believe children's immune systems could be overloaded by receiving too many vaccines at once, despite a lack of epidemiological evidence.(61) Individuals who refuse or delay vaccines due to their concerns often cluster geographically and socially, contributing to vaccine preventable disease outbreaks.(52, 62, 70) Vaccinomics has the potential to address vaccine hesitancy, through personalization of vaccine schedules and improved safety.(3) Vaccinomics could lead to increased vaccine hesitancy and refusal if individuals who learn they have twice the risk of an adverse outcome compared to others — 2 in 1 million versus 1 in 1 million — refuse vaccination, when the absolute risk remains very small. Alternatively, vaccinomics may alarm vaccine hesitant individuals, due to privacy concerns around genomics, or the because this approach is new and relatively less studied.

In 2017, we held a meeting with academic vaccinologists and federal agencies involved in vaccines, including representatives from the National Institutes of Health, Food and Drug Administration, Centers for Disease Control and Prevention, and Health Resources and Services Administration (National Vaccine Injury Compensation Program). The objective of the meeting was to discuss what policy issues might emerge throughout the lifecycle of vaccinomics, and where public input would be useful, even though vaccinomics may not be implemented in the

U.S. for 10-15 years. Discussions with vaccine stakeholders led us to identify the following policy questions that would benefit from public input:

- Who gets to access to (possible) personalized vaccines (and at what cost) for public health benefit?
- Should prioritization of vaccinomics research be placed on rare, serious, adverse reactions or common, mild adverse reactions? Instead, should subpopulation differences in vaccine response and contagiousness ("more contagious" and "more susceptible" populations) be considered for prioritization?
- Does the personalization of vaccines increase confidence in the safety and effectiveness of vaccine scheduling, dosing, and of vaccination more generally? Why?
- Should vaccinomics be prioritized over existing federal priorities for funding?

This study aimed to elucidate these public values around the policy implications of vaccinomics.

5.3 Methods

We conducted community meetings with initial plenary sessions and facilitated small discussion groups.

Community Meeting Recruitment

Three community meetings with nested discussion groups were held in Boulder, CO (two meetings in March 2018, each with 4 nested discussions), and Baltimore, MD (one meeting in April 2018, with 4 nested discussions). Boulder is a mostly Caucasian (87.9% versus 1.1% African American) urban community with a high prevalence of under-immunized children (3.3% of kindergarteners had ≥1 vaccine exemption in 2018-2019).(126) Baltimore has a large African

American (62.8% versus 31.8% Caucasian) population and is an urban environment (exemption data in Maryland are not publicly available).(127)

Using a multipronged recruitment strategy, parents and nonparents were purposively enrolled to approximate the sociodemographic profile of each city in terms of age, race/ethnicity, household income, and education. Parent status was only measured in Baltimore due to an oversight by the study team (n=28 parents, 7=nonparents). Recruitment took place through schools and libraries, and we reached out to community organization within our personal networks. Electronic and paper flyers were distributed to these organizations. Due to difficulty reaching enrollment targets in Baltimore, a Facebook advertisement was placed to enhance recruitment. This was not done for the meetings in Boulder. In both cities, recruiters targeted parents of school-aged children, as they make frequent vaccination-related decisions. Recruiters did not ask parents for their children's ages since parents of older children and nonparents were eligible to participate as well. Individuals were offered $50 Visa® gift card to participate in a 2-hour-long meeting on a Saturday or Sunday. Those with young children were also offered a $30 cash incentive for childcare.

Sociodemographic Questionnaire

Participants reported sociodemographic information via an online survey prior to attending community meetings. Though parents were targeted in recruitment, whether or not participants were parents and the ages of their children were only asked in the online questionnaire used in Baltimore, due to an oversight. Questionnaire data were cross tabulated by city.

Ethical Review

This project was determined to be nonhuman subjects research by the Johns Hopkins Institutional Review Board.

Vaccinomics Introduction

To educate participants about vaccinomics, we convened a large plenary session during which participants watched a four-minute-long animation, created by the study team (available from: https://preview.tinyurl.com/vaccinomics). Participants were not expected to have heard of vaccinomics before (unmeasured). After watching the video, a vaccine expert answered questions for approximately 10 minutes.

Group Discussions

To elucidate policy implications of vaccinomics, 10-15 participants were randomly assigned to groups for facilitated discussions. There were four discussion groups over two days in Boulder and four discussion groups on a single day in Baltimore. Participants could not hear other groups' discussions. Eight discussion groups in total were led by trained facilitators. In each group, a second team member took handwritten notes.

Discussions conducted using a standardized, semi-structured guide, designed to elicit the policy implications of vaccinomics, were audio recorded, and the recordings were professionally transcribed. Facilitators created a scenario and explained that genetic testing might reveal some people to be extra infectious or “super spreaders," who might be prioritized for vaccination in order to contain an infectious disease outbreak. Conversely, genetic testing might identify others as being unlikely to mount an adequate immune response to vaccination. These individuals might be prevented from being vaccinated to save limited supplies for those more likely to have a protective immune response. To understand acceptability of genetic screening that may be used to identify the approximately one in one million people at risk of

serious vaccine reactions, facilitators explained some people might be advised/prevented from getting a vaccine for their safety. Facilitators asked participants to comment on this approach.

Vaccine Confidence

We measured confidence in vaccine safety and effectiveness prior to educating participants about vaccinomics and at the end of the meeting to test the hypothesis that vaccine confidence would not change after discussing AEFIs and vaccinomics. In a large group setting, participants reported their confidence in vaccines for adults and babies by placing stickers along four spectra ranging from "not effective" to "very effective" and "not safe" to "very safe," with 10 unnumbered hash marks along the x axes. Participants explained the reasoning behind their stickers' placements on post-it notes adhered to a separate spectrum below where they placed below their stickers. Stickers were assigned a whole-number numeric value (0-10). The values of the pre- and post-discussion stickers were graphed and unpaired t-tests for the difference between the pre- and post-discussion means were separately estimated for the vaccine effectiveness and safety exercises, across all participants. Participants' handwritten post-it note comments from these exercises were thematically categorized.

Funding Priorities

To assess whether participants prioritized funding for vaccinomics compared to other health-related research priorities, they were asked to allocate $100 of play money between four options, as if they were a member of Congress. The first activity compared vaccinomics to other vaccine programs (free vaccines for low income children, development of new vaccines, and studies of vaccine safety and efficacy); the second compared vaccines and vaccinomics in combination to chronic diseases (cancer, heart disease, and diabetes). Participants divided their $100 in play money between four jars for each activity. The money was summed and divided by

the total amount of money allocated in each activity. This accounted for some participants not allocating all of their allotted funds.

Data Analysis

Iterative, thematic analyses influenced by Grounded Theory(130) were conducted on the transcripts from recorded discussion groups and written comments on vaccine confidence, using Atlas.ti®(131) for Windows and Microsoft Office®. Two people independently coded one transcript using open, descriptive codes.(130) Their coding was compared, and an agreed upon code list was subsequently used by the first author on all remaining transcripts. Data were recategorized using axial and selective codes. Transcripts were recoded as new codes emerged and the properties of the code list were refined. Memos were written throughout the process, describing the properties and dimensions of each code and summarizing emergent themes. Codes and themes were discussed with the project team, and iteratively revised.(130) Conclusions based on Grounded Theory(130) were compared to thematic notes taken immediately following the community meetings by a coauthor uninvolved in data analysis, to evaluate the consistency of our findings. Quantitative data on sociodemographic factors, vaccine safety and effectiveness, and funding priorities were analyzed using Stata, version 16®.(132)

5.4 Results

Study Population

Ninety-four participants were enrolled from Baltimore (n=35) and Boulder (n=59; **Table 1**). Seventy-two percent of participants were female (n=67). Over a third (35%) were 18-29, 21% 30-44, 1% 45-60, and 21% >60 years old. Two-thirds were White, not Hispanic, and 18% Black, not Hispanic. Holding a Bachelor's Degree (43%) or higher (15%) was common. Half of

participants had household annual income under $50,000 (n=47). Most Black, not Hispanic participants were from Baltimore. The results of seven of the eight discussion groups (10-15 people each) are reported (one group recording failed).

Emergent Themes

Vaccinomics' policy implications consisted of four interrelated constructs **(Figure 1).**

Vaccine prioritization*:* Prioritization for vaccination, especially during a vaccine shortage, may be based on genetics, to maximize effectiveness and safety. While some participants supported prioritization, most were opposed.

Agency**:** Participants were concerned that vaccinomics would dictate who should get vaccinated and should not, removing their agency to choose for themselves.

Personalization of Vaccine Schedules: Personalization was a subtheme of agency, prioritization, and stigma/discrimination in the scenario around vaccinomics leading to personalized immunization schedules.

Stigma/discrimination: Participants worried genetic information collected for the purposes of vaccinomics would not be kept private (a subtheme), and that they might be discriminated against or stigmatized as a result.

Vaccinomics Funding: Participants supported funding vaccinomics, versus other vaccine and chronic disease related options.

Vaccine Prioritization

This theme consisted of participants' responses regarding who should be prioritized and how they might react if they were not prioritized for vaccination. In response, a woman said:

> *I'd be fine prioritizing the other people who were more, either at risk of dying from the disease or at risk of spreading the disease. Source: Boulder 4*

Though some participants said prioritizing strangers or their grandchildren over themselves would be acceptable during a vaccine shortage, many participants objected that this would violate their right to make decisions for themselves by limiting their agency. Participants identified vaccine access and affordability, maximizing public health benefits, and race-based prioritization as important areas for consideration. One man thought prioritization bordered on discrimination. He said:

> *I was going to bring up the trust factor. But who is telling me I can't get the vaccine when there's this disease that's spreading through the population so quickly? So, issues of discrimination come up, issues of priority and in particular whatever age group, gender, et cetera. Source: Boulder 3*

This man and many others viewed prioritization as potentially limiting low income and minority groups' agency. He said:

> *Oh, yeah, people would freak out… You know, a bunch of White folks get vaccinated, but what happens to the Hispanic and Black populations…? They didn't get vaccinated. It could really play into like people suspecting foul play. It's like, okay, did they really try to get these super spreaders…?... And that would be an issue when giving power. Source: Boulder 2*

A woman similarly feared vaccinomics could exacerbate existing inequalities. She said:

> *Who gets [vaccinated]? For me, healthcare is between lower end of society are not getting the same level as the very rich. And I think this would become more of an economic thing where it's the health policy will be driven by pharmaceutical companies and insurance companies. Source: Boulder 1*

Participants feared vaccine prioritization based on race/ethnicity would exacerbate existing inequities in healthcare access and discrimination. Race-based prioritization was considered unacceptable.

Agency

Intertwined with prioritization, participants believed they had the right to choose whether they or their children were vaccinated. Several participants worried that implementing vaccine schedules based on genomics would mean that they would be mandated to get certain vaccines. A woman explained:

> *My main concern, that is if I'm identified as super spreader, is it forced on. And I don't want to get the vaccine then what? That's my big [concern]… Source: Boulder 1*

A woman worried her agency would be limited even if she was not identified as a potential super spreader. She explained:

> *[My concern is] not so much to do [with] genetic testing. If they have a genetic testing to also be able to look at it and determine whether or not [I'm a super spreader], but not have it be mandated by the government saying, "Well, you have this genome you have to have this done." Source: Boulder 1*

Similar to the woman quoted above who worried the government might mandate vaccination or other medical interventions based on her genetic test result, another woman indicated vaccinomics would decrease her confidence in the medical system. She said:

> *Woman: Yes, I think it'll be good because, like… maybe they could see it at all and see who carries that specific gene.*
>
> *Facilitator: … Concern that doesn't increase your level of confidence.*

Woman: Decreases just because it's this idea of choice versus being forced to do something… Source: Boulder 4

A woman explained it was essential to be given the information needed to make an informed decision, not just the principal of having agency that mattered. She said:

I think what's important is that that risk information be presented in a way people can easily understand. Out of 100 people those who don't get the vaccine who are like you, versus-- it's just how it's communicated. Of course, the whole public needs to understand risk better, in general. But it just needs to be correct and simple in the explanation. And then, I guess, you have to let people make their own decision if there's enough vaccine… Source: Boulder 3

One participant explained her decision-making process regarding the human papillomavirus vaccine (Gardasil):

…If they are a healthcare worker, they should be able to say, "I don't feel comfortable with taking this because I don't feel like it's been tested enough." I know with my son I don't want him to get the Gardasil because when he was younger, he got...[inaudible] So I just feel like everybody is different. …How one person reacts is not how another person reacts. And there's really no way to be able to tell. Source: Baltimore 1

A man noted individual-level agency would complicate implementation of prioritization. He said:

But in a real-world application, you wouldn't be able to, like, categorize all these people into one system and then also, like, force them to come in to the hospital to get their vaccinations, right… Because personal opinion comes into effect… Especially with anti-vax movements that – like, it would make sense but it wouldn't be practical. Source: Boulder 4

Participants felt they had a right to make vaccination decisions, regardless of the algorithms vaccinomics might suggest. See **Table 2** for additional agency quotations.

Personalization of Vaccine Schedules

A cross-cutting subtheme of agency, prioritization, and stigma/discrimination was that participants were interested in vaccinomics' potential to personalize vaccine schedules. They were instructed that personalization would not mean a new vaccine would be created for each individual, rather vaccine schedules would be refined for subgroups of the population based on population-level genomic information. Participants' comments about personalization were overwhelmingly positive, focused on the individual and community-level benefits of improved vaccine effectiveness. Drawing an analogy to stem cell research, a woman explained:

> *And it can be individualized. And I think what we're finding now with the stem cell research, the more you can individualize a treatment or a vaccine, the more effective it will be. Source: Boulder 2*

A woman noted the individual-level benefits and potential risks of discrimination stemming from vaccinomics were intertwined. She said:

> *I'd feel more comfortable if I had genetic testing that says that I'm not going to react adversely. Whereas when you're an infant you don't know what they're allergic to or not. You're just giving them vaccine and be like okay. But if you have that genetic testing my concern is more if that it gets out to insurance companies so then when that fact can be used adversely against me and not just for the benefit of my health. Source: Baltimore 1*

Personalization of vaccines was viewed favorably, but this was intertwined with vaccinomics' potential to contribute to stigma and discrimination. See **Table 3** for additional personalization quotations.

Stigma/Discrimination

Participants feared stigma and discrimination would result if genetic information collected to implement vaccinomics was not kept private and confidential. These fears were provoked by the idea that genetic testing might be required to benefit from vaccinomics. Facilitators explained widespread genetic testing might be used to help the one person out of every one million people vaccinated at risk of a serious adverse reaction, like paralysis or death. Despite its potential benefits, participants worried vaccinomics would lead to economic and racial discrimination, exacerbating inequities in healthcare access. A man explained:

> *…And who is going to... actually to obtain it? And that could be said for a lot of technologies, of course. Rich folks have it for a while and then over time we can get it to more broke folks. But it's like more of an immediate issue with vaccines.*
>
> *Source: Boulder 2*

A woman worried vaccinomics may only help some racial groups. She said:

> *And I think it's probably a predominantly White field so we have to be careful that the other races are getting what they need and that their risk factors are included in [vaccinomics]. Source: Boulder 4*

Participants feared that genetic information collected to implement vaccinomics would be used as the basis for discrimination by the U.S. government and health insurers. They noted historical cases in which individuals' rights had been violated, such as Henrietta Lacks, whose cervical cells were shared without her consent(178) and personal examples. A man living with AIDS said:

> *I live with AIDS and I've been working with AIDS treatment and vaccination and stuff for a long time and one of the issues that has come up is that collecting information about people's health is great as long as it stays between the doctor and the patient, but that isn't where it stays, and as soon as there is some record of something about your health*

eventually government or someone is going to find a way to get in there and find out. And sometimes that's used for really great reasons in terms of distributing resources for treatment and prevention and that sort of thing, but there is always this possibility that it could be used against you and there's also a certain amount of stigma attached to that. Source: Baltimore 2

These individuals worried that individuals in power and with access to their genetic results would violate patient confidentiality and they would be stigmatized/discriminated against as a result. Another man agreed, worrying a confidentiality breach could limit his access to healthcare. He explained:

So, I've got a lot of preexisting conditions, you know. I don't want to be-- them to say, "No, you can't have it," or, it's going to be so much it's I can't afford it. Source: Boulder 4

Many participants feared health insurance companies would discriminate against them based on their genetics. A woman said the risks of genetic testing may not be worthwhile. She suggested:

... It seems like to me DNA is so intensely private and personal, I mean, obviously, so personal, that if there were other areas of study that didn't require this mass culling of such personal information… Source: Boulder 4

Another participant worried social ostracism could result if he was revealed to be a super spreader. He said:

I think [vaccinomics] would be fantastic and I'd be all in favor of pursuing this. However, I can see some people's concerns would be being identified as a super spreader could ostracize you from a social perspective. Source: Boulder 1

See **Table 4** for additional stigma/discrimination quotations.

Funding Priorities

Participants favorably funded vaccinomics compared to other priorities (**Figures 2 and 3**). In the vaccines-related exercise, 28% of funds were allocated to vaccinomics, 26% to purchasing vaccines for low-income U.S. children, 25% to studies of vaccine safety and efficacy, and 21% to research and development of new vaccines **(Figure 2).** In the chronic disease research and development exercise, 34% of funding was allocated to vaccines and vaccinomics, 33% to cancer, 19% to diabetes, and 15% to heart disease **(Figure 3).** In making vaccine-related decisions, participants cited government mandates, personal experiences, pandemic prevention, and economic reasons.

Vaccine Confidence

Discussing vaccinomics, AEFIs and adverse reactions did not alter perceptions of vaccine safety and effectiveness. There was no statistical evidence of a difference in comparing mean scores pre versus post discussion for vaccine effectiveness or safety for children or adults (all $p>0.40$; **Table 5**). Written comments indicate most participants' vaccine confidence was unchanged, though some said their vaccine knowledge was positively increased due to the animation and discussions.

Several participants wrote pre-discussion that vaccines are more effective for babies than adults. Post-discussion, comments reflected no change in beliefs or slightly increased hope that vaccine safety and efficacy will improve in the future. Illustrative comments are shown in **Tables 6 and 7** (safety) and **Table 7 and 8** (effectiveness).

5.5 Discussion

This formative work illuminates public perceptions and values regarding vaccinomics and addresses calls to describe the implications of using genomics for infectious disease prevention.(179) We believe this is the first study to elucidate public views about vaccinomics. We found broad support for vaccinomics and these discussions of adverse events following immunization (AEFI) did not impact vaccine safety or effectiveness perceptions. Personalized vaccines and schedules were especially supported by those who knew someone with or had experienced an AEFI. Some participants feared information collected for vaccinomics would not be kept confidential, potentially leading to stigmatization/discrimination. They worried disclosure of genetic risk factors would lead to increased health insurance fees or lost coverage. Others worried vaccination would be mandatory for super spreaders and unvaccinated individuals would be discriminated against in the workplace, emphasizing the right to agency and disdain for compulsory vaccination.(100) The Genetic Information Nondiscrimination Act (GINA) is the only federal legislation prohibiting genetic discrimination by health insurers or employers.(101) Participants appeared unaware of this law. Comprehensive nondiscrimination policies may enhance vaccinomics participation and the likelihood that vaccinomics increases vaccine safety and effectiveness.(180)

Vaccinomics could lead to additional data on the safety and effectiveness of vaccines by genomic factors identifiable through laboratory testing and other factors that can be determined by self-report, like biological sex and race/ethnicity. Vaccine confidence may increase with personsalization of vaccine schedules. Compared to non-Hispanic Whites, minority populations are less trusting of vaccines, public health authorities, and pharmaceutical companies.(151, 157, 181) Low trust in vaccines is evidenced by low MMR coverage among racial/ethnic minorities.(182) Participants reported race/ethnicity-based prioritization could

exacerbate mistrust of vaccines and public health authorities, and that sex-based prioritization would be less problematic.

If differences in vaccine safety and efficacy are linked to biological sex, self-reported sex at birth could be used to assign the appropriate vaccine schedule. Alternatively, genetic testing for a rare marker might be used to screen out high-risk individuals. The HLA-DQB1*06:02 haplotype was associated with narcolepsy onset following vaccination against H1N1 in 2009 with the AS03-adjuvanted Pandemrix®.(183) If future studies show associations between genomics and adverse reactions, this information could inform subgroup-specific vaccine schedules.

Vaccinomics has the potential to increase vaccine confidence and acceptance, especially among populations with safety concerns. Participants, who experienced an AEFI or knew someone who had an AEFI, indicated they might be more trusting of vaccinomics than current vaccines. Vaccinomics may improve vaccine confidence among hesitant populations, potentially reducing the prevalence and clustering of under-immunized individuals, which are risk factors for vaccine preventable disease outbreaks.(52, 62, 70) There was no evidence that discussing AEFI made participants less confident in vaccines. Although this study showed some individuals with vaccine safety concerns were interested in vaccinomics' potential to personalize vaccine schedules, the system will need to be rigorously monitored to ensure the public's safety and confidence. Vaccinomics may make vaccine schedules more complicated, and its expected use of genomic data raises the potential for privacy violations. Robust safety surveillance may increase the public's trust and participation in vaccinomics.

Much remains to be determined about the feasibility of vaccinomics implementation. This study provides stakeholders with evidence that adults in disparate cities support vaccinomics, though they worry about its ethical, legal, social, and policy implications. These

findings were robust using methods influenced by Grounded Theory(130) and were separately identified from meeting notes a coauthor uninvolved in data analysis.

Strengths and Limitations

Data may not be generalizable nationwide, though the sample was socioeconomically diverse. Our methods prevented qualitative data from being analyzed by discussion group or sociodemographic characteristics. Results from one discussion group are excluded because the audio was not turned on. Facilitators and notetakers conveyed similar themes emerged from this group. Facilitators prevented individual participants from dominating discussions by calling on other participants and moving the discussion to other topics included in their semi-structured guide. Focus group discussions and activities conducted in group settings, including the vaccine confidence and the funding exercises, are inherently subject to social desirability bias.(184) Participants who saw more money in one jar, may have been tempted to add their money to that jar as well. Seeing that most respondents rated vaccine confidence highly may have influenced others to do the same. Participants were encouraged to make their selections based on their personal preferences and there was not a large group of other participants or study team members watching as they did so. In the second funding exercise, participants were confused by the options presented, questioning whether the Human Papillomavirus (HPV) vaccine fell under "vaccines and vaccinomics" or "cancer." Facilitators said “vaccines and vaccinomics” included the HPV vaccine and "cancer" included other aspects of prevention and treatment. Nondifferential misclassification may have resulted. Limitations of data collection methods precluded paired analyses, of pre- and post-discussion vaccine confidence ratings. Unpaired analyses strongly indicated there was no difference between the two time points, which was supported by discussion group and written comments.

Public Health Implications

Vaccine stakeholders should use these results to inform vaccinomics-related policies, including genetic nondiscrimination, with the goal of encouraging vaccinomics participation.(180) These results influenced the design of an online survey with 1,925 adult respondents demographically representative of the U.S. Results of both studies will be shared with vaccine stakeholders in 2020 to aid them in designing policies that foster vaccinomics participation. Genetic nondiscrimination legislation has positively influenced genetic testing uptake in Europe.(180) Efforts to make the U.S. residents aware of GINA(101) may increase participation in vaccinomics and genomics is general.

The social and economic costs of vaccine refusal are exceedingly high and can potentially be prevented by using vaccinomics to increase vaccine acceptance. A 2008 measles outbreak in California led to approximately $10,376/case in public sector spending and $775/case in spending by the affected family.(185) Vaccinomics may increase vaccine acceptance, preventing outbreaks. Vaccinomics could be targeted to areas at greatest risk of VPD, identified through mathematical models and geospatial statistics,(52, 53, 70, 186, 187) minimizing the community-wide effects of intentional under immunization.

5.6 Conclusions

Public health stakeholders should propose policies that will address constituents' concerns about vaccinomics, including confidentiality of genetic test results and the potential for increased stigma/discrimination. Despite some concerns, participants were hopeful about vaccinomics' potential to improve vaccine safety and effectiveness.

Funding

This work was supported by grant number RM1HG009038 from the National Human Genome Research Institute (all authors). The funder had no involvement in the design, implementation, analysis, interpretation, or reporting of this study.

5.7 Tables Chapter 5

Table 1. Sociodemographic distribution of the sample

		Baltimore n=35	Boulder n=59	Total N=94 (%)
Gender[1]				
	Female	24 (68.6)	43 (72.9)	67 (72.0)
Age Category (in years)[2]				
	18-29	6 (17.1)	26 (44.1)	32 (34.8)
	30-44	12 (34.3)	7 (11.9)	19 (20.7)
	45-59	12 (34.3)	8 (13.6)	20 (21.7)
	45-60	1 (2.9)	0 (0.0)	1 (1.1)
	≥61	3 (9.6)	16 (27.1)	19 (20.7)
Race/Ethnicity[3]				
	White, Not Hispanic	17 (48.6)	46 (78.0)	63 (67.0)
	Black, Not Hispanic	15 (42.9)	2 (3.4)	17 (18.1)
	Other	0 (0.0)	9 (15.3)	9 (9.6)
Education[4]				
	≤College degree	13 (37.1)	25 (52.4)	38 (41.8)
	Bachelor's degree	17 (48.6)	22 (37.3)	39 (42.9)
	Graduate degree	4 (11.4)	10 (16.9)	14 (15.4)
Household Income[5]				
	$0-$49,999	17 (48.6)	30 (50.8)	47 (50.0)
	$50,000-$99,999	6 (17.1)	14 (23.7)	20 (21.3)
	≥$100,000	5 (14.3)	10 (16.9)	15 (16.0)
	Unspecified	7 (20.0)	5 (8.5)	12 (12.8)
Age of Children[6] (in years)				
	<5	9 (25.7)	-	9 (25.7)
	5-18	15 (42.9)	-	15 (42.9)
	≥19	11 (31.4)	-	11 (31.4)
	No children	7 (20.0)	-	7 (20.0)

[1]Gender: 1 missing; [2]Age: 1 missing; [3] Race/ethnicity: 7 missing, other category includes 6 Asians, 1 Native Hawaiian/Other Pacific Islander, and 3 Hispanics; ; [4]Education: 3 missing; [5]Income: 1 missing; [6]Age of Children: only asked of Baltimore participants; multiple responses allowed to results sum to >100%.

Table 2. Agency: Quotations from Community Meetings

Speaker	Quotations	Source
Woman	*I feel like if you're not a super spreader and you're not really likely to get a bad reaction and so you don't get the vaccine. But it's only a probability that you might not get the disease and you have a bad reaction. So, if you don't get the vaccine and you still get the disease you are still a spreader. You're not a super spreader but you can still spread it to the people who didn't get the vaccine. I'm kind of just worried that once this comes out, you'll be like, 'Oh, I'm not obligated to get the vaccine,' there's going to be [a] huge population that don't have the vaccine. And once of those people get it, they can still spread it to a lot of people.*	Boulder 1
Woman	*I think you're also going get people the like "my body, I do what I want" kind of thing with it? Or, "you can't force me to" – you know what I mean? Like that whole legal thing would come into play.*	
Woman	*... Again, it should be a choice but that choice does affect other people's choices.*	
Woman	*I think it's great if you want to participate and provide your genes, but it's still a choice.*	
Man	*…I have sons and I want all of mine to be vaccinated because if the problem come down, they're the one that got something, not you making the call… I'm for any prevention method. Because you've got something. If you want to, you can say no, no, no. Right?... So, I'm much better with erring on the side of caution than sit back and not [vaccinate]. I'd feel; worse if... he got from something I could've prevented…*	Baltimore 1
Woman	*…I know when I took my kids to-- you know, if I question, it's like the doctor gets upset with me questioning. You know they've been around here for a long time. Whereas, I think, we need to acknowledge that there are concerns. And instead we need to be able to address those concerns and allow people the opportunity to say no.*	
Woman	*Woman: … having the super spreaders get the vaccine first, I guess the question is how does that happen. So if you're talking about a government mandate, that raises a whole lot of issues that I think are very thoughtful but maybe you could take a perspective of what if people voluntarily, if people knew that they were super spreaders and they volunteered to do that, maybe that would be a way. Facilitator: So you would be more comfortable if it was volunteer and not being told?* *Woman: Right, and that way it's not being forced because there might be people who know they're super spreaders who are like, "Okay, it makes sense, I should get the vaccine,' and that way we'll prevent this from being-- and that way it's not mandated by like intrusion into people's privacy."*	Baltimore 2
Man	*Man: I think the government-- should be mandatory by the state or the government, whichever way you want to put it. For instance, they've been hounding about phones while you're driving. And nobody stopped using their phones. And they go and kill people you. And they still out there with their phone in their face. So, if you don't make it mandatory and leave it to individual people, they're going to keep on doing what they're doing. They think it won't happen to them."* *Facilitator: "So you trust the government to put the schedules out there that will mandate people to get their vaccines?"* *Man: Yes. Once they prove it to the medical people prove their point. And I think it should be pushed on everybody.*	Baltimore 1

Table 3. Personalization of Vaccine Schedules: Quotations from Community Meetings

Speaker	Quotation	Source
Woman	*And it can be individualized. And I think what we're finding now with the stem cell research, the more you can individualize a treatment or a vaccine the more effective it will be.*	Boulder 2
Man	*I think the herd immunity is a big point, too. If you're able to understand their genomics and you're able to pretty much make this vaccine effective as possible, you'll be able to enhance the herd immunity effectiveness.*	
Man	*So, for this I think it would kind of ease your mind for a lot of these immunizations there's risks that are explained. This kind of showing that it would ease your mind on those risks to know you aren't that one in one million, if that makes sense.*	
Woman	*I would just say about the schedule, it's already really complex and there's already so much stuff. So, I think if a parent knows that that schedule is customized and catered to their specific child, I think it would make them more likely to do.*	
Woman	*So, you're essentially making it more complex. Each person has an individual schedule. But what if those individuals create, they own individual schedule like many people now make schedules that are different from the recommended schedules. So, then there's even more of a variance from the variance. And then it seems really complicated. And then would that whole theory work if people stray from that?*	Boulder 3
Woman	*…I think [vaccinomics] is probably a bad idea because like she said, it's going to get into a eugenics thing, survival of the fittest thing, you know, and it could be used to harm a lot of people. I don't think that's a good idea, but I like the first responder idea.*	

Table 4. Stigma Quotations from Community Meeting Discussions

Speaker	Quotation	Source
Woman	*So, I don't get how when people are either super spreaders or are deemed vulnerable, what would happen to them? … how would their lives change, the super spreaders, when they have to take a few years in quarantine…?*	Boulder 1
Man	*…Who is going to... actually to obtain it? And that could be said for a lot of technologies, of course. Rich folks have it for a while and then over time we can get it to more broke folks. But it's like more of an immediate issue with vaccines.*	
Woman	*…Say my child he gets this done and he's classified as a super spreader. Are the schools going to know about this? And does that cause our children to be segregated because they are super spreaders?"*	Baltimore 1
Woman	*And then even walking into the office with a mask on, then you're already putting everybody else on alert so that means stigma by itself. So, I think there will be a lot of stigma with vaccinomics if you know you are the super spreader, 'Oh, you're a super spreader, maybe you shouldn't come to work in flu season.' You know, you aren't seeing that."*	Baltimore 2
Woman	*… I seen people come in, bring their children in, like we can go to the emergency room and we might not get help because our policy might not pay for the emergency room visit and we still had to go out sick and not get treated or whatnot. And that's just how I feel because I'm like, poor or rich, we're still not getting the help that we need, that's just how I feel.*	

Table 5. Vaccine Confidence: Two Sample t-Test for the Equality of Means

		Mean (SE)[1]		P-value[2]
Effectiveness:[2]		Pre	Post	
	Adults	8.80 (3.35)	9.10 (3.46)	0.67
	Babies	8.80 (3.35)	9.00 (4.05)	0.86
Safety:[3]				
	Adults	9.10 (4.01)	8.40 (3.24)	0.55
	Babies	9.10 (4.01)	8.10 (3.29)	0.42

[1]SE: Standard Error; [2]P-value represents the probability that the two means are not equal
[2]Effectiveness: Pre-Babies: n=84; Post Babies: n=90; Pre Adults: n=88; Post Adults: n=91
[3]Safety: Pre Babies: n=92, Post Babies: n-81; Pre Adults: n=91, Post Adults: n=84

Table 6. Participants' Written Comments Explaining Pre versus Post-Discussion Vaccine Safety Ratings for Adults

Theme	Comment
Pre-Discussion	
Personal experience	*My cousin died of Guillain Barre syndrome - after swine flu shot* *From my personal experience, it is safe to adults*
Allergic reactions	*I think vaccines are safe for adults. The only issue is allergic reactions.*
Safety and manufacturing process	*They are not full live pathogens, so they do not cause harm*
Disease prevention	*They are safe because they help to eliminate the illness* *Vaccines help prevent illnesses that were once responsible for the death of a lot of people*
Scientific rigor	*They are very safe for most people. Extensive testing and years of use have shown little to no recourse or damage to mass people.*
Post Discussion	
Interested in vaccinomics' potential	*I became more concerned of the socio-political effects of vaccination that made me more concerned of the incidence of racism, insurance issues, status: immigration and deportations that can decrease safety among populations and thus effectiveness. But not the safety of effectiveness of the vaccine itself*
Vaccines getting safer	*Still very confident, vaccinomics seems to promote safety!*
Adverse reactions rarely occur	*It is safe. It is very rare to hear a about situation where people were harmed*

Table 7. Participants' Written Comments Explaining Pre versus Post-Discussion Vaccine Safety Ratings for Babies

Theme	Comment
Pre-Discussion	
Benefits of vaccines outweigh the risks	*I think the safety concerns of vaccines for children are overstated and the benefit (kid not getting sick & dying) outweighs the risk. Living baby>dead baby*
Vaccines keep babies safe	*Vaccines help to keep babies safe when they don't quite yet have the immunity to fight certain illnesses*
Generally safe: allergic reactions	*Overall, I think vaccines are safe for babies to prevent diseases in the future. The only issue is unknown allergic reactions. But the benefit is better than risk*
Generally safe: side effects AEFI are rare	*In my experience, babies can have short-term discomfort but vaccines are overall safe*
Generally safe: side effects AEFI are rare	*I don't like the chicken pox vaccine. I would have preferred my kids get their immunity by contracting it b/c its worse to get as an adult. I believe the motivating factor was to keep kids in school as opposed to for their health.* *Children that get chicken pox provide a natural booster for adults chicken pox is worse if your an adult & I worry that the vaccine will not protect them in adulthood. Many adults aren't always good at going to Dr. & keeping up w/ vaccines.*
Disease prevention	*It can keep babies healthy & avoid spreading illness*
Personal experience	*I received vaccines as a youngster and did not contract any childhood illnesses. They are safe*
Scientific rigor	*Vaccines are constantly tested and improved to avoid any negative consequences.* *They are made in a meticulous and precise way. There has been no significant scientific link to any negative effects.*
Post Discussion	
No change	*My opinions regarding the safety and effectiveness have not changed. But! I now have hope that they are destined to become safer & more effective. [drew a peace sign]* *No change, still think very safe. More research = increase safety*
Adverse reactions rarely occur	*There will always be some with adverse reactions*

Table 8. Participants' Written Comments Explaining Pre versus Post-Discussion Vaccine Effectiveness Ratings for Adults

Theme	Comment
Pre-Discussion	
VE greater for children than adults	*Vaccines don't work as well in adults than children bc of immune changes & being introduced to more*
Somewhat effective - vaccine dependent	*Depends on the vaccine but clearly the flu vaccine is limited in effectiveness year to year*
	I think that they're mostly very effective but it depends on the vaccine & the reaction of the person receiving the vaccine (allergies, etc)
	Vaccines are safe in the military. I had several and was in close contact with others. I didn't get ill for the vaccines.
	I think vaccines are effective but the adult immune system may have been exposed previously
Effective in adults	*Because adult has fully developed immune system, a 1 day old infant getting hep B vax won't respond as well as adult getting hep B vaccine*
	I think they're less effective than for children but still more effective than nothing
	Some vaccines do not create long term resistance which may decrease net effectiveness But when the vaccine is effective in a group; diseases are eradicated Small pox
Post Discussion	
Disease prevention	*Vaccines are the absolute best way to prevent pathological damage to our community proven by science*
Effective in adults	*May not be customized but still work*
	I think most vaccines are effective for adults the only ones that I don't think are as effective are created yearly like flu vaccines
	Im not convinced that they're more or less effective. but I'm hopeful but terrified for the future
	I think vaccines based on genes would be more effective. However, I feel more comfortable with vaccines that have been around for 20+ years
	For all questions after discussion - reinforced my beliefs in safety and experience of vaccines. No change in "dots" placement.
Change	*No significant change because I already do vaccinations and believe in the science. However, I think this will better inform the science.*

Table 9. Participants' Written Comments Explaining Pre versus Post-Discussion Vaccine Effectiveness Ratings for Babies

Theme	Comment
Pre-Discussion	
Adaptive immunity	*Vaccines are an effective way for babies to be exposed to antigens in a safe way so they can build up their adaptive immune system in order to contact later exposure to pathogen*
Vaccines improve immunity	*I think vaccines are most effective in babies because their immune systems are still developing*
Somewhat effective - timing	*Varies depending on age of baby & if Breastfed on not. Maternal antibodies interfere with VE & vax more effective once immune system is fully developed (after 2 yrs old?)*
Somewhat effective - vaccine dependent	*Seem very effective for major diseases, not so much for flu, etc*
Disease prevention	*We have smallpox vaccine & smallpox is eradicated; we have polio vaccine & disease is almost eradicated. Seems pretty effective to me*
Post Discussion	
Disease prevention	*Vaccines remain the best way to preventatively protect your children against the pathogen that will seek to harm them in their lives. (similar comment under Adults)*
Effective for babies	*It is effective, however, each person is going to respond differently* *Baby vaccines are effective. Polio and other diseases are being wiped out through vaccination. Keep all American kids safe.*
No change	*I still feel vaccines are best effective for babies* *No change, still think very effective. More research = increased effectiveness* *No significant change because I trust in the science and efficacy of vaccines and I did not get any new information. The science is maybe getting better*
Change	*As an epidemiologist, I have always had a positive view of vaccines and I think vaccinomics would make my opinion stronger* *I think vaccines based on genes would be more effective. However, the information must not be allowed to influence life & health insurance policies.* *The slides on/video said most vaccines (average) are only 80-90% effective & I didn't know that before (same comment appeared under Adults)*

5.8 Figures for Chapter 5

Figure 1.Emergent Themes

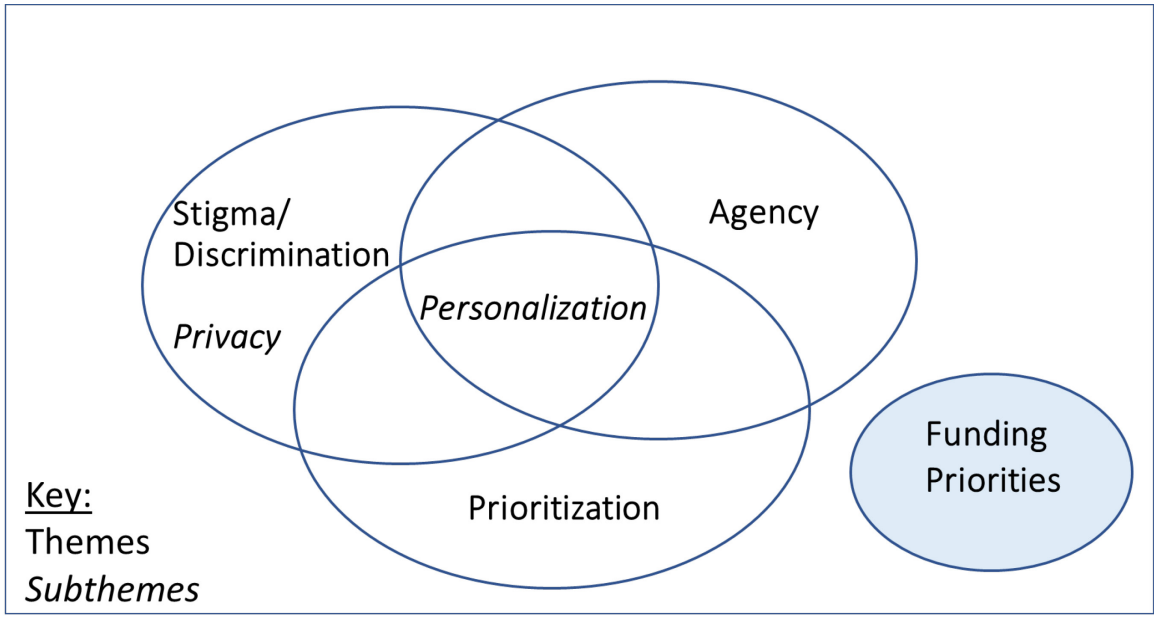


Figure 2. Vaccine-Related Funding Priorities

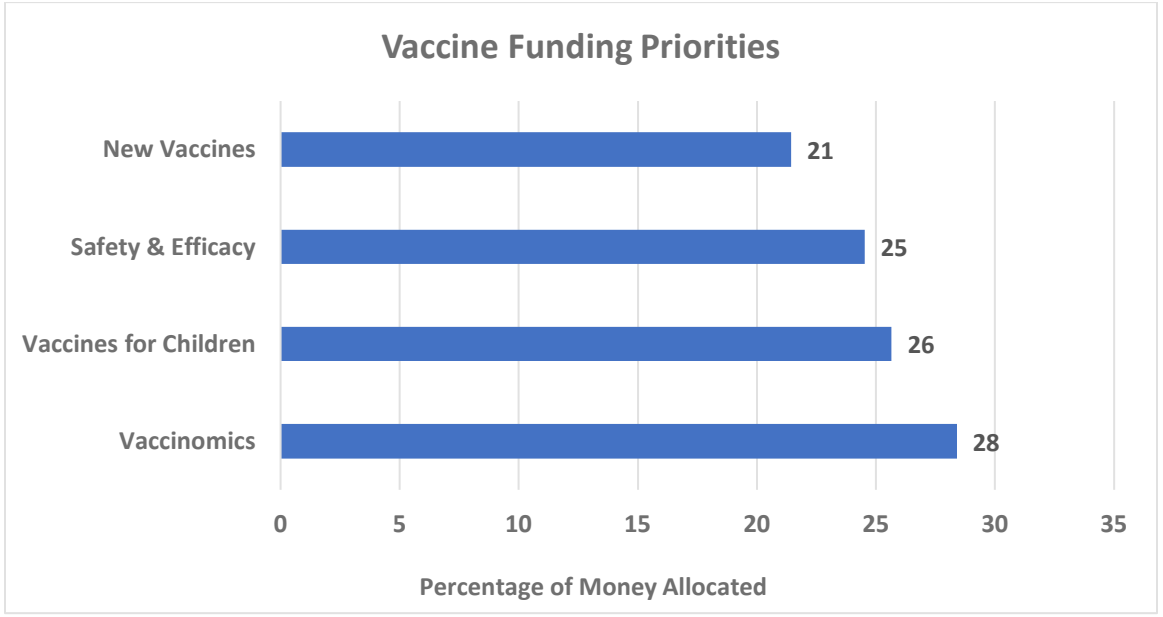
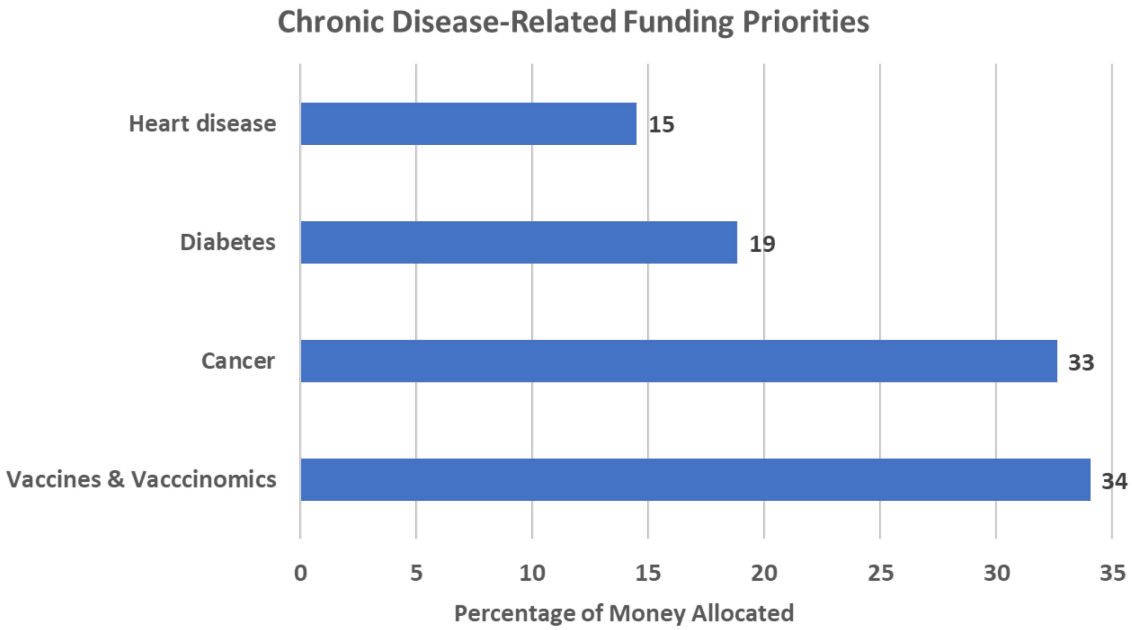


Figure 3.Chronic Disease-Related Funding Priorities



Chapter 6. Public values and the policy implications of vaccinomics: results of a cross-sectional survey in the United States

6.1 Abstract

Objective: Characterize public values informing vaccinomics policy.

Methods: Panel survey of adults ≥18 years old conducted in 2019. Within the survey, a four-minute-long animation explained vaccinomics. Sociodemographic, vaccine confidence, and uptake items were adapted from validated scales. Novel items measured vaccinomics-related values, support, and concerns. Participants indicated funding preferences for vaccinomics versus federal vaccine (safety and efficacy, new vaccines, free vaccines for children) and chronic disease (cancer, heart disease, and diabetes) priorities. Respondents indicated agreement with the statement "vaccines are very safe" at the beginning and end of the survey to measure the impact of discussing AEFI and vaccinomics. Data were weighted to the U.S. Census. Vaccinomics-related concerns were stratified by sociodemographic characteristics (age, parent status, household income, and education), vaccine hesitancy status, serious vaccine reaction experience, and trust in public health authorities. Unadjusted and adjusted prevalence ratios estimated associations with vaccinomics opposition.

Results: A majority (70.7%) of 1,925 respondents expected vaccinomics to increase their vaccine confidence. In bivariable analyses, vaccinomics support was ≥10% stronger among those without perceived vaccine reaction experience, with low vaccine hesitancy (among parents of teenagers and adults without minor children) and higher education, income, and trust in public health authorities. In multivariable models, low trust in public health authorities and experience with serious vaccine reactions were associated with expecting to feel angry if not prioritized for vaccination and agreement that vaccination is an individual's choice. Respondents supported

vaccinomics and funding for it compared to chronic disease and vaccine-related priorities. Vaccine safety perceptions did not change from the beginning to end of the survey.

Conclusion: Vaccinomics was supported across sociodemographic groups. Low trust in public health authorities and lack of perceived vaccine reactions were associated with opposition to vaccinomics. Federal agencies should allocate funding for vaccinomics-related research and implement policies that engender trust in public health.

6.2 Background

Vaccinomics is an emerging field that may improve vaccine development and use, through the application of advances in immunology and genomics to the study of vaccine response and development of vaccine candidates.(3) A subfield of vaccinomics, “adversomics” is the application of genomics to the study of adverse events following immunization (AEFI), which are events that are temporally associated with vaccination, but have not been determined to be causally associated.(29) For simplicity, "vaccinomics" encompasses adversomics here.(3)

There are many examples of genomic differences, including biological sex, race, and specific genetic loci, that are associated with immune response and vaccine adverse reactions.(24, 168-177) Vaccinomics is a new field, and its potential will not be fully realized in the near future. When it is implemented, there will be ethical, legal, and social implications, or more broadly termed, policy issues, that will arise. We have an opportunity to consider what these issues may be now, before vaccinomics is implemented. Early understanding of public values, preferences, and concerns can inform vaccinomics policy and development. The public could be influential in how vaccinomics is studied and implemented, impacting the research and development of new vaccines, clinical trials, licensure, recommendations for use, injury compensation and communications.

Vaccinomics could decrease vaccine hesitancy through improved safety and personalization of vaccine scedules, or increase it, due to privacy concerns around genomic data. The World Health Organization designated vaccine hesitancy as one of the top 10 threats to global health in 2019.(2) Serious vaccine reactions, like Guillain-Barre Syndrome (GBS), are exceedingly rare.(18, 44) There are an estimated 1-3 excess cases of GBS per 1 million persons vaccinated, which pales in comparison to the vaccine's benefits.(44) Despite the rarity of these events, many people worry about vaccine safety.(4, 6-12) People with vaccine safety concerns often worry that they or their children may be at increased risk of diseases with genetic risks-factors, including autoimmune diseases, asthma, and multiple sclerosis, or that children's immune systems could be overloaded by receiving too many vaccines at once, despite a lack of epidemiological evidence.(61, 68, 69) Those who refuse or delay vaccines, due to their concerns, often cluster geographically and socially, contributing to vaccine preventable disease outbreaks.(52, 62, 70). Vaccinomics may reduce vaccine hesitancy, through improved safety and personalization of vaccine schedules to subgroups of the population. Alternatively, vaccinomics may raise concerns among those who are not worried about vaccines now, or aggrevate concerns among those who mistrust current vaccines, due to the uncertainty around genomics.

This survey builds on formative work conducted with vaccine policymakers and community members. In 2017, we met with academic vaccinologists and representatives of federal agencies involved in vaccines, including the National Institutes of Health, Food and Drug Administration, Centers for Disease Control and Prevention, and Health Resources and Services Administration (National Vaccine Injury Compensation Program) to discuss what policy issues might emerge throughout the lifecycle of vaccinomics, and where public input would be useful, even though vaccinomics may not be implemented in the U.S. for 10-15 years. In 2019, we conducted community meetings in Boulder, Colorado and Baltimore, Maryland. Participants

were largely supportive of vaccinomics, but worried that without appropriate policy safeguards, vaccinomics could lead to stigmatization/discrimination through breaches of confidentiality and that genetically-based vaccine prioritization would reduce their agency to make vaccine-related decisions. Despite these concerns, the prospect of more personalized vaccine schedules, which may come through vaccinomics, was appealing, especially to those who reported experiencing AEFI.(188) This survey quantifies if vaccinomics-related concerns vary by region, vaccine hesitancy level, perceived AEFI experience, and sociodemographic factors. We aimed to characterize public values that could inform vaccinomics policy.

6.3 Methods

Recruitment and Consent

Respondents were recruited out of approximately 10 million Qualtrics panel participants using a double opt-in process.(133) All provided consent before answering survey items. Data were collected from January 22nd through February 11th, 2020. Quotas based on the American Community Survey,(135) Current Population Survey,(154) and 2010 Census(134) were included so that respondents would reflect the sociodemographic distribution of the U.S. Due to difficulty enrolling individuals with minority race/ethnicity, from the West, and in the lowest income, age, and education brackets, quotas were ignored when recruiting the last 400 (approximate) of 1,925 respondents.

Survey Content

Vaccinomics-related themes included vaccine schedule complexity, informed decision-making, more contagious and susceptible populations, funding, and implementation. Additional themes included vaccine confidence, trust, and genomics in general.

Survey items covered sociodemographic information, the ages of respondents' youngest children, vaccine attitudes and beliefs, trust in public health agencies, personal health, and

values around vaccinomics. Perceived experience with serious vaccine reactions was measured, defined as including, "permanent disability, hospitalization, life-threatening illness, or death." Respondents reported if they or anyone they knew experienced a perceived serious reaction. A four-minute-long animation embedded in the survey educated respondents about vaccinomics.

Vaccine hesitancy was measured using select items from previously validated scales.(137-140) PACV items were administered to parents of children ≤10 years old. Two sets of items were adapted from The Vaccination Confidence Scale(140) for parents of teenagers and other adults. Twenty items on trust in public health authorities ("trust" henceforth) were developed through a literature review.(141) One item measured concerns around the security of genetic test results. Most items used a 4-point Likert Scale.

Respondents were randomized with 50:50 probability to receive positively or negatively worded survey items about vaccinomics to minimize the effects of agreement bias. Items that came from preexisting scales were not presented in positive and negative forms. Survey content was revised for clarity and specificity after conducting cognitive interviews with 20 out of 131 pretest respondents.

Data Analyses

Data were weighted to the 2010 U.S. Census by region, Hispanic ethnicity, and race to facilitate making inferences about the U.S. population.(134) The distributions of survey weights were visualized using histograms and the adequacy of weighting was assessed by comparing the weighted data to the 2010 Census.(134)

Vaccine hesitancy data were converted to a score (range 0 to 100) using a linear transformation and visualized with histograms. The median in one of the three groups equaled zero, preventing dichotomization at that point. Instead, vaccine hesitancy scores for each group (parents of children ≤10 years old, parents of teenagers 11 to 17 years old, and adults without

minor children) were dichotomized at the weighted mean (low versus high hesitancy). The overall and stratified prevalence of low versus high vaccine hesitancy was assessed separately by age group (parents of children ≤10 years old, parents of teenagers, and adults without minor children) and by vaccinomics-related items. A two-sided t-test for survey data estimated the probability that the difference in mean vaccine safety score at the beginning versus end of the survey did not equal 0.

The binary trust in public health authorities variable (low versus high) was derived from a linear score of 14 items, dichotomized at the mean.(156) For vaccinomics items with both positive and negative wording, the distributions of each pair were compared. The scale of the negatively worded items was reversed and responses were combined with the positively worded items for analysis.

Using survey estimation procedures and Taylor-linearized variance estimates,(142) univariate and bivariable tabulations were conducted to characterize the associations between vaccinomics-related policy issues and sociodemographic factors, parent status, vaccine hesitancy, trust, and perceived experience with or knowing someone who reported a serious vaccine reaction ("serious reaction" henceforth). In stratified analyses, vaccinomics variables measured on a 4-point Likert Scale were dichotomized (strongly agree/agree versus strongly disagree/disagree; extremely likely/likely versus extremely unlikely/unlikely). Differences between groups ≥10% in bivariable analyses were identified as having potential policy implications and are noted in the Results.

Post hoc analyses were conducted to characterize support and opposition to vaccinomics. The proportion of respondents who indicated they would get vaccinated to protect others was cross-tabulated with the proportion who were vaccinated against influenza in 2019-2020 to determine if altruistic claims were matched by respondents' behaviors (vaccination

status was measured first). More in depth post hoc analyses characterized individuals who opposed vaccine prioritization. Two outcomes were explored: 1) those who thought they would be angry if not prioritized during a shortage due to being labeled "more contagious" or "more susceptible" and 2) those who believed vaccination was an individual's choice, even for "more contagious" and "more susceptible" individuals. We hypothesized vaccine hesitancy would be associated with these outcomes.

Prevalence ratios for potential opposition to prioritization were estimated by sociodemographic factors, parent status, trust, vaccine hesitancy (by age group: parents of young children, parents of teenagers, and adults without minor children), and serious reaction experience using the *glm* procedure for survey data, family(binomial), link(log). Factors associated with either outcome at $p<0.1$ in univariate regression were included in a saturated multivariable model, with an interaction term between age and trust. Backwards stepwise regression was used to identify parsimonious models with $p\leq0.05$. Respondents who answered "prefer not to answer" regarding their income or education were excluded from multivariable models in which these variables were included. Therefore, multivariable models only explored the association between expecting to feel angry and vaccine hesitancy for adults without minor children. As there was no association in univariate analyses between vaccination is an individual's choice and vaccine hesitancy for any age group, multivariable analyses excluded vaccine hesitancy.

This study had 96.9% power to detect a difference of 10% between two groups when the proportion in the reference group was 0.5 and there were 3 times as many respondents in one group compared to the other. Two-sided p-values were estimated using general tests of association. All analyses were conducted using Stata®, Version 16.(132)

Ethical Review

This work was ruled "exempt" by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

6.4 Results

Characteristics of the Study Population

The weighted mean response time for 1,925 respondents was 19.8 minutes (95% CI 18.8, 20.7). The weighted study population was 50.6% female, 61.8% White, non-Hispanic; 36.0% 18 to 34 years old, 62.9% had a child <18 years old, and 44.7% had a household annual income ≤$49,999. High vaccine hesitancy prevalence was 45.4% among parents of young children, 27.6% parents of teenagers, and among 37.7% adults without minor children (henceforth "other adults"). There was variability in the geographic distribution of respondents (Midwest: 22.2%, Northeast: 18.1%, South: 36.9%, West: 22.6%; **Table 1**). Less than a third of respondents previously underwent genetic testing (27.3%). Experiencing or knowing someone who had a serious vaccine reaction (henceforth "serious reaction") was common (76.5%). Among those with serious reaction experience, 85.7% were extremely likely/likely to participate in a biobank. Most of these respondents (81.9%) would be motivated to participate in biobanks with independent ethics oversight **(Table 2)**.

Broad Implications of Vaccinomics

Over ninety-one percent of all respondents expected vaccinomics to help them make informed decisions for themselves (91.7%) and their children (92.7%**; Table 3)**. Vaccine hesitancy among parents of teenagers (low: 97.7% versus high: 82.1%), adults without minor children (low: 96.1% versus high: 80.8%), and high trust (low: 85.8% versus 97.0%) were associated with ≥17% differences in respondents thinking vaccinomics would improve vaccine

decision-making for themselves. Low vaccine hesitancy among parents of young children was also associated with expecting vaccinomics to inform decision-making for one's child (low: 96.0% versus high: 84.9%; **Table 7**).

Most respondents expected vaccinomics to help others (82.6%), help themselves (75.8%), and improve their vaccine confidence compared to now (70.7%; **Table 3**). This belief was approximately 10% stronger among those with a household income >$150,000 compared to those with lower income, and among those with college equivalent or higher education compared to a high school degree or less (graduate degree: 78.7% versus high school: 65.7%; **Table 6**). Respondents without serious reaction experience (without: 73.9% versus with: 62.3%), with low vaccine hesitancy (parents of teenagers – low: 79.0% versus high: 62.8% and other adults – low: 75.3% versus high: 60.9%), and with high trust (high: 89.0 versus low: 61.6%) indicated vaccinomics would increase their vaccine confidence compared to the present **(Table 7).**

Even if vaccinomics leads to more complex vaccine schedules, 71.2% of respondents indicated they would support vaccinomics **(Table 3)**. There was ≥12% variance between groups among those with high versus low trust (84.1% versus 57.0%), without versus with serious reaction experience (75.2% versus 59.7%), among parents of teenagers with low versus high vaccine hesitancy (77.0% versus 63.4%) and adults without minor children (77.3% versus 61.1%; **Table 7**).

Most respondents (76.8%) would undergo genetic testing if it would help their healthcare provider know which vaccines were best for them **(Table 3).** Low vaccine hesitancy was associated with an increased likelihood of undergoing genetic testing among parents with young children (low: 79.0% versus high: 69.8%), parents of teenagers (low: 83.6% versus high: 61.7%), and other adults (low: 83.8% versus high: 66.6%). High trust (low: 63.3% versus high:

88.9%) and lack of vaccine reaction experience (without: 80.4% versus 64.5% with: **Table 7**) were also associated with higher willingness to undergo genetic testing.

Privacy

Approximately half of respondents indicated they would be concerned about the security of their genetic test result (56.3%), that their health insurance company would learn the result (45.6%), or that the U.S. government would learn the result (47.0%; **Table 3**). Less than a quarter of respondents worried their genetic test result would prevent them from getting a vaccine (22.0%; **Table 3**); however, concerns varied by level of education (graduate degree: 28.1% versus college experience: 18.7; **Table 6**), experience with serious vaccine reactions (with: 34.3% versus without: 18.3%) and trust in public health authorities (low: 39.1% versus high 20.8%; **Table 7**).

Discrimination

Although concern that one's DNA test result could lead to race/ethnic discrimination was low (29.0%; **Table 3**), results varied by level of trust (low: 39.1% versus high: 20.8%), experience with serious vaccine reactions (with: 43.0% versus without: 25.1%; **Table 7**), and race/ethnicity (White, non-Hispanic: 17.1%, Black, non-Hispanic: 4.4%, Other: 7.5%; data not shown).

Hypothetical Scenarios

If vaccines were in short supply, two-thirds of respondents strongly agreed/agreed more susceptible (74.5%) and contagious (75.7%) individuals should be prioritized for vaccination **(Table 4).** Support for prioritization of more susceptible individuals was 12-20% higher among those without serious reaction experience (without: 78.8% versus with: 59.2%), parents of teenagers with low vaccine hesitancy (low: 77.4% versus high: 66.2%), and those with high trust

(high: 84.1% versus low: 63.4%). Bivariable analyses regarding prioritizing more contagious individuals for vaccination followed the same trend **(Table 5).**

Less than half of respondents would be bothered if their doctor labeled them "more contagious" (41.3%) or expected being called "more susceptible" would hurt people (38.9%; **Table 4**). Those without serious reaction experience (without: 38.3% versus with: 50.8%) and low trust (low: 47.0% versus high: 36.9%) were more likely than others to indicate they would be bothered by the "more susceptible" and "more contagious" labels**.** When asked if these labels would hurt others, compared to oneself, the results were similar, but agreement that it would be bothersome differed by whether respondents had experienced serious reactions (without: 36.0% versus with: 45.2%) and level of trust (low: 47.0% versus high: 39.9%; **Table 5**).

Most respondents agreed (63.0%) vaccination should be an individual's choice and 23.2% expected to be angry if not prioritized for vaccination **(Table 4).** Overall, agreement with vaccination being an individual's choice was higher among those with serious reaction experience (without: 60.3% versus with: 73.9%), and higher education (graduate degree: 72.2% versus high school: 62.9%). Among parents of young children, those with low vaccine hesitancy more strongly believed vaccination was an individual's choice (low: 70.7% versus high: 61.6%; **Tables 5 and 11**).

Over half of respondents indicated they would get vaccinated to protect others (56.2%). In a post-hoc analysis, 39.5% of those strongly agreed/agreed they would get vaccinated to protect others also indicated they were vaccinated against influenza during the 2019-2020 season (data not shown).

Support for screening tests to identify individuals at increased risk of paralysis and death was high (64.3%), and 66.5% said their vaccine confidence would increase if the U.S. spent more to study vaccine safety and informed the public of the results **(Table 4).** In bivariable analyses,

those without serious vaccine reaction experience (without: 67.6% versus with: 56.6%) and high trust (high: 70.6% versus low: 57.3%) were associated with support for screening tests **(Table 7).** Support for screening tests to prevent serious reactions was stronger among respondents ≥55 years old (70.3%) compared to 18 to 34 years old (60.5%; **Table 6**).

Funding and Implementation Priorities

Over 75% of participants indicated vaccinomics should get more or an equal amount of money compared to current chronic disease (research and development for breast and prostate cancer, diabetes, and heart disease) and vaccine priorities (improved safety and effectiveness, buying vaccines for poor children, and supporting the use of vaccines in poor countries; **Table 8**). Half of respondents (49.6%) strongly agreed/agreed that the U.S. government should invest in making vaccines more effective rather than trying to reduce the occurrence of rare and serious events, like paralysis and death **(Table 4).**

Respondents indicated vaccinomics should be similarly implemented for children and adults, respectively, to improve vaccine safety and effectiveness (78.6%, 72.1%), identifying individuals at risk of serious reactions (61.0%, 61.7%), identifying those likely to be more contagious (54.0%, 54.3%), likely to be more susceptible (50.6%, 50.1%). Less than 15% thought genes should not be used in vaccine decisions for children (14.3%) or adults (13.7%; **Table 8**).

Regression Results

Two outcomes were explored as possible predictors of opposition to vaccine prioritization: 1) expecting to be angry if not prioritized for vaccination and 2) strongly agreeing/agreeing that vaccination is an individual's choice. Trust and experience with a vaccine

reaction were associated with both outcomes at p<0.05. Vaccine hesitancy was only associated with expecting to feel angry among adults without minor children **(Table 10).**

Expected to be Angry if not Prioritized

In bivariable analysis of all respondents, experience with a vaccine reaction, age, education, household income, parent status, trust, region, race/ethnicity were associated with expecting to feel angry. Vaccine hesitancy was only associated with expecting to feel angry at p<0.10 among adult without minor children. Among respondents with children <18 years old, expecting to be angry if not prioritized for vaccination was unassociated with vaccine hesitancy **(**p>0.1, **Table 9).** In multivariable analysis of the same group, experience with serious reactions, low trust in public health authorities, and high vaccine hesitancy were associated with expecting to feel angry if not prioritized (all p≤0.02). Respondents with serious reaction experience were more likely than those without this experience to indicate they would be angry if not prioritized, after controlling for level of vaccine hesitancy and trust (Prevalence Ratio [PR]: 1.84, 95% CI: 1.25, 2.70; p<0.01). High vaccine hesitancy (PR: 0.49; 95% CI: 0.32, 0.73; p<0.01) and low trust (PR: 0.67, 95% CI: 0.47, 0.96; p=0.02) were associated with lower prevalence of expecting to feel angry, controlling for other variables in the model **(Table 10)**.

Vaccination is an Individual's Choice

In bivariate analysis, vaccine reaction, age, parent status, household income, trust, and region, were associated with higher prevalence of agreement that vaccination is an individual's choice (all p≤0.10, **Table 9**). In multivariable analysis of all respondents, the prevalence of agreement was higher among those with vaccine reaction experience, low trust, a high school education, and parents of children <18 years old. After controlling for other variables in the model, respondents who had experience with a serious vaccine reaction were 15% (95% CI: 7%

to 25%; p<0.01) and those with low trust in public health authorities were 9% (95% CI: 2% to 16%; p=0.01) more likely to strongly agree/agree that vaccination is an individual's choice compared to other respondents **(Table 10).**

Vaccine Safety

Among all participants, the mean score increased by 0.10 (p<0.01) from the beginning of the survey to the end of the survey (range 0-3).

6.5 Discussion

These results indicate strong support for vaccinomics, and that vaccinomics may help bolster vaccine confidence. Respondents thought vaccinomics should get an equal amount or more funding compared to current federal priorities, and that it should similarly be implemented to help children and adults. Less than one third of respondents opposed genetically-based vaccine prioritization. In stratified analyses and multivariable regression, expected opposition to vaccinomics and vaccine prioritization was associated with low trust in public health authorities and experience with serious reactions. This suggests that bolstering trust in public health authorities might make adults more receptive to vaccinomics and genetically-based vaccine prioritization.

Serious V**accine Reactions**

A higher proportion of respondents than expected, based on the well-established safety profile of vaccines, indicated they personally experienced or knew someone who experienced a serious vaccine reaction.(18, 44) Although serious reactions were defined in the survey as including "permanent disability, hospitalization, life-threatening illness, or death," respondents may have reported experience with milder, yet concerning, events. The perception of having experience with life-threating events was associated with opposition to vaccine prioritization.

Trust in Public Health Authorities

Trust and experience with vaccine reactions were associated with expecting to feel angry if not prioritized and agreement that vaccination is an individual's choice. These factors may predict opposition to vaccinomics and genetically-based vaccine prioritization. This survey was conducted in January and February 2020, prior to COVID-19 being declared a pandemic by the WHO, or becoming the primary news topic in the U.S.(189) The hypothetical scenarios presented in the survey, where some people might be "more contagious" or "more susceptible" to infection and that vaccines may be in short supply, are now more realistic. As a result of the dire shortage of coronavirus tests, medical supplies, and hospital beds, nearly 90% of Americans were under stay-at-home orders in 2020.(190) Our finding that high trust in public health authorities is associated with higher trust in vaccinomics and support for vaccine prioritization might be stronger or weaker if the survey were fielded today. The head of the National Institute for Allergy and Infectious Diseases has stood by Mr. Trump regularly during COVID-19 press briefings from the White House.(191) Their physical proximity, frequency of joint appearances, and fact that these briefings are given from the White House may lead the public to perceive public health authorities and government officials as nearly the same. This perception may harm the public's trust in public health authorities, because trust in government has been on a 56-year-long decline.(192) This study indicates that in the absence of a pandemic, there was strong support for vaccinomics and that support was higher among those with high trust in public health authorities. If our survey were conducted again now, there may be even greater support for vaccinomics, or more fear about its policy implications, given the pandemic and that trust in public health authorities, like trust in government,(192) may vary over time.

Stigma/Discrimination

Based on formative work, we expected respondents to be more concerned about potential stigma/discrimination stemming from vaccinomics.(188) In formative meetings, 18% of respondents were Black, non-Hispanic and only 11% were in this study.(188) Although we set enrollment quotas for racial/ethnic minorities based on national-level estimates, quotas were unfilled for Hispanics and Asians. This lack of diversity may partially explain why concerns about racial/ethnic discrimination were not more prevalent. The lack of concern about racial/ethnic discrimination in the survey, compared to the community meeting, may also be related to differences in data collection. When one person expressed concerns about stigma/discrimination in the in-person discussion groups, this may have triggered agreement in others. In the survey, respondents answered in isolation from one another.

Vaccine Hesitancy and Serious Vaccine Reactions

The majority of respondents supported vaccinomics, though support was slightly lower among individuals with high vaccine hesitancy among two subgroups: parents of teenagers and adults without minor children. Among parents of young children, vaccine hesitancy was unassociated with the policy implications of vaccinomics. The slight increase (0.10 on 0-3 scale) in vaccine safety rating from the beginning versus the end of the survey was in a positive direction, but likely statistically significant due to a large sample size. There was no evidence that participants thought vaccines were less safe at the end, compared to the beginning, of the survey.

We expected those with high vaccine hesitancy and who had serious reaction experience to be more supportive of vaccinomics based on formative work.(188) Instead, we found most people were supportive of vaccinomics, regardless of their vaccine hesitancy status or experience with serious reactions. These findings may be due to differences in data collection

methods between the survey and formative work, and how vaccine hesitancy was measured by age group in the survey.(188) Vaccine hesitancy was not quantified in the formative study. Our observations in group discussion that vaccine hesitant individuals with AEFI experience supported vaccinomics may have been based on the presence of concerns along the vaccine hesitancy continuum,(4, 7, 8) but not high vaccine hesitancy and a tendency towards vaccine refusal. Participants in the formative study were asked to attend meetings about vaccines. Experience with AEFI may have motivated attendance, making our formative study participants less representative of the U.S. population compared to survey respondents. Though some of the PACV items administered here have been validated in other online panels, the PACV was originally designed for in-person administration.(137-139) Administering these items online may reduce their sensitivity to identify individuals with high vaccine hesitancy. The Vaccine Confidence Scale, which we adapted for respondents with teenagers and without minor children, was originally validated using an online panel.(140)

Representativeness of the Study Population

To assess the representativeness of our weighted results compared to the U.S. population, we included four items from the 2015-2016 NHANES in our survey and compared our results to the weighted NHANES data.(155) Despite differences in data collection and weighting methods, results were similar **(Appendix, Table 12).**(155) Data were also weighted and compared to the 2010 Census, allowing inferences to be made about the country as a whole.(134)

Strengths and Limitations

The original 15-item PACV and 5-item PACV Short Scale were developed for use in medical offices to screen parents of young children.(137, 138) The Vaccine Confidence Scale was developed for online administration, but with a 10-point Likert scale rather than the 4-point

scale used here.(140) Although the vaccine hesitancy items we used were previously demonstrated to have internal validity,(138) they may not have external validity when used among online panelists. Adapting these previously developed items may still have higher validity than de novo items created for this study. Though this is not a probability-based sample and the probabilities of selection and nonresponse were unavailable for use in weighting, data were weighted to the U.S. Census to facilitate making inferences about the U.S. population.(167) Weighted survey data were comparable to the 2010 Census and 2015-2016 NHANES results.(134, 167) Weighting inflates variance estimates compared to a simple random sample,(167) yet strong statistical associations were found in this analysis. Cross-sectional surveys are inherently limited by only collecting data at one point in time. If respondents' trust in public health authorities is sensitive to recent news, like the COVID-19 pandemic, or the sitting U.S. President, these results may not reflect how the public will feel when vaccinomics is implemented. Trust in public health authorities, associated with vaccinomics support in this study, may be lower, higher, or the same compared to now.

Public Health Implications

This is the second study to our knowledge of the policy implications of vaccinomics. Public policy leaders should consider these results in planning how to implement vaccinomics and engage interested adults. Simultaneously, skeptics will need to be assured that vaccinomics will not remove their agency to make vaccine-related decisions. Those promoting genetic testing and biobank participation should describe the role of Institutional Review Boards and other independent, ethical oversight to prospective participants, as most survey respondents said this kind of oversight made them more likely to participate in biobanks.

6.6 Conclusion

Respondents supported vaccinomics and funding for it compared to chronic disease and vaccine-related priorities. Trust in public health authorities and lack of experience with serious reactions were associated with opposition to vaccinomics. Federal agencies should allocate funding for vaccinomics-related research and implement policies that engender trust in public health authorities. This information will inform vaccinomics-related communications and policies, with the goal of making vaccinomics more appealing to the public and increasing the likelihood it is successful in making vaccination safer and more effective.

Funding

This study was supported by grant number RM1HG009038 from the National Human Genome Research Institute. The funder had no involvement in the design, implementation, analysis, interpretation, or reporting of this study.

6.7 Tables for Chapter 6

Table 1. Sociodemographic characteristics of the study population: weighted and unweighted

Sociodemographic Factors	Unweighted N=1,925 (%)	Weighted[10] %		Unweighted N=1,925 (%)	Weighted[10] %
Gender[1]			**Parent status[7]**		
Male	934 (48.5)	48.6	Child <18 years old	1,239 (64.4)	62.9
Female	976 (50.7)	50.6	Nonparent/older children (other adults)/prefer not to answer	686 (35.6)	37.1
Race/ethnicity[2]			**Youngest child's age (years)[8]**		
White, Non-Hispanic	1,136 (59.0)	61.8	≤5	323 (22.6)	22.2
Black, Non-Hispanic	230 (11.9)	11.4	6-10	401 (28.0)	27.7
Other	559 (29.0)	26.8	7-11	515 (36.0)	35.9
Respondent's Age (years)[3]			≥18	181 (12.6)	13.3
			Vaccine hesitancy: parents of children ≤10 years old[5]		
18-44	691 (36.0)	36.0			
35-54	661 (34.4)	33.4	Low	396 (54.7)	54.6
≥55	569 (29.6)	30.6	High	328 (45.3)	45.4
Region[4]			**Vaccine hesitancy: parents of children 11-17 years old[6]**		
Midwest	397 (20.6)	22.2	Low	376 (73.0)	72.4
Northeast	510 (26.5)	18.1	High	139 (27.0)	27.6
South	664 (34.5)	36.9	**Vaccine hesitancy: other adults[9]**		
West	35 (18.2)	22.6	Low	424 (61.8)	62.3
Household annual income[5]			High	262 (38.2)	37.7
$0-$49,999	855 (44.4)	44.7	**Science courses and training**		
$50,000-$99,999	508 (26.4)	26.7	High school	1,059 (55.0)	55.7
$100,000-$149,999	236 (12.3)	11.9	College	634 (32.9)	32.7
≥$150,000	290 (15.1)	14.8	Graduate/Continuing Education	315 (16.4)	15.8
Highest level of education[6]			Work/Training	267 (13.9)	13.7
≤High school degree	893 (46.4)	47.1	None of the above	149 (7.7)	7.7
≤College/Associate/Bachelor's degree	728 (37.8)	37.4	**Beginning vs. end of survey vaccine safety[12]**		
Masters/Profession/Doctorate degree	277 (14.4)	14.0	Mean difference	0.10	<0.01

[1]gender: n=15 "trans/prefer not to answer" [2]race/ethnicity: "other" includes 2 "don't know" Hispanic ethnicity, n=87 "prefer not to answer" race, n=25 Hawaiian/Pacific Islander, n=120 Asian, and n=89 American Indian/Alaskan Native (multiple responses allowed); [3]respondent's age: n=4 missing; [4]region: n=3 missing, n=3 "Puerto Rico/prefer not to answer"; [5]household annual income: n=36

missing, n=36 “prefer not to answer”; [6]education, n=27 missing, n=27 “prefer not to answer”; [7]parent status, baseline: n=2 missing combined with n=481=no; [8]age of youngest child: n=12 “prefer not to answer”; [9]vaccine hesitancy among parents of children ≤10 years old estimated using a composite score from items adapted from Opel et al.(137, 138), unweighted n=724; weighted n=705.73; [10]vaccine hesitancy among parents of children 11-17 years old estimated using a composite score from items adapted from Gilkey et al.(140), unweighted n=515; weighted n=507.03; [11]vaccine hesitancy among other adults measured based on Gilkey et al.(140), [12] Estimated mean difference using methods for survey weighted data; unweighted n=686; weighted n= 715. Taylor-linearized variance estimation for weighted survey data used. Unweighted N=1,925; Weighted N=1,927.87.

Table 2. The overall frequency and proportion of the study sample experienced with serious reactions to vaccines, genetic testing experience, and support for biobanks

Survey items		Weighted %
Have you or anyone you know ever had a serious reaction to a vaccine? Serious reactions include permanent disability, hospitalization, life-threatening illness, or death?[1]		
	No	76.5
	Yes	19.7
	Don't know	3.8
Among those who had or knew someone who had a serious reaction to a vaccine: If you had a rare, serious reaction to a vaccine, how likely would you be to let your doctor submit a sample from you (for example: a vial of blood or swab from your mouth) to a biobank?[2]		
	Extremely unlikely	6.0
	Unlikely	8.3
	Likely	36.0
	Extremely likely	49.7
Independent groups of scientists who are experts in research ethics and local community members oversee how biobanks manage people's information. Does having this kind of independent, research ethics oversight make you more likely to submit a sample to a vaccine biobank? [2]		
	No	10.6
	Yes	81.9
	Don't know	7.5
If Likely or extremely likely to give a sample: What is the primary reason you would participate in a vaccine biobank? [2]		
	To help others	50.4
	Interest in science and/or medicine	21.6
	It's the right thing to do	18.9
	To help myself	8.5
	Other	0.6

Table 2. Continued		Weighted %
Have you ever had your genes or DNA tested? For example, in your doctor's office or through an in-home test like 23andme, ancestry.com, or one purchased in a pharmacy?[3]		
	No	71.8
	Yes	27.3
If had DNA tested: Where were your genes or DNA tested? Select all that apply.[4]		
	I was tested in a doctor's office or other medical setting	62.4
	I used an in-home test (for example: through 23andme, ancestry.com, or one purchased in a pharmacy)	49.3
	Other	2.8
If had DNA tested: Did you share the gene or DNA test result with any of the following people? Select all that apply.[4]		
	Family	85.5
	Friends	34.1
	Co-worker	10.5
	My doctor, nurse, physician's assistant, a nurse practitioner, or a pharmacist	30.7
	My alternative medicine provider(s) (for example: chiropractor, naturopath, massage therapist, or acupuncturist)	9.0
Would you support a $0.25 fee on all vaccines to fund vaccinomics research? The $0.25 fee would mostly be paid by the government and health insurance companies, who pay for most people's vaccines now. It is unlikely you would have to pay more for vaccines because of this fee.		
	No	16.4
	Yes	70.8
	Don't know	12.8

[1]Serious reaction: Unweighted n=71 "don't know" included with n=1,465 "no"; [2]unweighted n=389 had a serious vaccine reaction and were asked these items; [3]unweighted n=17 (weighted proportion: 0.9%) "prefer not to answer; [4]unweighted n=535 had a DNA test and were asked these items; multiple responses allowed; results may not sum to 100%; Taylor-linearized variance estimation for weighted survey data used. Unweighted N=1,925; Weighted N=1,927.87.

Table 3. The overall frequency and proportion of participants' responses to questions about the ethical and policy implications of vaccinomics

	Unweighted N (%)					Weighted %
	Strongly Disagree	Disagree	Agree	Strongly Agree	Strongly Agree or Agree	Strongly Agree or Agree
Vaccinomics (based on genes/DNA) would help me make informed decisions about vaccines FOR MYSELF.	47 (2.4)	113 (5.9)	983 (51.1)	782 (40.6)	1,765 (91.7)	91.4
Asked of parents only: Vaccinomics (based on genes/DNA) would help me make informed decisions about vaccines FOR MY CHILD.[1]	31 (2.5)	54 (4.4)	626 (50.5)	528 (42.6)	1,154 (93.1)	92.7
I am afraid that my gene or DNA test result could prevent me from getting a vaccine.[2]	530 (27.5)	971 (50.4)	296 (15.4)	128 (6.6)	424 (22.0)	22.0
I am afraid that using genes or DNA in vaccine decisions could increase race/ethnic discrimination.[2]	509 (26.4)	848 (44(.1)	395 (20.5)	173 (9.0)	568 (29.5)	29.0
I would have my genes or DNA tested if it would help my doctor or another healthcare provider know which vaccines are best for ME.[2]	132 (6.9)	316 (16.4)	814 (42.3)	663 (34.4)	1,477 (76.7)	76.8
I am concerned my HEALTH INSURANCE COMPANY would learn my gene or DNA test result.[2]	297 (15.4)	751 (39.0)	577 (30.0)	300 (15.6)	877 (45.6)	45.6
I am concerned the U.S. GOVERNMENT would learn my gene or DNA test result.[2]	290 (15.1)	721 (37.5)	632 (32.8)	282 (14.6)	914 (47.5)	47.0
I would be concerned about the security of my gene or DNA test result[2]	247 (12.8)	582 (30.2)	726 (37.7)	370 (19.2)	1,096 (56.9)	56.3
I would support vaccinomics even if it made vaccine schedules more complex.[2]	123 (6.4)	431 (22.4)	1,003(52.1)	368 (19.1)	1,371 (71.2)	71.2
Vaccinomics would make me have more confidence in vaccines than I do now. [2]	148 (7.7)	429 (22.3)	955 (49.6)	393 (20.4)	1,348 (70.0)	70.7
Vaccinomics is likely to help other people.[2]	102 (5.3)	238 (12.4)	992 (51.5)	593 (30.8)	1,585 (82.3)	82.6
Vaccinomics is likely to help me.[2]	121 (6.3)	341 (17.7)	964 (50.1)	499 (25.9)	1,463 (76.0)	75.8

[1]Asked of unweighted n=1,239 parents of children<18 only; [2]These items had a positively and negatively worded version. The scale of the negatively worded items was reversed and combined with its positively phrased counterpart for analysis. Taylor-linearized variance estimation for survey data used for all data. Unweighted N=1,925; Weighted N=1,927.87.

Table 4. The overall frequency and proportion of participants' responses to questions about vaccine prioritization, screening tests, and government spending to improve vaccine safety

	Unweighted N (%)					Weighted %
Hypothetical 1	**Strongly Disagree**	**Disagree**	**Agree**	**Strongly Agree**	**Strongly Agree or Agree**	**Strongly Agree or Agree**
If there was a short supply of vaccine, it would make sense for the people "more susceptible" to infection to get it first.[1]	168 (8.7)	328 (17.0)	855 (44.4)	574 (29.8)	1,429 (74.2)	74.5
If there was a short supply of vaccine, it would make sense for the “more contagious” people to get it first.[1]	145 (7.5)	332 (17.2)	844 (43.8)	604 (31.4)	1,448 (75.2)	75.7
It would bother me if my doctor identified me as “more contagious” or "more susceptible."[1]	329 (17.1)	793 (41.2)	570 (29.6)	233 (12.1)	803 (41.7)	41.3
Getting vaccinated should be an individual’s choice, even if they are “more contagious” or "more susceptible."[1]	223 (11.6)	491 (25.5)	795 (41.3)	416 (21.6)	1,211 (62.9)	63.0
Identifying people as “more contagious” or "more susceptible will hurt people.[1]	340 (17.7)	822 (42.7)	542 (28.2)	221 (11.5)	763 (39.6)	38.9
	Extremely Unlikely	**Unlikely**	**Likely**	**Extremely Likely**	**Extremely Likely or likely**	**Extremely likely or likely**
If your genes or DNA showed you to be “more contagious” or likely to get other people sick, how likely would you be to get vaccinated to PROTECT OTHER PEOPLE?[1]	261 (13.6)	581 (30.2)	584 (30.3)	499 (25.9)	1,083 (56.3)	56.2

Table 4. Continued	Unweighted N (%)					Weighted %
	I would be angry because I would want the vaccine	I would be okay with this decision	I would not care because I would not want the vaccine anyway	Other	n/a	I would be angry because I would want the vaccine
If you were told you were NOT going to be among the first groups vaccinated during an infectious disease outbreak because your genetics showed you were not "more contagious" or "more susceptible" to infection, how might you react?[1]	453 (23.5)	1,264 (65.7)	162 (8.4)	46 (2.4)	n/a	23.2
Hypothetical 2	**Strongly Disagree**	**Disagree**	**Agree**	**Strongly Agree**	**Strongly Agree or Agree**	**Strongly Agree or Agree**
Screening tests that warn who is at increased risk of paralysis and death from vaccines will be worthwhile if they help predict who will have an adverse reaction.[1]	207 (10.8)	481 (25.0)	762 (39.6)	475 (24.7)	1,237 (64.3)	64.7
The U.S. government should invest in making vaccines more effective instead of trying to reduce the risk of very serious and rare events, like paralysis and death after getting a vaccine.[1]	294 (15.3)	676 (35.1)	686 (35.6)	269 (14.0)	955 (49.6)	50.0
My confidence in vaccines would increase if the U.S. government spent more money studying how safe vaccines are now and telling the public the results.[1]	172 (8.9)	473 (24.6)	856 (44.5)	424 (22.0)	1,280 (66.5)	66.9

[1]These items had a positively and negatively worded version. The scale of the negatively worded items was reversed and combined with its positively phrased counterpart for analysis. Taylor-linearized variance estimation for survey data used for all data. Unweighted N=1,925; Weighted N=1,927.87.

Table 5. Among people who agree/strongly agree with hypothetical scenarios, the frequency and proportion of participants' concerns related to vaccine prioritization and screening: stratified by experience with a serious vaccine reaction, vaccine hesitancy, and trust in public health authorities

	Weighted %														
				Vaccine Hesitancy											
	Serious Vaccine Reaction[2]			Parents of Young Children			Parents of Teenagers			Other Adults			Trust in PHA		
Hypothetical 1	**No**	**Yes**	**P-value**	**Low**	**High**	**P-value**	**Low**	**High**	**P-value**	**Low**	**High**	**P-value**	**Low**	**High**	**P-value**
If there was a short supply of vaccine, it would make sense for the people "more susceptible" to infection to get it first.[1]	78.8	59.2	<0.01	71.7	66.2	0.11	77.4	66.2	0.01	82.1	75.6	0.03	63.4	84.1	<0.01
If there was a short supply of vaccine, it would make sense for the “more contagious” people to get it first.[1]	80.6	60.6	<0.01	71.2	72.9	0.62	80.3	69.1	<0.01	78.1	75.6	0.45	64.4	85.0	<0.01
It would bother me if my doctor identified me as “more contagious” or "more susceptible." [1]	38.3	50.8	<0.01	44.9	46.0	0.77	41.2	48.9	0.12	35.6	38.2	0.50	47.0	36.9	<0.01
Getting vaccinated should be an individual’s choice, even if they are “more contagious” or "more susceptible."[1]	60.3	73.9	<0.01	70.7	61.6	0.01	62.8	62.6	0.97	60.8	56.5	0.26	66.7	59.5	<0.01
Identifying people as “more contagious” or "more susceptible will hurt people.[1]	36.0	45.2	<0.01	42.4	43.0	0.88	37.5	46.0	0.08	31.4	44.3	<0.01	49.6	30.6	<0.01

Table 5 Continued	Serious Vaccine Reaction[2]			Parents of Young Children			Parents of Teenagers			Other Adults			Trust in PHA		
Hypothetical 1	**No**	**Yes**	**P-value**	**Low**	**High**	**P-value**	**Low**	**High**	**P-value**	**Low**	**High**	**P-value**	**Low**	**High**	**P-value**
If your genes or DNA showed you to be "more contagious" or likely to get other people sick, how likely would you be to get vaccinated to PROTECT OTHER PEOPLE?[1]	57.7	50.1	0.03	53.5	55.8	0.54	59.0	54.7	0.37	62.7	47.3	<0.01	52.8	59.4	<0.01
Hypothetical 2															
Screening tests that warn who is at increased risk of paralysis and death from vaccines will be worthwhile if they help predict who will have an adverse reaction.[1]	67.6	56.6	<0.01	65.7	59.5	0.09	66.2	59.7	0.17	67.5	62.6	0.19	57.3	70.6	<0.01
The U.S. government should invest in making vaccines more effective instead of trying to reduce the risk of very serious and rare events, like paralysis and death after getting a vaccine.[1]	50.4	49.5	<0.56	52.3	50.6	0.67	48.4	48.2	0.97	49.1	47.7	0.73	49.7	49.5	0.92

Table 5 Continued	Serious Vaccine Reaction[2,6]			Parents of Young Children[3]			Parents of Teenagers[4]			Other Adults[5]			Trust in PHA[6]		
Hypothetical 2	**No**	**Yes**	**P-value**	**Low**	**High**	**P-value**	**Low**	**High**	**P-value**	**Low**	**High**	**P-value**	**Low**	**High**	**P-value**
My confidence in vaccines would increase if the U.S. government spent more money studying how safe vaccines are now and telling the public the results.[1]	70.0	57.7	<0.01	67.2	61	0.08	68.6	57.6	0.02	75.0	60.3	<0.01	57.8	74.4	<0.01
If you were told you were NOT going to be among the first groups vaccinated during an infectious disease outbreak because your genetics showed you were not "more contagious" or "more susceptible" to infection, how might you react? Please check all that apply.[1]															
I would be angry because I would want the vaccine.	20.8	34.4	<0.01	26.8	29.9	0.35	27.4	21.6	0.18	20.3	11.5	<0.01	28.3	19.2	<0.01

[1]These items had a positively and negatively worded version. The scale of the negatively worded items was reversed and combined with its positively phrased counterpart for analysis. [2]Serious Reactions: unweighted n=71 "don't know" responses combined with n=1,465 "no" for analysis; [3]Parents of Young Children: unweighted n=724; weighted n=706; [4]Parents of Teenagers: unweighted n=515, weighted n=507; [5]Other adults: weighted n=686, unweighted n=706, includes unweighted n=2 "prefer not to answer" parent status" and unweighted n=12 "prefer not answer" child's age; Taylor-linearized variance estimation for weighted survey data used; p-values estimated using two-sided general tests of association. [6]Unweighted N=1,925; Weighted N=1,927.87.

Table 6. Among people who agree/strongly agree with hypothetical scenarios, the frequency and proportion of participants' concerns about the ethical and policy implications of vaccinomics: stratified by sociodemographic characteristics

	Weighted %															
	Parent Status[2]			Highest level of Education[3]				Household Annual Income[4]					Respondent's Age (years)[5]			
	Child ≤18 years old	No/prefer not to ans.	P-value	≤High school deg.	≤College degree	Graduate degree	P-Value	≤$49,999	$50,000-$99,999	$100,000-$149,999	≥$150,000	P-value	18-44	35-54	≥55	P-Value
Vaccinomics (based on genes/DNA) would help me make informed decisions about vaccines FOR MYSELF.[1]	92.0	90.4	0.22	89.3	93.4	95.4	<0.01	89.4	92.8	92.3	96.8	<0.01	88.2	93.0	93.4	<0.01
Asked of parents only: Vaccinomics (based on genes/DNA) would help me make informed decisions about vaccines FOR MY CHILD.[1]	92.7	n/a	n/a	89.9	93.9	96.7	<0.01	89.9	94.1	93.7	97.6	<0.01	90.7	93.1	96.2	0.05
I am afraid that I might not be able to get a vaccine because of my genes or DNA.[1]	22.4	21.3	0.60	22.4	18.7	28.1	<0.01	20.5	20.2	23.5	26.0	0.19	27.6	21.8	15.6	<0.01
I am afraid that using genes or DNA in vaccine decisions could increase race/ethnic discrimination.[1]	29.6	28.1	0.51	28.7	27.2	33.4	0.17	28.9	28.9	29.6	28.1	0.99	32.4	30.0	24.2	<0.01

Table 6 Continued	Child ≤18 years old	No/prefer not to ans.	P-value	≤High school deg.	≤College degree	Graduate degree	P-value	≤$49,999	$50,000-$99,999	$100,000-$149,999	≥$150,000	P-value	18-44	35-54	≥55	P-value
Screening tests that warn who is at increased risk of paralysis and death from vaccines will be worthwhile if they help predict who will have an adverse reaction.[1]	64.0	65.7	0.47	63.4	68.7	59.8	0.02	64.9	61.8	70.8	64.9	0.14	60.5	63.9	70.3	<0.01
The U.S. government should invest in making vaccines more effective instead of trying to reduce the risk of very serious and rare events, like paralysis and death after getting a vaccine.[1]	50.3	49.4	0.69	49.4	49.7	51.1	0.89	50.4	46.9	54.1	52.3	0.27	49.8	51.8	48.3	0.48
I would have my genes or DNA tested if it would help my doctor or another healthcare provider know which vaccines are best for ME.[1]	76.5	77.3	0.67	73.7	79.6	82.7	<0.01	75.0	79.5	76.3	78.3	0.27	71.5	74.5	85.7	<0.01
I would support vaccinomics even if it made vaccine schedules more complex.[1]	71.0	71.0	0.98	70.5	72.1	72.8	0.69	70.3	72.8	68.1	75.2	0.26	69.0	70.4	74.5	0.09
Vaccinomics would make me have more confidence in vaccines than I do now.[1]	71.2	71.2	0.56	65.7	74.7	78.7	<0.01	67.7	70.9	70.8	80.7	<0.01	66.8	72.3	73.7	0.02
Vaccinomics is likely to help other people.[1]	82.1	83.6	0.42	81.1	84.2	84.4	0.21	81.2	85.1	81.4	84.7	0.23	75.4	83.1	90.5	<0.01
Vaccinomics is likely to help me.[1]	78.0	72.1	<0.01	71.5	79.7	80.7	<0.01	76.2	71.4	83.1	78.1	<0.01	70.1	77.7	80.4	<0.01

[1]These items had a positively and negatively worded version. The scale of the negatively worded items was reversed and combined with its positively phrased counterpart for analysis [2]parent status: no/prefer not to answer includes n=2 "prefer not to answer; [3]education: n=3 "prefer not to answer," ≤college includes some college, Associate's or Bachelor's Degree; [4]income: n=4 "prefer not to answer"; [5]age: n=4 "prefer not to answer." Taylor-linearized variance estimation for survey data used for all data; p-values estimated using two-sided general tests of association. Unweighted N=1,925; Weighted N=1,927.87.

Table 7. Among people who agree/strongly agree with hypothetical scenarios, the frequency and proportion of participants' concerns about the ethical and policy implications of vaccinomics: stratified by experience with a serious vaccine reaction, vaccine hesitancy, and trust in public health authorities

	Weighted %														
				Vaccine Hesitancy											
	Serious vaccine reaction[2]			Parents of young children			Parents of teenagers			Other adults			Trust in PHA		
	No	Yes	P-value	Low	High	P-value	Low	High	P-value	Low	High	P-value	Low	High	P-value
Vaccinomics (based on genes/DNA) would help me make informed decisions about vaccines FOR MYSELF.	91.9	92.2	<0.01	95.2	86.9	<0.01	97.6	83.5	<0.01	96.2	80.9	<0.01	85.8	97.0	<0.01
Asked of parents only: Vaccinomics (based on genes/DNA) would help me make informed decisions about vaccines FOR MY CHILD.	92.3	95.0	0.04	96.7	87.5	<0.01	97.7	83.2	N/A	<0.01	N/A	N/A	89.4	96.7	<0.01
I am afraid that I might not be able to get a vaccine because of my genes or DNA.[1]	18.3	34.3	<0.01	23.0	22.9	0.97	19.4	27.3	0.05	18.9	25.6	0.04	31.0	13.9	<0.01
I am afraid that using genes or DNA in vaccine decisions could increase race/ethnic discrimination.[1]	25.1	43.0	<0.01	31.8	32.0	0.96	26.6	31.7	0.26	26.7	30.5	0.27	39.1	20.8	<0.01
Screening tests that warn who is at increased risk of paralysis and death from vaccines will be worthwhile if they help predict who will have an adverse reaction.[1]	67.6	56.6	<0.01	65.7	59.5	0.09	66.2	59.7	0.17	67.5	62.6	0.19	57.3	70.6	<0.01

Table 7. Continued	Serious vaccine reaction[2,6]			Parents of young children[3]			Parents of teenagers[4]			Other adults[5]			Trust in PHA[6]		
	No	Yes	P-value	Low	High	P-value	Low	High	P-value	Low	High	P-value	Low	High	P-value
Vaccinomics is likely to help me.[1]	79.6	64.4	<0.01	79.5	72.6	0.03	83.2	71.9	<0.01	79.5	61.1	<0.01	61.6	89.0	<0.01
Vaccinomics would make me have more confidence in vaccines than I do now.[1]	73.9	62.3	<0.01	71.2	65.2	0.09	77.1	61.9	<0.01	75.0	60.3	<0.01	56.5	82.3	<0.01
Vaccinomics is likely to help other people.[1]	86.0	72.3	<0.01	81.6	77.1	0.14	91.0	69.1	<0.01	87.3	76.7	<0.01	69.7	93.8	<0.01
The U.S. government should invest in making vaccines more effective instead of trying to reduce the risk of very serious and rare events, like paralysis and death after getting a vaccine.[1]	50.4	49.5	0.56	52.3	50.6	0.66	48.4	48.2	0.97	49.1	47.7	0.73	49.7	49.5	0.92
My confidence in vaccines would increase if the U.S. government spent more money studying how safe vaccines are now and telling the public the results.[1]	70.0	57.7	<0.01	67.2	61.0	0.08	68.6	57.6	0.02	75.0	60.3	<0.01	57.8	74.4	<0.01
I would have my genes or DNA tested if it would help my doctor or another healthcare provider know which vaccines are best for ME.[1]	80.4	64.5	<0.01	79.8	71.6	0.01	82.2	62.6	<0.01	83.7	66.8	<0.01	63.3	88.9	<0.01
I would support vaccinomics even if it made vaccine schedules more complex.[1]	75.2	59.7	<0.01	72.2	67.7	0.18	76.1	64.0	<0.01	77.1	61.5	<0.01	57.0	84.1	<0.01

[1]These items had a positively and negatively worded version. The scale of the negatively worded items was reversed and combined with its positively phrased counterpart for analysis. [2]Serious Reactions: unweighted n=71 "don't know" responses combined with n=1,465 "no" for analysis; [3]Parents of Young Children: unweighted n=724; weighted n=706; [4]Parents of Teenagers: unweighted n=515, weighted n=507; [5]Other adults: weighted n=686, unweighted n=706, includes unweighted n=2 "prefer not to answer" parent status" and unweighted n=12 "prefer not answer" child's age; Taylor-linearized variance estimation for weighted survey data used; p-values estimated using two-sided general tests of association. [6]Unweighted N=1,925; Weighted N=1,927.87.

Table 8. The overall frequency and proportion of how respondents prefer the U.S. government prioritize funding and implement vaccinomics

	Weighted %		
If you were making decisions about how the U.S. government spends money, would vaccinomics get more, an equal amount or less money than:	**More**	**Equal**	**Less**
Breast and prostate cancer research and development	37.3	49.1	13.6
Diabetes research and development	34.2	53.4	12.4
Heart disease research and development	38.2	47.9	13.8
If you were making decisions about how the U.S. government spends money, would vaccinomics get more, an equal amount or less money than:			
Studies about safety and effectiveness of current vaccines	39.0	55.4	5.5
Buying vaccines for U.S. children whose families cannot afford them	42.5	48.4	9.1
Supporting the use of vaccines for children in poor countries	39.7	48.6	11.7
If vaccinomics could make personalized vaccine recommendations available in the next 15 years, how should this information be used for CHILDREN? [1]			**Yes**
To make vaccines safer and more effective for all children			78.6
To identify children most likely to have serious and dangerous reactions to vaccines			61.0
To identify children most likely to be more contagious			54.0
To identify children most likely to be more susceptible			50.6
Genes or DNA should NOT be used to make decisions about vaccines for children			14.3
None of the above			4.4
If vaccinomics could make personalized vaccine recommendations available in the next 15 years, how should it be used for ADULTS? [1]			
To make vaccines safer and more effective for all adults			72.1
To identify adults most likely to have serious and dangerous reactions to vaccines			61.7
To identify adults most likely to be more contagious			54.3
To identify adults most likely to be more susceptible			50.1
Genes should NOT be used to make decisions about vaccines for adults			13.7
None of the above			4.5

[1]Multiple responses allowed; percentages may not sum to 100%; Taylor-linearized variance estimation for weighted survey data used. Unweighted N=1,925; Weighted N=1,927.87.

Table 9. Bivariable analysis of factors that may be associated with opposition to vaccinomics and prioritization: expecting to feel angry if not prioritized for vaccination and strongly agreeing/agreeing that vaccination is an individual's choice

	Bivariable Analyses			
	Expecting to Feel Angry		Individual's Choice	
	PR (95% CI)[9]	P-value	PR (95% CI)[9]	P-value
Experience with a serious vaccine reaction[1]				
No/Don't know	Ref		Ref	
Yes	1.68 (1.41, 2.00)	<0.01	1.23 (1.14, 1.32)	<0.01
Education[2]				
≤High school degree	Ref		Ref	
≤College degree	0.94 (0.78, 3.17)	0.51	0.95 (0.88, 1.03)	0.23
Graduate degree	1.41(1.14, 1.76)	<0.01	1.15 (1.05, 1.26)	<0.01
Parents of children <18 years old				
No/Prefer not to answer	Ref		Ref	
Yes	1.59 (1.31, 1.93	<0.01	1.10 (1.02, 1.18)	0.02
Age (years)[3]				
18-34	Ref		Ref	
35-54	2.46 (1.91, 3.17)	<0.01	1.09 (0.99, 1.19)	0.07
≥55	2.14 (1.65, 2.78)	<0.01	1.13 (1.03, 1.23)	<0.01
Vaccine hesitancy among parents of young children[4]				
Low	Ref		Ref	
High	1.08 (0.85, 1.37)	0.53	0.86 (0.77, 0.97)	0.01
Vaccine hesitancy: parents of teenagers[5]				
Low	Ref		Ref	
High	0.81 (0.56, 1.17)	0.25	1.01 (0.87, 1.17)	0.92
Vaccine hesitancy: adults without minor children[6]				
Low	Ref		Ref	
High	0.58 (0.39, 0.86)	<0.01	0.94 (0.82, 1.07)	0.33

Table 9, Continued	Bivariable Analyses			
	Expecting to Feel Angry		Individual's Choice	
	PR (95% CI)[9]	P-value	PR (95% CI)[9]	P-value
Household annual income[7]				
≤$49.999	Ref		Ref	
$50,000-$99,999	1.18 (0.96, 1.46)	0.12	1.06 (0.97, 1.16)	0.19
$100,000-$149,999	1.22 (0.94, 1.60)	0.14	1.10 (0.98, 1.23)	0.09
≥$150,000	1.58 (1.27, 1.97)	<0.01	1.15 (1.05, 1.27)	<0.01
Trust in public health authorities				
Low	Ref		Ref	
High	0.70 (0.50, 0.99)	0.04	0.89 (0.83, 0.96)	<0.01
Region[8]				
Midwest	Ref		Ref	
Northeast	1.38 (1.07, 1.78)	0.01	1.09 (0.98, 1.21)	0.10
South	1.25 (0.98, 1.60)	0.08	1.10 (0.99, 1.21)	0.08
West	1.32 (1.00, 1.73)	0.05	1.12 (1.00, 1.25)	0.05
Race/ethnicity				
White, non-Hispanic	Ref		Ref	
Black, non-Hispanic	1.48 (1.18, 1.87)	<0.01	0.98 (0.88, 1.10)	0.79
Other	1.24 (1.03, 1.49)	0.02	1.00 (0.92, 1.08)	0.99

[1]n=71 "don't know" responses combined with 1,465 "no" for analysis; [2]Education: unweighted n=27 missing; ≤college includes some college, Associate's or Bachelor's Degree; [3]Age: unweighted n=27 4 missing; [4]Parents of young children: unweighted n=724, Weighted N= 705.73; 5Parents of teenagers: unweighted n=515, weighted n= 507.03; [6]Adults without minor children: unweighted n= 686, weighted n=715.12; [7]Household annual income: unweighted n=36 missing; [8]Region: unweighted n=3 missing; [9]Prevalence Ratios (PR) and 95% Confidence Interval (95% CI) estimated using log binomial regression for survey data. Taylor-linearized variance estimation used. Taylor-linearized variance estimation used; p-values estimated using general tests of association. Unweighted N=1,925; Weighted N=1,927.87.

Table 10. Multivariable associations between expected opposition to vaccinomics and prioritization: expecting to feel angry if not prioritized for vaccination and strongly agreeing/agreeing that vaccination is an individual's choice

	Multivariable Analyses: Parsimonious Models			
	Expecting to Feel Angry[3]		Individual's Choice	
	aPR (95% CI)	P-value	aPR (95% CI)	P-value
Experience with a serious vaccine reaction[1]				
No/Don't know	Ref		Ref	
Yes	1.84 (1.25, 2.70)	<0.01	1.16 (1.07, 1.25)	<0.01
Trust in public health authorities				
Low	Ref		Ref	
High	0.67 (0.47, 0.96)	0.02	0.91 (0.84, 0.98)	0.01
Vaccine hesitancy among other adults				
Low	Ref			
High	0.49 (0.32, 0.73)	<0.01	N/A	
Education[2]				
≤High school			Ref	
≤College	N/A		0.93 (0.86, 1.01)	0.09
Graduate degree	N/A		1.11 (1.01, 1.21)	0.04
Parents of children <18 years old				
No/Prefer not to answer			Ref	
Yes	N/A		1.09 (1.01, 1.17)	0.04

[1]n=71 "don't know" responses combined with 1,465 "no" for analysis; [2]Education: unweighted n=27 missing; ≤college includes some college, Associate's or Bachelor's Degree; [3]Expecting to feel angry: education and parent status excluded due to p<0.05 in saturated multivariable analysis (see Appendix). Unweighted N=686 adults without minor children included; Weighted N=715.12; [4]Individual choice: Vaccine hesitancy among other adults excluded due to p>0.05 in univariate analysis (Table 9). Adjusted Prevalence Ratios (aPR) and 95% Confidence Interval (95% CI) estimated using log binomial regression for survey data and the difficult option to facilitate model convergence. Taylor-linearized variance estimation used; p-values estimated using general tests of association. Unweighted N=1,925; Weighted N=1,927.87.

6.8 Appendix for Chapter 6

Table 11. The frequency and proportion of participants' concerns related to vaccine prioritization and screening: stratified by sociodemographic factors

	Weighted %															
	Parent Status[2]			Education[3]				Household Annual Income[4]					Age (years)[5]			
Hypothetical 1	**Child ≤18 Years old**	**No/Not answered**	**P-values**	**≤High School**	**≤College**	**Graduate Degree**	**P-value**	**≤$49,999**	**$50,000-$99,999**	**$100,000-$149,999**	**≥$150,000**	**P-value**	**18-44**	**35-54**	**≥55**	**P-value**
If there was a short supply of vaccine, it would make sense for the people "more susceptible" to infection to get it first.[1]	71.3	79.9	<0.01	72.4	79.5	68.6	<0.01	73.3	77.5	78.1	70.3	0.07	64.9	74.2	86.7	<0.01
If there was a short supply of vaccine, it would make sense for the “more contagious” people to get it first.[1]	74.6	77.5	0.16	73.4	79.8	72.8	<0.01	74.4	76.8	78.9	74.9	0.49	67.3	74.8	86.7	<0.01
It would bother me if my doctor identified me as “more contagious” or "more susceptible."[1]	44.2	36.5	<0.01	42.9	36.6	47.5	<0.01	43.1	39.4	38.5	42.1	0.44	46.1	44.9	31.4	<0.01
Getting vaccinated should be an individual’s choice, even if they are “more contagious” or "more susceptible."[1]	65.1	59.4	0.02	62.9	59.9	72.2	<0.01	60.0	63.6	65.9	69.1	0.04	63.8	66.1	58.6	0.03
Identifying people as “more contagious” or "more susceptible will hurt people.[1]	40.6	36.0	0.05	41.1	34.8	43.0	0.01	39.3	37.9	39.6	38.6	0.96	44.4	41.3	30.0	<0.01

Table 11, Continued	Parent Status			Education[2]				Household Annual Income[3]					Age (years)[4]			
Hypothetical 1	**Child ≤18 Years old**	**No/Not answered**	**P-values**	**≤High School**	**≤College**	**Graduate Degree**	**P-value**	**≤$49,999**	**$50,000-$99,999**	**$100,000-$149,999**	**≥$150,000**	**P-value**	**18-44**	**35-54**	**≥55**	**P-value**
If your genes or DNA showed you to be "more contagious" or likely to get other people sick, how likely would you be to get vaccinated to PROTECT OTHER PEOPLE? [1]	55.7	57.0	0.58	54.3	56.2	60.3	0.23	55.2	55.6	55.5	59.4	0.67	56.3	57.6	54.3	0.52
Hypothetical 2																
Screening tests that warn who is at increased risk of paralysis and death from vaccines will be worthwhile if they help predict who will have an adverse reaction.[1]	64.0	65.7	0.47	63.4	68.7	59.8	0.02	64.9	61.8	70.8	64.9	0.14	60.5	63.9	70.3	<0.01
The U.S. government should invest in making vaccines more effective instead of trying to reduce the risk of very serious and rare events, like paralysis and death after getting a vaccine.[1]	50.3	49.4	0.69	49.4	49.7	51.1	0.89	50.4	46.9	54.1	52.3	0.27	50.2	48.2	51.7	0.48

Table 11, Continued	Parent Status[1]			Education[2]				Household Annual Income[3]					Age (years)			
	Child ≤18 Years old	No/Not answered	P-values	≤High School	≤College	Graduate Degree	P-value	≤$49,999	$50,000-$99,999	$100,000-$149,999	≥$150,000	P-value	18-44	35-54	≥55	P-value
My confidence in vaccines would increase if the U.S. government spent more money studying how safe vaccines are now and telling the public the results.[4]	65.3	69.6	0.06	66.3	69.6	61.9	0.07	68.5	65.3	68.6	64.1	0.42	65.3	64.9	71.1	0.41
If you were told you were NOT going to be among the first groups vaccinated during an infectious disease outbreak because your genetics showed you were not "more contagious" or "more susceptible" to infection, how might you react? Please check all that apply.[1]																
I would be angry because I would want the vaccine.	26.9	16.9	<0.01	23.3	21.0	31.5	<0.01	19.9	23.5	24.4	31.4	<0.01	29.9	26.0	12.1	<0.01

[1]These items had a positively and negatively worded version. The scale of the negatively worded items was reversed and combined with its positively phrased counterpart for analysis [2]parent status: no/prefer not to answer includes n=2 "prefer not to answer; [3]education: n=3 "prefer not to answer, "≤college includes some college, Associates or Bachelor's Degree ; [4]income: n=4 "prefer not to answer"; [5]age: n=4 "prefer not to answer." Taylor-linearized variance estimation for survey data used for all data; p-values estimated using two-sided general tests of association. Unweighted N=1,925; Weighted N=1,927.87

Table 12. Comparison of Vaccinomics National Survey Population to NHANES

Below are the population values for a few NHANES items, used to compare the occurrence of health behaviors in our sample vs. the US overall. However, NHANES consists of a phone interview & in person exam, and is weighted based on probability of selection and nonresponse, which we could not do. Both NHANES and our sample are weighted to the Census.

	Vaccinomics National Survey			NHANES
	Unweighted Analysis		Weighted Analysis	Weighted Analysis
Sociodemographic Factors	**N=1,925**	**%**	**%**	**%**
Would you say your health in general is…?[1]				
Very good	553	28.7	28.0	33.4
Good	1,140	59.2	59.5	39.7
Poor	203	10.5	11.0	16.9
Don't know	29	1.5	1.5	0
IN THE PAST 12 MONTHS, I worried whether the food in my home would run out before getting money to buy more[1]				
Often true	362	18.8	19.0	8.7
Sometimes true	650	33.8	33.3	17.8
Never true	913	47.4	47.8	73.3
Do you consider yourself now to be…?[1]				
Fat or overweight	721	37.4	37.4	52.3
Too thin	165	8.6	8.4	4.9
About the right weight	987	51.3	51.4	42.6
Don't know	52	2.7	2.8	0.2
Have you smoked at least 100 cigarettes in your entire life?[1]				
No	931	48.4	48.5	57.1
Yes	961	49.9	49.9	42.8
Don't know	33	1.7	1.6	0.1

[1]Adapted from NHANES 2015-2016 questionnaire.

Chapter 7. Discussion

7.1 Summary of Results

Understanding barriers to influenza coverage could help inform vaccinomics implementation.(3, 14-17) Our findings could help improve influenza vaccine and vaccinomics-related confidence and participation. Now that healthcare systems are overburdened by COVID-19, using influenza vaccines to minimize hospitalizations is especially important.(193) Vaccine hesitancy is common, especially for influenza vaccines.(7, 8, 73, 125, 141, 144, 151-153, 157, 194) Vaccinomics has the potential to improve influenza vaccine development and use.(3, 23) We conducted community meetings to understand public values around current vaccines and vaccinomics. Emergent themes included genetically-based vaccine prioritization, personalization of vaccine schedules, agency, and stigma/discrimination. Participants supported funding for vaccinomics compared to federal vaccine and chronic disease priorities. Next, we investigated variability in emergent themes using a panel survey, demographically representative of the U.S. We measured vaccinomics support, vaccine hesitancy, and potential associations with influenza vaccination. Most respondents had ≥1 vaccine concern, and influenza vaccination was higher among those who used complementary/alternative medicine (CAM) and had some college education or higher. High vaccine hesitancy was associated with lower vaccination prevalence compared to low hesitancy, among most respondents. There was no indication vaccine confidence altered from the beginning to the end of the community meetings or survey.

Influenza vaccines are often misperceived as new and untested, and many parents worry the vaccine could make them ill, in addition to general vaccine safety concerns, such as pain at the injection site.(6, 9-12, 72, 94, 152, 194-196) Vaccine hesitant populations might fear vaccinomics as being new and untested as well. Alternatively, vaccinomics might assuage hesitant population's concerns through increased personalization. Immunologic data indicates

there are sex differences in immune response to influenza vaccination, which could influence vaccine safety.(22-24) Vaccinomics could play a role in improving influenza vaccines through the development of novel vaccine candidates, adjuvants, and personalized vaccine schedules.(17, 27) For these reasons, influenza vaccines are a prime target for vaccinomics and were the focus here.(23)

We held a stakeholder meeting in 2017 to discuss what kinds of information we could collect that would be useful to decision-makers. In 2018 we held community meetings to characterize public values around key themes raised by stakeholders: privacy of genetic test results, vaccine prioritization, personalization of vaccine schedules, stigmatization/discrimination of vulnerable populations, and agency in vaccine decision-making. These findings informed an online panel survey, where we found broad support for vaccinomics.

Community meeting and survey participants supported vaccinomics in general, especially its potential to improve vaccine safety and effectiveness. Vaccine confidence was unaltered by discussing vaccinomics and adverse events following immunization in-person or asking about these issues in the survey. Despite this, vaccine concerns were common. College and graduate education were associated with higher vaccination prevalence compared to high school. These findings are congruent with some national estimates,(25, 152) but not others, as we did not find an association between race/ethnicity and vaccination in multivariable models.(194) Five findings were surprising:

1) >50% of parents with young children reported children receive too many vaccines.
2) Vaccine hesitancy was unassociated with influenza vaccination among parents of young children.
3) Nearly 20% of survey respondents perceived experiencing serious vaccine reactions, or knowing someone who had.

4) Use of complementary/alternative medicine was associated with higher vaccination, compared to nonuse.
5) Vaccinomics support was associated with a lack of serious vaccine reaction experience and low vaccine hesitancy.

Understanding these associations may inform efforts to improve influenza vaccination coverage and vaccinomics implementation.

Most survey respondents indicated they had ≥1 vaccine concerns, comparable to a study that reported 77% of parents of children aged ≤6 years old had at least one concern.(4) A higher proportion of respondents in this study indicated children receive too many vaccines. We used different wording and included parents of slightly older children than the prior study. They conducted a mailed panel survey in 2011 and we conducted an online panel survey in 2020.(4) National-level vaccine hesitancy data have not been published in the peer-reviewed literature since 2011. In a 2019 Gallup poll, 84% parents indicated childhood vaccination was important, the same proportion as in 2015 (84%), but 10% lower than agreed with this statement in 2001 (94%).(6) It is unclear whether the observed differences between our study and the 2011 survey are due to changes over time, selection bias, or measurement methods.

Vaccine hesitancy is a known predictor of vaccine refusal and delay,(7, 8, 94, 125) and was associated with a lower prevalence of influenza vaccination among parents of teenagers and adults without minor children. Although >50% of parents of young children reported children receive too many vaccines, the dichotomized hesitancy variable was not associated with vaccination prevalence. This may be due to how we measured vaccine hesitancy or selection bias. We used a greater number of items adapted from the PACV and PACV Short Scale (n=9) than were adapted from the Vaccine Confidence Scale for parents of teenagers (n=6) and adults without minor children (n=5).(137, 138, 140) If additional items did not increase

sensitivity, their inclusion could have inflated the denominator (total potential score) compared to the numerator (individual's earned score), which was the basis of classifying people as having "low" or "high" hesitancy. This may have introduced unnecessary variance and information bias into our estimates. Use of an online panel survey may also have led to selection bias, which could have been greater for parents of young children compared to other groups. Recruiting parents of young children took longer than for other groups, indicating respondents may have differed from nonrespondents in meaningful ways.

Formative research suggested those who had vaccine safety concerns and experience with adverse events following immunization (AEFI) were especially interested in vaccinomics potential to personalize vaccine schedules. In the survey, the opposite was true: those who did not think they had serious vaccine reactions were more supportive of vaccinomics. However, there was broad support for vaccinomics among respondents, including those who reported experience with serious adverse reactions. Vaccine hesitancy falls along a continuum,(4, 7, 8) and our in-person observation may have been based on people having some vaccine concerns, but not having "high" vaccine hesitancy as quantified among survey respondents. It was surprising how many survey respondents thought they had experienced, or knew someone who experienced, a serious vaccine reaction. Funding for tailored, culturally-appropriate patient education about common, nonserious vaccine reactions, in addition to influenza vaccines in general, may help dispel misperceptions and improve vaccine coverage. Though standardized, mass messaging has shown limited success in increasing influenza vaccination rates,(197, 198) individualized messaging through apps is under study.(199, 200)

7.2 Strengths and Limitations

Social desirability bias is common in focus groups and surveys,(165, 184) though we tried to mitigate this by using a standardized facilitator's guide and asking open-ended questions

in the formative study. In the survey, we randomized participants to receive positively or negatively phrased items and used neutral language to try to minimize bias. A double opt-in process was used for survey enrollment to reduce the risk of multiple responses per person; however, panelists must volunteer for the panel before being invited to respond.(133) This makes the survey results subject to selection bias. Furthermore, selection bias may have resulted in survey respondents having a greater interest in vaccines and genomics than is average.

Quotas were used to enroll a sample demographically representative of the U.S. Weighted data were similar to the U.S. Census and NHANES, despite differences in data collection and weighting procedures.(134, 155) Data were collected at one point in time and are subject to social desirability and selection bias as all data were self-reported. The degree to which vaccine hesitancy estimates may be biased is unknown, as the most recent estimates were published in 2011.(4) These are the first national estimates of vaccinomics support. Vaccine hesitancy is disparately measured across studies.(4-6, 137, 138, 140, 153, 157, 201-203) Our vaccine hesitancy items were adapted from previously validated scales, which should minimize information bias in this construct.(137, 138, 140)

It is unlikely that participants heard of vaccinomics before joining this study, though this was unmeasured. Though we attempted to introduce vaccinomics with neutral language, our excitement for this topic may have swayed in-person participants and come across in the 4-minute-long animation used during in-person meetings and in the survey. Respondents may be biased by our behaviors.

Community meeting data collection methods prevented data from being analyzed by discussion group or sociodemographic characteristics. Additionally, an error in recording

prevented one discussion group from being analyzed. Nondifferential misclassification of funding priorities data may have resulted from participant confusion.

7.3 *Public Health Implications*

If we can improve childhood and adult influenza vaccine uptake, this has the potential to drastically reduce hospitalizations(148) and save billions of dollars,(204) which is especially needed now that healthcare systems are overburdened by COVID-19.(193) This may be possible through personalized educational interventions and vaccinomics. We identified influenza vaccine attitudes and beliefs that do not favor vaccination and subpopulations that can be targeted. Having a high school education or lower and being a CAM nonuser, were associated with lower vaccination prevalence. Younger adults have more negative vaccine attitudes and beliefs than older adults.(152) Education-level appropriate, individualized communications should target adults with high school education or lower and young age.(152) CAM nonusers had lower vaccine prevalence, and are likely to be racial/ethnic minorities and have lower socioeconomic status than CAM users.(158) How to reach these populations and what kinds of information will resonate with them, remains to be determined.

Vaccine stakeholders should use the community meeting and survey results to inform vaccinomics-related policies, with the goal of encouraging vaccinomics participation. We will share our results with vaccine stakeholders in 2020. Vaccinomics' skeptics need to be assured vaccinomics will not remove their agency to make vaccine-related decisions. Genetic nondiscrimination legislation positively influenced genetic testing uptake in Europe.(180) Efforts to make the U.S. residents aware of the Genetic Information Nondiscrimination Act(101) may increase participation in vaccinomics and genomics is general. Discrimination was a prevalent concern in community meetings, but less so in the survey. Those promoting genetic testing and biobank participation should describe the role of Institutional Review Boards and other

independent, ethical oversight to prospective participants, as most survey respondents said this kind of oversight increased the likelihood they would participate in biobanks.

Vaccine safety is widely mistrusted, and could be improved through vaccinomics.(3) Increasing awareness of vaccine safety resources (Vaccine Safety Datalink, Vaccine Adverse Events Reporting System, and Vaccine Injury Compensation Program) may improve confidence now. Survey respondents indicated they would have higher confidence if the government studied vaccine safety and shared the results with the public. Increased awareness of these programs might improve the public's confidence in vaccine safety.

7.4 Overall Conclusions

Public health authorities should explore partnerships with CAM providers to improve vaccine attitudes, beliefs and coverage, and research how to reach disadvantaged populations. Future research should further explore drivers of influenza vaccination decision-making,(205) as increasing influenza vaccination could have widespread public health benefits. Federal funding and policies aimed at improving trust in public health authorities, incorporating public values, and addressing sociodemographic disparities in vaccine coverage are needed. Federal funding and policies that raise awareness of federal vaccine safety oversight programs may improve vaccine confidence, and policies that engender trust in public health authorities may improve vaccinomics support.

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Chapter 9. Appendices

9.1 Appendix 1: Facilitator and Recorder's Guide

Small Group: Hypotheticals questions, Spectrum question, and Priorities exercise

Time scheduled: 60 minutes total (30 minutes for Hypotheticals, 10 minutes for Spectrum, 20 minutes for Priorities)

Date: **Facilitator name:**

Recorder name:

Guidance for Facilitators & Recorders: Use paint chips to poll participants. Instruct participants to face paint chips towards recorder.

	Break Out Group	
	Males	**Females**
Total Participants		
With kids 0-11 (red)		
With kids 11-18 (yellow)		
With kids >18 (green)		

Guidance for Facilitators & Recorders:

- *These discussions will follow the explanatory animation video and Q&A.*
- *We will break into groups and have facilitated discussions.*
- *There will be a facilitator and a recorder for each break-out group.*
- *The facilitators will guide the discussion based on the interests of the group (as long as it's ELSI-relevant), it isn't necessary (or expected) that we get to all the questions below. The organizers believe it more important to follow interesting conversation threads and*

then ask additional prompts and follow-up questions, all building off of participant comments.

- *You do not need to record participant names. However, if it is pertinent that they are a parent or of a certain age, etc., you can indicate this.*

FACILITATOR & RECORDER OVERVIEW – HYPOTHETICAL 1 (approximately 15 minutes)

Hypothetical 1: ***Facilitators to review the Hypothetical with the Group (use handouts)***

- **Imagine this winter there's a disease outbreak that is spreading easily and quickly.**
- **The disease has serious consequences in that it makes people very sick and they could die.**
- **There is a vaccine for it, but there is a limited supply initially, so we need to decide who gets the vaccine first and who needs to wait a bit to get it.**
- **Vaccinomics will let you prioritize giving the vaccine to "super spreaders" and those most at risk for serious consequences first.**

Hypothetical 1 PROMPTS:

Facilitators: After asking PROMPT 1 below, feel free to follow the group's interests. Prompts 2-8 are optional.

1. **What do you care about (worried about, comforted by) in the scenario described? And why?**

2. **Does applying vaccinomics (targeting super spreaders and those most vulnerable) make sense to you as a strategy?**

3. **How might you react to learn that you are a super spreader or vulnerable and will receive the vaccine, versus you aren't and you won't receive the vaccine (or at least not as soon)?**

4. **Are there upsides/downsides you can imagine to vaccinomics?**

5. **Some have wondered whether the customizing of vaccines will increase or decrease vaccination rates? What do you think? Does it have the potential to increase or decrease trust?**

6. **If doctors and public health practitioners need to know your genetics to implement a vaccinomics approach, does that raise issues for you? Is it worth sharing this information? Are there safeguards that are important to you?**

7. **If a vaccinomics approach results in more complicated vaccine schedule (because perhaps girls need to go more often, or boys need X,Y,Z for example…) or that members of your family might have different vaccine plans, is that ok? What does it make you think about…?**

8. **Certain genes are associated with race or gender. Therefore, the distribution of vaccines could be prioritized in that way. Are there issues that could arise when some get the vaccine and others do not?**

RECORDER WORKSHEET

*Note to recorders: Facilitators will press to understand the underlying reasons as to why participants have certain views. Please take special care to record **why** participants have the particular perspective they do.*

Hypothetical 1 - PROMPT 1 (Required)

1. **What do you care about (worried about, comforted by) in the scenario described? And why?**

Hypothetical 1 - PROMPTS 2-8 (Optional)

2. **Does applying vaccinomics (targeting super spreaders and those most vulnerable) make sense to you as a strategy?**

3. **How might you react to learn that you are a super spreader or vulnerable and will receive the vaccine, versus you aren't and you won't receive the vaccine (or at least not as soon)?**

   Reminder re: super spreader (described in video): someone who is more likely to spread a pathogen (stuff that makes you sick, like germs) to others. For example, they might spread more flu virus when they sneeze than other people do. This might make them more infectious to others.

Hypothetical 1 - PROMPTS 2-8 (Optional) continued:

4. **Are there upsides/downsides you can imagine to vaccinomics?**

Hypothetical 1 - PROMPTS 2-8 (Optional) continued:

5. **Some have wondered whether the customizing of vaccines will increase or decrease vaccination rates? What do you think? Does it have the potential to increase or decrease trust?**

6. **If doctors and public health practitioners need to know your genetics to implement a vaccinomics approach, does that raise issues for you? Is it worth sharing this information? Are there safeguards that are important to you?**

Hypothetical 1 - PROMPTS 2-8 (Optional) continued:

7. **If a vaccinomics approach results in more complicated vaccine schedule (because perhaps girls need to go more often, or boys need X, Y, Z for example…) or that members of your family might have different vaccine plans, is that ok? What does it make you think about…?**

   Hypothetical 1 (continued)

8. **Certain genes are associated with race or gender. Therefore, the distribution of vaccines could be prioritized in that way. Are there issues that could arise when some get the vaccine and others do not?**

FACILITATOR & RECORDER OVERVIEW – HYPOTHETICAL 2 (Approximately 15 minutes)

Hypothetical 2: Facilitators to review the Hypothetical with the Group (use handouts)

A new and serious contagious disease has emerged.

The vaccine being developed is safe for almost everyone.

However, 1 in 1 million people will have a bad reaction to the VACCINE and could be permanently paralyzed or die.

Vaccinomics may help us learn who would have a bad reaction to the vaccine (based on genetic markers) and advise them not to get it. Instead of 1 in 1million, we could reduce the risk to closer to 0 in 1 million.

Facilitators: After asking PROMPT 1 below, feel free to follow the group's interests. Prompts 2-3 are optional.

What do you care about (worried about, comforted by) in the scenario described? And why? What are your thoughts?

Does applying vaccinomics (understanding those who might react badly and suggesting they don't get the vaccine) make sense to you as a strategy?

Does applying vaccinomics change your level of confidence in the government's response to this outbreak?

RECORDER WORKSHEET

Note to recorders: Facilitators will press to understand the underlying reasons as to why participants have certain views. Please take special care to record why participants have the particular perspective they do.

Hypothetical 2, Prompt 1 (Required):

What do you care about (worried about, comforted by) in the scenario described? And why? What are your thoughts?

Hypothetical 2, Prompts 2-3 (Optional):

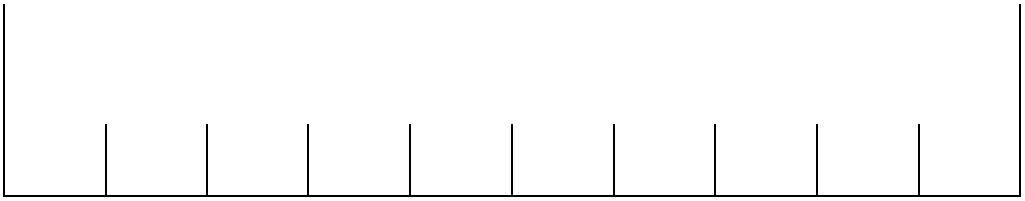
Does applying vaccinomics (understanding those who might react badly and suggesting they don't get the vaccine) make sense to you as a strategy?

Does applying vaccinomics change your level of confidence in the government's response to this outbreak?

RECORDER WORKSHEET

SMALL GROUP SPECTRUM QUESTION (Approximately 10 minutes): Based on what you've learned in the video and our discussion, would vaccinomics change your level of confidence in the safety and effectiveness of vaccines?

Facilitators: This question is really important. Have some discussion about this question… Try to rephrase the question a few ways to ensure they understand it. Essentially, if vaccinomics worked all of the ways we hope it would. And if we were better able to tailor vaccines to different genes, does that tailoring to individuals/groups instill greater confidence in the safety and effectiveness of vaccines?



NOTE: Facilitators will use their handout sheet to record the dots.

Comments

*Note to recorders: Facilitators will press to understand the underlying reasons as to **why** participants have certain views. Please take special care to record **why** participants have the particular perspective they do.*

<u>RECORDER WORKSHEET</u> -- SMALL GROUP SPECTRUM DISCUSSION (continued)

SMALL GROUP SPECTRUM QUESTION: Based on what you've learned in the video and our discussion, would vaccinomics change your level of confidence in the safety and effectiveness of vaccines?

FACILITATOR & RECORDER OVERVIEW -- PRIORITIES EXERCISE

Resources and priorities (20 minutes total)

Facilitator instructions to the group: We know resources are limitless and decision-makers have to make choices about how to allocate funds for different research priorities. Given limited resources, we are interested in your advice on how do we make choices about what research to advance? It would be helpful to understand your collective priorities.

For this next exercise, we are going to: 1. Have a discussion about resources and you have the chance to influence each other. Preview: We are going to talk about vaccinomics among other vaccine priorities and then vaccinomics among other public health priorities. And 2. Then you will take your play money and "vote with your dollars" by allocating your budget among different priorities.

Priorities Scenario 1: You have $100 to split among the ways we currently spend money on vaccines, plus the addition of vaccinomics:

1. **New vaccines**
2. **Studies about safety and effectiveness of current vaccines**
3. **Buying vaccines for U.S. kids**
4. **Investing in the science of vaccinomics**

Priorities Scenario 2: You have $100 to split among other public health priorities. Vaccinomics is included in the vaccine priority. How would you divide your $100 among these four priorities?

1. **Vaccine research and development, to include developing vaccinomics**
2. **Cancer research and development**

3. **Diabetes research and development**
4. **Heart disease research and development**

<u>RECORDER WORKSHEET – PRIORITIES EXERCISE (10 minutes)</u>

Priorities Scenario 1: You have $100 to split among the ways we currently spend money on vaccines, plus the addition of vaccinomics:

1. **New vaccines**
2. **Studies about safety and effectiveness of current vaccines**
3. **Buying vaccines for children U.S. kids**
4. **Investing in the science of vaccinomics**

Note to facilitators: After 5-7 minutes discussion, let them divide up their money into the jars.

Priorities Scenario 1 - PARTICIPANT COMMENTS

*Note to recorders: Facilitators will press to understand the underlying reasons as to **why** participants have certain views. Please take special care to record **why** participants have the particular perspective they do.*

RECORDER WORKSHEET – PRIORITIES EXERCISE (10 minutes)

Priorities Scenario 2: You have $100 to split among other public health priorities. Vaccinomics is included in the vaccine priority. How would you divide your $100 among these four priorities?

1. **Vaccine research and development, to include developing vaccinomics**
2. **Cancer research and development**
3. **Diabetes research and development**
4. **Heart disease research and development**

Note to facilitators: After 5-7 minutes discussion, let them divide up their money into the jars.

Priorities Scenario 2 - PARTICIPANT COMMENTS

*Note to recorders: Facilitators will press to understand the underlying reasons as to **why** participants have certain views. Please take special care to record **why** participants have the particular perspective they do.*

9.2 Appendix 2: Community Meeting Wall Chart Spectrum Exercises

WELCOME!

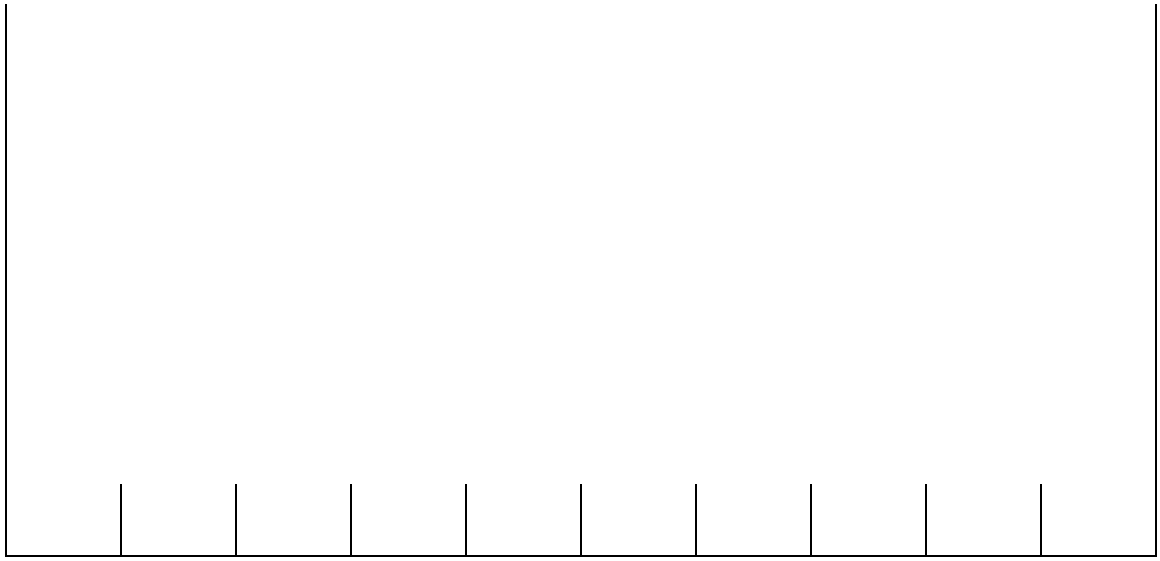
We want to understand some of your views about vaccine effectiveness and vaccine safety BEFORE we have a mash-up conversation about vaccinomics. We ask about how you think about effectiveness and vaccines for yourself, but also for babies.

Pssst! You'll want to bring your envelope along for this…

Just so you know, these aren't questions about knowledge, they are questions about your view on issues regarding vaccines.
Facilitators will walk you through the questions and we are especially eager to have any discussion with you about what factors you considered as you placed your dot along the spectrum line.

Thanks!

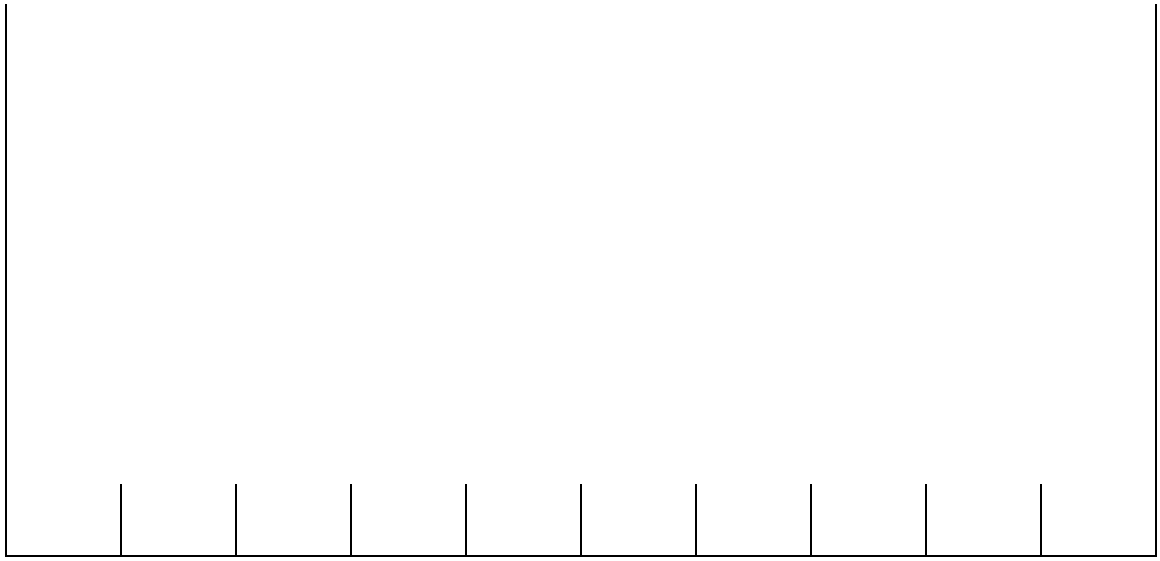
Your view: In general, how effective do you think vaccines are *for adults*? Please put a dot along this spectrum.



Share with us: why did you place your dot where you did and what factors you were considering?

(Facilitator to add post-it notes here with any answers to "why")

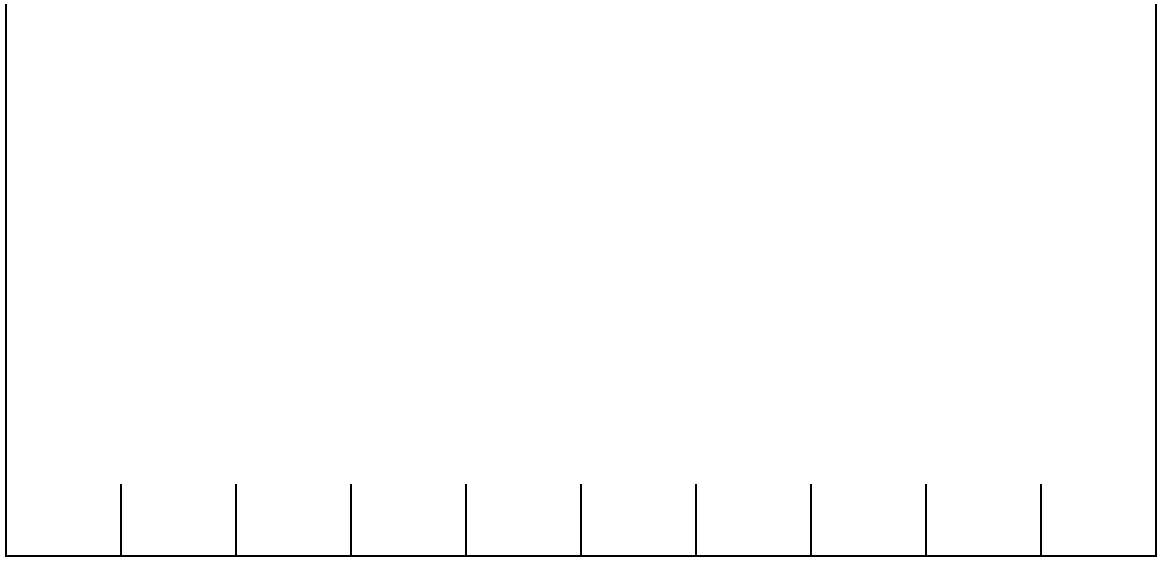
Your view: In general, how effective are the vaccines *for babies*? Please put a dot along this spectrum.



Share with us: why did you place your dot where you did and what factors you were considering?

(Facilitator to add post-it notes here with any answers to "why")

Your view: In general, how safe do you think vaccines are *for adults*? Please put a dot along this spectrum.

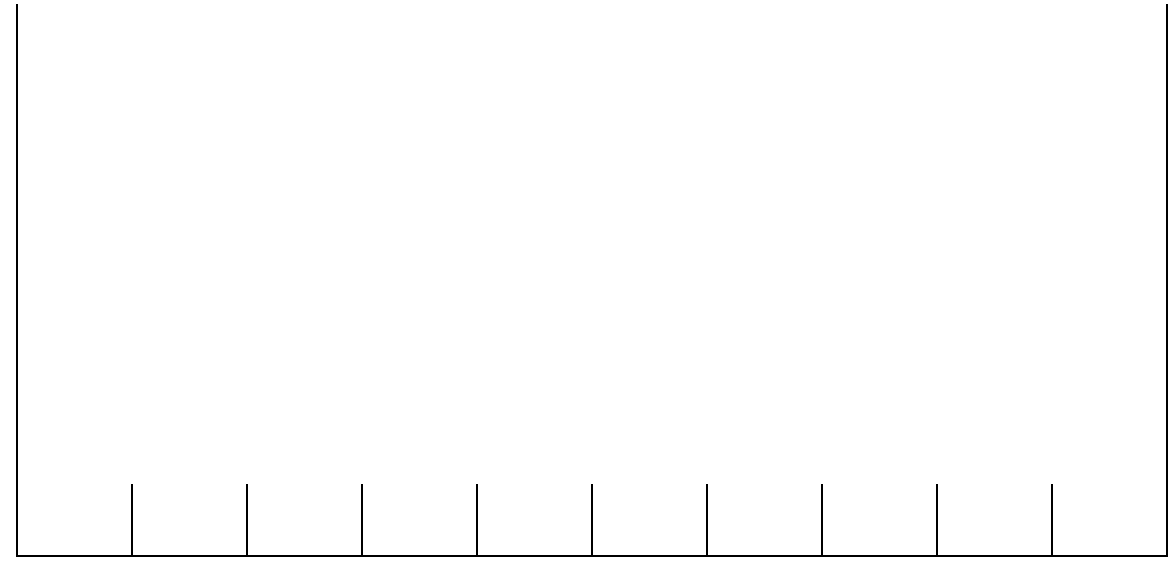


Not safe **Very safe**

Share with us: why did you place your dot where you did and what factors you were considering?

(Facilitator to add post-it notes here with any answers to "why")

Your view: In general, how safe do you think vaccines are *for babies*? Please put a dot along this spectrum.



Share with us: why did you place your dot where you did and what factors you were considering?

(Facilitator to add post-it notes here with any answers to "why")

9.3 Appendix 3: Community Meeting Sociodemographic Questionnaire

Vaccinomics Registration for [City: Boulder/Baltimore]

Please fill out this quick survey about yourself so we can obtain a representative balance of perspectives based on **[City: Boulder/Baltimore/Denver]'s demographic population.**

1. What is your first and last name [text field]
2. Please Indicate how you'd like to be contacted about the upcoming session by either listening your phone # and/or email address below:

    Phone call reminder [text field]

    Text reminder [text field]

    Email reminder [text field]
3. What age group do you fall into? [radio buttons]

    18-29

    30-44

    45-59

    ≥60

    I prefer not to answer
4. What is your gender? [radio buttons]

    Male

    Female

    I prefer not to answer
5. Other (please specify) [text field]What is your race/ethnicity? (Please choose all that apply) [checkboxes]

    American Indian or Alaska Native

    Asian

Black/African American

Hispanic/Latino

Native Hawaiian or Other Pacific Islander

White/Caucasian

I prefer not to answer

Other (please specify) [text field]

6. What is the highest level of education you have completed? [radio buttons]

Doctoral or professional degree

Master's Degree

Bachelor's Degree

Associate's Degree

Some College

High school diploma or equivalent

Some high school

I prefer not to answer

7. What is your approximate average household income? [radio buttons]

$0-$49,999

$50,000-$99,999

$100,000-$149,999

>$150,000

I prefer not to answer

8. How did you hear about this meeting (Please check all that apply).

Flyer

Social media/Facebook group

In person

From friends or family

Other (please specify below) [text field]

9. Do you have children? (Please choose all that apply) *[Asked of Baltimore Participants only]*

Infant younger than 5 years old

Child 5 to 18 years old

Child above 18 years old

No children

I prefer not to answer

Thank you for answering the vaccinomics screening questions. Using the contact information, you provided, we'll follow-up to let you know if you are a good fit for the meeting. If you are a good fit, you will receive a $50 Visa gift card for your time and refreshments will be served at the meeting. We will also use your contact information remind you about the meeting a couple days in advance. In the meantime, if you have any questions or concerns, please email Janesse at janesse@23-four.com.

9.4 Appendix 4. Vaccinomics National Survey

Last Edited 1/17/20

Not Visible to Respondents: Question numbers won't be visible to respondents to avoid confusing them when there are skip patterns. Instead, progress bars showing percentage of the survey completed will be used. Whenever questions are labeled **A) or B)** after the question number, this indicates there is a positive and negative phrasing of the item. Participants will be **randomized to receive A) or B) with 50-50 cumulative probability**.

Not Visible to Respondents: PART 1 – CONSENT: ALL

We (a research team at Johns Hopkins University) have a grant from the National Institutes of Health (NIH) to study what people think about new ways to make vaccines (shots) and recommendations about who gets which vaccines. We are asking you to spend about 15 minutes:

- Answering some questions about vaccines
- Watching a 4-minute-long video
- Answering questions about the video's content, vaccines, your health, and personal background

There is no direct benefit to you from being in this study. This study may influence funding for vaccine research and public health policies about vaccines. We will do all that we can to protect your confidentiality. There is a small risk your privacy is violated. Someone outside the research team may get access to your survey responses. The risk that someone identifies you as a survey participant is minimal since we will not have your name or contact information. Information we collect from you will either be encrypted or password protected.

By clicking YES below, you give your consent to answer the survey questions. Click NO if you do not consent to answer these questions. Even if you consent to answer the questions now, you do not have to finish the survey. Just close your browser to end the survey at any time.

1. Do you consent to answer the survey questions?
- ❍ Yes
- ❍ No→ skip to closing statement

Not Visible to Respondents: PART 2 – Demographics: ALL

Please answer a few questions about yourself. This helps us compare those who take our survey to the population of the U.S. overall. All answers will be confidential.

2. What experience do you have with science? Select all that apply.
- □ High school-level courses
- □ College-level courses
- □ Graduate school-level or continuing education courses
- □ Work experience or training
- □ None of the above

3. What state do you live in? Please select a state from the dropdown menu below:
- Alabama
- Alaska
- Arizona
- Arkansas
- California
- Colorado
- Connecticut
- Delaware
- District of Columbia
- Florida
- Georgia
- Hawaii
- Idaho
- Illinois
- Indiana
- Iowa
- Kansas
- Kentucky
- Louisiana
- Maine
- Maryland
- Massachusetts
- Michigan
- Minnesota

- Mississippi
- Missouri
- Montana
- Nebraska
- Nevada
- New Hampshire
- New Jersey
- New Mexico
- New York
- North Carolina
- North Dakota
- Ohio
- Oklahoma
- Oregon
- Pennsylvania
- Rhode Island
- South Carolina
- South Dakota
- Tennessee
- Texas
- Utah
- Vermont
- Virginia
- Washington
- West Virginia
- Wisconsin
- Wyoming
- Puerto Rico
- Prefer not to answer

4. How old are you? Select the appropriate age range.

- ❍ 18-24 years
- ❍ 25-34 years
- ❍ 35-44 years
- ❍ 45-54 years
- ❍ 55-64 years
- ❍ 65 or older
- ❍ Prefer not to answer

5. What is your gender?

- ❍ Male
- ❍ Female
- ❍ Transgender
- ❍ Prefer not to answer

6. Are you Hispanic?

- ❍ Yes
- ❍ No
- ❍ Prefer not to answer

7. What is your race? Select all that apply.

- ☐ White
- ☐ Black or African American
- ☐ American Indian or Alaskan Native
- ☐ Asian
- ☐ Native Hawaiian or Pacific Islander
- ☐ Prefer not to answer

8. What is the highest level of education you have completed?

- ❍ High school graduate, GED, some high school or less
- ❍ Associate's Degree, some college, or Bachelor's Degree (for example: AA, AS, BA, or BS)
- ❍ Master's, Professional, or Doctorate degree (for example: MA, MS, MBA, MD, DDS, PhD, or JD)
- ❍ Prefer not to answer

9. What was your approximate average household income IN THE PAST 12 MONTHS? Please include wages, salary, commissions, bonuses, or tips from all jobs. Report amount before deductions for taxes, bonds, dues, or other items.

- ❍ $0-$49,999
- ❍ $50,000-$99,999
- ❍ $100,000-$149,999
- ❍ $150,000 or more
- ❍ Prefer not to answer

Not Visible to Respondents: Continue to PART 3 – Parent Status.

Not Visible to Respondents: PART 3 – Parent Status For all survey respondents:

10. Are you a parent or legal guardian of a child?

- ❍ Yes → CONTINUE TO Q11
- ❍ No → SKIP TO PART 5
- ❍ Prefer not to answer → SKIP TO PART 5

11. How old is the youngest child in your household?

- ❍ 5 years old or younger→ CONTINUE TO PART 4
- ❍ 6 to 10 years old → CONTINUE TO PART 4
- ❍ 11-17 years old→ CONTINUE TO PART 4
- ❍ 18 years or older → SKIP TO PART 5
- ❍ Prefer not to answer → SKIP TO PART 5

Not Visible to Respondents:

IF QUOTA IS FILLED, GO TO PART 27 – CLOSING STATEMENT

OTHERWISE, RESPONDENTS WILL GET PART 4 OR PART 5 DEPENDING ON ANSWERS TO Q10 AND Q11 ABOVE

Not Visible to Respondents: PART 4 – Ask of all parents of children <18

12. Did your youngest child get the flu vaccine **THIS year** (2019-2020)?

- ❍ Yes, he/she is vaccinated
- ❍ I plan to get him/her vaccinated
- ❍ No, NOT planning to get him/her vaccinated
- ❍ Don't know

13. Did your youngest child get the flu vaccine **LAST year** (2018-2019)?

- ❍ Yes
- ❍ No
- ❍ Don't know

PART 5: Ask of nonparent, parents of children>18, parents who prefer not to give their child's age

14. Did you get the flu vaccine **THIS year** (2019-2020)?

- ❍ Yes, I'm vaccinated
- ❍ I plan to get vaccinated
- ❍ No, NOT planning to get vaccinated
- ❍ Don't know

15. Did you get the flu vaccine **LAST year** (2018-2019)?

- ❍ Yes
- ❍ No
- ❍ Don't know

Not Visible to Respondents: PART 6 – Complementary/Alternative Medicine & Trust in Doctors – ALL

16. Have you or members of your family (spouse/partner or children) used the services of a chiropractor, acupuncturist, or other complementary/alternative medicine provider in the last five years?

- ❍ Yes→ CONTINUE TO Q17
- ❍ No→SKIP TO Q18
- ❍ Don't know →SKIP TO Q18

17. What type of alternative medicine was used? **Select all that apply.**

- ▪ Acupuncture
- ▪ Biofeedback or hypnosis
- ▪ Chiropractic
- ▪ Essential oils
- ▪ Folk remedies
- ▪ Herbal therapies
- ▪ High-dose megavitamins
- ▪ Homeopathy
- ▪ Imagery or energy healing
- ▪ Spiritual healing
- ▪ Other (please specify:_____)

PART 6a -Not visible to respondents: For parents of kids<18:

We are interested in your opinions about vaccines (shots) and your YOUNGEST child's vaccination history. Your child's doctor or nurse gives vaccines like MMR (measles, mumps and rubella) or polio to help keep your child from getting sick. Please think about vaccines other than the flu or influenza when answering.

PART 6b - Not visible to respondents: For other respondents:

We are interested in your opinions about the FLU VACCINE or FLU SHOT given to ADULTS. Please indicate how strongly you agree or disagree with each statement.

PART 6c -Not visible to respondents: Q18 & Q20 asked of ALL

	Strongly Disagree	Disagree	Agree	Strongly Agree	Don't Know
18. I trust the information I receive from doctors about vaccines.	❍	❍	❍	❍	❍
19. I can openly discuss my questions about vaccines with my doctor.	❍	❍	❍	❍	❍

	Strongly Disagree	Disagree	Agree	Strongly Agree
20. Vaccines are very safe	❍	❍	❍	❍

Not Visible to Respondents: PART 7 – Vaccine Concern Questions for PARENTS/GUARDIANS OF CHILDREN ≤10 YEARS OLD

Please answer each question about your YOUNGEST child.

Please think about vaccines other than the flu or influenza when answering.

21. Have you ever delayed having your child get a vaccine (not including the flu vaccine) for reasons other than illness or allergy?	Yes	No	Don't Know
22. Have you ever decided not to have your child get a vaccine (not including the flu vaccine) for reasons other than illness or allergy?	Yes	No	Don't Know

Please indicate your child's vaccination status:

	Vaccinated on time	Vaccinated with delay	Plan to Vaccinate on time	Plan to vaccinate with delay	NOT Planning to Vaccinate	Don't Know
23. MMR (prevents measles, mumps, and rubella)	❍	❍	❍	❍	❍	❍

Not Visible to Respondents: Part 8 – Questions for Parents of Children<6 Years Old

Please answer each question about your YOUNGEST child.

Please think about vaccines other than the flu or influenza when answering.

	Strongly Disagree	Disagree	Agree	Strongly Agree
24. Children get more vaccines than are good for them.	❍	❍	❍	❍
25. It is better for children to develop immunity by getting sick than by getting a vaccine.	❍	❍	❍	❍
26. It is better for children to get fewer vaccines at the same time.	❍	❍	❍	❍

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	Not at all hesitant	Not too hesitant	Somewhat hesitant	Very hesitant	Don't Know
27. Overall, how hesitant about childhood vaccines are you?	❍	❍	❍	❍	❍

Not Visible to Respondents: PART 9 – Questions for - Parents of children 11-17

Please answer each question about your YOUNGEST child.

Please think about vaccines other than the flu or influenza when answering.

	Strongly Disagree	Disagree	Agree	Strongly Agree
28. Vaccines are necessary to protect the health of teenagers	❍	❍	❍	❍
29. Vaccines do a good job in preventing the diseases they are intended to prevent	❍	❍	❍	❍
30. If I do not vaccinate my child, he/she may get a disease such as pertussis or human papillomavirus (HPV) and cause other people to get sick	❍	❍	❍	❍

Please indicate your YOUNGEST child's vaccination status:

	Vaccinated on time	Vaccinated with delay	Plan to Vaccinate on time	Plan to vaccinate with delay	NOT Planning to Vaccinate	Don't Know
31. Meningococcal (prevents meningitis)	❍	❍	❍	❍	❍	❍

PART 10: VACCINATION QUESTIONS FOR ALL PARENTS KIDS<18

Please indicate your YOUNGEST child's vaccination status:

	Vaccinated on time	Vaccinated with delay	Plan to Vaccinate on time	Plan to vaccinate with delay	NOT Planning to Vaccinate	Don't Know
32. DTaP (prevents diphtheria, pertussis, and tetanus)	❍	❍	❍	❍	❍	❍
33. Varicella (prevents the chickenpox)	❍	❍	❍	❍	❍	❍

	Strongly Disagree	Disagree	Agree	Strongly Agree
34. The Centers for Disease Control and Prevention (CDC) and professional medical associations' recommended vaccine schedule is a good fit for my child.	❍	❍	❍	❍

Not Visible to Respondents: PART 11 – Adapted for Vaccinomics - Nonparents, parents of children≥18, & those who prefer not to give their child's age

We are interested in your opinions about the FLU VACCINE or FLU SHOT given to ADULTS. Please indicate how strongly you agree or disagree with each statement.

	Strongly Disagree	Disagree	Agree	Strongly Agree
35. Vaccines are necessary to protect the health of adults.	❍	❍	❍	❍
36. Vaccines do a good job in preventing the diseases they are intended to prevent	❍	❍	❍	❍
37. If I do not get vaccinated, I may get influenza or the flu and cause other people to get sick.	❍	❍	❍	❍

NOT VISIBLE TO RESPONDENTS: PART 12 – VACCINE CONCERNS – ALL

Not Visible to Respondents: Randomize each participant to either the positive (A) or negative (B) version of each question with 50-50 cumulative probability of each version.

	Strongly Disagree	Disagree	Agree	Strongly Agree
38. A) I trust pharmaceutical companies to make very safe and effective vaccines.	❍	❍	❍	❍
39. B) I do NOT trust pharmaceutical companies to make very safe and effective vaccines.	❍	❍	❍	❍
40. A) I am more likely to trust vaccines that have been around for a while than newer vaccines.	❍	❍	❍	❍
41. B) I am NOT more likely to trust vaccines that have been around for a while than newer vaccines.	❍	❍	❍	❍

Not Visible to Respondents: PART 13 – Embed vaccinomics animation here for ALL to see

Please watch a 4-minute-long animation here: [embed video]

If the video does not automatically play, please click this link: **https://tinyurl.com/vaccinomics**

Not Visible to Respondents: Vaccines PART 14 – ALL

42. According to the video, do genes or DNA influence how people respond to vaccines?

- ❍ Yes
- ❍ No
- ❍ Don't know

43. Have you or anyone you know ever had a serious reaction to a vaccine? Serious reactions include permanent disability, hospitalization, life-threatening illness, or death.

- ❍ Yes
- ❍ No
- ❍ Don't know

44. Have you heard of the following resources before? Select all that apply.

- ☐ Vaccines Injury Compensation Program (VICP)
- ☐ Vaccine Adverse Events Reporting System (VAERS)
- ☐ National Vaccine Safety Hotline (NVSH)
- ☐ Not aware of VICP, VAERS, or NVSH

45. If Had a Serious Reaction to a Vaccine (Q43=YES): Did you or your provider report the reaction to the Vaccine Adverse Events Reporting System (VAERS) or the Vaccines Injury Compensation Program (VICP)?

- ❍ Yes
- ❍ No
- ❍ Don't know

Not Visible to Respondents: PART 15 – Biobank

Not Visible to Respondents: If had a serious reaction to a vaccine (Q43=YES), Asked Q46-Q48. Otherwise, SKIP to Genetic Testing Section (PART 16).

A vaccine biobank holds biological samples from people (such as a vial of blood or a swab from inside the mouth) for long-term research purposes.

- The goal is to understand how and why people have bad reactions to vaccines and whether genes or DNA play a role.
- Biobank samples may be used along with vaccinomics to make vaccines safer and more effective.

	Extremely Unlikely	Unlikely	Likely	Extremely Likely
46. If you had a rare, serious reaction to a vaccine, how likely would you be to let your doctor submit a sample from you (for example: a vial of blood or swab from your mouth) to a vaccine biobank?	❍	❍	❍	

47. Independent scientists and community members who are experts in research ethics oversee how biobanks manage people's information. Does having this kind of independent, research ethics oversight make you more likely to submit a sample to a vaccine biobank?

- ❍ Yes
- ❍ No
- ❍ Don't know

48. If Likely or Extremely Likely to Give Sample: What is the primary reason you would participate in a vaccine biobank?

- ❍ To help others
- ❍ Interest in science and/or medicine
- ❍ It's the right thing to do
- ❍ To help myself
- ❍ Other (please specify): _____

Not Visible to Respondents: PART 16 – Genetic Testing: ALL

49. Have you ever had your genes or DNA tested? For example, in your doctor's office or through an in-home test like 23andme, ancestry.com, or one purchased in a pharmacy?

- ❍ Yes
- ❍ No
- ❍ Prefer not to answer

54. If had DNA tested: Where were your genes or DNA tested? Select all that apply.

- ☐ I was tested in a doctor's office or other medical setting
- ☐ I used an in-home test (for example: through 23andme, ancestry.com, or one purchased in a pharmacy)
- ☐ Other (please specify):_____

55. If had DNA tested: Did you share the gene or DNA test results with any of the following people? Select all that apply.

- ☐ Family
- ☐ Friends
- ☐ Co-workers
- ☐ My doctor, nurse, physician's assistant, a nurse practitioner, or a pharmacist
- ☐ My alternative medicine provider(s) (for example: chiropractor, naturopath, massage therapist, or acupuncturist)

Not Visible to Respondents: PART 17 – ELSI: ALL

In the future, genes or DNA might influence 1) how vaccines are made and 2) who is recommended to get which vaccine dose (vaccine schedules). Please indicate how strongly you agree or disagree with each statement.				
	Strongly Disagree	**Disagree**	**Agree**	**Strongly Agree**
56. A) I am afraid that my	❍	❍	❍	❍

gene or DNA test result could prevent me from getting a vaccine.				
57. B) I am NOT afraid that my gene or DNA test result could prevent me from getting a vaccine.	❍	❍	❍	❍
58. A) I am afraid that using genes or DNA in vaccine decisions could increase race/ethnic discrimination.	❍	❍	❍	❍
59. B) I am NOT afraid that using genes or DNA in vaccine decisions could increase race/ethnic discrimination	❍	❍	❍	❍

- **As a reminder, implementing vaccinomics means using people's genetic information to personalize vaccine schedules.**
- **The goal of vaccinomics is to make vaccines even safer and more effective.**

Please indicate how strongly you agree or disagree with each statement:				
	Strongly Disagree	**Disagree**	**Agree**	**Strongly Agree**
60. <u>NOT VISIBLE TO RESPONDENTS: SKIP IF NOT A PARENT</u> Vaccinomics (based on genes/DNA) would help me make informed decisions about vaccines FOR MY CHILD	❍	❍	❍	❍
61. Vaccinomics (based on genes/DNA) would help me make informed decisions about vaccines FOR MYSELF	❍	❍	❍	❍

<u>Not Visible to Respondents: PART 18– Public Health Authorities: ALL</u>
Public health authorities include local and state health departments, the Centers for Disease Control and Prevention (CDC), and Food and Drug Administration (FDA).

Please indicate how strongly you agree or disagree with each statement:	Strongly Disagree	Disagree	Agree	Strongly Agree
62. They do everything they should to protect the health of the population	❍	❍	❍	❍
63. They are partly responsible for the illegal drug problems in this country	❍	❍	❍	❍
64. They base recommendations on the best available science	❍	❍	❍	❍
65. They do not respond appropriately to emergencies and disasters	❍	❍	❍	❍
66. They are concerned about all people, without caring about who has more or less money	❍	❍	❍	❍
67. They waste money on health problems	❍	❍	❍	❍
68. They ensure the public is protected against diseases	❍	❍	❍	❍
69. They provide skewed information	❍	❍	❍	❍
50. They keep trying the same things to help the public, even when they don't work very well	❍	❍	❍	❍
70. They sometimes hide information from the public	❍	❍	❍	❍
71. They are not always able to help the health of the public	❍	❍	❍	❍
72. They were responsible for creating HIV and AIDS	❍	❍	❍	❍
73. They make unhelpful recommendations."	❍	❍	❍	❍
74. They use resources well	❍	❍	❍	❍
75. They accurately inform the public of both health risks and benefits of medicines	❍	❍	❍	❍
76. They believe in what they recommend for the public	❍	❍	❍	❍
77. They quickly help the public with health problems	❍	❍	❍	❍
78. They are more concerned about some racial and ethnic groups than other groups	❍	❍	❍	❍

79. They provide the public with complete and accurate information about important health issues	❍	❍	❍	❍
80. They come up with new ideas to solve health problems	❍	❍	❍	❍

Not Visible to Respondents: Part 19 – Vaccinomics: ALL

- **As a reminder, implementing vaccinomics means using people's genetic information to personalize vaccine schedules.**
- **The goal of vaccinomics is to make vaccines even safer and more effective.**

81. Would you support a $0.25 fee on all vaccines to fund vaccine safety studies, including vaccinomics research? The $0.25 fee would mostly be paid by the government and health insurance companies, who pay for most people's vaccines now. It is **unlikely you would have to pay more for vaccines** because of this fee.

- ❍ Yes
- ❍ No
- ❍ Don't know

Not Visible to Respondents: PART 20– Hypothetical 1: ALL

- **Imagine this winter there is a disease that is spreading easily and quickly.**
- **The disease makes people very sick, and they could die.**
- **There is a vaccine for it, but there is a limited supply of the vaccine.**
- **Not everyone can get the vaccine right away.**
- **Some people are "more contagious." They are more likely get someone else sick than the average person.**
- **In the future, scientists might be able to use genes or DNA to identify who is "more contagious."**

Please indicate how strongly you agree or disagree with each statement.

	Strongly Disagree	Disagree	Agree	Strongly Agree
82. A) If there was a short supply of vaccine, it would make sense for the people "more susceptible" to infection to get it first.	❍	❍	❍	❍
83. B) If there was a short supply of vaccine, it would NOT make sense for the people "more susceptible" to infection to get it first.	❍	❍	❍	❍
84. A) If there was a short supply of vaccine, it would make sense for the "more contagious" people to get it first.	❍	❍	❍	❍

	Strongly Disagree	Disagree	Agree	Strongly Agree
85. B) If there was a short supply of vaccine, it would NOT make sense for the “more contagious” people to get it first.	❍	❍	❍	❍
86. A) It would bother me if my doctor identified me as “more contagious” or "more susceptible."	❍	❍	❍	❍
87. B) It would NOT bother me if my doctor identified me as “more contagious” or "more susceptible."	❍	❍	❍	❍
88. A) Getting vaccinated should be an individual’s choice, even if they are “more contagious” or "more susceptible"	❍	❍	❍	❍
89. B) Getting vaccinated should NOT be an individual’s choice. Public health authorities should decide if “more contagious” or "more susceptible" people need to get vaccinated.	❍	❍	❍	❍
90. A) Identifying people as “more contagious” will hurt people.	❍	❍	❍	❍
91. B) Identifying people as “more contagious” or "more susceptible" will NOT hurt people.	❍	❍	❍	❍

Please indicate how strongly you agree or disagree with each statement.	Extremely Unlikely	Unlikely	Likely	Extremely Likely
92. A) If your genes or DNA showed you to be “more contagious” or likely to get other people sick, how likely would you be to get vaccinated to PROTECT OTHER PEOPLE?	❍	❍	❍	❍
93. B) If your genes or DNA showed you to be “more susceptible” or likely to get infected, how likely would you be to forgo vaccination so that others could get vaccinated?	❍	❍	❍	❍

94. If you were told you were NOT going to be among the first groups vaccinated during an infectious disease outbreak because your genetics showed you were not predisposed to be "more contagious" or "more susceptible" to infection, how might you react?

❍ I would be angry because I would want the vaccine

- ❍ I would be okay with this decision
- ❍ I would not care because I would not want the vaccine anyway
- ❍ Other: please specify_____

Not Visible to Respondents: PART 21 – Hypothetical 2: ALL

- **Imagine a new and serious contagious disease emerges.**
- **The vaccine being developed is safe for ALMOST everyone.**
- **However, 1 person in 1 million people vaccinated will have a serious reaction to the VACCINE.**
- **They could become paralyzed or die FROM THE VACCINE.**
- **Vaccinomics may use genes or DNA to help us predict and prevent who may get paralysis or die from the vaccine.**
- **Certain people would be told not to get specific vaccines for their safety.**
- **Instead of 1 person in 1 million people vaccinated getting paralysis or dying, the risk could be reduced to be closer to 0 people in 1 million people vaccinated getting paralysis or dying.**

In the questions below, the U.S. government includes the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and the National Institutes of Health (NIH).

Please indicate how strongly you agree or disagree with each statement.	Strongly Disagree	Disagree	Agree	Strongly Agree	
95. A) Screening tests that warn who is at increased risk of paralysis and death from vaccines will be worthwhile if they help predict who will have an adverse reaction.	❍	❍	❍	❍	❍
96. B) Screening tests that warn who is at increased risk of paralysis and death from vaccines will NOT be worthwhile unless they can help predict who will have an adverse reaction.	❍	❍	❍	❍	❍
97. A) The U.S. government should invest in making vaccines more effective instead of trying to reduce the risk of very serious and rare events, like paralysis and death after getting a vaccine.	❍	❍	❍	❍	❍
98. B) The U.S. government should invest in reducing the risk of very serious and rare events, like paralysis and death after getting a vaccine,	❍	❍	❍	❍	❍

Please indicate how strongly you agree or disagree with each statement.	Strongly Disagree	Disagree	Agree	Strongly Agree	
instead of making vaccines more effective.					
99. A) My confidence in vaccines would increase if the U.S. government spent more money studying how safe vaccines are now and telling the public the results.	❍	❍	❍	❍	❍
100. B) My confidence in vaccines would NOT increase if the U.S. government spent more money studying how safe vaccines are now and telling the public the results.	❍	❍	❍	❍	❍

Not Visible to Respondents: PART 22 – ELSI Concerns: ALL

- **You've learned genes or DNA may help researchers and doctors predict who is:**
  - **Likely to become severely ill and possibly die from an infectious disease**
  - **Likely to be more contagious or susceptible to infection**
  - **Most likely to have a very rare (1 person in 1 million people vaccinated) but serious reaction like being paralyzed or dying after vaccination**

Please indicate how strongly you agree or disagree with each statement.
Not Visible to Respondents: Will randomize participants to get items labeled A or B with 50-50 cumulative probability. They will not see both versions.

	Strongly Disagree	Disagree	Agree	Strongly Agree	
101. A) I would have my genes or DNA tested if it would help my doctor or another healthcare provider know which vaccines are best for ME.	❍	❍	❍	❍	❍
102. B) I would NOT have my genes or DNA tested even if it would help my doctor or another healthcare provider know which vaccines are best for ME.	❍	❍	❍	❍	❍
103. A) I am concerned my HEALTH INSURANCE COMPANY would learn my gene or DNA test result.	❍	❍	❍	❍	❍

104. B) I am NOT concerned my HEALTH INSURANCE COMPANY would learn my gene or DNA test result.	❍	❍	❍	❍	❍
105. A) I am concerned the U.S. GOVERNMENT would learn my gene or DNA test result.	❍	❍	❍	❍	❍
106. B) I am NOT concerned the U.S. GOVERNMENT would learn my gene or DNA test result.	❍	❍	❍	❍	❍
107. A) I would be concerned about the security of my gene or DNA test result	❍	❍	❍	❍	❍
108. B) I would NOT be concerned about the security of my gene or DNA test result	❍	❍	❍	❍	❍

- **As a reminder, implementing vaccinomics means using people's genetic information to personalize vaccine schedules.**
- **The goal of vaccinomics is to make vaccines even safer and more effective.**

Please indicate how strongly you agree or disagree with each statement.

	Strongly Disagree	Disagree	Agree	Strongly Agree
109. A) I would support vaccinomics even if it made vaccine schedules more complex	❍	❍	❍	❍
110. B) I would NOT support vaccinomics if it made vaccine schedules more complex	❍	❍	❍	❍
111. A) Vaccinomics would make me have more confidence in vaccines than I do now.	❍	❍	❍	❍
112. B) Vaccinomics would NOT make me have more confidence in vaccines than I do now.	❍	❍	❍	❍
113. A) Vaccinomics is likely to help other people.	❍	❍	❍	❍
114. B) Vaccinomics is UNLIKELY to help other people.	❍	❍	❍	❍
115. A) Vaccinomics is likely to help me.	❍	❍	❍	❍

	Strongly Disagree	Disagree	Agree	Strongly Agree
116. B) Vaccinomics is UNLIKELY to help me.	❍	❍	❍	❍

Not Visible to Respondents: PART 23 – Vaccine Safety: for Parents of Children <18

NOT VISIBLE TO RESPONDENTS: If a parent of child<18:
Please answer about your YOUNGEST child as you did earlier in the survey.
Please think about vaccines other than the flu or influenza when answering.

Not Visible to Respondents: PART 24 – Vaccine Safety: for Parents of Children <18
We are interested in your opinions about the FLU VACCINE or FLU SHOT given to ADULTS.
Please indicate how strongly you agree or disagree with the statement below, like you did at the beginning of the survey.

ALL GET Q117

	Strongly Disagree	Disagree	Agree	Strongly Agree
117. Vaccines are very safe	❍	❍	❍	❍

Not Visible to Respondents: PART 25 – Funding Priorities: ALL
The next few questions ask which issues you think the U.S. government should invest money in studying.

If you were making decisions about how the U.S. government spends money, would vaccinomics get more, an equal amount or less money than:	Vaccinomics should get:		
	More	Equal	Less
118. Breast and prostate cancer research and development	❍	❍	❍
119. Diabetes research and development	❍	❍	❍
120. Heart disease research and development	❍	❍	❍

- **As a reminder, implementing vaccinomics means using people's genetic information to personalize vaccine schedules.**
- **The goal of vaccinomics is to make vaccines even safer and more effective.**

The goal of vaccinomics is to make vaccines even safer and more effective. If you were making decisions about how the U.S. government spends money, would vaccinomics get more, an equal amount or less money than each of the options below:	Vaccinomics should get:		
	More	Equal	Less
121. Studies about safety and effectiveness of current vaccines	❍	❍	❍
122. Buying vaccines for U.S. children whose families cannot afford them	❍	❍	❍
123. Supporting the use of vaccines for children in poor countries	❍	❍	❍

124. If vaccinomics could make personalized vaccine recommendations available in the next 15 years, how should this information be used for CHILDREN? Select all that apply.

- ☐ To make vaccines safer and more effective for all children
- ☐ To identify children most likely to have serious and dangerous reactions to vaccines
- ☐ To identify children most likely to be more contagious
- ☐ To identify children most likely to be more susceptible to infection
- ☐ Genes or DNA should NOT be used to make decisions about vaccines for children
- ☐ None of the above

125. If vaccinomics could make personalized vaccine recommendations available in the next 15 years, how should it be used for ADULTS? Select all that apply.

- ☐ To make vaccines safer and more effective for all adults
- ☐ To identify adults most likely to have serious and dangerous reactions to vaccines
- ☐ To identify adults most likely to be more contagious
- ☐ To identify adults most likely to be more susceptible to infection
- ☐ Genes should NOT be used to make decisions about vaccines for adults
- ☐ None of the above

Not Visible to Respondents: PART 26 – Personal Health: ALL

The next section includes questions about your health and behaviors. This helps us compare those who take our survey to the population of the U.S. overall. All answers will be confidential.Would you say your health in general is . . .?

- ❍ Very good
- ❍ Good
- ❍ Poor
- ❍ Don't know

126. IN THE PAST 12 MONTHS, I worried whether the food in my home would run out before getting money to buy more.

- ❍ Often true
- ❍ Sometimes true
- ❍ Never true

127. Do you consider yourself now to be. . .?

- ❍ Fat or overweight
- ❍ Too thin
- ❍ About the right weight
- ❍ Don't know

128. Have you smoked at least 100 cigarettes in your entire life?

- ❍ Yes
- ❍ No
- ❍ Don't know

Not Visible to Respondents: PART 27 – Closing Statement: ALL

Thank you for answering the survey questions. We truly appreciate your help!

Chapter 10. Biographical Statement

Jennifer E. Gerber, MSc is a PhD Candidate in the Department of International Health's Global Disease Epidemiology and Control Program at Johns Hopkins Bloomberg School of Public Health. Her research focuses on vaccine hesitancy, vaccine uptake, and the policy implications of using genomics to change vaccine development and use, ("vaccinomics") in the United States. Jennifer collaborates with the Berman Institute for Bioethics to study the acceptability and policy implications of genomic testing for the prevention and treatment of infectious disease in hospital settings. Previously, Jennifer worked on epidemiologic studies of oral HPV incidence and persistence as an employee of Johns Hopkins' Department of Epidemiology and on studies of influenza vaccine effectiveness and safety as an employee of a contract research organization. In this role, Jennifer also evaluated the availability of medical and behavioral health services for high-risk populations and evaluated emergency response policies and communications platforms. Jennifer earned Certificates in Vaccine Science and Policy, current Good Clinical Practice, and teaching at Johns Hopkins in 2019, received the Mary and Carl Taylor award from the Department of International Health, and mentored a high school student interested in vaccines. She earned a Master of Science (MSc) in Epidemiology at the London School of Hygiene and Tropical Medicine in 2011 and a Bachelor of Arts in Anthropology, *magna cum laude,* from Tufts University in 2007. Her birthdate is April 9, 1985.