Community-Based Values for 2009 Pandemic Influenza A H1N1 Illnesses and Vaccination-Related Adverse Events

Tara A. Lavelle1,2, Martin I. Meltzer3, Achamyeleh Gebremariam4, Kara Lamarand4, Anthony E. Fiore3, Lisa A. Prosser4

1 Ph.D. Program in Health Policy, Harvard University, Cambridge, Massachusetts, United States of America, 2 The Center for Health Decision Science, Harvard School of Public Health, Boston, Massachusetts, United States of America, 3 Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, 4 Child Health Evaluation and Research Unit, Division of General Pediatrics, University of Michigan Health System, Ann Arbor, Michigan, United States of America

Abstract

Objective: To evaluate community-based values for avoiding pandemic influenza (A) H1N1 (pH1N1) illness and vaccination-related adverse events in adults and children.

Methods: Adult community members were randomly selected from a nationally representative research panel to complete an internet survey (response rate = 65%; n = 718). Respondents answered a series of time trade-off questions to value four hypothetical health state scenarios for varying ages (1, 8, 35, or 70 years): uncomplicated pH1N1 illness, pH1N1 illness-related hospitalization, severe allergic reaction to the pH1N1 vaccine, and Guillain-Barré syndrome. We calculated descriptive statistics for time trade-off amounts and derived quality adjusted life year losses for these events. Multivariate regression analyses evaluated the effect of scenario age, as well as respondent socio-demographic and health characteristics on time trade-off amounts.

Results: Respondents were willing to trade more time to avoid the more severe outcomes, hospitalization and Guillain-Barré syndrome. In our adjusted and unadjusted analyses, age of the patient in the scenario was significantly associated with time trade-off amounts (p-value<0.05), with respondents willing to trade more time to prevent outcomes in children versus adults. Persons who had received the pH1N1 vaccination were willing to trade significantly more time to avoid hospitalization, severe allergic reaction, and Guillain-Barré syndrome, controlling for other variables in adjusted analyses.(p-value<0.05)

Conclusions: Community members placed the highest value on preventing outcomes in children, compared with adults, and the time trade-off values reported were consistent with the severity of the outcomes presented. Considering these public values along with other decision-making factors may help policy makers improve the allocation of pandemic vaccine resources.

Introduction

In April 2009, the first influenza pandemic in over forty years began in North America; the causative virus was 2009 pandemic influenza (A) H1N1 (pH1N1). Under guidance from the Advisory Committee for Immunization Practices (ACIP), the Centers for Disease Control and Prevention recommended target groups for vaccination [1]. A vaccine became available during October 2009, and a program was implemented on an emergency basis to reduce the impact of the expanding pandemic.

Vaccination programs, such as the one implemented for pH1N1, involve an inherent trade-off of risks. Vaccinating for a particular disease reduces the risk of infectious illness, but introduces new risks of vaccine-related adverse events. The acceptability of a vaccination program depends in part on how the public values the potential risks and benefits of vaccination. By examining the likelihood of these risks and benefits, as well the value of prevention, decision makers can determine the potential value of a public vaccination program. When pH1N1 vaccine recommendations were made in the U.S. the only studies reporting community values associated with influenza illness and vaccination were based on data from seasonal influenza [2,3,4]. Outcomes related to pH1N1 illness and vaccination may be valued differently, however. We present in this study estimates of community-based values for avoiding adult and pediatric health events related to pH1N1 illness and vaccination.
Methods

Ethics Statement
This study was reviewed and provided with exempt status by the University of Michigan institutional review board. All study data were de-identified; no informed consent was required by the board in order for individuals to participate in the study.

Overview
We used the time trade off (TTO) approach to evaluate community-based values for avoiding pH1N1 illness and vaccination-related adverse events in adults and children. The TTO method estimates the value each respondent puts on avoiding a particular health outcome by estimating their willingness to trade quantity of life for quality of life. For example, a TTO question may value diabetes prevention by measuring the amount of time a person would be willing to give up from her life span to avoid living with diabetes (living instead a reduced number of years without diabetes). The resulting TTO values can be interpreted as subjective measures of quality of life, and are the basis for constructing quality adjusted life years (QALYs). QALYs are created by weighting a segment of time spent in a specific health state by the quality of life value associated with that health state. QALYs have been used to measure the morbidity associated with chronic illness over an extended time period [5]. In our study, to value the morbidity associated with the health states of pH1N1 illness and vaccination-related adverse events, we used TTO responses from our survey to calculate short-term QALY losses.

Study participants
We randomly sampled adult community members to complete an internet survey from a research panel designed to be statistically representative of the U.S. general adult population. The survey was administered by Knowledge Networks (Menlo Park, CA), which currently recruits new research panel members by mail from a published address-based sample frame that covers approximately 98% of U.S. households [6]. Non-internet households who choose to join the panel are provided with internet access and a laptop computer. Households who use their own computer and internet service to answer online surveys administered by Knowledge Networks receive small monthly stipends in exchange for their participation [7]. Demographic information collected for all new panel members includes gender, age, ages of their household members, race/ethnicity, income, and education level.

Study Procedures
Participation in the study required completion of a 15-minute survey during January 2010. Respondents answered a series of TTO questions to value hypothetical health state scenarios describing: uncomplicated pH1N1 illness, pH1N1 illness-related hospitalization, severe allergic reaction to the pH1N1 vaccine, and Guillain-Barré syndrome, a potential vaccine-related adverse event. Each of the 4 health state scenarios had 4 versions; each referencing a hypothetical person aged 1, 8, 35, and 70 years. Respondents were randomly assigned to value 2 different ages for each of the 4 scenarios, for a total of 8 TTO questions. The different age versions of each health state scenario were identical except for the description of usual activities, which included school/daycare for children and work/household responsibilities for adults. We instructed respondents to imagine a family member or friend that closely matched the age description in the scenario at hand. Respondents were also asked whether they had been vaccinated for pH1N1 or seasonal influenza, and whether they or anyone else in their family had ever experienced pH1N1 or seasonal influenza illness or an influenza vaccination-related adverse event.

TTO estimation
We used a modified bidding algorithm, combining binary and open ended response questions, to measure TTO amounts. This method is less prone to non-response problems compared to a single open ended question [8]. After presenting one age-specific health event related to pH1N1 illness or vaccination, we first asked respondents whether they would trade a fixed amount of time from the end of their life in exchange for avoiding the health event. (Figure 1) The amount of time that the respondents were asked to trade was randomized to reduce anchoring bias, with initial TTO amounts ranging from 2 days to 2 months for uncomplicated flu and severe allergic reaction outcomes, and 2 weeks to 1 year for hospitalization and Guillain-Barré syndrome outcomes. A follow up binary question offered a higher TTO amount if the initial response was “yes,” and a lower TTO amount if the initial response was “no.” These two binary questions were followed by an open-ended question which asked respondents for the maximum amount of time they would trade from the end of their life (in days, weeks, months, and years) to avoid the health state in question; this maximum TTO value was used for all analyses.

Analyses
We calculated descriptive statistics for TTO data, including means, medians, 5th and 95th percentiles, minimums and maximums. Confidence intervals around mean values were estimated using bootstrapping with replacement procedures [9]. We used the Kruskal-Wallis non-parametric test in unadjusted analyses to evaluate whether median values differed by scenario age. All summary statistics used unweighted data, due to the similarity between unweighted and weighted summary statistics. In our primary analysis, TTO amounts greater than life expectancy were reset to equal the respondent’s life expectancy, and we evaluated the effect of this in sensitivity analyses.

As respondents were asked their willingness to trade time from the end of their life, we adjusted for the potential impact of time preference by using a 3% discount rate to calculate discounted TTO values [5,10]. Dividing the respondents’ discounted TTO amount by their discounted life expectancy allowed us to calculate a short term QALY loss associated with the temporary health state in question.

To evaluate the association between TTO amounts and respondent/scenario characteristics, we used a generalized estimating equation negative binomial regression model. This type of regression model is bounded at 0 to account for the lower limit of TTO responses and adjusts for the correlations associated with multiple evaluations per respondent [11]. Using the undiscounted TTO amounts reported for the four different health states as the dependent variables, the four final regression models each included as independent variables: scenario age, gender, respondent age, education, race/ethnicity, having a child under the age of 18, vaccination status, and experience with the health state in question. The goodness of fit of each model was measured using a test of concordance between the observed and predicted TTO values [12].

Results

Respondents
The survey was sent to 1,110 members of the survey panel. Of those invited by email to participate in the online survey, 65%
completed the survey (n = 718); 9% of respondents were eliminated from the primary analysis due to missing or invalid responses, leaving a final analysis sample size of n = 659. Observations were excluded from the analysis if TTO amounts were missing for more than half (4 or more) of the scenarios (n = 56), the responses in all four time metrics were equivalent (n = 2), or the TTO amount was nonsensical (e.g., 999999 months) (n = 1).

Demographic characteristics among those who responded to the survey were statistically different from those who did not respond to the survey for all demographic characteristics except location (country region and metropolitan status). Compared to non-responders, responders were more likely to be male, white, married, aged 45 or older, college educated, and earn more than $35,000 annually; respondents were also less likely to have a child under the age of 18 years. (p<0.05 for all)

Respondent characteristics included in the primary analysis are summarized in Tables 1, and 2. Without survey weights, 30% of respondents were male, 56% were married, 78% were white, non-Hispanic, 33% had a child under the age of 18 living at home, and 84% rated themselves in excellent/very good or good overall health. Forty two percent of all respondents had received the seasonal flu vaccine in the previous 12 months, and 21% had received the pH1N1 vaccine in this time period. Thirty one percent of respondents reported that they had experienced seasonal influenza themselves, and 18% had a family member who had experienced this illness at some point in the past. Three percent of respondents had experienced pH1N1 illness themselves, and 5% had a family member who had experienced this illness. Only a small fraction of respondents (1–2%, depending on question) reported that they had experienced a hospitalization related to influenza, or a side effect from an influenza vaccine, either personally or through a family member.

Descriptive statistics
Respondents were willing to trade a median of 7 undiscounted days to avoid a hospitalization related to pH1N1 influenza and 30 days to avoid Guillain-Barré syndrome, compared to a median of 2 and 4 undiscounted days to avoid uncomplicated pH1N1 illness and severe allergic reaction, respectively (Table 3). Due to the right skewed distribution for TTO amounts in all 4 health states (unsymmetrical, with the greatest proportion of respondents willing to trade 0 days), mean values were substantially higher and more variable than median values.

| Time trade-off question | Sample health state scenarios |
|-------------------------|-------------------------------|
| In the following questions, we will describe a scenario. When reading the scenario we would like you to think about a family member or friend that closely fits the age description of the scenario. After reading the scenario we would like you to think about what portion of your life, if any, you would be willing to trade off from the end of your life to avoid the situation described. When answering the following questions we would like you to personally imagine the situation. | For 1 year old child | For 35 year old adult |
| • Include the value of preventing the pain, suffering, inconvenience, and lost time for productive activities (paid work or work in the home) or leisure. | Uncomplicated H1N1 illness: | | Hospitalization: |
| Assume that you personally have [insert remaining years from life table left to live]. What portion of your life, if any, would you be willing to trade off from the end of your life to avoid this scenario in a [insert scenario age]? You can choose any amount of time in days, weeks, months or years. | For this next set of questions, we would like you to think of a 1 year old child in your family. During an episode of H1N1 flu: | For this next set of questions, we would like you to think of a 35 year old adult in your family. During an episode of H1N1 flu: | |
| Would you be willing to trade off 10 days in order to avoid this scenario? [Yes/No] | • The child is tussy and has a high fever. The child feels tired, has body aches and has coughing. | • The person has a high fever. The person feels tired, has body aches and has coughing. | |
| If No: Would you be willing to trade off 5 days? [Yes/No] | • The child is sick for a total of 1 week. | • The person has difficulty breathing. | |
| If Yes: Would you be willing to trade off 3 weeks? [Yes/No] | • For 3 days, the child has difficulty doing normal activities like playing and is unable to attend daycare or school. | After a couple of days of not getting any better, the person is hospitalized. | |
| What is the most time you would be willing to trade off? You may answer in more than one time category, but please note that your final answer will be totaled. (i.e. if you fill in 6 months and 1 year, your final answer will be 1 ½ years). You can also choose to trade no time. | • The child completely recovers and has no more problems related to having the flu. | At the hospital the person is given an IV for fluids and oxygen to help with breathing problems. They are treated for pneumonia with medication. | |
| __ days __ weeks __ months __ years | Guilain-Barré Syndrome: | After 1 week in the hospital, the person returns home. | |
| | Think back to the 1 year old child. About 2 weeks after receiving a vaccine: | After the hospitalization, it takes 1 more week for the person to return to normal activities like going to work or taking care of household responsibilities. The person completely recovers and has no more problems related to having the flu. | |
| | • The child experiences severe muscle weakness in his or her legs followed in his or her arms. | Severe allergic reaction: | |
| | • The child's hands and feet have cramps, tingling and numbness. The weakness spreads to the shoulders, face and chest. It becomes difficult to breath. | Think back to the 35 year old adult. About 5 minutes after receiving the vaccine: | |
| | • The child is very tussy and uncomfortable. | • The person develops flushing, sweating and swelling of the face. | |
| | • The child needs to be hospitalized for testing including a spinal tap (a needle is inserted into the spine to take fluid for the testing.) | • The person begins wheezing, has shortness of breath and difficulty breathing. | |
| | • While in the hospital the child is put on a machine to help with breathing. | • 911 is called and the person is taken by ambulance to the nearest hospital. At the hospital the person is admitted for an allergic reaction. | |
| | • After 2 weeks in the hospital, the child is sent home. | • The person is treated with medicines (antihistamines and steroid medications), given oxygen to help with breathing and IV for fluids. | |
| | • Recovery is gradual. In 1 year the child returns to usual health. | • The person is discharged the next day. | |

Figure 1. Time trade off question with sample health scenarios.
doi:10.1371/journal.pone.0027777.g001
Respondents were willing to trade a mean of 291 and 376 undiscounted days to avoid pH1N1-related illnesses and vaccination-related adverse events in children, compared to adults. Respondents were willing to trade a median of 3 and 14 undiscounted days to avoid pH1N1 illness and hospitalization in a 1 year old child, but were only willing to trade a median of 2 and 7 days to avoid these outcomes in a 70 year old adult. Likewise, respondents were willing to trade a median of 7 and 60 undiscounted days to prevent a severe vaccine allergic reaction and Guillain-Barré syndrome in a 1 year old child, but were only willing to trade a median of 2 and 28 days, to avoid these same outcomes in a 70 year old adult. (Table 3)

The median values for the loss in QALYs from pH1N1 illness and vaccination-related adverse events also exhibited a significant difference by scenario age (p-value<0.05 for all health states). (Table 4) For example, pH1N1-related hospitalization was associated with a 0.0007 median QALY loss for a 1 year old and a 0.0003 median QALY loss for a 70 year old. Likewise, Guillain-Barré syndrome was associated with a 0.0039 median QALY loss for a 1 year old and a 0.0012 median QALY loss for a 70 year old. Mean values were consistently higher and more variable than median values. (Table 4)

Regression analyses

After adjusting for respondent characteristics, the 1 year and 8 year old scenario ages were significantly associated with greater TTO amounts (compared with the 35 year old scenario age) in all four final regression models. (p-values<0.05, Table 5) Seventy year old scenario age was significantly associated with lower TTO amounts (compared to the 35 year scenario age) in the final regression models for hospitalization and Guillain-Barré syndrome outcomes. For all four health states, having less than a college degree was significantly associated with greater TTO amounts. (Table 5) Other demographic characteristic associations were not consistent across outcomes, however. Compared with a white, non-Hispanic reference group, being Hispanic or black, non-Hispanic, was significantly associated with greater TTO amounts for uncomplicated pH1N1 illness and allergic reaction only. Being over the age of 30 was significantly associated with greater TTO amounts. (Table 5) Seventy year old scenario age was significantly associated with lower TTO amounts (compared to the 35 year scenario age) in the final regression models for hospitalization and Guillain-Barré syndrome outcomes.

Respondent health characteristic associations were also inconsistent predictors of TTO amounts. Experience with uncomplicated pH1N1 illness and Guillain-Barré syndrome was significantly associated with greater TTO amounts for those respective health states, but experience with pH1N1-related hospitalization and severe allergic reaction was not significantly associated with the TTO amounts for these outcomes. Compared to respondents that had not been vaccinated for pH1N1, those that had been vaccinated were willing to trade significantly more time to avoid a pH1N1-related hospitalization (p-value = 0.03) but were also willing to trade more time to avoid both vaccination related adverse events. (p-value<0.05 for both).

Respondent’s gender, and having a child under 18, did not significantly impact TTO responses. Concordance coefficients, used to measure the goodness of fit of our models, ranged from 0.071 to 0.129. All coefficients were significantly greater than zero, indicating that there was a significant and positive correlation between our observed and predicted TTO values. (Table 5) Sensitivity analyses which excluded respondents who traded

---

Table 1. Respondent demographic characteristics (n = 659).

| Characteristic                  | Unweighted | Weighted$^1$ |
|--------------------------------|------------|--------------|
| Gender                         |            |              |
| Male                           | 49.9%      | 49.8%        |
| Female                         | 50.1%      | 50.2%        |
| Age                            |            |              |
| 18–29                          | 15.9%      | 20.6%        |
| 30–44                          | 24.4%      | 27.7%        |
| 45–59                          | 33.9%      | 27.7%        |
| 60+                            | 25.8%      | 24.0%        |
| Education                      |            |              |
| Less than High School          | 11.2%      | 12.4%        |
| High School                    | 33.6%      | 30.3%        |
| Some College                   | 26.4%      | 28.3%        |
| Bachelor’s degree or higher    | 28.8%      | 29.0%        |
| Race                           |            |              |
| White, Non-Hispanic            | 77.7%      | 70.4%        |
| Black, Non-Hispanic            | 7.7%       | 10.4%        |
| Other, Non-Hispanic            | 2.6%       | 5.4%         |
| Hispanic                       | 10.2%      | 12.7%        |
| 2+ races, Non-Hispanic         | 1.8%       | 1.1%         |
| Marital Status                 |            |              |
| Married                        | 55.5%      | 52.3%        |
| Single (never married)         | 21.5%      | 23.3%        |
| Divorced                       | 11.1%      | 12.8%        |
| Widowed                        | 6.1%       | 5.0%         |
| Separated                      | 1.2%       | 2.0%         |
| Living with partner            | 4.6%       | 4.6%         |
| Household Income               |            |              |
| <3 times poverty level         | 44.3%      | 43.2%        |
| ≥3 times poverty level         | 45.4%      | 45.3%        |
| Don’t Know                     | 10.3%      | 11.5%        |
| Regions                        |            |              |
| Northeast                      | 19.3%      | 19.1%        |
| Midwest                        | 21.5%      | 20.4%        |
| South                          | 36.1%      | 37.8%        |
| West                           | 23.1%      | 22.7%        |
| Global Health                  |            |              |
| Excellent/Very Good            | 47.6%      | 45.8%        |
| Good                           | 36.0%      | 38.1%        |
| Fair                           | 13.5%      | 13.4%        |
| Poor                           | 2.9%       | 2.7%         |
| Child Under 18 Living at Home  | 32.5%      | 32.5%        |
| TTO questions hard to answer   | 51.0%      | 51.4%        |
| Households with Internet       | 62.2%      | 63.6%        |

$^1$ Post stratification weights were provided by Knowledge Networks to account for sampling and non-response bias.

doi:10.1371/journal.pone.0027777.t001
amounts larger than life expectancy yielded very similar results to the primary analysis, which included these respondents with their TTO amounts reset to their life expectancy (results not shown).

**Discussion**

This study reports community values for avoiding pH1N1 illness-related outcomes and vaccination-related adverse events in the U.S. On average, respondents’ values for avoiding pH1N1-related health events and vaccination-related adverse events were aligned with the portrayed severity of these events in our survey. Compared to pH1N1 illness-related hospitalization, respondents were willing to trade less time to avoid uncomplicated pH1N1 illness and a severe allergic reaction from vaccination, across all scenario ages. Respondents were willing to trade the greatest amount of time to avoid the most severe outcome, Guillain-Barré syndrome. This relative ranking of these TTO values across outcomes is consistent with previous findings for outcomes associated with seasonal influenza illness and vaccine related adverse events [3]. In regression analyses, 1 year and 8 year old scenario ages were consistently associated with greater TTO amounts, indicating that the public may give preference to preventing pH1N1 illness and vaccine-related health outcomes in children compared with adults. These data are consistent with earlier findings that indicate that community members may prefer to prioritize child health [3,13,14].

These findings are also consistent with the ACIP’s recommendations in July of 2009 which stated that children and young adults aged 6 months–25 years should be among those prioritized for pH1N1 vaccination, and that children 6 month–4 years should be one of the groups prioritized under a scenario of limited vaccine supply [1]. These recommendations were made based on data of disease prevalence and risk of complications, and some limited data from community engagement exercises performed as part of pandemic preparedness [15]. Also considering these new preference data obtained from community members after the recent pH1N1 influenza pandemic may help policy makers better define key target groups to prioritize for vaccination during the next influenza pandemic.

Our analysis also indicates that certain characteristics of community members may be significant predictors of health state valuations. In adjusted analyses, we found that respondents with less than a bachelor’s degree were willing to trade significantly more time than those with a higher level of education to avoid all four health states, controlling for other variables in a multivariate regression. This finding is not consistent with values elicited for seasonal influenza, and may represent a finding that is important to note in light of the novel nature of pH1N1 compared to seasonal influenza [3]. Hispanic and black, non-Hispanic respondents were also willing to trade significantly more time than white respondents to avoid uncomplicated pH1N1 illness and severe allergic reaction. This statistical association between respondent race and health state valuation is consistent with values elicited from community members for seasonal influenza and other health states [3,16]. Although no consensus exists regarding the cause of the association, one possible explanation is

| Characteristic | Unweighted | Weighted 1 |
|----------------|------------|------------|
| Received pH1N1 Vaccine in past 12 months | 20.8% | 19.8% |
| Received Seasonal Influenza Vaccine in past 12 months | 41.7% | 40.2% |
| Experienced pH1N1 Influenza Illness, Self | 3.2% | 4.3% |
| Experienced pH1N1 Influenza Illness, Family Member | 5.3% | 5.3% |
| Experienced Seasonal Influenza Illness, Self | 31.2% | 32.3% |
| Experienced Seasonal Influenza Illness, Family Member | 17.5% | 17.7% |
| Experienced pH1N1-Related Hospitalization, Self | 0.2% | 0.1% |
| Experienced pH1N1-Related Hospitalization, Family member | 1.8% | 1.8% |
| Experienced Seasonal Influenza-Related Hospitalization, Self | 0.8% | 1.3% |
| Experienced Seasonal Influenza-Related Hospitalization, Family Member | 2.6% | 3.0% |
| Experienced Severe Allergic Reaction to pH1N1 vaccine, Self | 0.5% | 0.5% |
| Experienced Severe Allergic Reaction to pH1N1 vaccine, Family Member | 0.2% | 0.1% |
| Experienced Severe Allergic Reaction to Seasonal Influenza vaccine, Self | 1.4% | 1.5% |
| Experienced Severe Allergic Reaction to Seasonal Influenza vaccine, Family Member | 1.2% | 1.2% |
| Experienced pH1N1 Guillain-Barré Syndrome, Self | 0.3% | 0.4% |
| Experienced pH1N1 Guillain-Barré Syndrome, Family Member | 0.0% | 0.0% |
| Experienced Seasonal Influenza Guillain-Barré Syndrome, Self | 0.2% | 0.2% |
| Experienced Seasonal Influenza Guillain-Barré Syndrome, Family Member | 0.3% | 0.6% |

1 Post stratification weights were provided by Knowledge Networks to account for sampling and non-response bias.

doi:10.1371/journal.pone.0027777.t002
Table 3. Time-tradeoff amounts for 2009 pandemic influenza (A) H1N1 illness and vaccination-related adverse events.

| Health Scenario                              | Undiscounted time-tradeoff amounts (days from end of life) | Discounted (3%) time-tradeoff amounts (days) |
|----------------------------------------------|----------------------------------------------------------|---------------------------------------------|
|                                              | n  | Mean | 95% CI | Median | p-value | 5th | 95th | min – max | Mean | 95% CI | Median | p-value | 5th | 95th | min – max |
| Uncomplicated pH1N1 illness                  |    |      |        |        |         |     |      |          |      |        |        |         |     |      |          |
| 1-year old                                   | 296 | 415  | 268–668 | 3      | 0       | 182  | 0 – 13514 | 24.2 | 145–406 | 1.1   | 0     | 87.0  | 0 – 8217 |
| 8-year old                                   | 345 | 261  | 170–432 | 3      | 0       | 131  | 0 – 13514 | 137.0 | 81–242  | 1.2   | 0     | 458.1 | 0 – 8217 |
| 35-year old                                  | 349 | 155  | 103–244 | 1      | 0       | 73   | 0 – 6940  | 75.5 | 48–135  | 0.30  | 0     | 391.8 | 0 – 5310 |
| 70-year old                                  | 307 | 85   | 59–126  | 2      | 0       | 47   | 0 – 2726  | 43.2 | 20–66   | 0.72  | 0     | 252.4 | 0 – 1508 |
| All ages                                     | 1477| 226  | 177–293 | 2      | 0.0177  | 0    | 731    | 0 – 13514 | 118.0 | 95.5  | 0.66  | 0.0436 | 0    | 222.3 | 0 – 8217 |
| pH1N1 illness-related hospitalization        |    |      |        |        |         |     |      |          |      |        |        |         |     |      |          |
| 1-year old                                   | 297 | 442  | 303–682 | 14     | 0       | 182  | 0 – 13514 | 24.2 | 153–394 | 5.1   | 0     | 940.0 | 0 – 8217 |
| 8-year old                                   | 342 | 374  | 258–558 | 14     | 0       | 182  | 0 – 13514 | 190.4 | 126–316 | 4.5   | 0     | 877.7 | 0 – 8217 |
| 35-year old                                  | 358 | 242  | 159–400 | 7      | 0       | 73   | 0 – 10958 | 125.2 | 80–222  | 1.9   | 0     | 497.5 | 0 – 6906 |
| 70-year old                                  | 307 | 108  | 79–157  | 7      | 0       | 44   | 0 – 3653  | 52.04| 36–77   | 2.6   | 0     | 245.1 | 0 – 1650 |
| All ages                                     | 1304| 291  | 235–362 | 7      | 0.0003  | 0    | 1391   | 0 – 13514 | 151.7 | 115–197| 3.2   | 0.0007 | 0    | 527.8 | 0 – 8217 |
| Severe allergic reaction                     |    |      |        |        |         |     |      |          |      |        |        |         |     |      |          |
| 1-year old                                   | 291 | 313  | 196–516 | 7      | 0       | 91   | 0 – 13514 | 183.3 | 108–330 | 2.9   | 0     | 392.7 | 0 – 8217 |
| 8-year old                                   | 341 | 307  | 208–499 | 6      | 0       | 169  | 0 – 13514 | 156.0 | 96–259  | 2.1   | 0     | 608.5 | 0 – 8217 |
| 35-year old                                  | 352 | 180  | 112–321 | 2      | 0       | 545  | 0 – 10958 | 94.02| 54–189  | 0.50  | 0     | 251.5 | 0 – 7266 |
| 70-year old                                  | 301 | 88   | 64–141  | 2      | 0       | 500  | 0 – 3653  | 40.03 | 28–62   | 0.82  | 0     | 245.1 | 0 – 1650 |
| All ages                                     | 1285| 222  | 176–289 | 4      | 0.0002  | 0    | 731    | 0 – 13514 | 118.0 | 90–160 | 1.2   | 0.0147 | 0    | 337.3 | 0 – 8217 |
| Guillain-Barré Syndrome                      |    |      |        |        |         |     |      |          |      |        |        |         |     |      |          |
| 1-year old                                   | 292 | 527  | 391–774 | 60     | 0       | 219  | 0 – 13514 | 279.3 | 189–421 | 26.7  | 0     | 941.1 | 0 – 8217 |
| 8-year old                                   | 340 | 488  | 362–685 | 60     | 0       | 200  | 0 – 13514 | 243.2 | 170–373 | 22.0  | 0     | 960.5 | 0 – 8217 |
| 35-year old                                  | 351 | 330  | 229–479 | 30     | 0       | 109  | 0 – 10958 | 173.2 | 118–276 | 8.4   | 0     | 543.6 | 0 – 7266 |
| 70-year old                                  | 303 | 158  | 122–244 | 28     | 0       | 545  | 0 – 6544  | 73.45| 56–114  | 8.0   | 0     | 283.7 | 0 – 3351 |
| All ages                                     | 1286| 376  | 317–454 | 30     | 0.0001  | 0    | 1641   | 0 – 13514 | 192.3 | 157–244| 13.6  | 0.0001 | 0    | 614.9 | 0 – 8217 |

1Using unweighted data.

2To generate confidence intervals around our mean values, we used bootstrap re-sampling of size equal to the sample size (approximately 1300, depending on the health state) with 3000 iterations. From each of the 3000 bootstrap samples generated, we calculate the overall means and means by scenario age to create a sampling distribution around the original mean values.

3Kruskal-Wallis test evaluated whether median values differed by scenario age.

doi:10.1371/journal.pone.0027777.t003
that respondents without a usual source of care may demonstrate a stronger preference to avoid illness. Previous research has shown that compared to white individuals, Hispanic and black individuals are less likely to have a doctor's office as their usual source of care, regardless of insurance coverage, family income and geographic region [17,18]. As we did not measure usual source of care, it is possible that this variable confounded the race association found in our analysis. Future research should assess respondents' usual source of care and parse out its contribution, along with race and other factors, to health state preferences.

An important limitation of this study is that we used a stated preference approach to value health states. These stated preferences may not reflect the actual choices that these respondents may make when faced with a choice between accepting or rejecting vaccination. In addition, we used the TTO approach for valuing health states, but other methods may have produced different results [19]. As with most vignettes used to estimate preferences, the scenarios used in our survey were concise descriptions of complex health events; adding additional dimensions of health to these vignettes may have influenced respondents’ valuations [20].

We also do not know the generalizability of these results. Our measurement of public values for health states related only to this influenza pandemic, and may not relate to more severe influenza pandemics. Another limitation is that both the timing of our survey and the representativeness of the sample may not have been optimal for determining truly representative public values. The survey was fielded after the fall epidemic had passed and the vaccination program had been initiated, and so may not reflect the important public values that were relevant during the time that vaccination program decisions were being made. Data have shown that the public’s concern about getting sick from pH1N1 as well as their concern about the safety risks associated with vaccination declined over the duration of the epidemic [21]. Also, compared to non-respondents, our respondents were more likely to be college educated, married, white, older males, and thus may have reported values different from a more population representative sample.

In this study we measured values for health outcomes related to pH1N1 illness and vaccination from the general U.S. public, and not specifically from those that have experienced pH1N1 illness. Previous studies have found that compared to a sample of persons

| Loss in QALYs                                      | n  | Mean | Lower bound | Upper bound | Median | p-value | 5th | 95th | Percentile Range | Range |
|----------------------------------------------------|----|------|-------------|-------------|--------|---------|-----|-----|------------------|-------|
| Uncomplicated pH1N1 illness                        |    |      |             |             |        |         |     |     |                  |       |
| 1-year old                                         | 296| 0.0394| 0.0251      | 0.0625      | 0.0001 | 0.1708  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 8-year old                                         | 345| 0.0218| 0.0132      | 0.0377      | 0.0001 | 0.0907  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 35-year old                                        | 349| 0.0138| 0.0085      | 0.0247      | 0.0000 | 0.0551  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 70-year old                                        | 307| 0.0092| 0.0059      | 0.0159      | 0.0001 | 0.0427  | 0   | 0.5226 |                  | 0 – 0.5226 |
| All ages                                           | 1297| 0.0207| 0.0156      | 0.0267      | 0.0001 | 0.0211  | 0   | 0.8020 |                  | 0 – 1.0000 |
| pH1N1 illness-related hospitalization              |    |      |             |             |        |         |     |     |                  |       |
| 1-year old                                         | 297| 0.0391| 0.0266      | 0.0613      | 0.0007 | 0.1851  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 8-year old                                         | 342| 0.0304| 0.0200      | 0.0477      | 0.0006 | 0.1174  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 35-year old                                        | 358| 0.0217| 0.0140      | 0.0362      | 0.0003 | 0.1125  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 70-year old                                        | 307| 0.0104| 0.0073      | 0.0160      | 0.0003 | 0.0496  | 0   | 0.4034 |                  | 0 – 0.4034 |
| All ages                                           | 1304| 0.0253| 0.0202      | 0.0320      | 0.0004 | 0.1118  | 0   | 1.0000 |                  | 0 – 1.0000 |
| Severe allergic reaction                            |    |      |             |             |        |         |     |     |                  |       |
| 1-year old                                         | 291| 0.0317| 0.0195      | 0.0536      | 0.0003 | 0.0853  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 8-year old                                         | 341| 0.0251| 0.0162      | 0.0401      | 0.0003 | 0.1017  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 35-year old                                        | 352| 0.0166| 0.0092      | 0.0325      | 0.0001 | 0.0496  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 70-year old                                        | 301| 0.0074| 0.0051      | 0.0114      | 0.0001 | 0.0366  | 0   | 0.2183 |                  | 0 – 0.2183 |
| All ages                                           | 1285| 0.0201| 0.0156      | 0.0266      | 0.0002 | 0.0691  | 0   | 1.0000 |                  | 0 – 1.0000 |
| Guillain-Barre Syndrome                             |    |      |             |             |        |         |     |     |                  |       |
| 1-year old                                         | 292| 0.0475| 0.0329      | 0.0692      | 0.0039 | 0.1533  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 8-year old                                         | 340| 0.0391| 0.0281      | 0.0584      | 0.0034 | 0.1381  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 35-year old                                        | 351| 0.0300| 0.0204      | 0.0460      | 0.0012 | 0.1300  | 0   | 1.0000 |                  | 0 – 1.0000 |
| 70-year old                                        | 303| 0.0135| 0.0103      | 0.0194      | 0.0012 | 0.0640  | 0   | 0.4433 |                  | 0 – 0.4433 |
| All ages                                           | 1286| 0.0325| 0.0268      | 0.0403      | 0.0019 | 0.1236  | 0   | 1.0000 |                  | 0 – 1.0000 |

1Using unweighted data.
2To generate confidence intervals around our mean values, we used bootstrap re-sampling of size equal to the sample size (approximately 1300, depending on the health state) with 3000 iterations. From each of the 3000 bootstrap samples generated, we calculate the overall means and means by scenario age to create a sampling distribution around the original mean values.
3Kruskal-Wallis test evaluated whether median values differed by scenario age.
doi:10.1371/journal.pone.0027777.t004

Table 4. Loss in quality adjusted life years (QALYs) for 2009 pandemic influenza (A) H1N1 illness and vaccination-related adverse events.
who have not experienced an ill health state, those who have experienced it are typically willing to trade less time to avoid the illness [22,23,24]. Many of these studies, however, have focused on chronic illnesses, and there is limited evidence as to how experience or familiarity with a short term health state may influence preferences for avoiding these health outcomes. Van Hoek, et al. estimated a 0.008 QALY loss attributable to pH1N1 in a sample of confirmed pH1N1 cases using the EQ-5D questionnaire. This QALY loss among those who have experienced pH1N1 illness is difficult to compare to our results, however, because it averages over a sample of confirmed cases with and without complications [25]. In our adjusted analyses, we found that those who experienced uncomplicated pH1N1 illness or Guillain-Barré syndrome were willing to trade significantly more time to avoid these health states compared with those without experience. (p-value <0.05 for both) More research is needed to determine if such differences can be measured among other experienced temporary health states.

Our findings suggest that the community-based values for avoiding health events related to pH1N1 illness and vaccination are consistent with the severity of the outcomes. These data also suggest that the public places a greater value on preventing outcomes in children, compared to adults, consistent with previous findings from seasonal influenza. The valuations derived from

Table 5. Multivariate regression results: Time trade-off amounts by scenario age, sociodemographics, illness experience, and vaccination status, predicted number of days traded.

| Predictors | Uncomplicated pH1N1 Illness \( ^1 \) | pH1N1 Illness-related Hospitalization \( ^1 \) | Severe Allergic Reaction \( ^1 \) | Guillain-Barré Syndrome \( ^1 \) |
|-----------|-------------------------------------|---------------------------------|-------------------------------|---------------------------|
| Predictor  | Estimate \( SE \)             | Estimate \( SE \)                | Estimate \( SE \)              | Estimate \( SE \)         |
| Scenario Age |                                    |                                 |                               |                           |
| 1 year     | 212.06* \( SE 37.01 \)          | 315.06* \( SE 58.43 \)         | 179.30* \( SE 27.74 \)        | 362.55* \( SE 37.06 \)   |
| 8 years    | 133.87* \( SE 22.99 \)          | 251.47* \( SE 38.29 \)         | 178.54* \( SE 29.05 \)        | 333.34* \( SE 31.00 \)   |
| 35 years   | 88.78 \( SE 14.85 \)            | 181.07 \( SE 30.35 \)          | 102.06 \( SE 16.23 \)         | 242.78 \( SE 25.73 \)    |
| 70 years   | 82.08 \( SE 14.85 \)            | 122.77* \( SE 20.45 \)         | 80.64 \( SE 13.96 \)          | 189.30* \( SE 18.70 \)   |
| Gender     |                                    |                                 |                               |                           |
| Male       | 134.10 \( SE 26.92 \)           | 200.55 \( SE 41.21 \)          | 108.78 \( SE 20.23 \)         | 229.98 \( SE 29.66 \)    |
| Female     | 104.70 \( SE 17.07 \)           | 208.23 \( SE 32.77 \)          | 146.69 \( SE 27.87 \)         | 322.87 \( SE 41.48 \)    |
| Respondent Age |                                    |                                 |                               |                           |
| 18–29 yrs | 42.86 \( SE 12.81 \)            | 122.78 \( SE 47.80 \)          | 77.00 \( SE 20.49 \)          | 164.66 \( SE 31.36 \)    |
| 30–44 yrs | 127.30* \( SE 43.66 \)          | 262.50 \( SE 85.75 \)          | 123.10 \( SE 44.75 \)         | 321.42* \( SE 76.84 \)   |
| 45–59 yrs | 119.70* \( SE 29.61 \)          | 215.97 \( SE 52.96 \)          | 143.05 \( SE 35.93 \)         | 277.05* \( SE 47.67 \)   |
| 60 & above | 207.41* \( SE 51.82 \)          | 205.09 \( SE 44.66 \)          | 153.84 \( SE 40.95 \)         | 312.47* \( SE 54.33 \)   |
| Education  |                                    |                                 |                               |                           |
| <High School | 307.60* \( SE 112.78 \)         | 271.93* \( SE 82.06 \)         | 197.52* \( SE 55.70 \)        | 328.23* \( SE 68.15 \)   |
| High School | 231.97* \( SE 55.77 \)          | 322.30* \( SE 69.34 \)         | 295.44* \( SE 77.68 \)        | 512.44* \( SE 97.07 \)   |
| Some College | 159.83* \( SE 34.98 \)          | 266.07* \( SE 75.05 \)         | 125.63* \( SE 30.76 \)        | 239.68* \( SE 44.32 \)   |
| Bachelors & above | 37.24 \( SE 10.28 \)          | 84.92 \( SE 22.89 \)          | 40.57 \( SE 10.34 \)          | 139.32 \( SE 19.30 \)   |
| Race/Ethnicity |                                |                                 |                               |                           |
| White, Non- Hispanic | 100.84 \( SE 16.67 \)          | 179.64 \( SE 28.27 \)          | 102.87 \( SE 16.67 \)         | 248.76 \( SE 25.90 \)    |
| Black, Non- Hispanic | 538.04* \( SE 192.98 \)       | 456.50 \( SE 206.98 \)         | 299.25* \( SE 87.33 \)        | 406.62 \( SE 125.60 \)   |
| Other, Non- Hispanic | 55.84 \( SE 27.92 \)          | 143.50 \( SE 65.01 \)          | 113.87 \( SE 39.06 \)         | 246.96 \( SE 133.04 \)   |
| Hispanic   | 383.92* \( SE 109.84 \)         | 342.61 \( SE 125.27 \)         | 342.63* \( SE 117.27 \)       | 421.06 \( SE 132.49 \)   |
| Children <18 yrs |                                |                                 |                               |                           |
| No         | 144.92 \( SE 29.99 \)           | 216.02 \( SE 42.25 \)          | 132.97 \( SE 26.97 \)         | 244.80 \( SE 32.11 \)    |
| Yes        | 98.31 \( SE 21.74 \)            | 182.12 \( SE 44.81 \)          | 116.23 \( SE 24.89 \)         | 340.97 \( SE 62.31 \)    |
| Experience with Illness (self/family) |                                |                                 |                               |                           |
| No         | 78.28 \( SE 12.19 \)            | 201.51 \( SE 26.82 \)          | 125.72 \( SE 17.08 \)         | 271.10 \( SE 24.55 \)    |
| Yes        | 236.97* \( SE 54.85 \)          | 298.85 \( SE 144.91 \)         | 221.94 \( SE 106.39 \)        | 1234.26* \( SE 688.48 \) |
| pH1N1 Vaccination Status |                                |                                 |                               |                           |
| No         | 115.07 \( SE 17.92 \)           | 177.67 \( SE 27.00 \)          | 108.86 \( SE 16.52 \)         | 242.64 \( SE 24.51 \)    |
| Yes        | 189.87 \( SE 46.87 \)           | 347.31* \( SE 90.24 \)         | 231.03* \( SE 64.04 \)        | 425.03* \( SE 92.75 \)   |

*p-value <0.05; indicates statistical difference of value compared to the reference group.

Reference group.

Model goodness-of-fit concordance coefficients and confidence intervals- uncomplicated pH1N1 illness: 0.129 (95% CI 0.090, 0.168), pH1N1 illness-related hospitalization: 0.071 (95% CI: 0.051,0.092), Severe Allergic Reaction: 0.095 (95% CI: 0.071,0.118), Guillain-Barré syndrome: 0.112 (95% CI: 0.089,0.135).
these data can be used along with other decision-making factors during the development of pandemic influenza vaccination programs in the U.S. and the allocation of future pandemic vaccine supplies.

Acknowledgments

The views expressed are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention.

References

1. National Center for Immunization and Respiratory Diseases (2009) Use of influenza A (H1N1) 2009 monovalent vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). 2009. MMWR Recomm Rep 58: 1–6.
2. Prosser LA, Bridges CB, Uyeki TM, Rego VH, Ray GT, et al. (2005) Values for preventing influenza-related morbidity and vaccine adverse events in children. Health Qual Life Outcomes 3: 18.
3. Prosser LA, Payne K, Rusnak D, Shi P, Uyeki T, et al. (2011) Valuing health across the lifespan: health state preferences for seasonal influenza illnesses in patients of different ages. Value Health 14: 133–143.
4. Johnston SS, Rousculp MD, Palmer LA, Chu BC, Mahadevia PJ, et al. (2010) Employees’ willingness to pay to prevent influenza. Am J Manag Care 16: e205–214.
5. Gold MR (1996) Cost-effectiveness in health and medicine. New York: Oxford University Press. xiii. 425 p.

Author Contributions

Conceived and designed the experiments: TAL LAP MIM AEF. Analyzed the data: AG. Wrote the paper: TAL LAP MIM AEF KL.