How Does the Public Evaluate Vaccines for Low-Incidence, Severe-Outcome Diseases? A General-Population Choice Experiment

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Abstract

Background Because immunizing large numbers of healthy people could be required to reduce a relatively small number of infections, disease incidence has a large impact on cost effectiveness, even if the infection is associated with very serious health outcomes. In addition to cost effectiveness, the US Advisory Committee on Immunization Practices requires evidence of stakeholders' values and preferences to help inform vaccine recommendations. This study quantified general-population preferences for vaccine trade-offs among disease severity, disease incidence, and other vaccine features.

Methods We developed a best-practice discrete choice experiment survey and administered it to 1185 parents of children aged 12–23 years and 1203 young adults aged 18–25 years from a national opt-in consumer panel. The data were analyzed using exploded-logit latent-class analysis.

Results Latent-class analysis identified two classes with similar relative-importance weights in both samples. One of the two classes represented about half the samples and had preferences consistent with well-structured, logically ordered, and acceptably precise stated-preference utility. Preferences for the other half of the samples were poorly defined over the ranges of vaccine and disease attributes evaluated. Both parents and young adults in the first class evaluated protection from a disease with 1 in 100 incidence and full recovery at home as having statistically the same preference utility as a disease with 1 in 1 million incidence requiring hospitalization and resulting in permanent deafness.

Conclusions The results suggest that vaccines that protect against low-incidence, severe-outcome diseases, provide 'peace of mind' benefits not captured by standard health-outcome metrics. The fact that half the respondents had poorly defined vaccine preferences is a reminder of the challenges of implementing patient-centric vaccine decision making.

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Key Points for Decision Makers

The value of low-incidence, severe-outcome diseases for about half of a large sample of the US public was found to be much larger than typically is indicated in cost-effectiveness assessments.

The value of vaccines to protect against low-incidence, severe-outcome diseases is at least as large as vaccines against high-incidence, less severe-outcome diseases.

About half of the same sample had unexpectedly ordered and imprecise vaccine preferences. This result is consistent with the well-known problematic state of vaccine knowledge and vaccination decision making among a substantial portion of the US public.

1 Introduction

In the United States (US) the Advisory Committee on Immunization Practices (ACIP) provides expert external advice and guidance to the Centers for Disease Control (CDC) on controlling vaccine-preventable diseases. Key factors considered in developing recommendations include the balance of benefits and harms, type of evidence, and health-economic analyses [1]. The ACIP also requires evidence of stakeholders' values and preferences for the purpose of informing vaccine recommendations [2].

The evaluation framework requires that the evidence includes a 'summary of findings of cost-effectiveness analyses (CEAs) of the vaccine in the target population'. CEA compares the costs of providing immunizations with the health benefits of reducing infection incidence. Even if the infection is associated with very serious health outcomes, including death, sufficiently small incidence will result in a vaccine having such a high cost per case avoided that it would fail a conventional cost-effectiveness test.

An international panel of clinical and health economic experts concluded that "the currently prevailing logic of cost-effectiveness … was considered deficient as it does not capture well-established social preferences regarding health care resource allocation" [3]. Erickson and colleagues proposed a comprehensive framework that went beyond cost effectiveness for evaluating new vaccines [4]. To be useful, such a framework should provide guidance on how to compare diseases with low incidence but high fatality and severe-sequelae rates with diseases with high incidence, low fatality rates, and mild sequelae. The authors suggest that evaluations of immunization programs should include acceptability as indicated by 'public perception of disease risk, severity, fear, and demand for disease control'.

Such public perceptions of value can be significantly different than those obtained with conventional CEA methods. For example, Prosser et al. [5] found that US parents and other adults would pay $500 to reduce the risk of pneumococcal meningitis from 21 per 100,000 to 6 per 100,000, which is equivalent to approximately $3.3 million per case avoided, orders of magnitude larger than conventional cost-effectiveness thresholds.

This study aimed to better understand and quantify the patient and population benefit-risk trade-off preferences among vaccine attributes, particularly with regard to disease incidence and sequelae severity. A secondary interest of this study is to compare vaccination preferences of parents of teen-age and college-age children with the preferences of college-age individuals themselves for certain infectious diseases for which college-age individuals are at elevated risks.

2 Materials and Methods

2.1 Study Design

An online survey used a discrete choice experiment to elicit respondents' evaluations of tradeoffs among vaccine attributes [6, 7]. The study design followed good research practices for health-related choice-experiment studies [8]. Vaccine attributes and levels were identified and defined in consultation with clinical experts and pretested in face-to-face interviews with 18 adult parents of at least one child between the ages of 16 and 25 years, and seven young adults between the ages of 18 and 25 years. All pretest interviews were conducted by at least two experienced interviewers using a think-aloud protocol in which respondents were asked to read the survey instrument aloud and were encouraged to express their thoughts related to survey information materials and questions. Details on the pretest interviews are contained in Appendix A in the electronic supplementary material (ESM).

The final web-enabled survey instrument included choice questions that required respondents to evaluate constructed vaccines, which were defined by five attributes. Three of these attributes related to the disease that the vaccine is protective against:

- Effect of the disease (*Effect*)
- How many people get the disease each year (*Rate*)
- How the disease spreads (*Mode*)

The remaining two attributes describe the vaccine itself:

- How long the vaccine lasts (*Duration*)
- Cost to you (*Cost*)

Each of these five attributes can assume one of three or more levels, which are shown in Table 1. Each unique vaccine profile in the choice questions was described based on the level assigned for each attribute.

Because our goal is to understand respondents' willingness to accept tradeoffs between disease severity and incidence, we do not name any diseases in the direct choice-experiment questions. Respondents could have reactions to disease labels that would confound the experiment. However, various combinations of disease attribute levels can describe a wide range of vaccine-preventable diseases, such as seasonal influenza, invasive meningococcal disease, pertussis, and herpes zoster.

Experimentally constructed vaccine profiles were arranged in pairs, and respondents were asked to choose one of four options: (1) a vaccine to protect against disease A; (2) a vaccine to protect against disease B; (3) vaccines to

Table 1 Attributes and attribute levels used in the discrete choice experiment

Attribute	Levels
Effect of the disease	Moderately ill—full recovery at home: People feel moderately ill for about 1 week but can recover at home. They will not have any long-term problems because of the disease
	Severely ill—full recovery after hospital stay: People feel severely ill and spend 2 weeks in hospital. They will not have any long-term problems because of the disease
	Total deafness: People become severely ill and spend 2 weeks in hospital. Even after receiving the best interventions, people become permanently deaf. They cannot hear at all in any situation and hearing aids do not work
	Lose both legs: People become severely ill and spend 2 weeks in hospital. Even after receiving the best interventions, the infection damages people's legs so badly that they must be amputated
	Permanent brain damage: People become severely ill and spend 2 weeks in hospital. Even after receiving the best interventions, people have permanent brain damage and depend on others for feeding, toileting, dressing, and walking
	Death: People become severely ill and spend 2 weeks in hospital. Even after receiving the best intervention, people die from the disease
How many people get the disease and its effects each year	1 in 100 (1 person in a neighborhood) 1 in 1000 (1 person in a village) 1 in 10,000 (1 person in a small town) 1 in 100,000 (1 person in a medium-sized city) 1 in 1,000,000 (1 person in a large city)
Mode of exposure	Airborne: People could get the disease if they breathe air containing germs after an infected person coughs or sneezes
	Casual contact: Some germs are spread through casual contact with doorknobs, desks, toys, or railings that an infected person has touched
	Personal contact: Some germs can only spread through personal contact such as kissing, or sharing straws, drinks, or eating utensils with an infected person
How long the vaccine lasts	1 year 5 years 10 years
Cost to you	$50 $100 $300 $500

protect against both disease A and disease B; or (4) neither vaccine. If 'Both' or 'Neither' was selected, respondents were asked which vaccine they thought was more important. Thus, the response data consist of three possibilities: one vaccine is preferred to both another vaccine and to no vaccine, no vaccine is preferred to either of two vaccines, or both vaccines are preferred to no vaccine with an indication of which vaccine is more important. The last case provides a complete ordering of the three alternatives. Figure 1 shows an example choice question.

An experimental design determined how attribute levels were combined to describe disease profiles and profile pairings in each choice question. The experimental design was generated using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA) to optimize D-efficiency and maximize the statistical power available to estimate the preference or utility weight for each attribute level. Research on experimental subdesigns has found gains in efficiency from using multiple designs in the same study [9]. We developed two flat-prior designs, one of which optimized on main effects and one of which accommodated an interaction between

disease severity and incidence rate. Each design contained 32 subsets of three unique choice questions each. Respondents were randomly assigned to two subsets, one from each group. This procedure resulted in six trade-off questions for each respondent. SAS code used to generate the experimental design is contained in Appendix B in the ESM.

The final web-enabled survey instrument included several important features in addition to the preference elicitation and treatment experience questions, which were designed to both aid respondents in interpreting the survey and to provide indications of respondent comprehension and consistency. These additional features included informed consent, detailed attribute descriptions that could be recalled in pop-up windows by mousing over attribute labels, comprehension and reflection questions, a risk tutorial, and practice choice questions. The final web-enabled survey also collected respondents' demographic information, perceptions of risk of infectious disease with different degrees of severity and risk, attitudes and behaviors toward vaccines, and judgments about the value of receiving MenB vaccine-related information directly from a physician. This study received

Fig. 1 Example choice question

	Disease A	Disease B
Effect of the disease	Death	Deafness
How many people get the disease and its effects each year	1 in 1,000 (1,000 in 1 million)	1 in 100,000 (10 in 1 million)
How the disease spreads	Personal Contact	Personal Contact
How long the vaccine lasts	10 years	5 years
Cost to you	$50 ($5 per year of protection)	$300 ($60 per year of protection)

If you could choose a vaccine to protect yourself from one, both, or neither of these diseases, what would you choose?
- ○ Vaccine for disease A
- ○ Vaccine for disease B
- ○ Vaccines for both disease A and disease B
- ○ I would not choose either vaccine.

[If selected "both" or "neither"]
Which vaccine do you think is <u>more</u> important?

- ○ Vaccine for Disease A is more important
- ○ Vaccine for Disease B is more important

approval from a major research university Institutional Review Board.

2.2 Data Collection

The final version of the survey instrument was programmed by IPSOS, a market research company, for web-enabled administration. Members of the IPSOS national opt-in consumer panel were invited, via email or via their personalized online portal, to participate in the online survey. Panelists were eligible for the study if they met a basic set of inclusion criteria, i.e. ability to read and understand English, and being either a young adult aged 18–25 years or a parent of at least one child aged 12–25 years. Survey responses were

collected during three phases. Two soft launches collected data in July and August 2019. After each soft launch, these preliminary data were assessed to check that randomization processes were working properly and that attribute ranges were wide enough to induce tradeoffs among all the attributes. IPSOS fielded the final survey between 22 August and 2 October 2019. Demographics for the soft-launch samples can be found in Table S1 of the ESM.

2.3 Statistical Analysis

We performed recommended internal-validity tests on the data to assess data quality [10]. We identified respondents who always chose the alternative with the better level of a

single attribute, always chose the vaccine alternative in the same position (either A or B) or provided incorrect responses to quiz questions testing respondent comprehension of the attributes included in the choice questions [10]. Any of these response patterns can indicate that respondents were inattentive, did not understand the survey, or were using simplifying heuristics to avoid evaluating each choice question in detail. Additionally, we identified respondents who always selected either the 'Neither vaccine' or 'Both vaccines' alternative in every choice question. While this pattern of responses might be caused by inattention, it can also be an expression of very strong preferences for or against vaccines in general. We used probit models to test for systematic relationships between these strongly vaccine-hesitant or pro-vaccine choice patterns and respondent characteristics.

The main analysis evaluated the responses to the vaccine choice questions. Logit models were used to understand how respondents' choices between vaccines (including 'Both' and 'Neither') were associated with the characteristics of each vaccine option. Results from these models indicate the effect that changes in disease and vaccine characteristics would have on respondents' choices; thus, they are considered a measure of relative importance or utility of specific attribute levels in the questions. Latent-class, log-odds parameter estimates can be interpreted as relative utility weights. The utility specification used in the analysis is shown in Eq. 1:

$$U_{ij} = \beta_{ij}^{\text{Effect}}\text{Effect} + \beta_{ij}^{\text{Rate}}\ln(\text{Rate}) + \beta_{ij}^{\text{Rate}\times\text{Effect}}[\ln(\text{Rate}) \times \text{Effect}]$$
$$+ \beta_{ij}^{\text{Duration}}\text{Duration} + \beta_{ij}^{\text{Mode}}\text{Mode} + \beta_{ij}^{\text{Cost}}\text{Cost} + \gamma_i Z$$

$$(1)$$

where i indexes individuals with class-i preferences and j indexes vaccine profiles. Variable names are defined above. All vaccine variables are categorical vectors except for Rate, and continuous Rate is interacted with the Effect categories. Z is a vector of individual covariates.

Only differences in preference estimates between levels of the same attribute are interpretable and represent that specific change's relative importance in determining observed choices. Because choice-model preference estimates are confounded with a model-specific scale factor, raw utility weights cannot be directly compared between models [11]. However, utility weights can be rescaled relative to a consistent set of attribute differences; this normalizes cross-model scale differences and facilitates comparison and interpretation.

Because choice alternatives not only included 'Vaccine A', 'Vaccine B', or 'Neither vaccine' but also the option of choosing 'Both vaccines', the standard choice model requires modification. Appendix C in the ESM shows how sequential or 'exploded' logit was adapted for this question format. There are likely to be scale differences among the A/B vaccine alternatives and the 'Both' and 'Neither' alternatives.

Furthermore, it is likely there are scale differences between the A/B alternatives in the first question and the A/B alternatives in the second question generated from the 'Both' and 'Neither' choices. To account for heteroskedasticity in the two-stage question format, we obtained random-parameter estimates for alternative-specific constants corresponding to choosing one of the two vaccine alternatives, 'Both alternatives', and 'Neither alternative'. Hensher et al. [12] derived a formula for converting the random-parameter standard-deviation estimates to corresponding scale values. We also estimated scale controls for 'Both' and 'Neither' variants of the second question. After controlling for scale in the first question, the second-question scale estimates were not significantly different from 1, which is the normalized scale for the A/B alternatives in the first question. Hence, we report scale results only for the scale-adjusted first question.

The model specification assumed that observed respondent choices were the result of differences in the levels of each disease and vaccine attribute that define each choice alternative, and that were experimentally controlled. Furthermore, the models were structured to allow the importance of disease incidence to vary with the effects of the vaccine-preventable diseases. Furthermore, each class of respondents in the latent-class model was allowed to have unique importance weights. Because we quantified the values of vaccines that protect against diseases with different exposure risks and severity in a common preference-utility metric, we were able to identify combinations of risk and disease severity that yield similar vaccine preference values for respondents within each class. The resulting similar-utility bands enable comparisons between values for vaccines against high-incidence/low-severity diseases versus low-incidence/high-severity diseases.

In accordance with good-practice guidance to account for heterogeneity in respondents' preferences, we used latent-class analysis to estimate relative importance weights for each attribute level [13]. Latent-class analysis identifies classes of respondents with similar preferences; results give both the relative importance of the vaccine attributes within each class as well as the probability that each respondent is assigned to a given class. The number of latent classes included in the final models is based on several criteria, including the Bayesian information criterion (BIC), interpretability of results, and model parsimony.

We estimated 2-, 3-, 4-, and 5-class models with the same specification. The 3-class model had the smallest BIC, but as noted, BIC should not be the only criterion for selecting a latent-class specification. Class 1 in the 3-class model is essentially the same as Class 1 in the 2-class model. The second class in the 2-class model is split into two classes in the 3-class model. The larger of those classes is similar to Class 2 in the 2-class model. The third class is much smaller. It is not as strongly disordered but all the severities

Table 2 Selected demographic and attitude variables, survey respondents, compared with the US population

Characteristic	Parents (n = 1185)	US population	Young adults (n = 1203)	US population
Age, years	58.4	45.7	21.8	20.6
Female (%)	50.1	50.0	76.1	49.5
Minority (%)	10.6	25.4	22.7	26.8
4 years of college or more (%)	47.3	39.1	26.3	8.8
Income < $25,000 (%)	11.3	12.1	25.9	24.3
Income > $100,000 (%)	24.0	42.7	10.9	15.1
Vaccines are necessary to protect health (% agree or strongly agree)	3.9		6.9	
People receive too many vaccines (% agree or strongly agree)	12.8		18.9	
Get the flu shot every, or nearly every, year (%)	61.8		43.4	

US population statistics are provided for reference only and are drawn from Census.gov

have similar importance. Thus, the 3-class model provides no quantitative or qualitative insights that are not shown in the 2-class model.

Relationships among class-membership probabilities and respondent characteristics were estimated with preference parameters and included sociodemographic, vaccine attitude, vaccination history, and internal validity variables. Data from the young-adult and parent samples were analyzed separately. Analyses used Stata SE version 16 (StataCorp LLC, College Station, TX, USA) and Latent GOLD version 5.1 (Statistical Innovations, Arlington, MA, USA).

3 Results

3.1 Sample and Validity Tests

We obtained observations from 1185 parents and 1203 young adults. Table 2 contains selected demographic and attitude characteristics of the samples. For reference, Table 2 also contains basic demographic data for the US population for the relevant age bands, according to the US Census Bureau. In general, the parent sample was older, oversampled White non-minority people and contained a lower proportion of high-income (<$100,000 annual income) respondents compared with the general US population. The young-adult sample contained more women and more people with 4-year college degrees than the general population.

Overall, the sample contained very few inconsistencies in the validity tests. In the parent sample, 2.3% of respondents failed all of the comprehension questions, 2% always selected the same alternative (either A or B) in the vaccine choice questions, and 28.5% always selected the vaccine with the better level of a single attribute. In the young-adult sample, 4.8% of respondents answered all the comprehension questions incorrectly, 2.1% always selected the same alternative (either A or B) in the vaccine choice questions,

and 27.8% always selected the vaccine with the better level of a single attribute.

3.2 Vaccine Hesitancy and Pro-Vaccine Correlates

Only about 3% of the sample (69 respondents) indicated strongly vaccine-hesitant preferences by selecting the 'Neither vaccine' alternative in every question, while 19% (453 respondents) indicated strongly pro-vaccine preferences by always choosing 'Both vaccines'. Table 3 contains results of probit analysis that evaluates relationships between respondent demographic characteristics and non-variant responses; while an extensive list of possible covariates was included in the model, only significant covariates are included in Table 3 because of space constraints. Parents under age 65 years, parents whose children were older, and lower-income parents and young adults were more likely to select the 'Neither vaccine' alternative in every question. On the other hand, lower-income respondents and those who selected White as their race were also more likely to always select 'Both vaccines'. Vaccine-hesitant respondents were more likely to say that they did not need a doctor to help make vaccine decisions, while pro-vaccine respondents were more likely to say they did need such help. Finally, in terms of survey mechanics, vaccine-hesitant respondents were more likely to incorrectly answer a quiz question on their understanding of a probability graphic, and pro-vaccine respondents were less likely to rush through the survey in less than 7 min.

3.3 Latent Classes and Attribute Importance

For subsequent analysis, we dropped the 47 parents and 22 young adults who chose 'Neither vaccine' in all choice questions, giving us analysis samples of n = 1138 and n = 1181, respectively. Based on the criteria described above, models with two classes provided the most appropriate fit for the choice data. Estimated class-membership proportions for

Table 3 Probit analysis of vaccine-hesitant and pro-vaccine respondents. Statistically significant determinants of likelihood of always choosing the 'No vaccine' alternative (vaccine-hesitant, 3% of the sample) or always choosing the 'Both vaccines' alternative (pro-vaccine, 19% of the sample) in every question

Variable	Vaccine-hesitant		Pro-vaccine	
	Coefficient	p value	Coefficient	p value
Constant	− 2.189	0.00	− 1.0331	0.00
Parent	0.732	0.00	0.288	0.00
Children aged < 18 years	− 0.380	0.02		
Age > 65 years	− 0.458	0.01		
Income	− 0.411	0.00		
Income < $70,000			0.170	0.005
Minority			− 0.158	0.049
Do not need doctor to help make vaccine decisions	0.331	0.02	− 0.205	0.033
Fail probability quiz	0.365	0.00		
Survey duration < 7 min			− 0.588	0.007
	n = 2386		n = 2386	

Class 1 and Class 2 were 65% and 35%, respectively, for parents, and 55% and 45%, respectively, for young adults.

Table 4 compares covariate analysis of latent-class membership probabilities for the parent and young-adult samples. In both samples, respondents who completed the survey in less than 10 min were less likely to be grouped in Class 1. Younger parents and parents with adult children were more likely to be grouped into Class 1. Limited educational attainment and minority status were significantly correlated with Class 1 membership for young adults, but minority status was uncorrelated with Class 1 membership for parents.

Those who more frequently chose the 'Both vaccines' option were more likely to have Class 1 preferences.

Finally, class membership was also related to respondents' perception of the value of vaccine information provided by physicians. In both samples, respondents who placed greater value on receiving information about vaccines from their doctor were more likely to have Class 1 preferences. Similarly, respondents who had not discussed a MenB vaccine with their doctors and those who expressed higher concern about physicians not discussing a MenB vaccine were also more likely to have Class 1 preferences. In the young-adult sample, respondents with Class 1 preferences were more likely to agree to pay for more time with their physician to discuss a MenB vaccine.

The two latent classes had distinct preference patterns that were similar between the parent and young-adult samples. Figure 2a and b compare the 2-class relative utility weights and 95% confidence intervals for parent (Fig. 2a) and young-adult (Fig. 2b) samples. These figures compare three disease effects: recover fully at home in 1 week with moderate illness (Home), recover fully in hospital in 2 weeks with serious illness (Hospital), and die in hospital after 2 weeks with serious illness (Death). Three levels—total deafness, lose both legs, and permanent brain damage—are omitted from Fig. 2 due to space constraints; preference weights for all levels are included in ESM Tables S2a and S2b and in Fig. 3. The results reported here were obtained by rescaling the log-odds relative utility weights from each class and population, such that preferences for a 1 in 1 million chance of recovery at home had a weight of zero, and a 1 in 100 chance of death had a weight of 10. All other weights were scaled proportionately in relation to this difference to preserve the relative importance of changes in the attributes. Table 1 in the ESM contains all of the raw coefficient estimates.

Table 4 Covariate analysis of class 1 latent-class membership probabilities[a]

| Covariate	Parent sample (n = 1138)		Young-adult sample (n = 1181)	
	Coefficient	p value	Coefficient	p value
Age > 55 years	− 0.847	0.00	–	–
Parent with child aged < 18 years	− 0.847	0.00	–	–
Minority	0.292	0.22	− 0.692	0.00
High school education or less	− 1.598	0.00	− 1.153	0.00
Reported having discussion with doctor about MenB vaccines	− 0.775	0.00	− 1.004	0.00
Concerned (4 or more on a 7-point feeling scale ranging from 'unconcerned' to 'angry') if the doctor does not discuss MenB vaccines	0.380	0.00	0.538	0.00
Accepted specified cost to pay for additional time to discuss the vaccine with the doctor	− 0.411	0.00	− 0.165	0.02
Accepted specified cost to pay for MenB vaccine	0.696	0.000	0.481	0.00
Spent less than 10 min taking the survey	− 2.034	0.010	− 1.612	0.00

[a]All covariates are 0/1 indicator variables
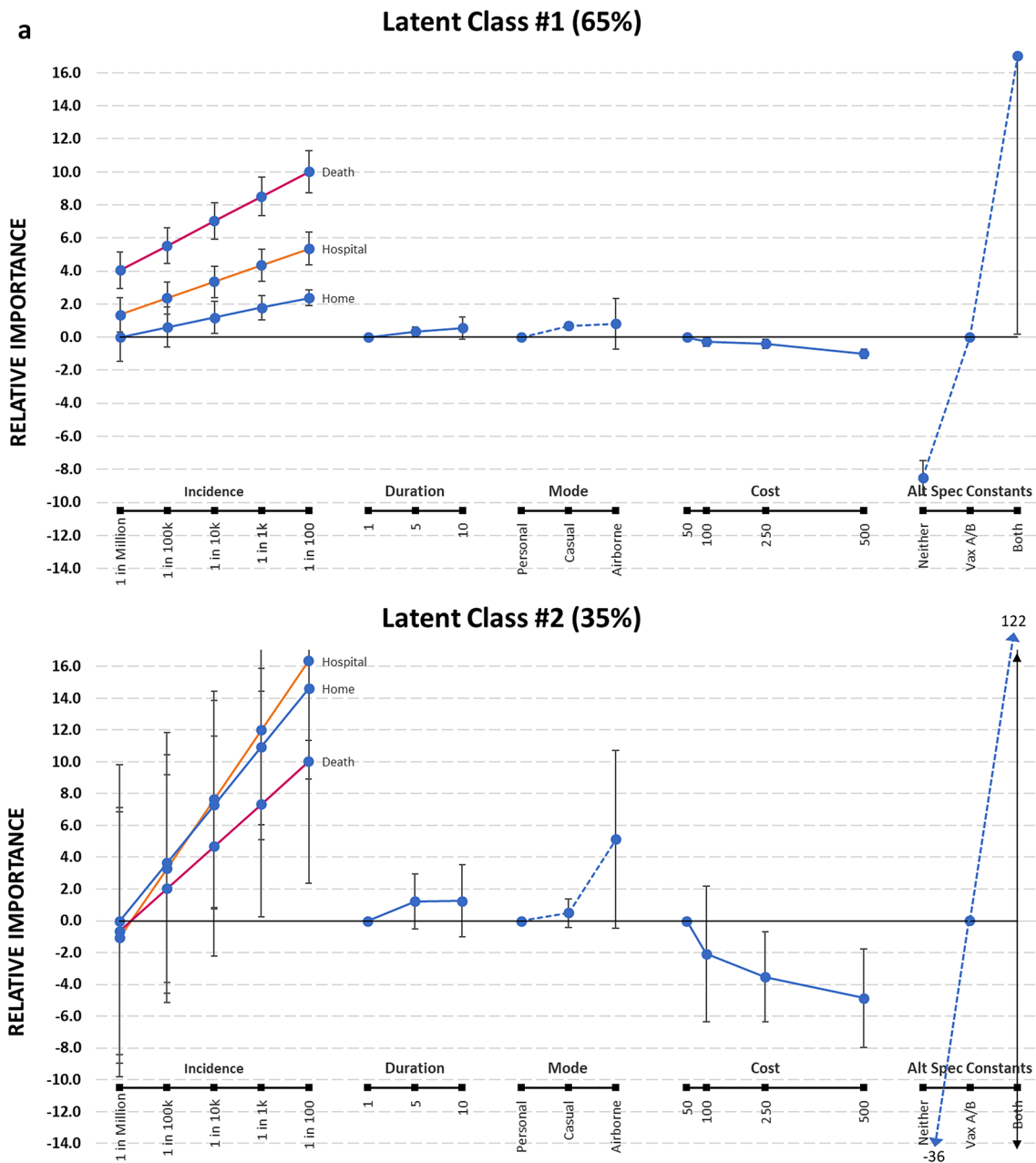
Fig. 2 a Latent-class estimates, parent sample (95% confidence intervals). Preference estimates for Class 1 incidence preferences are logically ordered with good precision, however Class 2 incidence preferences are not logically ordered and imprecise. Pro-vaccine preferences are much weaker for Class 2. The large negative value for the 'Neither' (no vaccine choice) option indicates strong pro-vaccine preferences. The alternative-specific constant for choosing both vaccines in the first question is insignificantly different than choosing one of the two vaccines for both classes. The endpoints for the confidence interval for 'Both' in Class 2 is ± 137. **b** Latent-class estimates, young-adult sample (95% confidence intervals). Results are qualitatively similar to that of the parent sample. Precision of the 'Both vaccines' parameter is very poor for both classes. 'Neither vaccine' is significant and strongly negative for both classes relative to choosing one of the two vaccines in the first question. The endpoints for the confidence interval for 'Both' in Class 2 is ± 177

Class 1 estimates for both parent and young-adult samples are well-ordered for severity-incidence interactions. Vaccines that prevent higher-incidence diseases with more severe effects are preferred to vaccines that prevent lower-incidence diseases with less severe effects. Duration of protection, mode of transmission, and cost are relatively unimportant compared with severity-incidence interactions. For example, for young adults evaluating a vaccine against a disease from which most people will recover at home, the importance of obtaining protection against the disease would
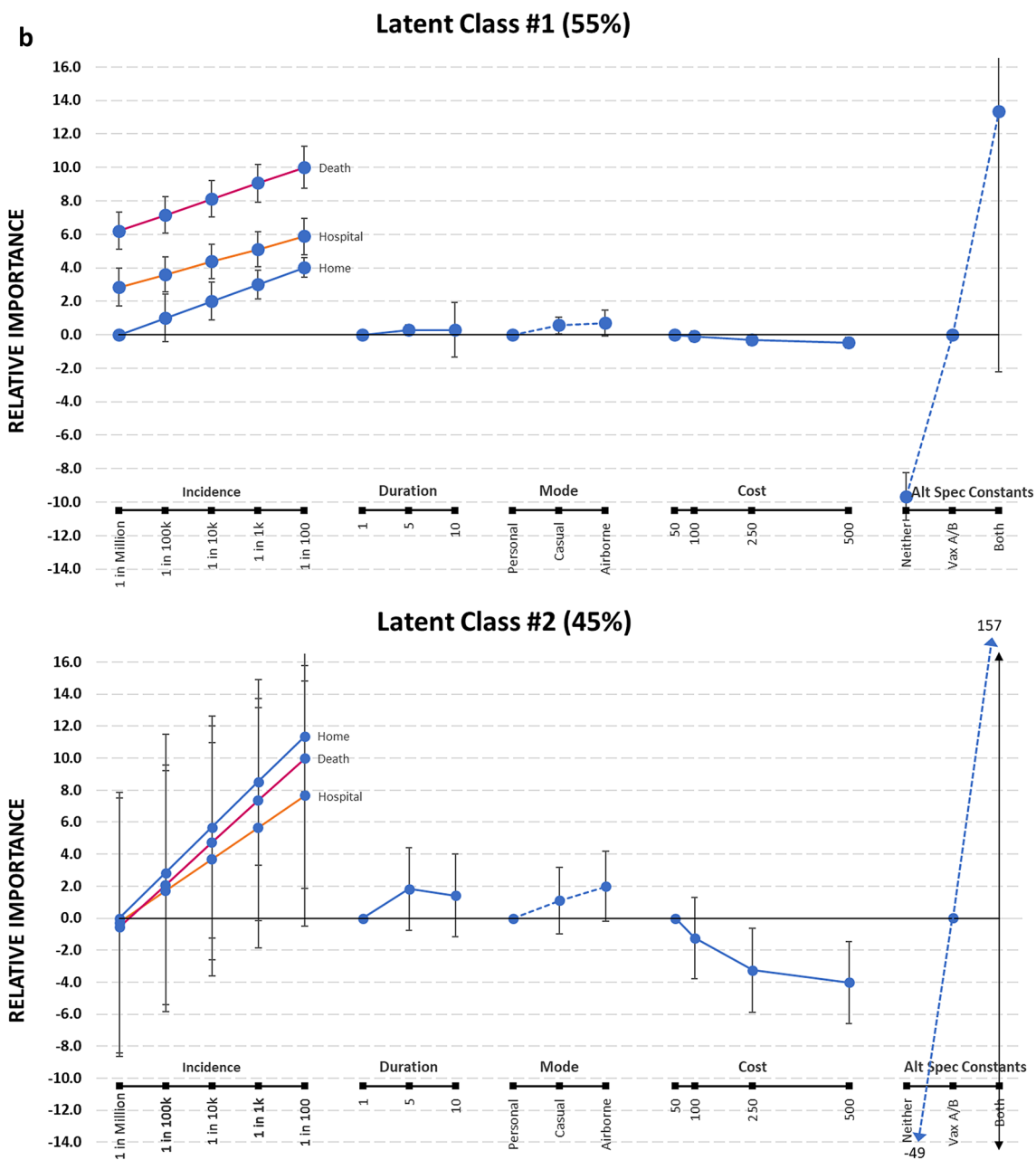
Fig. 2 (continued)

increase by about 1.89 if the disease incidence increased to 1 in 10,000 from 1 in 1 million. By contrast, the importance of obtaining protection from a disease spread through personal contact increases by 0.72 if the disease was airborne. Thus, young adults considered the importance of the change in incidence from 1 in 1 million to 1 in 10,000 to be 2.6 times more important than the difference between transmission through personal contact and airborne contact. For parents, the same increase in incidence is about 1.35 times more important than airborne contact (weight 1.16 vs. 0.86). For both samples, the importance weight for the 'Neither

vaccine' is strongly negative, indicating that the mean vaccine shown in the study design was strongly preferred to no vaccine. Estimate precision was similar in both samples for severity-incidence interactions, but parent-sample confidence intervals are much wider for other attributes compared with the very precise young-adult estimates.

Figure 3 provides an alternative way to visualize preferences for vaccines for diseases with varying combinations of severity and incidence, again divided for the parent (Fig. 3a) and young-adult (Fig. 3b) samples with Class 1 preferences. In Fig. 3, disease incidence ranging from lowest to highest

Fig. 3 **a** Constant-utility bands for severity-incidence combinations, parent sample Class 1. The charts show bands of similar utility or value of protection. Combination A describes a vaccine for an infection with high incidence and low severity, such as the annual influenza virus. Combination B describes a vaccine for an infection with very low incidence but very serious sequelae. Both A and B lie on the same similar-utility band. Points within bands are not statistically significantly different. **b** Constant-utility bands for severity-incidence combinations, young-adult sample Class 1
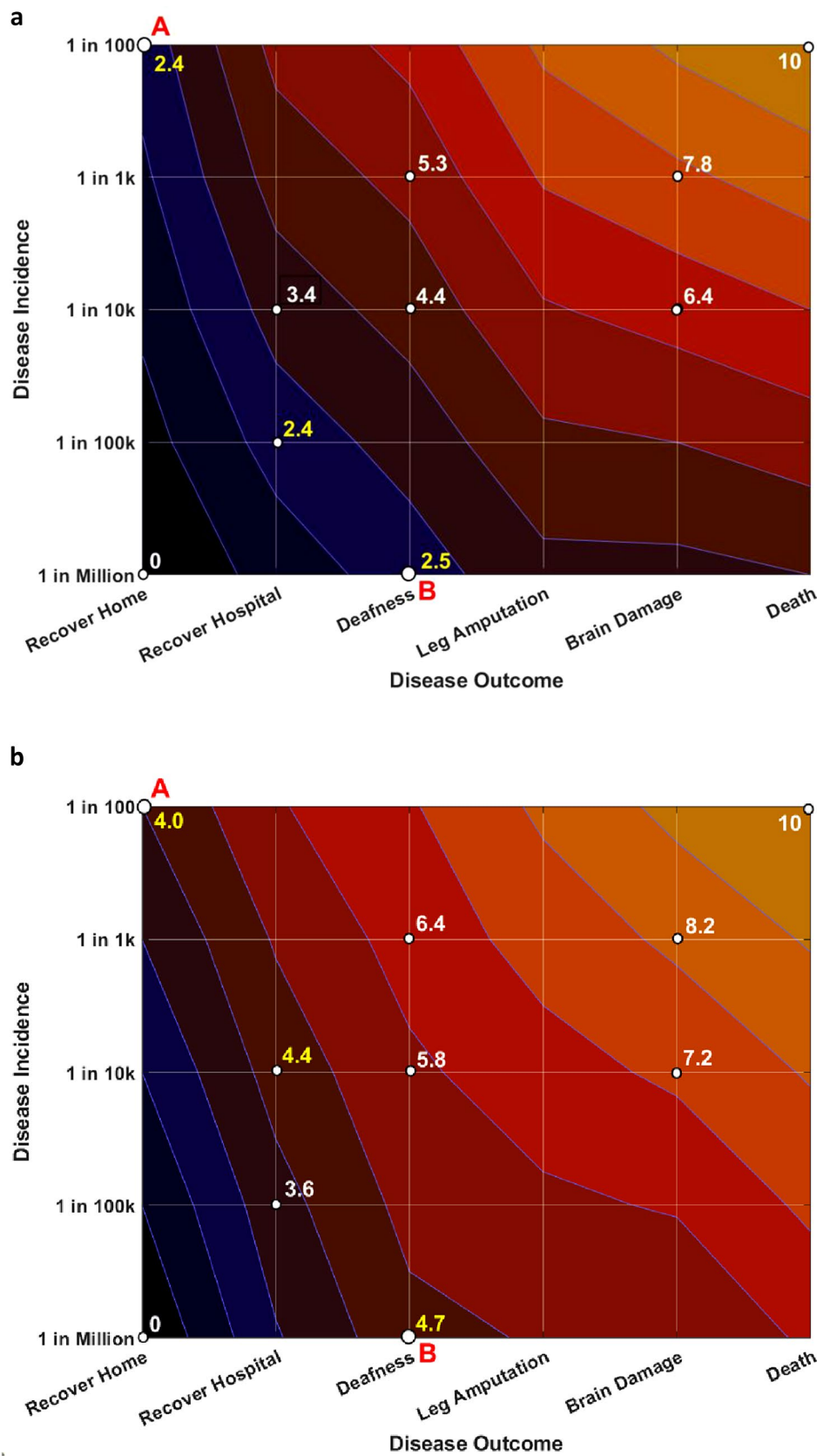
is plotted on the vertical axis, while disease severity based on the five qualitative categories included in the survey is plotted on the horizontal axis. Preferences for each combination included in the survey are plotted in the two-dimensional space in a contour map, with less-preferred vaccines (for diseases with low severity and low incidence) closer to the lower left-hand corner and the most-preferred vaccines closer to the upper right-hand corner. Thus, moving progressively to the right or upward indicates higher preference-utility 'elevations'. Utility weights in this space are grouped into constant-utility curves or bands, which are graded by color and indicate the sets of severity-incidence combinations that are of similar preference utility. While differences in utility levels within each band are not statistically significant, differences in utility levels close to each other in different bands could also be statistically insignificant. For both figures, the bands do not cross, indicating that, given a specific severity, respondents consistently prefer protection against higher-incidence diseases, and given a specific incidence, respondents prefer protection against diseases with more serious long-term effects. The bands also slope downward, indicating that respondents would accept trade-offs involving increases in disease incidence only if they are paired by decreases in disease-outcome severity. However, the bands are steeper for the young-adult sample, indicating they would accept larger increases in incidence for a given reduction in severity than the parent sample. This pattern indicates young-adult respondents were more tolerant of contagion risks than parent respondents.

Point A in each figure corresponds to the utility of a vaccine against a disease with 1 in 100 incidence and an expectation of full recovery after 1 week at home, a profile similar to the seasonal influenza virus. Point B corresponds to the utility of a vaccine against a disease with 1 in 1 million incidence resulting in permanent deafness. For the parent sample, the high-incidence/low-severity vaccine lies on the same constant-utility band as the low-incidence/high-severity vaccine. Points A and B for the young-adult sample have higher utility levels than the corresponding points for the parent sample. For young adults, a vaccine protecting against a condition resulting in deafness lies on a higher constant-utility band than a vaccine protecting against a condition such as the seasonal influenza virus. Several other specific preference-utility values for disease incidence and severity combinations are also included in the figure for reference.

In contrast to the well-ordered Class 1 preferences, Class 2 preferences exhibit unexpected ordering for some severity-incidence combinations and wide confidence intervals for these attributes. For example, for the approximately 45% of young adults with Class 2 preferences, none of the disease severity-incidence combinations are statistically significantly different from one another. Hence, for respondents with Class 2 preferences, we cannot quantify the difference

in value for obtaining protection from diseases that result in death and those resulting in full recovery at home, or on diseases that occur in 1 in 100 people and 1 in 1 million. Consequently, it is not useful to display the Class 2 results in a figure analogous to Fig. 3.

The 'Neither vaccine' alternative, while still negative, was of a much smaller magnitude in Class 2 compared with Class 1. However, it was not statistically significantly different from zero in any of the models. Interestingly, although the duration, mode, and cost attributes have lower average-preference utility for Class 2 than Class 1, the confidence intervals are generally smaller in Class 1, particularly in the young-adult sample.

4 Discussion

4.1 Policy Implications

The findings from this research suggest three lessons about public preferences for vaccines for low-incidence, severe-outcome diseases in the US, all of which are important for how the ACIP interprets evidence on stakeholders' perspectives. First, the US public wants vaccines to protect against low-incidence, severe-outcome diseases and values these vaccines at least as much as vaccines against high-incidence but less-severe diseases. This preference-based finding stands in contrast to analyses based on conventional QALY frameworks. For many respondents, vaccinations against severe but low-incidence diseases have a value comparable with vaccines against common but less consequential diseases. One interpretation of this result is that vaccines that protect against low-incidence, severe-outcome diseases provide 'peace of mind' benefits that are not captured by standard health-outcome metrics.

Second, our latent-class analysis illustrates the difficulties in evaluating and interpreting preferences among a heterogeneous population. While only a small minority of respondents failed our built-in logical consistency checks, approximately 35–45% of our samples had Class 2 preference patterns, which featured unexpected ordering and imprecise vaccine preferences. This result appears to be consistent with the well-known problematic state of vaccine knowledge and vaccination decision making among a substantial portion of the US public. In contrast, Class 1 preferences indicate that 55–65% of our samples placed a well-defined value on vaccines much larger than is typically indicated in CEA assessments.

Third, our findings suggest that an ACIP recommendation for shared clinical decision making may not be successful, especially for people with Class 2 preferences. The observed response patterns imply that changes in CDC vaccine messaging and shared decision-making approaches may be

necessary to help many people make informed vaccination decisions.

4.2 Limitations

Hypothetical choices do not have the same emotional and financial consequences as real choices. Thus, there is always potential for hypothetical bias in choice-experiment studies. This study adhered to best practices for limiting hypothetical bias by framing the preference elicitation in a realistic context, defining vaccine attributes carefully, and minimizing the cognitive effort required to evaluate vaccine alternatives.

Because this study was conducted prior to the coronavirus disease 2019 (COVID-19) pandemic and increased awareness of vaccine development, testing, and approval procedures, we must acknowledge the possibility that people's current attitudes toward vaccines could be different from the attitudes expressed in this survey. Moreover, it is not clear what impact population-wide increases in pandemic-related stress and anxiety, alongside greater awareness of public-health policies and programs, might have on the public's overall assessment of vaccine-preventable diseases.

Based on general opinion surveys about vaccine attitudes, we expected to find a larger proportion of vaccine-hesitant respondents. While we observed only about 3% of respondents rejected all the vaccine alternatives, we found that about half of both the parent and young-adult samples had implausible, uninformative preferences for vaccine-attribute trade-offs. This result is consistent with much of the population's known ambiguous attitudes toward vaccines [14–16].

Our sample sizes are considerably larger than most published choice-experiment studies [7, 17]. While our samples were proportionately similar to the general population on several dimensions, members of large consumer panels are not necessarily representative of the general US population. Nevertheless, the large sample sizes facilitated identifying statistically significant personal-characteristic covariates that help explain class-membership probabilities and preference patterns.

5 Conclusions

This study demonstrates the value that a large sample of respondents places on achieving protection against vaccine-preventable diseases with varying incidence and disease-severity characteristics. It demonstrates that many respondents place considerable value on achieving protection against low-incidence but severe diseases. These population preferences could be relevant for informing vaccine recommendations to better align with the public's desire to access vaccines against rare but serious diseases.

Declarations

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