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Quantifying the public's view on social value judgments in vaccine decision-making

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Title: Quantifying the public's view on social value judgments in vaccine decision-making: a discrete choice experiment

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Abstract: Vaccination programs generate direct protection, herd protection and, occasionally, side effects, distributed over different age groups. This study elicits the general public's view on how to balance these outcomes in funding decisions for vaccines. We performed an optimal design discrete choice experiment with partial profiles in a representative sample (N=1499) of the public in the United Kingdom. Using a panel mixed logit model, we quantified, for four different types of infectious disease, the importance of a person's age during disease, how disease was prevented—via direct vaccine protection or herd protection—and whether the vaccine induced side effects. Our study shows clear patterns in how the public values vaccination programs. These diverge from the assumptions made in public health and cost-effectiveness models that inform decision-making. We found that side effects and infections in newborns and children were of primary importance to the perceived value of a vaccination program. Averting side effects was, in any age group, weighted three times as important as preventing an identical natural infection in a child whereas the latter was weighted six times as important as preventing the same infection in elderly aged 65-75 years. These findings were independent of the length or severity of the disease, and were robust across respondents' backgrounds. We summarize these patterns in a set of preference weights that can be incorporated into future models.

Reply to reviewers

We would like to thank both reviewers for their extensive and constructive feedback. This has substantially improved our paper. Below we respond point-by-point to their comments.

Reviewer #1: SSM-D-18-01397

Quantifying the public's view on social value judgements in vaccine decision making-a discrete choice experiment I've read with great interest the manuscript "Quantifying the public's view on social value judgements in vaccine decision making: a discrete choice experiment". The manuscript starts with describing that the usual framework of cost-effectiveness analysis does not consider alternatives regarding the public's view on value judgements in vaccine decision making. The authors have performed a discrete choice experiment in order to examine the importance of different age groups in the program's overall evaluation and the extent to which it matters whether these age groups are affected by either direct, herd or side effects. By quantifying these preferences and translating these into preference weights for health outcomes, they hope to incorporate these into a future economic evaluation framework. The choice experiment was conducted among a representative sample, recruited from a commercial panel, in the UK. Five attributes were chosen: direct effects of vaccination, targeted age of the vaccination programme, side effects related to vaccination, herd effects, the age group affected by the herd effects. It was an unlabelled design. The diseases were also unnamed but described based on the dimensions and level of the EQ-5D-3L. Four different disease profiles were presented: severe(lasting nine days), severe (lasting sixty days), mild (lasting nine days) and mild (lasting sixty days). The design was a D-optimal in a Bayesian framework. Results showed that vaccine induced side-effects and infections in young children were considered the most important when assessing a program's value. Averting side-effects of the vaccine was weighted three times that of preventing an identical natural infection in any age groups. Vaccination programs that prevent disease in children were weighted six times that of programmes preventing a disease in older adults.
As I've said before, I've read the manuscript with great interest and thought the manuscript was overall well written. However, I think the manuscript could benefit from a more in-depth and thorough explanation of not only the process of selecting the attributes/levels but also the discussion of the results.

Below you find my comments more in detail:

Introduction:

- *The authors state that the CEA framework neglects key value judgements needed to evaluate vaccine programmes. Although they refer to a multiple of references, I would like to see a concrete example of which key values are missing and how this is taken into consideration within this discrete choice experiment.*

Reply: We agree that the development of the specific research question in the introduction was insufficiently clear and also insufficiently focused towards the concrete context of vaccines. It was also not entirely clear how our DCE provided answers to these problems. We have rewritten parts of the introduction to make it more focused and concrete, including examples and we have added a starting paragraph before the methods section to explain how our DCE can provide answers.

In the introduction:
"There is a growing literature about the limits of CEA in assessing the value of vaccination [9-15].

One important criticism is that CEA is limited in how it values the consequences of vaccination. Summary outcome measures [such as e.g. infections prevented or Quality-Adjusted Life Years (QALYs) gained] neglect the particular social context in which these outcomes occur. Nonetheless, such contextual features are important aspects to consider when evaluating a vaccination strategy [….] There are qualitative differences between these direct, herd and side effects. Creating herd protection can be of particular ethical value (e.g. to protect vulnerable groups who otherwise cannot protect themselves) and there is a profound psychological impact of vaccine-induced side effects. Moreover, the distribution of these three different effect types over different age groups is important. […] Several notable examples illustrate that this broader social context of health outcomes needs to be considered in vaccine decision-making [18]. For instance, vaccines against rotavirus (Rotashield®) and pertussis (whole cell pertussis vaccine) were withdrawn from many countries because of a perceived risk of side effects, even though from a medical perspective the benefit from vaccination largely outweighed any potential risk [19-21]. Also, despite persuasive economic and public health benefits of childhood influenza vaccination, few countries have actually implemented such a preventive strategy, due in large part to concerns about the social acceptability and equity of targeting vaccination at children to protect the wider population [22]. And, in many countries introduction of an effective varicella vaccination program has been delayed because of concerns about the possible 'exogenous boosting effect' and its social repercussions, i.e. that reduced chickenpox transmission among children (due to varicella vaccination) might temporarily increase shingles incidence among older generations [23]. Misjudging ethical norms and social sensitivities in vaccination policy by over-relying on CEA can have important implications…"

In the methods:
"DCEs are a widely used survey method to quantify individuals' preferences [35, 36] (for a general review of applications, see [37]). Participants are presented with a series of choices, usually between two goods described by the same attributes but differing in their attribute levels. By observing respondents' preferred choices, researchers can infer how the value of the competing options is determined by the attributes of the product. In our case, we observe how people prioritize between vaccination programs based on the number of direct, herd and side effects generated by the program, and their distribution over different age groups. This allows us to estimate a utility function that describes how the public values vaccination programs, taking into account the different types of vaccine effect and their distribution."

Methods:

- *I miss a clear description of the selection of the attributes and the levels. Why were these specific 5 attributes chosen?*

Reply: This is an important point and it is in fact a substantial part of the work we did for this DCE. We agree that this aspect of the DCE should be more extensively described in the paper. We have now included more motivating discussion regarding the choice of attributes and levels.

"To develop the final attributes and levels of the vaccine programs included in the DCE, we followed a three stage iterative process. We performed a literature search of other vaccine-related DCEs to assess the choice context and which attributes and levels were considered. These attributes were disease incidence, case fatality risk, economic impact, duration of illness and duration of vaccine protection, severity of illness and severity of side effects, and various personal characteristics including age, gender and willingness/ability to get vaccinated. [40-44] From this list, we took the combination of attributes that was, in combination with the four disease profiles, best suited to answer our research question. We presented several versions to a convenience sample of lay persons, colleagues and collaborators at the market research company in a pilot questionnaire, which we revised in response to received comments. We re-iterated this process

until we found the right form for the DCE from which, with a relatively simple set of in total five core attributes (Table 1), we could robustly calculate preference weights."

"After the design, we tested our survey among a pilot sample of the online panel (N=69) to confirm that respondents could fully understand and complete the survey. Based on the feedback from this pilot sample we judged that the experiment was understandable and that no further changes were needed."

- *How realistic is it that the side effects were presented as identical to an episode of the disease a vaccine usually prevents? For me, it is not clear although the authors partly explain this in the discussion. However, the whole issue nowadays is that an increasing number of people think the benefit of a vaccine (i.e. preventing the disease) does not outweigh the "perceived" risks of the vaccine itself. This leads to a reduced uptake with potentially devastating consequences. My point is: how valid are the results of this study if the provided attributes do not provide the information that is necessary to make an informed choice regarding priority setting for a vaccine programme?*

Reply: The reviewer makes an excellent point. Indeed, the fact that respondents might 'overestimate' the importance of the side effects is in essence one of the subjects of this DCE. And indeed, we saw that there was a cluster of respondents who were more vaccine skeptical and gave higher weight to side effects. Evidence on the severity of side effects relative to the disease itself does vary, with most side effects typically less severe, however with exceptions. Several vaccines can have (although rarely) severe side effects, often more severe than the disease the vaccine is preventing - eg. Guillian-Barre syndrome, anaphylaxis, intussusception etc. But the risk of these severe events is much less than the risk reduction in getting the disease after getting vaccinated. We opted for equal severity between prevented disease and induced side effects because this simplification reduced the need for respondents to simultaneously trade-off two disease severity profiles as well as the number of cases, likely improving the reliability of our results. To mitigate this issue that the reviewer correctly highlights, our questionnaire included a difference in the size of the direct impact and side effects—including an at least 10-fold lower disease burden linked to side-effects compared to the prevented disease burden. Indeed, turning the overall effect of side effects by total burden in this manner allowed us to more simply compare the weight of side effects to direct or herd effects (without having to convert these health effects to e.g. QALYs). We have further clarified this point in the revised manuscript.

In the methods section:
"The side effects of vaccination were presented in the DCE as identical to an episode of the disease that the vaccine usually prevents, in order to enable a direct comparison between the three effect types. Not doing so would have meant using a second health profile within one choice option (one for the disease and one for the side effects) and this would also have made the experiment substantially more difficult for the participants."

And in the study limitations:
"There are several limitations. We did not include any mortality effects, nor did we include a difference in severity between the three vaccine effects, even though this would be more realistic (as side effects of vaccines are usually milder than the disease being prevented). We chose not to include these aspects because we wanted to avoid increasing the complexity of the survey and reducing the validity of the respondents' answers by adding a second disease profile. Also, keeping the disease outcome constant over age groups and effects enabled trade-offs that were wholly

reflective of the preference between age groups and effects instead of also reflecting additional considerations about disease severity."

- *So, I would like to see a description of the qualitative process undertaken before the design of the DCE. For example: were qualitative interviews conducted with vaccination experts or people who are in favour or against vaccination? This would make it clear whether the selected attributes correspond with the missing information the public needs in order to make a valid judgement regarding priority setting for a vaccine programme. I could imagine that for example information about the long term effectiveness of a vaccine or protection duration could make a difference. For the attribute levels: the authors refer to expert opinion but again for me it is not clear what kind of experts were asked. The authors also refer to other DCE's although these were almost all disease-specific, referring to rotavirus or HPV vaccination. It is not clear how the levels from these choice experiments can easily translate to the ones used in this study.*

Reply: We agree that more info was needed on the process of selecting attributes and levels, see our response below. In fact, we think that constructing the list of 5 attributes for 4 different diseases was a merit of the design of this DCE. We used various inputs for this process and followed a trial and error approach towards finding the best possible form. We relied on our own judgment as researchers in this field and our assessment of the choice data that were needed to answer our research question, other DCEs in the literature but also on the feedback from colleagues and friends in earlier trial rounds and a pilot (N=69) in a later stage. Other DCEs were indeed context-specific but they gave us information on how various dimensions of health effect (e.g. mortality vs morbidity, competing dimensions of illness, side effects, etc.) were presented and traded-off, which personal attributes of vaccine recipients were included (age, gender, etc), etc. Some attributes with relevance in a wider assessment could be included indirectly, for example vaccine effectiveness could be modulated through the reduction in incidence of the disease. As with the nature of these questionnaires, a balance had to be struck between attribute inclusion and tractability for the respondent. We added the following in the methods section to provide more info on the process:

"To develop the final attributes and levels of the vaccine programs included in the DCE, we followed a three stage iterative process. We performed a literature search of other vaccine-related DCEs to assess the choice context and which attributes and levels were considered in other studies. These attributes were disease incidence, case fatality risk, economic impact, duration of illness and duration of vaccine protection, severity of illness and severity of side effects, and various personal characteristics including age, gender and willingness/ability to get vaccinated. [40-44] From this list, we took the combination of attributes that was, in combination with the four disease profiles, best suited to answer our research question. We presented several versions to a convenience sample of lay persons, colleagues and collaborators at the market research company in a pilot questionnaire, which we revised in response to received comments. We re-iterated this process until we found the right form for the DCE from which, with a relatively simple set of in total five core attributes (Table 1), we could robustly calculate preference weights."

"After the design, we tested our survey among a pilot sample of the online panel (N=69) to confirm that respondents could fully understand and complete the survey. Based on the feedback from this pilot sample we judged that the experiment was understandable and that no further changes were needed."

Results:

- *If I understand correctly, the cluster analysis revealed two group of respondents, one who attached no importance to the number of side-effects and another group who valued this*

highly. For cluster 1, it seems that the only predictor was no hesitancy on vaccination although the explained variance was low. However, I wonder if the authors also performed an analysis to examine what was the predictor for the highly valued side effects in cluster 2. Is it possible that these are people who are very hesitant for vaccination?

Reply: Thank you for this observation. Our previous phrasing was incomplete; the cluster 2 results were not mentioned whereas we in fact compared cluster 1 with cluster 2 in the analysis. We have changed this in the revised manuscript as follows:

"We used a logistic regression to determine predictors of cluster membership. Cluster 1, which attached almost no importance to the number of side effects, was characterized by high values on the VHS, indicating little hesitancy (p<0.0001). *On the other hand, cluster 2 who valued side effects more highly, was characterized by higher degrees of hesitancy on the VHS*. However, the predictive power of this association for membership of the group was small (McFadden's pseudo R2=0.6%), implying that there is much unexplained heterogeneity in the importance placed on side effects."

Discussion:

- *the authors state that their study is the first one to quantify social value judgements in vaccine. Although this makes it difficult to compare their results with other studies, they indicate that one of their findings is in line with theoretical expectations about cognitive heuristics like loss aversion, act-omission bias and hyperbolic discounting. My question is: why and could the authors explain this more in detail? What is for example the link between their findings and hyperbolic discounting or act-omission bias?*

Reply: Thank you for this comment. We have expanded the text as follows, and hope this is clearer.

"The finding that individuals weighted one averted instance of a side effect equal to about three similarly severe natural infections in children can be explained with general theory on decision-making. For instance, well-documented psychological phenomena such as 'loss aversion' (58) (overvaluing risks and losses over opportunities and gains), the 'act-omission bias' (59) (judging the effects of an act—becoming vaccinated—differently from identical effects resulting from an omission—becoming infected), or 'hyperbolic discounting' (60) (overvaluing the present—in which side effects occur—over the future—in which disease prevention will occur) suggest that people put an extraordinary weight on side effects when evaluating a vaccination strategy."

- *Then the authors state that it is important to study which aspects of health policy choices matter most to the public. They mention that in particular public trust, goodwill and participation are key to success and that one has to be aware of the sensitivities surrounding vaccination. My question is: explain more to what extent your results might help to take away the sensitivities surrounding vaccination? The problem nowadays is that public trust or goodwill are often related to perceptions of risks (and not the actual risk of vaccination), a misconception about the severity of the disease like thinking that measles is an innocent virus that has no severe consequences. How are the selected five attributes direct effects of vaccination, targeted age of the vaccination programme, side effects related to vaccination, herd effects, the age group affected by the herd effects related to these issues?*

Reply: We have expanded the text on how our results could be used in practice.

"Our findings provide empirical evidence on how to set vaccine priorities in line with public preferences. There is an important debate over the extent to which the public's opinion should drive resource allocation in healthcare (see e.g. [67, 68]). But, many believe that the values of the public, who pays for healthcare, should at least somehow be acknowledged in the decision-making process. In the context of vaccination, where public support and participation is key to success, this concern becomes particularly crucial. Therefore, our results can be useful additions to vaccine appraisals. They can provide guidance in specific epidemiological cases where CEA does not provide the answers needed. For instance, our results would suggest that, despite their attractiveness in terms of cost-effectiveness, the public may not support a childhood influenza vaccination program that mainly benefits adults or elderly (), because preventing side effects in vaccinated children is preferred over preventing disease burden among adults and elderly. Furthermore, our study suggests that a childhood varicella-zoster vaccination program, in the case that it protects children against varicella disease at the expense of increased zoster in the elderly (the 'exogenous boosting hypothesis'), might be justifiable. In contrast, previous analyses where QALY loss for children are weighted equally to those for the elderly find that the increased burden in the elderly offsets the QALY gains in children and determine the program not cost-effective (23 77).

Our results can also be directly incorporated into economic evaluations as sensitivity analyses to better align the underlying assumptions of CEA with the values of the population. Our estimated preference weights can be used in decision-analytic models as a parameter to weight QALYs or infections according to their 'social value'. This would re-adjust the (equal) weight that QALYs receive in CEA according to how important people think that the age of the QALY-recipient is and whether the benefit was generated through direct protection, herd immunity or (avoiding) side-effects. There is an increased interest in such 'extended', 'distributive' or 'equity-weighted' economic evaluation (see e.g. 7 36 70-75), but, to our knowledge, such studies do not exist for the evaluation of vaccines. Our estimates are developed particularly for this context, and provide an opportunity to do so."

Reviewer #2:

Thank you for the opportunity to review your interesting research. Overall this is a well written manuscript on an important topic.

- *Line 153 - did you pre-test your graphics to ensure comprehensibility and that it is measuring what you are expecting it to?*

Reply: Yes, we extensively tested the graphics and the wordings of the attributes and levels, first in groups of lay people and colleagues in our departments and among collaborators at the market research company and finally in a pilot of 69 online trial-participants. We have explained this piloting process more extensively in the revised manuscript.

"To develop the final attributes and levels of the vaccine programs included in the DCE, we followed a three stage iterative process. We performed a literature search of other vaccine-related DCEs to assess the choice context and which attributes and levels were considered in other studies. These attributes were disease incidence, case fatality risk, economic impact, duration of illness and duration of vaccine protection, severity of illness and severity of side effects, and various personal characteristics including age, gender and willingness/ability to get vaccinated. [40-44] From this list, we took the combination of attributes that was, in combination with the four disease profiles, best suited to answer our research question. We presented several versions to a convenience sample of lay persons, colleagues and collaborators at the market research company in a pilot questionnaire, which we revised in response to received comments. We re-iterated this process

until we found the right form for the DCE from which, with a relatively simple set of in total five core attributes (Table 1), we could robustly calculate preference weights.."

"After the design, we tested our survey among a pilot sample of the online panel (N=69) to confirm that respondents could fully understand and complete the survey. Based on the feedback from this pilot sample we judged that the experiment was understandable and that no further changes were needed."

- *Line 162 - what criteria did you use to choose your 45 choice sets?*

Reply: We have used the Bayesian D-optimal design criterion to generate the 45 choice sets of the DCE. This is also stated in the text at the end of Section 2.3, but for clarity, we added the following explanation:

"The Bayesian D-optimal design then results in the smallest possible standard errors for the utility estimates at the given sample size".

- *Line 183 - This is a rather generic sentence that does not give information about your pilot testing - were there any major or minor changes that resulted from your pilot testing? I am curious especially in how participants understood the attributes with a risk component - which as you know, can be interpreted quite differently between individuals depending on how you frame your attribute and levels. Did participants suggest the graphics used for direct effects, side effects and indirect effects?*

Reply: We agree and have added more information in the revised manuscript on the process of pilot testing. We attempted to circumvent the problems related to risk by not including explicit risk-attributes, such as risk of disease, and instead include visual aids. As we did require some risk difference between attributes we chose to present the absolute number of prevented cases within the DCE, which is a combination of a risk of disease and a vaccine effectiveness. We helped the responders to differentiate between the numerical quantities by presenting graphical representations of the numbers in bars and blocks. We settled on the graphics within the iterative process of study design – a choice that highlights the order of magnitude difference between direct and side effects. Nevertheless, it might make a difference when we name the number of people without side effects rather than the complement with side effects (framing effects). However we think that our choice was defensible based on two considerations. First, we wanted to quantify the weight respondents placed on side effects and therefore we chose to frame side effects explicitly to ensure that people traded off vaccine-induced illness with natural infection, rather than neglect side effects and focus on the positive benefits. Second, our pilot testing showed that our framing made respondents reason in the way we anticipated: they clearly balanced good outcomes with negative ones. We agree that this point deserves more attention and we have therefore added the following to the Discussion section on study limitations in the revised manuscript.

"We also chose to present the number of side effects rather than its complement: the number of vaccinated people without side effects. This framing may have played a role in the observed weight for side effects and the other framing would have likely generated lower estimates. We however wanted people to explicitly trade-off side effects with protective benefits."

- *Line 188 - 50 pence for a 12 minute survey seems very low to me? Is this the usual rate?*

Reply: This is indeed the usual rate that is applied by the market research company we recruited.

- *Line 232 - you mention 1546 started the questionnaire - how many survey links were sent out? i.e. the true response rate would be the number potentially eligible as your denominator.*

Reply: In total there were 1950 surveys send out of which 1546 completed the full survey. We clarified this in the text as follows.

"A total of 1546 respondents out of 1950 (79%) who were sent the questionnaire completed it, of which 47 (3%) indicated that the questions were too difficult or their answers invalid, leaving 1499 questionnaires for analysis."

- *Line 295 - you state your findings were robust across respondent characteristics - can you provide this information as supplemental information?*

Reply: Yes, we have now updated the manuscript accordingly and provide an extensive robustness check of the modelling results in Appendix D.

Discussion - I know your choice sets are not specific to any disease but use general descriptors for severity. However, doesn't the specific type of disease actually impact on preferences? e.g. I suspect people would view a cancer vaccine (e.g. HPV) quite differently from a vaccine for influenza, all things being equal as measured by your 5 attributes. There is something inherent in the disease itself that might be worth exploring for future studies. But in your manuscript, might be worth a few sentences to discuss this possibility.

Reply: Thank you for this suggestion. We have now raised this issue in the discussion with the study limitations.

"Also, we used generic disease profiles based on a description in EQ-5D terms to minimize respondents making personal associations to the disease and vaccine (e.g. 'flu' or 'whooping cough'), but this may also have increased the level of abstraction and reduced the level of personal involvement. A suggestion for further research is to repeat our study with named diseases and to test whether our finding that the disease profile did not matter to people's preferences is confirmed."

- *Line 368 - how specifically can other researchers use your preference weights in their models? can you give a concrete example? do you mean these weights can be used change WTP thresholds?*

Reply: We think that our results could be used experimentally to 'weight' QALYs in a decision model for vaccines according to public preferences over the weight of QALYs. CEA counts QALYs and assumes that all QALYs are equally valuable but our results (in line with other more general studies) suggest that this is not the case. Our preference weights could be used to provide an additional layer of information to these QALYs, about their 'social value'. A QALY gained in a child would therefore weigh more than one gained in an adult. This is of course contentious but it provides, in our opinion, useful information for vaccine decision making where health interests between generations sometimes need to be traded off. We have added some more sentences on this in the new manuscript and suggested some examples.

"For instance, our results would suggest that, despite their attractiveness in terms of cost-effectiveness, the public may not support a childhood influenza vaccination program that mainly benefits adults or elderly [69], because preventing side effects in vaccinated children is preferred over preventing disease burden among adults and elderly. Furthermore, our study suggests that a

childhood varicella-zoster vaccination program, in the case that it protects children against varicella disease at the expense of increased zoster in the elderly (the 'exogenous boosting hypothesis'), might be justifiable. In contrast, previous analyses where QALY loss for children are weighted equally to those for the elderly find that the increased burden in the elderly offsets the QALY gains in children and determine the program not cost-effectiveOur findings can provide an empirical evidence base about how to set vaccine priorities in line with public preferences., because preventing side effects in vaccinated children is preferred highly over preventing disease burden among adults and elderly. [23, 70]"

And:

"Our results can also be directly incorporated into economic evaluations (e.g. as sensitivity analyses), to better align the underlying assumptions of CEA with the values of the population. The preference weights we illustrated in Figure 3 can be used in decision-analytic models as a parameter to weight QALYs or infections according to their 'social value'. This would re-adjust the (equal) weight that QALYs receive in CEA according to how important people think that the age of the QALY-recipient is and whether it was generated through direct protection, herd immunity or (avoiding) side-effects. There is an increased interest in such 'extended', 'distributive' or 'equity-weighted' economic evaluation (see e.g. [7, 34, 71-76]), but, to our knowledge, such studies are inexistent for the evaluation of vaccines. Our estimates are developed particularly for this context, and provide an opportunity to do so."

- *Table 1 - there is a big difference in the having children demographics between the study population and the UK population - any potential impact on your results?*

Reply: 42% is the percentage of UK families living with dependent children (<18 years old), which should be compared to 35% (both the 11% (0-4 yo) and 24% (5-20 yo) in the sample), so there is not a large difference in demographics between the sample and the UK population. Moreover, when we include parental status as a covariate in the model we see no significant effects of parental status (See supplementary material provided with this revision).

- *Table 1 - last row - 'participant affected by poor health' - seems like quite a significant proportion (27%) - how was poor health defined? - any potential impact on preferences?*

Reply: Poor health consisted of the following three answers: (1) neither I nor my close friends or family are affected by poor health, (2) I consider myself affected by poor health and (3) I am not affected but close friends or family are affected by poor health. The exact nature of "poor health" was left to the respondent rather than defined by us. However, this respondent characteristic had no impact on preferences, as indicated by a non-significant interaction effect with any of the attributes in the model. See supplementary material.

- *Table 2 - can you discuss the interpretation of your interaction results in your text in more detail?*

Reply: Thank you for this suggestion. We agree and we have added a new paragraph and a new figure to the revised manuscript. The interaction terms cannot easily be understood based on the estimates in the table but should be interpreted in terms of marginal utilities, consisting of the sum of the main effects of the two attributes involved and the interaction itself. We have added a new figure depicting the interaction between the two age groups and added the following to the results section:

"Figure 4 illustrates the interaction between the age of the vaccinated group and the age of the herd immunity recipients (see Table 3). This interaction should be understood as the additional utility that is given to (or taken away from) a vaccination program, purely depending on the particular combination of age groups that are involved, regardless of the magnitude of direct, indirect or side effects that are being generated. It presents the attractiveness of particular intergenerational vaccination strategies. Whereas a CEA perspective would consider all possible age combinations equally attractive (as long as they lead to the same number of infections prevented), our sample had clear intergenerational preferences over vaccination strategies. Any age group was deemed acceptable to vaccinate when there were herd immunity benefits for newborns. To generate herd immunity for adults, infants were the most attractive age group. To generate it to protect the elderly >80, adults were deemed most appropriate. The least attractive intergenerational combination was vaccinating elderly >80 while generating herd immunity in adults 30-50 years. The most attractive age combination was vaccinating children while generating herd immunity in newborns."

- *Figure 3 - I am a bit confused with your utility weights for side effects - aren't these supposed to be negative? Or is the label supposed to be "prevention of side effects?"?*

Reply: The QALYs for side effects are in principle negative but we presented them as a 'weighting factor' for QALYs that could be used in a decision model. In that case these QALYs are already being 'lost' and it's our weighing factor that multiplies this loss. We added the following clarifications:

"Similarly, a vaccination strategy reduces its utility by causing side effects: reducing 34 side effects in children equals 100 prevented cases among the same age group."

And also:

"The mean weight for side effects across all ages was -2.93, meaning that avoiding one vaccine-induced infection was weighted equally to avoiding around three natural infections among children."

- *Appendix B - any internal tests of validity incorporated into your experimental design?*

Reply: There were no internal tests incorporated in our experimental design, apart from our explicit question whether participants understood the questionnaire. The ultimate test of the internal validity of the design lies with the quality and reliability of responses that we observed. The preciseness of the estimates we obtained justifies the priors we used for the Bayesian design construction (see appendix C), which were based upon extensive deliberation amongst the authors. We have extensively piloted the different choice sets amongst colleagues until the choice sets were balanced in the level of complexity and as such manageable to make meaningful trade-offs. Afterwards, only a small minority of respondents (N=47 or 3%) indicated that the choice sets were too difficult, and these respondents were excluded from the analysis. Moreover, the research company pledged to only include 'serious' responders based on previous experiences, time taken for the survey, etc.

MINOR CHANGES

- *Line 69 - please clarify your last phrase 'contestable perspective on them' - do you mean they only consider the healthcare perspective*

Reply: We agree that this statement was unclear and unnecessary and we have deleted this sentence from the introduction

- *A figure or table of all attributes with levels might be helpful.*

Reply: We have added a new table with all attributes and levels to the revised manuscript (Table 1).

Quantifying the public's view on social value judgments in vaccine decision-making: a discrete choice experiment

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Abstract

Vaccination programs generate direct protection, herd protection and, occasionally, side effects, distributed over different age groups. This study elicits the general public's view on how to balance these outcomes in funding decisions for vaccines. We performed an optimal design discrete choice experiment with partial profiles in a representative sample (N=1499) of the public in the United Kingdom. Using a panel mixed logit model, we quantified, for four different types of infectious disease, the importance of a person's age during disease, how disease was prevented—via direct vaccine protection or herd protection—and whether the vaccine induced side effects. Our study shows clear patterns in how the public values vaccination programs. These diverge from the assumptions made in public health and cost-effectiveness models that inform decision-making. We found that side effects and infections in newborns and children were of primary importance to the perceived value of a vaccination program. Averting side effects was, in any age group, weighted three times as important as preventing an identical natural infection in a child whereas the latter was weighted six times as important as preventing the same infection in elderly aged 65-75 years. These findings were independent of the length or severity of the disease, and were robust across respondents' backgrounds. We summarize these patterns in a set of preference weights that can be incorporated into future models.

Keywords

Priority-setting; age; side effects, herd protection, cost-effectiveness analysis, decision making; discrete choice experiment; preference weight, vaccination

1. Introduction

Economic evaluation methods such as cost-effectiveness analysis (CEA) are common components in public funding decisions for vaccines [1, 2]. They feature in the standard evidence considered by e.g. the Advisory Committee on Immunization Practices in the US, the Joint Committee on Vaccination and Immunization in England, the World Health Organization and non-governmental organizations such as the Bill & Melinda Gates Foundation [3]. At the same time, it is widely acknowledged that these evaluation frameworks have important shortcomings and that they alone offer insufficient basis for making fair and efficient vaccine funding decisions [4-8]. There is a growing literature about the limits of CEA in assessing the value of vaccination [9-15].

One important criticism is that CEA is limited in how it values the consequences of vaccination. Summary outcome measures [such as e.g. infections prevented or Quality-Adjusted Life Years (QALYs) gained] neglect the particular social context in which these outcomes occur. Nonetheless, such contextual features are important aspects to consider when evaluating a vaccination strategy. Vaccination induces disease protection in those who become vaccinated, but it also creates *herd* protection (or indirect effects in third parties because of reduced pathogen transmission [16]) and, occasionally, adverse clinical *side* effects. There are qualitative differences between these direct, herd and side effects. Creating herd protection can be of particular ethical value (e.g. to protect vulnerable groups who otherwise cannot protect themselves) and there is a profound psychological impact of vaccine-induced side effects. Moreover, the *distribution* of these three different effect types over different age groups is important. Side effects can be concentrated in one age group despite indirect protection from reduced transmission benefitting

either the wider population, or in some cases a different age group entirely [17]. Examples include protecting the elderly through childhood influenza vaccination or future generations through a *polio* eradication program. Such broader, distributive aspects of vaccination are important but they remain neglected in standard cost-effectiveness or public health impact models.

Several notable examples illustrate that this broader social context of health outcomes needs to be considered in vaccine decision-making [18]. For instance, vaccines against rotavirus (Rotashield®) and pertussis (whole cell pertussis vaccine) were withdrawn from many countries because of a perceived risk of side effects, even though from a medical perspective the benefit from vaccination largely outweighed any potential risk [19-21]. Also, despite persuasive economic and public health benefits of childhood influenza vaccination, few countries have actually implemented such a preventive strategy, due in large part to concerns about the social acceptability and equity of targeting vaccination at children to protect the wider population [22]. And, in many countries introduction of an effective varicella vaccination program has been delayed because of concerns about the possible 'exogenous boosting effect' and its social repercussions, i.e. that reduced chickenpox transmission among children (due to varicella vaccination) might temporarily increase shingles incidence among older generations [23].

Misjudging ethical norms and social sensitivities in vaccination policy by over-relying on CEA can have important implications. It may affect the perceived equity of a program, its support by the public and its long-term sustainability [13, 24-26] [27, 28]. It can invoke public backlash to the vaccine, leading to reduced uptake, increased vaccine hesitancy and reduced overall effectiveness of the program [29-31]. Therefore, an empirical evidence-base is needed about the public's view on the key

value judgments that need to be made in vaccine funding decisions [9, 10, 12, 32, 33]. Such evidence can complement formalized appraisals like CEA, stimulate deliberation and discussion on how to prioritize vaccines within a budget constraint and, moreover, it can be explored whether such evidence can become quantitatively integrated into formal decision frameworks in some sort of 'extended' or 'weighted' CEA [7, 34].

The objective of this study is to address this challenge by analyzing how the population in the United Kingdom prioritizes vaccination programs and to investigate whether its values diverge from the assumptions that are implicitly underlying CEA. We use a discrete choice experiment (DCE) among a representative sample of the population in the United Kingdom (UK) to investigate, for four different types of infectious diseases, the role played by different age groups in a program's overall evaluation and the extent to which it matters whether these age groups are affected by either direct, herd or side effects. We summarize these findings into a set of social preference weights for health outcomes (e.g. QALYs) that could be incorporated into economic evaluation or public health impact models.

2. Methods

DCEs are a widely used survey method to quantify individuals' preferences [35, 36] (for a general review of applications, see [37]). Participants are presented with a series of choices, usually between two goods described by the same attributes but differing in their attribute levels. By observing respondents' preferred choices, researchers can infer how the value of the competing options is determined by the attributes of the product. In our case, we observe how people prioritize between

vaccination programs based on the number of direct, herd and side effects generated by the program, and their distribution over different age groups. This allows us to estimate a utility function that describes how the public values vaccination programs, taking into account the different types of vaccine effect and their distribution.

2.1 Choice context

For all of their choices, respondents were randomly assigned one of four disease scenarios (see **Appendix A**). These were introduced before the start of the DCE. After five choice sets this disease was presented again to the respondent as a reminder. The four disease profiles were described as (1) severe—lasting nine days, (2) mild—lasting nine days, (3) severe—lasting 160 days, and (4) mild—lasting 160 days. Influenza and pertussis were used as proxies for an acute severe and a longer lasting milder disease, respectively [38, 39]. To avoid participants' preconceived ideas, the diseases were unnamed and only described to participants by means of severity using the generic descriptors of the dimensions of a standard instrument to measure health-related quality of life, the EuroQoL EQ-5D-3L, based on average reported values for both influenza and pertussis [38, 39]. To exclude considerations about age differences in remaining life expectancy, we explicitly told the participants that the diseases were not fatal.

Before every choice set we told respondents the following: "*the government has to choose between two vaccination programs that will each be used in 100 000 people. Considering your conviction about vaccination policy, which program do you think*

the government should choose? Both options are equally costly, and identical in every way except for the following 5 differences."

2.2 Attributes and levels of vaccination programs

To develop the final attributes and levels of the vaccine programs included in the DCE, we followed a three stage iterative process. We performed a literature search of other vaccine-related DCEs to assess the choice context and which attributes were typically considered. These attributes were disease incidence, case fatality risk, economic impact, duration of illness and duration of vaccine protection, severity of illness and severity of side effects, and various personal characteristics including age, gender and willingness/ability to get vaccinated. [40-44] From this list, we took the attributes that were, in combination with the four disease profiles, best suited to answer our research question. We presented several attribute combinations to a convenience sample of lay persons, colleagues and collaborators at the market research company in a pilot questionnaire, which we revised in response to received comments. We re-iterated this process until we found the right form for the DCE from which, with a relatively simple set of in total five core attributes (**Table 1**), we could robustly calculate preference weights.

The first two attributes described the age group targeted for vaccination and magnitude of the direct effects among those vaccinated. The third attribute described the number of side effects occurring among those vaccinated. The side effects of vaccination were presented in the DCE as identical to an episode of the disease that the vaccine usually prevents, in order to enable a direct comparison between the three effect types. Not doing so would have meant using a second health profile

within one choice option (one for the disease and one for the side effects) and this would also have made the experiment substantially more difficult for the participants. The fourth and fifth attribute described the magnitude of the herd effects and the age group that received them. We decided to focus only on the morbidity aspects of illness because including mortality would require additional attributes for infected people in order to account for their differing life expectancy.

For direct and herd protection we used 1000, 3000 or 5000 disease episodes prevented per 100,000 people vaccinated (an attack rate of 1-5% for a vaccine with a 100% efficacy), and for side effects 100, 300 or 500 disease episodes per 100,000 people vaccinated (an attack rate of 0.1-0.5%). For direct protection and side effects, we considered the following three age groups: children aged between 3 months and 3 years of age, adults aged between 30 and 50 years, and elderly aged between 65 and 75 years. The age groups for herd protection represented groups that, in the case of the first two, are often difficult to vaccinate for immunological reasons: young children under 3 months, elderly above 80 years and unvaccinated adults between 30 and 50 years.

(insert **Table 1**)

We depicted both the age group and quantity of cases avoided or caused by vaccination using simple graphics [45] (**Figure 1**). To explicitly investigate the assumption whether individuals ultimately look at the total impact of the program and to reduce the chance that respondents would adhere to a simple counting heuristic

without reflection, we presented the net number of disease cases averted for each strategy separately (the sum of direct and herd effects minus side effects).

(insert **Figure 1)**

2.3 Experimental design of the choice sets

The design of a DCE refers to the number and composition of choice sets presented to each participant [46]. A set of 45 choice sets was selected out of the 58,806 possible choice sets (see **Appendix B** for more info on the selection process) and distributed over three survey versions, so to limit the number of choice sets to be completed per respondent to 15. Therefore, each of the four disease profiles was represented in three different surveys (see **Figure 2**).

(Insert **Figure 2)**

The choice alternatives (i.e. profiles) themselves were '*partial* profiles' [47, 54]. We varied and highlighted the levels of two to four of the five attributes in the choice sets and kept the remaining attribute(s) constant so that respondents did not have to simultaneously trade-off all five dimensions per choice (see **Appendix B**). Limiting the cognitive burden for respondents in a DCE increases the validity and reliability of their answers [48]. The design we generated was 'D-optimal' in a Bayesian framework fitting with a multinomial logit (MNL) model for the attributes' main effects and six interactions between the two age attributes (direct and herd effects) and the

three magnitude attributes we deemed to be important *a priori*. We chose a Bayesian framework to integrate prior information on the respondents' likely preferences [49] (see **Appendix C**). The Bayesian D-optimal design then results in the smallest possible standard errors for the utility estimates at the given sample size.

2.4 Sample

After the design, we tested our survey among a pilot sample of the online panel (N=69) to confirm that respondents could fully understand and complete the survey. Based on the feedback from this pilot sample we judged that the experiment was understandable and that no further changes were needed.

From a consumer panel of 1 million UK members, 9613 random panelists were approached to participate in "a scientific study on resource allocation in healthcare". Of these people, 4144 (43%) responded to the invitation. We recruited 1950 of them to fulfill predetermined quotas to provide a representative sample of the UK population in terms of gender, socio-economic strata (indicated by the occupation of the head of the household), age groups (20-29, 30-39, 40-49, 50-59, 60+ years), and urban vs. rural background.

The DCE was conducted in November 2016. An email containing a link to the survey website was sent to participants and by clicking on the link respondents consented to participate, although they were free to stop or close the survey at any point. All respondents received a nominal incentive for study completion (£0.50 per 12-minute questionnaire). Before completing the DCE, respondents were asked to administer a survey tool to measure vaccine hesitancy [50], and were asked social-demographic questions and whether they have or had children. After the DCE, we asked about

their experience with severe diseases, their interpretation of the validity of the answers they provided and the overall difficulty of the DCE survey.

We obtained informed consent from all respondents and ethical approval of the study from the Ethics Committee of the London School of Hygiene & Tropical Medicine (Ref 10335). We conducted the research in accordance with the Code of Conduct of the Market Research Society, which ensured that information is collected for research purposes only, is kept confidential, and respondent anonymity is guaranteed.

2.5 Data analysis

To quantify the weight of the five attributes and their levels in the utility attributed to a vaccination strategy, a panel mixed logit model (fitted by the Hierarchical Bayes method [51]) was used (see **Table 3**). The model involved seven main effects: four related to the two three-level categorical attributes describing the utility impact of a change in the targeted age group in direct and herd effects, and three related to the continuous attributes describing the impact of a change in the absolute number of disease cases via direct effects, side effects and herd effects. Besides these seven main effects the model also includes attribute interaction effects, indicating the additional change in utility because of a particular combination of attribute levels. We computed the overall significance of the attributes using likelihood ratio (LR) tests and measured the relative importance of the attributes by the logworth statistic (i.e. $-\log_{10}$ (p-value of the LR-test)). The coefficients of the logit model were obtained by estimating the *a priori* model, i.e. the model with the utility function that seemed most appropriate when planning the DCE, and subsequently dropping the non-significant

model terms until we obtained a *final* model in which all effects had significant explanatory value at the 5% level. Models were fitted using the JMP 13 Pro Choice platform (based on 10,000 iterations, with the last 5000 used for estimation) assuming normally distributed parameters with no correlation between the attributes. Combining the main and interaction effects, this model allows calculating the additional utility of a vaccination program generated per additional health effect, i.e. per type of effect per age group (see the nine variations in **Table 3**). The 95% confidence intervals for the equity weights were estimated using the Delta method [52].

We investigated heterogeneity in respondents' preferences in two ways. First, by exploring the influence of the observed respondent characteristics on the average preferences and, second, by studying the unobserved preference heterogeneity by means of a hierarchical cluster analysis on the subject-specific estimates resulting from the Hierarchical Bayes approach. We favoured this two-stage modelling method as it performs equally well as one-stage modelling methods such as latent class modelling [53] while enabling us to parsimoniously derive the preference weights and their 95% confidence intervals.

3. Results

3.1 Response

A total of 1546 respondents out of 1950 (79%) who were sent the questionnaire completed it, of which 47 (3%) indicated that the questions were too difficult or their answers invalid, leaving 1499 questionnaires for analysis. Our final sample was sufficiently representative of the UK population in terms of gender, family size, socio-economic status and education level (**Table 2**).

(insert **Table 2**)

3.2 Main effects and calculated weights

Across all questionnaires, respondents made a total of 22,485 choices between vaccination programs. There was no significant effect observed of which of the three survey versions a participant received. Respondents did not systematically choose the program with the highest overall public health impact, i.e. the total of all prevented cases including direct, herd and side effects. In fact, only 99 respondents (6.6%) consistently opted for the most effective program in all of their choice sets. However, about half the respondents (738/1499) chose the most effective alternative in at least 70% of their choices, indicating that the total effect on the disease burden is important, but not the only factor in prioritizing vaccination programs.

Table 3 presents an overview of the incremental utility of the main effects and interactions. The vaccination program that was least preferred (i.e. yielding minimum utility) was one that targeted the elderly (65-75y), generated the lowest number of prevented cases, the highest number of side effects, and the lowest number of cases prevented via herd protection in unvaccinated adults. The most preferred program (i.e. yielding maximum utility) was one that targeted children, generated the highest

number of prevented cases, the lowest number of side effects, and the highest number of cases prevented via herd protection in newborns.

(insert **Table 3**)

Using the same logit model, we then calculated preference weights for each effect type per age group. These weights act as a multiplicative factor to transform identical clinical symptoms into health effects with equal value in the public's view. We compared the additional utility of a vaccination program that is generated through preventing one specific disease case relative to the utility gained through directly preventing a single disease case via vaccinating a child (**Figure 3**). These preference weights reveal important patterns. First, preventing side effects of vaccination was highly preferable to preventing natural infections, even though the symptoms were equal in length and severity. The mean weight for side effects across all ages was -2.93, meaning that avoiding one vaccine-induced infection was weighted equally to avoiding around three natural infections among children. This finding was consistent whether side effects occurred in children (-2.95 (95% CI: -3.21; -2.69)), adults (-3.16 (95% CI: -3.51; -2.81)) or the elderly (-2.68 (95% CI: -2.98; -2.37)). Second, respondents preferred vaccination programs that prevented disease among newborns and children compared with those for adults and the elderly, even though the prevented disease burden was similar. One episode prevented in a newborn via herd protection was considered about twice as valuable as directly protecting an adult via vaccination. Third, the extent to which respondents preferred protecting adults and the elderly depends on the type of benefit conferred

by the program. Direct effects were the preferred mode of protection for adults whereas herd effects were preferred for the elderly. Reducing disease burden by directly vaccinating adults (aged 30-50 years) was weighted equally to reducing disease burden in the elderly (aged 80+ years) via herd effects [0.75 (0.64; 0.85) compared to 0.67 (0.58; 0.76), respectively]. In contrast, reducing disease burden in adults (aged 30-50 years) by herd effects counted equally to reducing disease burden in elderly (aged 65-75 years) directly via vaccination (0.12 (0.03; 0.20) compared to 0.16 (0.06; 0.25), respectively).

(insert **Figure 3**)

From these results, we also calculated the number of infections needed to avert in order to obtain equal utility as that from protecting 100 children directly via vaccination (**Table 4**). Avoiding 100 infections in children via vaccination was considered equivalent to protecting 632 elderly (65-75 years) or 134 adults. In turn, these outcomes were equivalent to protecting 71 newborns, 865 adults or 150 elderly (>80y) via herd protection. Similarly, a vaccination strategy reduces its utility by causing side effects. Avoiding 34 side effects in children generates the same utility as preventing 100 natural infections among the same age group.

(insert **Table 4**)

Figure 4 illustrates the significant interaction in our model between the age of the vaccinated group and the age of the herd protection recipients (see **Table 3**). This interaction must be understood as the additional utility that is given to (or taken away from) a vaccination program depending on the particular combination of age groups that are involved, regardless of the magnitude of direct, herd or side effects that are being generated. It presents the attractiveness of particular intergenerational vaccination strategies. Whereas a CEA perspective would consider all possible age combinations equally attractive (as long as they lead to the same number of infections prevented), our sample had clear intergenerational preferences over vaccination strategies. Any age group was deemed acceptable to vaccinate when there were herd protection benefits for newborns. To generate herd protection for adults, children were the most attractive age group. To generate it to protect the elderly >80, adults were deemed most appropriate. The least attractive intergenerational combination was vaccinating elderly 65-75 years while generating herd protection in adults 30-50 years. The most attractive age combination was vaccinating children while generating herd protection in newborns.

(insert **Figure 4**)

3.3 Preferences across disease types and respondents

As shown in **Appendix D**, our results remained robust across all four different disease types: the equity weights were statistically equivalent, regardless of whether the condition was mild vs. severe or acute vs. chronic (indicated by a non-significant interaction effect in our model between the attributes and the disease type). Also, the

appendix illustrates that our findings also remained robust across most respondent characteristics: gender, age, occupation, level of education, urban-rural, socio-economic background, experience with severe illness or parental status. Although individuals with a low degree of vaccine hesitancy (indicated by high values on the 'vaccine hesitancy scale' (VHS) [50]) attributed less importance to side effects ($p<0.0001$), this effect was relatively small (a 10 unit increase in the VHS score (on a scale from 10 to 50) led to a 10% decrease in absolute magnitude of the utility for side effects (~0.03)).

The hierarchical cluster analysis of the individual preferences (see methods) revealed two distinct groups of respondents: one group (N=564, *Cluster 1*) who attached almost no importance to the number of side effects (with a mean weight of -0.91 for side effects) and a larger group (N=935, *Cluster 2*) who valued this attribute fairly highly (with a mean weight of -4.40) (**Table 3**). This clustering explains the relatively high variation across respondents for the weight estimate for side effects (the standard deviation to mean absolute value ratio of 0.043 for side effects is almost twice the ratio for direct and herd effects). We used a logistic regression to determine predictors of cluster membership. Cluster 1, who attached almost no importance to the number of side effects, was characterized by high values on the VHS, indicating little hesitancy ($p<0.0001$). On the other hand, cluster 2, who valued side effects more highly, was characterized by higher degrees of hesitancy on the VHS. However, the predictive power of this association for membership of the group was small (McFadden's pseudo R^2=0.6%), implying that there is much unexplained heterogeneity in the importance placed on side effects.

385

4. Discussion

In this study, we used a discrete choice experiment to analyse and quantify how the public values the outcomes of vaccination programs. We observed several general preference patterns, which were robust across different lengths and severities of disease and respondent characteristics (socio-economic background, age, education and parenthood). We observed that most respondents did not make choices purely based on how to minimize the number of infections. In particular, individuals, on average, weighted one averted instance of a side effect equal to about three similarly severe natural infections in children and weighted one averted health outcome in children up to six times more than preventing similarly severe health outcomes in the elderly. Interestingly, our study has disentangled this latter phenomenon from the type of effect as we observed a different weight given to protecting older people depending on whether the benefits were directly vs. indirectly received. Our results support a duty of care principle to provide herd protection for the elderly and an aversion to protecting adults who are better able to protect themselves. The weight given to side effects when evaluating a vaccination program was divisive, splitting our sample into two clusters.

Our study, as far as we are aware, is the first of its kind to quantify the important social value judgements that need to be made in vaccine funding decisions. Although this limits comparability, our findings are in line with what can be learned from other study domains. The finding that individuals weighted one averted instance of a side effect equal to about three similarly severe natural infections in children can be explained with general theory on decision-making. For instance, well-documented psychological phenomena such as ‘loss aversion’ [55] (overvaluing risks and losses over opportunities and gains), the ‘act-omission bias’ [56] [judging the effects of an

411 act (becoming vaccinated) differently from identical effects resulting from an
412 omission (becoming infected)], or 'hyperbolic discounting' [57] [overvaluing the
413 present (in which side effects occur) over the future (in which disease prevention will
414 occur)] suggest that people put an extraordinary weight on side effects when
415 evaluating a vaccination strategy. Moreover, also empirical studies that have
416 investigated people's (stated) choices about whether or not they would personally
417 become vaccinated with a particular vaccine (e.g. [43, 58]) generated findings that
418 highlight the extraordinary weight of side effects. The preference given to health
419 benefits in younger people (newborns and children), up to six-fold, is also in line with
420 related studies on 'ageism' in other contexts of healthcare priority-setting (reviewed
421 in [59] and discussed elsewhere, e.g. [60, 61]).

422 It is important to study which aspects of health policy choices matter most to the
423 public. This is especially true in vaccination where public trust, goodwill and
424 participation are sensitive and key to success [62]. There is a growing concern that
425 public and political trust in scientific evidence is eroding, particularly in the context of
426 vaccination [63-65]. By being aware of the sensitivities around vaccination, decision
427 makers can understand and address some of the root causes of vaccine hesitancy,
428 adapt to concerns of the population and improve responses in communication
429 strategies.[66] Our findings provide empirical evidence on how to set vaccine
430 priorities in line with public preferences. There is an important debate over the extent
431 to which the public's opinion should drive resource allocation in healthcare (see e.g.
432 [67, 68]). But, many believe that the values of the public, who pays for healthcare,
433 should at least somehow be acknowledged in the decision-making process. In the
434 context of vaccination, where public support and participation is key to success, this
435 concern becomes particularly crucial. Therefore, our results can be useful additions

to vaccine appraisals. They can provide guidance in specific epidemiological cases where CEA does not provide the answers needed. For instance, our results would suggest that, despite their attractiveness in terms of cost-effectiveness, the public may not support a childhood influenza vaccination program that mainly benefits adults or elderly [69], because preventing side effects in vaccinated children is preferred over preventing disease burden among adults and elderly. Furthermore, our study suggests that a childhood varicella-zoster vaccination program, in the case that it protects children against varicella disease at the expense of increased zoster in the elderly (the 'exogenous boosting hypothesis'), might be justifiable. In contrast, previous analyses where QALY losses for children are weighted equally to those for the elderly find that the increased burden in the elderly offsets the QALY gains in children and determine the program not cost-effective [23, 70].

Our results can also be directly incorporated into economic evaluations as sensitivity analyses to better align the underlying assumptions of CEA with the values of the population. Our estimated preference weights can be used in decision-analytic models as a parameter to weight QALYs or infections according to their 'social value'. This would re-adjust the (equal) weight that QALYs receive in CEA according to how important people think that the age of the QALY-recipient is and whether the benefit was generated through direct protection, herd immunity or (avoiding) side effects. There is an increased interest in such 'extended', 'distributive' or 'equity-weighted' economic evaluation (see e.g. [7, 34, 71-76]), but, to our knowledge, such studies do not exist for the evaluation of vaccines. Our estimates are developed particularly for this context, and provide an opportunity to do so.

There are several limitations. We did not include any mortality effects, nor did we include a difference in severity between the three vaccine effects, even though this

would be more realistic (as side effects of vaccines are usually milder than the disease being prevented). We chose not to include these aspects because we wanted to avoid increasing the complexity of the survey and reducing the validity of the respondents' answers by adding a second disease profile. Also, keeping the disease outcome constant over age groups and effects enabled trade-offs that were wholly reflective of the preference between age groups and effects instead of also reflecting additional considerations about disease severity. We also chose to present the number of side effects rather than its complement the number of vaccinated people *without* side effects. This framing may have played a role in the observed weight for side effects. The alternative framing would probably have drawn less attention to side effects and might have generated smaller weights. We however wanted people to make explicit trade-offs between side effects with protective benefits and chose for the more direct framing. Using the alternative is a suggestion for further research. Also, we used generic disease profiles based on a description in EQ-5D terms to minimize respondents making personal associations to the disease and vaccine when we would have named the diseases (e.g. 'flu' or 'whooping cough'), but this may also have increased the level of abstraction and reduced the level of personal involvement. A suggestion for further research is to repeat our study with named diseases and to test whether our finding that the disease profile did not matter to people's preferences is confirmed. Another limitation is that, while our sample was broadly representative of the UK population, it was recruited from an online panel where membership may be associated with unobserved characteristics (e.g. interest in technology).

In conclusion, our study demonstrates clear and robust preference patterns in how people value the impact of vaccination programs. A large majority of respondents

had a strong preference to minimize side effects and to prevent disease among newborns and children. Our observations provide quantitative evidence about public preferences around important and sensitive but neglected trade-offs in vaccine policy decision-making, and can hopefully inspire further research and discussion.

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Table 1. Attributes and levels used in the DCE

Attribute	Level
Age of vaccinated group (N=100 000)	Children (3 months - 3 years)
	Adults (30-50 years)
	Elderly (65-75 years)
Disease episodes prevented in vaccinated group	1000 cases
	3000 cases
	5000 cases
Number of vaccine-induced side-effects	100 cases
	300 cases
	500 cases
Disease episodes prevented via herd protection	1000 cases
	3000 cases
	5000 cases
Age of people receiving herd protection	Newborns (<3 months)
	Adults (30-50 years)
	Elderly (>80 years)

656

657 **Table 2: Respondent characteristics.**

	Sample	UK population*
Total recruited	1546	
Excluded for analysis	47	
Included in the analysis	1499 (100%)	
Gender		
Male	703 (47%)	49%
Female	796 (53%)	51%
Age (years)		
20-29	296 (20%)	13%
30-39	285 (19%)	13%
40-49	288 (19%)	14%
50-59	308 (21%)	13%
60 and over	322 (21%)	23%
Living in a city with more than 10,000 inhabitants	1011 (67%)	83%
Social grades based on the profession of the highest paid household member		
A (upper middle class)	85 (6%)	4%
B (middle class)	297 (20%)	23%
C1 (lower middle class)	385 (26%)	27%
C2 (skilled working class)	330 (22%)	21%
D (working class)	72 (5%)	16%
E (non-working)	330 (22%)	9%
Education level		
No qualifications	48 (3%)	15%
Secondary education	322 (21%)	14.2%
Post-secondary education	288 (19%)	14.5%
Vocational qualification	254 (17%)	20.3%
Undergraduate degree, Post-graduate degree & Doctorate	427 (39%)	30%

Not sure	2 (0.1%)	/
Having children		
No children	585 (39%)	42%
Children aged 0-4 years	168 (11%)	42%**
Children aged 5-20 years	358 (24%)	/
Children aged over 20 years	388 (26%)	15%
Exposure to poor health		
Participant affected by poor health	407 (27%)	
Close friends or family of the participant affected by poor health	470 (31%)	
Neither participant nor close friends nor family affected by poor health	622 (41%)	

*UK population data 2016: Office for National Statistics https://www.gov.uk/government/publications

**Percentage of UK families living with dependent children (<18 years old)

675

676 **Table 3. Attributes that affected respondent choices, based on panel mixed logit model estimates (means and standard**
677 **deviations) with p-values from likelihood ratio (LR) tests for significant attribute effects.**

Model term		Posterior mean	Posterior std dev	Subject std dev	P-value
Cases prevented in unvaccinated by herd effects (per 1000 cases)		0.715	0.018	0.101	<0.0001
Cases prevented in vaccinated by direct effects (per 1000 cases)		0.619	0.018	0.100	<0.0001
Cases of side effects in vaccinated (per 100 cases)		-0.285	0.012	0.110	<0.0001
Age of unvaccinated	[Newborns <3m]	0.614	0.048	0.090	<0.0001
	[Adults 30-50y]	-0.597	0.043	0.105	
	[Elderly >80y]	*-0.017*	NA	NA	
Age of unvaccinated*Cases prevented in vaccinated by direct effects	[Newborns <3m]	-0.043	0.009	0.054	<0.0001
	[Adults 30-50y]	0.071	0.009	0.041	
	[Elderly >80y]	*-0.028*	NA	NA	
Age of vaccinated	[Children 3m-3y]	0.305	0.040	0.063	<0.0001
	[Adults 30-50y]	0.142	0.048	0.062	
	[Elderly 65-75y]	*-0.446*	NA	NA	
Age of unvaccinated*Age of vaccinated	[Newborns <3m]* [Children 3m-3y]	-0.131	0.036	0.053	<0.0001
	[Newborns <3m]* [Adults 30-50y]	-0.210	0.041	0.065	
	[Newborns <3m] [Elderly 65-*	*0.341*	NA	NA	

	75y]				
	[Adults 30-50y]* [Children 3m-3y]	0.250	0.052	0.044	
	[Adults 30-50y]* [Adults 30-50y]	-0.079	0.049	0.045	
	[Adults 30-50y] [Elderly 65-75y]*	*-0.171*	NA	NA	
	[Elderly >80y] [Children 3m-3y]*	*-0.119*	NA	NA	
	[Elderly >80y] [Adults 30-50y]*	*0.289*	NA	NA	
	[Elderly >80y] [Elderly 65-75y]*	*-0.170*	NA	NA	
Age of vaccinated*Cases of side effects in vaccinated	[Children 3m-3y]	-0.032	0.008	0.040	<0.0001
	[Adults 30-50y]	-0.037	0.009	0.044	
	[Elderly 65-75y]	*0.069*	NA	NA	
Age of unvaccinated*Cases prevented in unvaccinated by herd effects	[Newborns <3m]	0.052	0.009	0.048	<0.0001
	[Adults 30-50y]	-0.005	0.008	0.043	
	[Elderly >80y]	*-0.047*	NA	NA	
Age of vaccinated*Cases prevented in vaccinated by direct effects	[Children 3m-3y]	0.051	0.010	0.044	<0.0001
	[Adults 30-50y]	-0.032	0.009	0.037	
	[Elderly 65-75y]	*-0.019*	NA	NA	

678 Note: Mean estimates corresponding to the last level of an attribute, either as a main effect or involved in an interaction, are italicized and calculated as minus
679 the sum of the estimates for the other levels of that attribute; NA means ‘not assigned’.

Table 4. Number of infections to prevent to gain equal utility, with 95% confidence intervals.

Age group of vaccine effect	Direct effects	Herd effects	Side effects
Newborns (<3 months)	NA	**71** [66; 76]	NA
Children (3 months – 3 years)	**100** [index]	NA	**-34** [-37; -31] Cluster 1: -221 [-340; -102] Cluster 2: -21 [-23; -20]
Adults (30–50 years)	**134** [115; 153]	**865** [242; 1487]	**-32** [-35; -28] Cluster 1: -72 [-93; -51] Cluster 2: -23 [-25; -20]
Elderly (65–75 years)	**632** [255; 1010]	NA	**-37** [-42; -33] Cluster 1: -113 [-163; -64] Cluster 2: -25 [-27; -22]
Elderly (>80 years)	NA	**150** [130; 169]	NA

Note: Cluster 1 and 2 have 564 and 935 respondents, respectively; NA refers to combinations of attribute levels not included in the choice profiles.

Figure 1. Example of a choice set.

Figure 2. Schematic representation of the different arms of the questionnaire. For each disease stratum, there was also an equal sampling over the socio-economic groups (25% A+B; 25% C1; 25% C2; 25% E+D).

Figure 3. Utility weights representing public preferences for identical health outcomes with different attributes, with 95% confidence intervals.

Figure 4. Intergenerational preferences: interaction effects between the age group vaccinated and the age group receiving herd protection effects. Marginal utility values consist of main effects of the attributes involved and their interaction effect..

*Revised manuscript (clean) EXCLUDING AUTHOR DETAILS
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Quantifying the public's view on social value judgments in vaccine decision-making: a discrete choice experiment

Abstract

Vaccination programs generate direct protection, herd protection and, occasionally, side effects, distributed over different age groups. This study elicits the general public's view on how to balance these outcomes in funding decisions for vaccines. We performed an optimal design discrete choice experiment with partial profiles in a representative sample (N=1499) of the public in the United Kingdom. Using a panel mixed logit model, we quantified, for four different types of infectious disease, the importance of a person's age during disease, how disease was prevented—via direct vaccine protection or herd protection—and whether the vaccine induced side effects. Our study shows clear patterns in how the public values vaccination programs. These diverge from the assumptions made in public health and cost-effectiveness models that inform decision-making. We found that side effects and infections in newborns and children were of primary importance to the perceived value of a vaccination program. Averting side effects was, in any age group, weighted three times as important as preventing an identical natural infection in a child whereas the latter was weighted six times as important as preventing the same infection in elderly aged 65-75 years. These findings were independent of the length or severity of the disease, and were robust across respondents' backgrounds. We summarize these patterns in a set of preference weights that can be incorporated into future models.

Keywords

Priority-setting; age; side effects, herd protection, cost-effectiveness analysis, decision making; discrete choice experiment; preference weight, vaccination

1. Introduction

Economic evaluation methods such as cost-effectiveness analysis (CEA) are common components in public funding decisions for vaccines [1, 2]. They feature in the standard evidence considered by e.g. the Advisory Committee on Immunization Practices in the US, the Joint Committee on Vaccination and Immunization in England, the World Health Organization and non-governmental organizations such as the Bill & Melinda Gates Foundation [3]. At the same time, it is widely acknowledged that these evaluation frameworks have important shortcomings and that they alone offer insufficient basis for making fair and efficient vaccine funding decisions [4-8]. There is a growing literature about the limits of CEA in assessing the value of vaccination [9-15].

One important criticism is that CEA is limited in how it values the consequences of vaccination. Summary outcome measures [such as e.g. infections prevented or Quality-Adjusted Life Years (QALYs) gained] neglect the particular social context in which these outcomes occur. Nonetheless, such contextual features are important aspects to consider when evaluating a vaccination strategy. Vaccination induces disease protection in those who become vaccinated, but it also creates *herd* protection (or indirect effects in third parties because of reduced pathogen transmission [16]) and, occasionally, adverse clinical *side* effects. There are qualitative differences between these direct, herd and side effects. Creating herd protection can be of particular ethical value (e.g. to protect vulnerable groups who otherwise cannot protect themselves) and there is a profound psychological impact of vaccine-induced side effects. Moreover, the *distribution* of these three different effect types over different age groups is important. Side effects can be concentrated in one age group despite indirect protection from reduced transmission benefitting

either the wider population, or in some cases a different age group entirely [17]. Examples include protecting the elderly through childhood influenza vaccination or future generations through a *polio* eradication program. Such broader, distributive aspects of vaccination are important but they remain neglected in standard cost-effectiveness or public health impact models.

Several notable examples illustrate that this broader social context of health outcomes needs to be considered in vaccine decision-making [18]. For instance, vaccines against rotavirus (Rotashield®) and pertussis (whole cell pertussis vaccine) were withdrawn from many countries because of a perceived risk of side effects, even though from a medical perspective the benefit from vaccination largely outweighed any potential risk [19-21]. Also, despite persuasive economic and public health benefits of childhood influenza vaccination, few countries have actually implemented such a preventive strategy, due in large part to concerns about the social acceptability and equity of targeting vaccination at children to protect the wider population [22]. And, in many countries introduction of an effective varicella vaccination program has been delayed because of concerns about the possible 'exogenous boosting effect' and its social repercussions, i.e. that reduced chickenpox transmission among children (due to varicella vaccination) might temporarily increase shingles incidence among older generations [23].

Misjudging ethical norms and social sensitivities in vaccination policy by over-relying on CEA can have important implications. It may affect the perceived equity of a program, its support by the public and its long-term sustainability [13, 24-26] [27, 28]. It can invoke public backlash to the vaccine, leading to reduced uptake, increased vaccine hesitancy and reduced overall effectiveness of the program [29-31]. Therefore, an empirical evidence-base is needed about the public's view on the key

value judgments that need to be made in vaccine funding decisions [9, 10, 12, 32, 33]. Such evidence can complement formalized appraisals like CEA, stimulate deliberation and discussion on how to prioritize vaccines within a budget constraint and, moreover, it can be explored whether such evidence can become quantitatively integrated into formal decision frameworks in some sort of 'extended' or 'weighted' CEA [7, 34].

The objective of this study is to address this challenge by analyzing how the population in the United Kingdom prioritizes vaccination programs and to investigate whether its values diverge from the assumptions that are implicitly underlying CEA. We use a discrete choice experiment (DCE) among a representative sample of the population in the United Kingdom (UK) to investigate, for four different types of infectious diseases, the role played by different age groups in a program's overall evaluation and the extent to which it matters whether these age groups are affected by either direct, herd or side effects. We summarize these findings into a set of social preference weights for health outcomes (e.g. QALYs) that could be incorporated into economic evaluation or public health impact models.

2. Methods

DCEs are a widely used survey method to quantify individuals' preferences [35, 36] (for a general review of applications, see [37]). Participants are presented with a series of choices, usually between two goods described by the same attributes but differing in their attribute levels. By observing respondents' preferred choices, researchers can infer how the value of the competing options is determined by the attributes of the product. In our case, we observe how people prioritize between

vaccination programs based on the number of direct, herd and side effects generated by the program, and their distribution over different age groups. This allows us to estimate a utility function that describes how the public values vaccination programs, taking into account the different types of vaccine effect and their distribution.

2.1 Choice context

For all of their choices, respondents were randomly assigned one of four disease scenarios (see **Appendix A**). These were introduced before the start of the DCE. After five choice sets this disease was presented again to the respondent as a reminder. The four disease profiles were described as (1) severe—lasting nine days, (2) mild—lasting nine days, (3) severe—lasting 160 days, and (4) mild—lasting 160 days. Influenza and pertussis were used as proxies for an acute severe and a longer lasting milder disease, respectively [38, 39]. To avoid participants' preconceived ideas, the diseases were unnamed and only described to participants by means of severity using the generic descriptors of the dimensions of a standard instrument to measure health-related quality of life, the EuroQoL EQ-5D-3L, based on average reported values for both influenza and pertussis [38, 39]. To exclude considerations about age differences in remaining life expectancy, we explicitly told the participants that the diseases were not fatal.

Before every choice set we told respondents the following: "*the government has to choose between two vaccination programs that will each be used in 100 000 people. Considering your conviction about vaccination policy, which program do you think*

the government should choose? Both options are equally costly, and identical in every way except for the following 5 differences."

2.2 Attributes and levels of vaccination programs

To develop the final attributes and levels of the vaccine programs included in the DCE, we followed a three stage iterative process. We performed a literature search of other vaccine-related DCEs to assess the choice context and which attributes were typically considered. These attributes were disease incidence, case fatality risk, economic impact, duration of illness and duration of vaccine protection, severity of illness and severity of side effects, and various personal characteristics including age, gender and willingness/ability to get vaccinated. [40-44] From this list, we took the attributes that were, in combination with the four disease profiles, best suited to answer our research question. We presented several attribute combinations to a convenience sample of lay persons, colleagues and collaborators at the market research company in a pilot questionnaire, which we revised in response to received comments. We re-iterated this process until we found the right form for the DCE from which, with a relatively simple set of in total five core attributes (**Table 1**), we could robustly calculate preference weights.

The first two attributes described the age group targeted for vaccination and magnitude of the direct effects among those vaccinated. The third attribute described the number of side effects occurring among those vaccinated. The side effects of vaccination were presented in the DCE as identical to an episode of the disease that the vaccine usually prevents, in order to enable a direct comparison between the three effect types. Not doing so would have meant using a second health profile

within one choice option (one for the disease and one for the side effects) and this would also have made the experiment substantially more difficult for the participants. The fourth and fifth attribute described the magnitude of the herd effects and the age group that received them. We decided to focus only on the morbidity aspects of illness because including mortality would require additional attributes for infected people in order to account for their differing life expectancy.

For direct and herd protection we used 1000, 3000 or 5000 disease episodes prevented per 100,000 people vaccinated (an attack rate of 1-5% for a vaccine with a 100% efficacy), and for side effects 100, 300 or 500 disease episodes per 100,000 people vaccinated (an attack rate of 0.1-0.5%). For direct protection and side effects, we considered the following three age groups: children aged between 3 months and 3 years of age, adults aged between 30 and 50 years, and elderly aged between 65 and 75 years. The age groups for herd protection represented groups that, in the case of the first two, are often difficult to vaccinate for immunological reasons: young children under 3 months, elderly above 80 years and unvaccinated adults between 30 and 50 years.

(insert **Table 1**)

We depicted both the age group and quantity of cases avoided or caused by vaccination using simple graphics [45] (**Figure 1**). To explicitly investigate the assumption whether individuals ultimately look at the total impact of the program and to reduce the chance that respondents would adhere to a simple counting heuristic

without reflection, we presented the net number of disease cases averted for each strategy separately (the sum of direct and herd effects minus side effects).

(insert **Figure 1)**

2.3 Experimental design of the choice sets

The design of a DCE refers to the number and composition of choice sets presented to each participant [46]. A set of 45 choice sets was selected out of the 58,806 possible choice sets (see **Appendix B** for more info on the selection process) and distributed over three survey versions, so to limit the number of choice sets to be completed per respondent to 15. Therefore, each of the four disease profiles was represented in three different surveys (see **Figure 2**).

(Insert **Figure 2)**

The choice alternatives (i.e. profiles) themselves were '*partial* profiles' [47, 54]. We varied and highlighted the levels of two to four of the five attributes in the choice sets and kept the remaining attribute(s) constant so that respondents did not have to simultaneously trade-off all five dimensions per choice (see **Appendix B**). Limiting the cognitive burden for respondents in a DCE increases the validity and reliability of their answers [48]. The design we generated was 'D-optimal' in a Bayesian framework fitting with a multinomial logit (MNL) model for the attributes' main effects and six interactions between the two age attributes (direct and herd effects) and the

three magnitude attributes we deemed to be important *a priori*. We chose a Bayesian framework to integrate prior information on the respondents' likely preferences [49] (see **Appendix C**). The Bayesian D-optimal design then results in the smallest possible standard errors for the utility estimates at the given sample size.

2.4 Sample

After the design, we tested our survey among a pilot sample of the online panel (N=69) to confirm that respondents could fully understand and complete the survey. Based on the feedback from this pilot sample we judged that the experiment was understandable and that no further changes were needed.

From a consumer panel of 1 million UK members, 9613 random panelists were approached to participate in "a scientific study on resource allocation in healthcare". Of these people, 4144 (43%) responded to the invitation. We recruited 1950 of them to fulfill predetermined quotas to provide a representative sample of the UK population in terms of gender, socio-economic strata (indicated by the occupation of the head of the household), age groups (20-29, 30-39, 40-49, 50-59, 60+ years), and urban vs. rural background.

The DCE was conducted in November 2016. An email containing a link to the survey website was sent to participants and by clicking on the link respondents consented to participate, although they were free to stop or close the survey at any point. All respondents received a nominal incentive for study completion (£0.50 per 12-minute questionnaire). Before completing the DCE, respondents were asked to administer a survey tool to measure vaccine hesitancy [50], and were asked social-demographic questions and whether they have or had children. After the DCE, we asked about

their experience with severe diseases, their interpretation of the validity of the answers they provided and the overall difficulty of the DCE survey.

We obtained informed consent from all respondents and ethical approval of the study from the Ethics Committee of the London School of Hygiene & Tropical Medicine (Ref 10335). We conducted the research in accordance with the Code of Conduct of the Market Research Society, which ensured that information is collected for research purposes only, is kept confidential, and respondent anonymity is guaranteed.

2.5 Data analysis

To quantify the weight of the five attributes and their levels in the utility attributed to a vaccination strategy, a panel mixed logit model (fitted by the Hierarchical Bayes method [51]) was used (see **Table 3**). The model involved seven main effects: four related to the two three-level categorical attributes describing the utility impact of a change in the targeted age group in direct and herd effects, and three related to the continuous attributes describing the impact of a change in the absolute number of disease cases via direct effects, side effects and herd effects. Besides these seven main effects the model also includes attribute interaction effects, indicating the additional change in utility because of a particular combination of attribute levels. We computed the overall significance of the attributes using likelihood ratio (LR) tests and measured the relative importance of the attributes by the logworth statistic (i.e. $-\log_{10}$ (p-value of the LR-test)). The coefficients of the logit model were obtained by estimating the *a priori* model, i.e. the model with the utility function that seemed most appropriate when planning the DCE, and subsequently dropping the non-significant

model terms until we obtained a *final* model in which all effects had significant explanatory value at the 5% level. Models were fitted using the JMP 13 Pro Choice platform (based on 10,000 iterations, with the last 5000 used for estimation) assuming normally distributed parameters with no correlation between the attributes. Combining the main and interaction effects, this model allows calculating the additional utility of a vaccination program generated per additional health effect, i.e. per type of effect per age group (see the nine variations in **Table 3**). The 95% confidence intervals for the equity weights were estimated using the Delta method [52].

We investigated heterogeneity in respondents' preferences in two ways. First, by exploring the influence of the observed respondent characteristics on the average preferences and, second, by studying the unobserved preference heterogeneity by means of a hierarchical cluster analysis on the subject-specific estimates resulting from the Hierarchical Bayes approach. We favoured this two-stage modelling method as it performs equally well as one-stage modelling methods such as latent class modelling [53] while enabling us to parsimoniously derive the preference weights and their 95% confidence intervals.

3. Results

3.1 Response

A total of 1546 respondents out of 1950 (79%) who were sent the questionnaire completed it, of which 47 (3%) indicated that the questions were too difficult or their answers invalid, leaving 1499 questionnaires for analysis. Our final sample was sufficiently representative of the UK population in terms of gender, family size, socio-economic status and education level (**Table 2**).

(insert **Table 2**)

3.2 Main effects and calculated weights

Across all questionnaires, respondents made a total of 22,485 choices between vaccination programs. There was no significant effect observed of which of the three survey versions a participant received. Respondents did not systematically choose the program with the highest overall public health impact, i.e. the total of all prevented cases including direct, herd and side effects. In fact, only 99 respondents (6.6%) consistently opted for the most effective program in all of their choice sets. However, about half the respondents (738/1499) chose the most effective alternative in at least 70% of their choices, indicating that the total effect on the disease burden is important, but not the only factor in prioritizing vaccination programs.

Table 3 presents an overview of the incremental utility of the main effects and interactions. The vaccination program that was least preferred (i.e. yielding minimum utility) was one that targeted the elderly (65-75y), generated the lowest number of prevented cases, the highest number of side effects, and the lowest number of cases prevented via herd protection in unvaccinated adults. The most preferred program (i.e. yielding maximum utility) was one that targeted children, generated the highest

number of prevented cases, the lowest number of side effects, and the highest number of cases prevented via herd protection in newborns.

(insert **Table 3**)

Using the same logit model, we then calculated preference weights for each effect type per age group. These weights act as a multiplicative factor to transform identical clinical symptoms into health effects with equal value in the public's view. We compared the additional utility of a vaccination program that is generated through preventing one specific disease case relative to the utility gained through directly preventing a single disease case via vaccinating a child (**Figure 3**). These preference weights reveal important patterns. First, preventing side effects of vaccination was highly preferable to preventing natural infections, even though the symptoms were equal in length and severity. The mean weight for side effects across all ages was -2.93, meaning that avoiding one vaccine-induced infection was weighted equally to avoiding around three natural infections among children. This finding was consistent whether side effects occurred in children (-2.95 (95% CI: -3.21; -2.69)), adults (-3.16 (95% CI: -3.51; -2.81)) or the elderly (-2.68 (95% CI: -2.98; -2.37)). Second, respondents preferred vaccination programs that prevented disease among newborns and children compared with those for adults and the elderly, even though the prevented disease burden was similar. One episode prevented in a newborn via herd protection was considered about twice as valuable as directly protecting an adult via vaccination. Third, the extent to which respondents preferred protecting adults and the elderly depends on the type of benefit conferred

by the program. Direct effects were the preferred mode of protection for adults whereas herd effects were preferred for the elderly. Reducing disease burden by directly vaccinating adults (aged 30-50 years) was weighted equally to reducing disease burden in the elderly (aged 80+ years) via herd effects [0.75 (0.64; 0.85) compared to 0.67 (0.58; 0.76), respectively]. In contrast, reducing disease burden in adults (aged 30-50 years) by herd effects counted equally to reducing disease burden in elderly (aged 65-75 years) directly via vaccination (0.12 (0.03; 0.20) compared to 0.16 (0.06; 0.25), respectively).

(insert **Figure 3**)

From these results, we also calculated the number of infections needed to avert in order to obtain equal utility as that from protecting 100 children directly via vaccination (**Table 4**). Avoiding 100 infections in children via vaccination was considered equivalent to protecting 632 elderly (65-75 years) or 134 adults. In turn, these outcomes were equivalent to protecting 71 newborns, 865 adults or 150 elderly (>80y) via herd protection. Similarly, a vaccination strategy reduces its utility by causing side effects. Avoiding 34 side effects in children generates the same utility as preventing 100 natural infections among the same age group.

(insert **Table 4**)

Figure 4 illustrates the significant interaction in our model between the age of the vaccinated group and the age of the herd protection recipients (see **Table 3**). This interaction must be understood as the additional utility that is given to (or taken away from) a vaccination program depending on the particular combination of age groups that are involved, regardless of the magnitude of direct, herd or side effects that are being generated. It presents the attractiveness of particular intergenerational vaccination strategies. Whereas a CEA perspective would consider all possible age combinations equally attractive (as long as they lead to the same number of infections prevented), our sample had clear intergenerational preferences over vaccination strategies. Any age group was deemed acceptable to vaccinate when there were herd protection benefits for newborns. To generate herd protection for adults, children were the most attractive age group. To generate it to protect the elderly >80, adults were deemed most appropriate. The least attractive intergenerational combination was vaccinating elderly 65-75 years while generating herd protection in adults 30-50 years. The most attractive age combination was vaccinating children while generating herd protection in newborns.

(insert **Figure 4**)

3.3 Preferences across disease types and respondents

As shown in **Appendix D**, our results remained robust across all four different disease types: the equity weights were statistically equivalent, regardless of whether the condition was mild vs. severe or acute vs. chronic (indicated by a non-significant interaction effect in our model between the attributes and the disease type). Also, the

appendix illustrates that our findings also remained robust across most respondent characteristics: gender, age, occupation, level of education, urban-rural, socio-economic background, experience with severe illness or parental status. Although individuals with a low degree of vaccine hesitancy (indicated by high values on the 'vaccine hesitancy scale' (VHS) [50]) attributed less importance to side effects ($p<0.0001$), this effect was relatively small (a 10 unit increase in the VHS score (on a scale from 10 to 50) led to a 10% decrease in absolute magnitude of the utility for side effects (~0.03)).

The hierarchical cluster analysis of the individual preferences (see methods) revealed two distinct groups of respondents: one group (N=564, *Cluster 1*) who attached almost no importance to the number of side effects (with a mean weight of -0.91 for side effects) and a larger group (N=935, *Cluster 2*) who valued this attribute fairly highly (with a mean weight of -4.40) (**Table 3**). This clustering explains the relatively high variation across respondents for the weight estimate for side effects (the standard deviation to mean absolute value ratio of 0.043 for side effects is almost twice the ratio for direct and herd effects). We used a logistic regression to determine predictors of cluster membership. Cluster 1, who attached almost no importance to the number of side effects, was characterized by high values on the VHS, indicating little hesitancy ($p<0.0001$). On the other hand, cluster 2, who valued side effects more highly, was characterized by higher degrees of hesitancy on the VHS. However, the predictive power of this association for membership of the group was small (McFadden's pseudo R^2=0.6%), implying that there is much unexplained heterogeneity in the importance placed on side effects.

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4. Discussion

In this study, we used a discrete choice experiment to analyse and quantify how the public values the outcomes of vaccination programs. We observed several general preference patterns, which were robust across different lengths and severities of disease and respondent characteristics (socio-economic background, age, education and parenthood). We observed that most respondents did not make choices purely based on how to minimize the number of infections. In particular, individuals, on average, weighted one averted instance of a side effect equal to about three similarly severe natural infections in children and weighted one averted health outcome in children up to six times more than preventing similarly severe health outcomes in the elderly. Interestingly, our study has disentangled this latter phenomenon from the type of effect as we observed a different weight given to protecting older people depending on whether the benefits were directly vs. indirectly received. Our results support a duty of care principle to provide herd protection for the elderly and an aversion to protecting adults who are better able to protect themselves. The weight given to side effects when evaluating a vaccination program was divisive, splitting our sample into two clusters.

Our study, as far as we are aware, is the first of its kind to quantify the important social value judgements that need to be made in vaccine funding decisions. Although this limits comparability, our findings are in line with what can be learned from other study domains. The finding that individuals weighted one averted instance of a side effect equal to about three similarly severe natural infections in children can be explained with general theory on decision-making. For instance, well-documented psychological phenomena such as ‘loss aversion’ [55] (overvaluing risks and losses over opportunities and gains), the ‘act-omission bias’ [56] [judging the effects of an

411 act (becoming vaccinated) differently from identical effects resulting from an
412 omission (becoming infected)], or 'hyperbolic discounting' [57] [overvaluing the
413 present (in which side effects occur) over the future (in which disease prevention will
414 occur)] suggest that people put an extraordinary weight on side effects when
415 evaluating a vaccination strategy. Moreover, also empirical studies that have
416 investigated people's (stated) choices about whether or not they would personally
417 become vaccinated with a particular vaccine (e.g. [43, 58]) generated findings that
418 highlight the extraordinary weight of side effects. The preference given to health
419 benefits in younger people (newborns and children), up to six-fold, is also in line with
420 related studies on 'ageism' in other contexts of healthcare priority-setting (reviewed
421 in [59] and discussed elsewhere, e.g. [60, 61]).

422 It is important to study which aspects of health policy choices matter most to the
423 public. This is especially true in vaccination where public trust, goodwill and
424 participation are sensitive and key to success [62]. There is a growing concern that
425 public and political trust in scientific evidence is eroding, particularly in the context of
426 vaccination [63-65]. By being aware of the sensitivities around vaccination, decision
427 makers can understand and address some of the root causes of vaccine hesitancy,
428 adapt to concerns of the population and improve responses in communication
429 strategies.[66] Our findings provide empirical evidence on how to set vaccine
430 priorities in line with public preferences. There is an important debate over the extent
431 to which the public's opinion should drive resource allocation in healthcare (see e.g.
432 [67, 68]). But, many believe that the values of the public, who pays for healthcare,
433 should at least somehow be acknowledged in the decision-making process. In the
434 context of vaccination, where public support and participation is key to success, this
435 concern becomes particularly crucial. Therefore, our results can be useful additions

436 to vaccine appraisals. They can provide guidance in specific epidemiological cases
437 where CEA does not provide the answers needed. For instance, our results would
438 suggest that, despite their attractiveness in terms of cost-effectiveness, the public
439 may not support a childhood influenza vaccination program that mainly benefits
440 adults or elderly [69], because preventing side effects in vaccinated children is
441 preferred over preventing disease burden among adults and elderly. Furthermore,
442 our study suggests that a childhood varicella-zoster vaccination program, in the case
443 that it protects children against varicella disease at the expense of increased zoster
444 in the elderly (the 'exogenous boosting hypothesis'), might be justifiable. In contrast,
445 previous analyses where QALY losses for children are weighted equally to those for
446 the elderly find that the increased burden in the elderly offsets the QALY gains in
447 children and determine the program not cost-effective [23, 70].

448 Our results can also be directly incorporated into economic evaluations as sensitivity
449 analyses to better align the underlying assumptions of CEA with the values of the
450 population. Our estimated preference weights can be used in decision-analytic
451 models as a parameter to weight QALYs or infections according to their 'social
452 value'. This would re-adjust the (equal) weight that QALYs receive in CEA according
453 to how important people think that the age of the QALY-recipient is and whether the
454 benefit was generated through direct protection, herd immunity or (avoiding) side
455 effects. There is an increased interest in such 'extended', 'distributive' or 'equity-
456 weighted' economic evaluation (see e.g. [7, 34, 71-76]), but, to our knowledge, such
457 studies do not exist for the evaluation of vaccines. Our estimates are developed
458 particularly for this context, and provide an opportunity to do so.

459 There are several limitations. We did not include any mortality effects, nor did we
460 include a difference in severity between the three vaccine effects, even though this

would be more realistic (as side effects of vaccines are usually milder than the disease being prevented). We chose not to include these aspects because we wanted to avoid increasing the complexity of the survey and reducing the validity of the respondents' answers by adding a second disease profile. Also, keeping the disease outcome constant over age groups and effects enabled trade-offs that were wholly reflective of the preference between age groups and effects instead of also reflecting additional considerations about disease severity. We also chose to present the number of side effects rather than its complement the number of vaccinated people *without* side effects. This framing may have played a role in the observed weight for side effects. The alternative framing would probably have drawn less attention to side effects and might have generated smaller weights. We however wanted people to make explicit trade-offs between side effects with protective benefits and chose for the more direct framing. Using the alternative is a suggestion for further research. Also, we used generic disease profiles based on a description in EQ-5D terms to minimize respondents making personal associations to the disease and vaccine when we would have named the diseases (e.g. 'flu' or 'whooping cough'), but this may also have increased the level of abstraction and reduced the level of personal involvement. A suggestion for further research is to repeat our study with named diseases and to test whether our finding that the disease profile did not matter to people's preferences is confirmed. Another limitation is that, while our sample was broadly representative of the UK population, it was recruited from an online panel where membership may be associated with unobserved characteristics (e.g. interest in technology).

In conclusion, our study demonstrates clear and robust preference patterns in how people value the impact of vaccination programs. A large majority of respondents

had a strong preference to minimize side effects and to prevent disease among newborns and children. Our observations provide quantitative evidence about public preferences around important and sensitive but neglected trade-offs in vaccine policy decision-making, and can hopefully inspire further research and discussion.

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653 **Table 1. Attributes and levels used in the DCE**

Attribute	Level
Age of vaccinated group (N=100 000)	Children (3 months - 3 years)
	Adults (30-50 years)
	Elderly (65-75 years)
Disease episodes prevented in vaccinated group	1000 cases
	3000 cases
	5000 cases
Number of vaccine-induced side-effects	100 cases
	300 cases
	500 cases
Disease episodes prevented via herd protection	1000 cases
	3000 cases
	5000 cases
Age of people receiving herd protection	Newborns (<3 months)
	Adults (30-50 years)
	Elderly (>80 years)

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657 **Table 2: Respondent characteristics.**

	Sample	UK population*
Total recruited	1546	
Excluded for analysis	47	
Included in the analysis	1499 (100%)	
Gender		
Male	703 (47%)	49%
Female	796 (53%)	51%
Age (years)		
20-29	296 (20%)	13%
30-39	285 (19%)	13%
40-49	288 (19%)	14%
50-59	308 (21%)	13%
60 and over	322 (21%)	23%
Living in a city with more than 10,000 inhabitants	1011 (67%)	83%
Social grades based on the profession of the highest paid household member		
A (upper middle class)	85 (6%)	4%
B (middle class)	297 (20%)	23%
C1 (lower middle class)	385 (26%)	27%
C2 (skilled working class)	330 (22%)	21%
D (working class)	72 (5%)	16%
E (non-working)	330 (22%)	9%
Education level		
No qualifications	48 (3%)	15%
Secondary education	322 (21%)	14.2%
Post-secondary education	288 (19%)	14.5%
Vocational qualification	254 (17%)	20.3%
Undergraduate degree, Post-graduate degree & Doctorate	427 (39%)	30%

Not sure	2 (0.1%)	/
Having children		
No children	585 (39%)	42%
Children aged 0-4 years	168 (11%)	42%**
Children aged 5-20 years	358 (24%)	/
Children aged over 20 years	388 (26%)	15%
Exposure to poor health		
Participant affected by poor health	407 (27%)	
Close friends or family of the participant affected by poor health	470 (31%)	
Neither participant nor close friends nor family affected by poor health	622 (41%)	

*UK population data 2016: Office for National Statistics https://www.gov.uk/government/publications

**Percentage of UK families living with dependent children (<18 years old)

675

676 **Table 3. Attributes that affected respondent choices, based on panel mixed logit model estimates (means and standard**
677 **deviations) with p-values from likelihood ratio (LR) tests for significant attribute effects.**

Model term		Posterior mean	Posterior std dev	Subject std dev	P-value
Cases prevented in unvaccinated by herd effects (per 1000 cases)		0.715	0.018	0.101	<0.0001
Cases prevented in vaccinated by direct effects (per 1000 cases)		0.619	0.018	0.100	<0.0001
Cases of side effects in vaccinated (per 100 cases)		-0.285	0.012	0.110	<0.0001
Age of unvaccinated	[Newborns <3m]	0.614	0.048	0.090	<0.0001
	[Adults 30-50y]	-0.597	0.043	0.105	
	[Elderly >80y]	*-0.017*	NA	NA	
Age of unvaccinated*Cases prevented in vaccinated by direct effects	[Newborns <3m]	-0.043	0.009	0.054	<0.0001
	[Adults 30-50y]	0.071	0.009	0.041	
	[Elderly >80y]	*-0.028*	NA	NA	
Age of vaccinated	[Children 3m-3y]	0.305	0.040	0.063	<0.0001
	[Adults 30-50y]	0.142	0.048	0.062	
	[Elderly 65-75y]	*-0.446*	NA	NA	
Age of unvaccinated*Age of vaccinated	[Newborns <3m]* [Children 3m-3y]	-0.131	0.036	0.053	<0.0001
	[Newborns <3m]* [Adults 30-50y]	-0.210	0.041	0.065	
	[Newborns <3m] [Elderly 65-*	*0.341*	NA	NA	

	75y]				
	[Adults 30-50y]* [Children 3m-3y]	0.250	0.052	0.044	
	[Adults 30-50y]* [Adults 30-50y]	-0.079	0.049	0.045	
	[Adults 30-50y] [Elderly 65-75y]*	*-0.171*	NA	NA	
	[Elderly >80y] [Children 3m-3y]*	*-0.119*	NA	NA	
	[Elderly >80y] [Adults 30-50y]*	*0.289*	NA	NA	
	[Elderly >80y] [Elderly 65-75y]*	*-0.170*	NA	NA	
Age of vaccinated*Cases of side effects in vaccinated	[Children 3m-3y]	-0.032	0.008	0.040	<0.0001
	[Adults 30-50y]	-0.037	0.009	0.044	
	[Elderly 65-75y]	*0.069*	NA	NA	
Age of unvaccinated*Cases prevented in unvaccinated by herd effects	[Newborns <3m]	0.052	0.009	0.048	<0.0001
	[Adults 30-50y]	-0.005	0.008	0.043	
	[Elderly >80y]	*-0.047*	NA	NA	
Age of vaccinated*Cases prevented in vaccinated by direct effects	[Children 3m-3y]	0.051	0.010	0.044	<0.0001
	[Adults 30-50y]	-0.032	0.009	0.037	
	[Elderly 65-75y]	*-0.019*	NA	NA	

Note: Mean estimates corresponding to the last level of an attribute, either as a main effect or involved in an interaction, are italicized and calculated as minus the sum of the estimates for the other levels of that attribute; NA means ‘not assigned’.

680 **Table 4. Number of infections to prevent to gain equal utility, with 95%**
681 **confidence intervals.**

Age group of vaccine effect	Direct effects	Herd effects	Side effects
Newborns (<3 months)	NA	**71** [66; 76]	NA
Children (3 months – 3 years)	**100** [index]	NA	**-34** [-37; -31] Cluster 1: -221 [-340; -102] Cluster 2: -21 [-23; -20]
Adults (30–50 years)	**134** [115; 153]	**865** [242; 1487]	**-32** [-35; -28] Cluster 1: -72 [-93; -51] Cluster 2: -23 [-25; -20]
Elderly (65–75 years)	**632** [255; 1010]	NA	**-37** [-42; -33] Cluster 1: -113 [-163; -64] Cluster 2: -25 [-27; -22]
Elderly (>80 years)	NA	**150** [130; 169]	NA

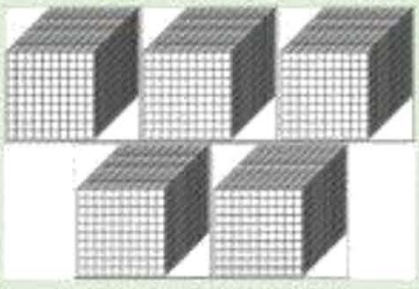
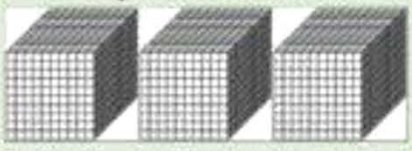
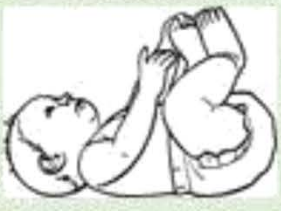
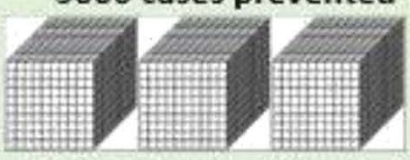
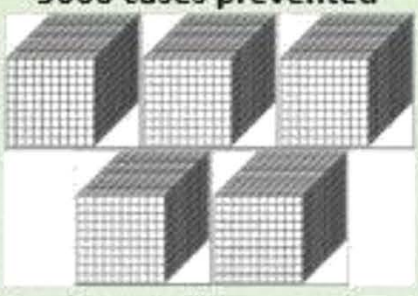
682 Note: Cluster 1 and 2 have 564 and 935 respondents, respectively; NA refers to combinations of
683 attribute levels not included in the choice profiles.
684

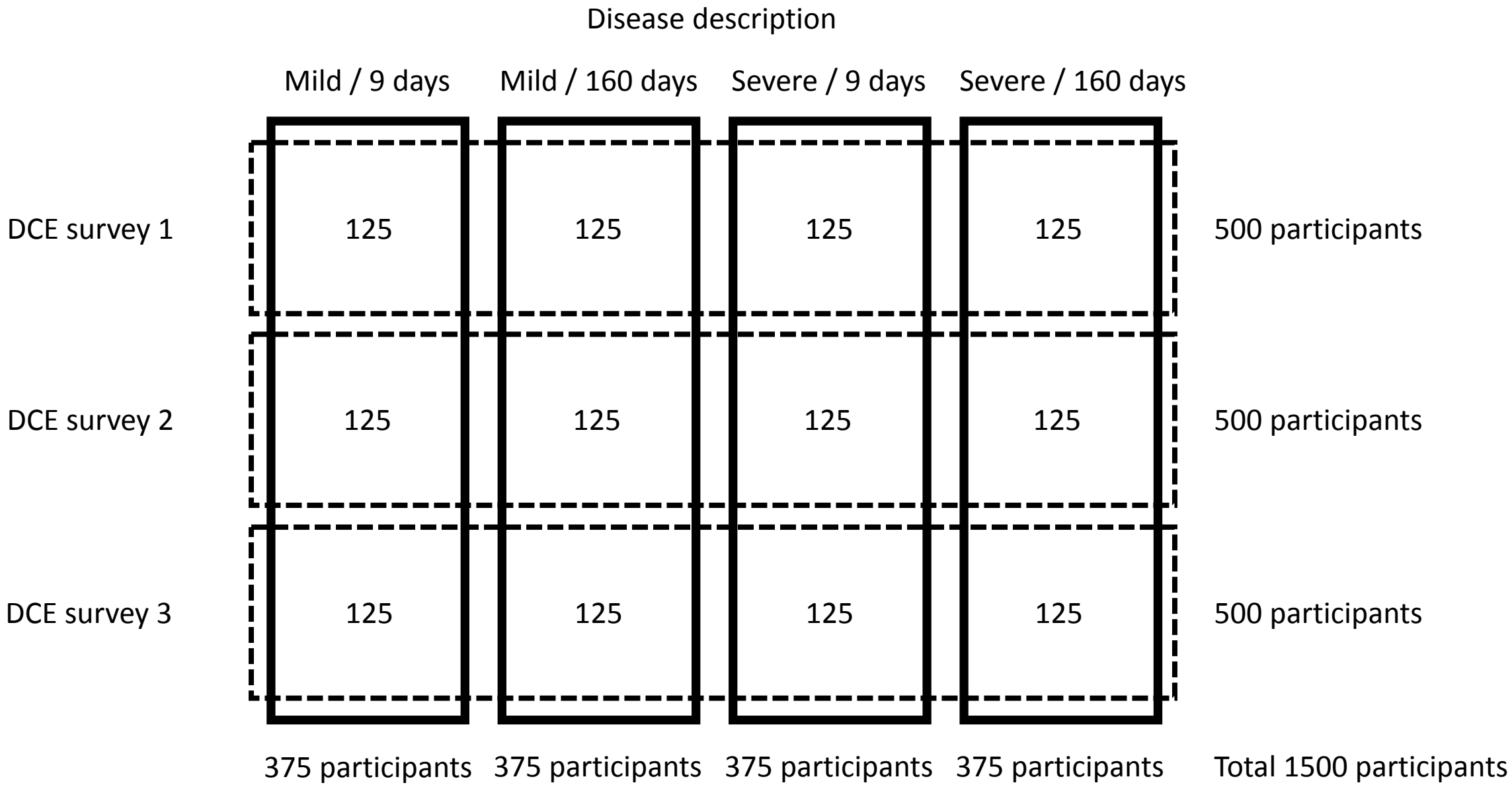
Figure 1. Example of a choice set.

Figure 2. Schematic representation of the different arms of the questionnaire. For each disease stratum, there was also an equal sampling over the socio-economic groups (25% A+B; 25% C1; 25% C2; 25% E+D).

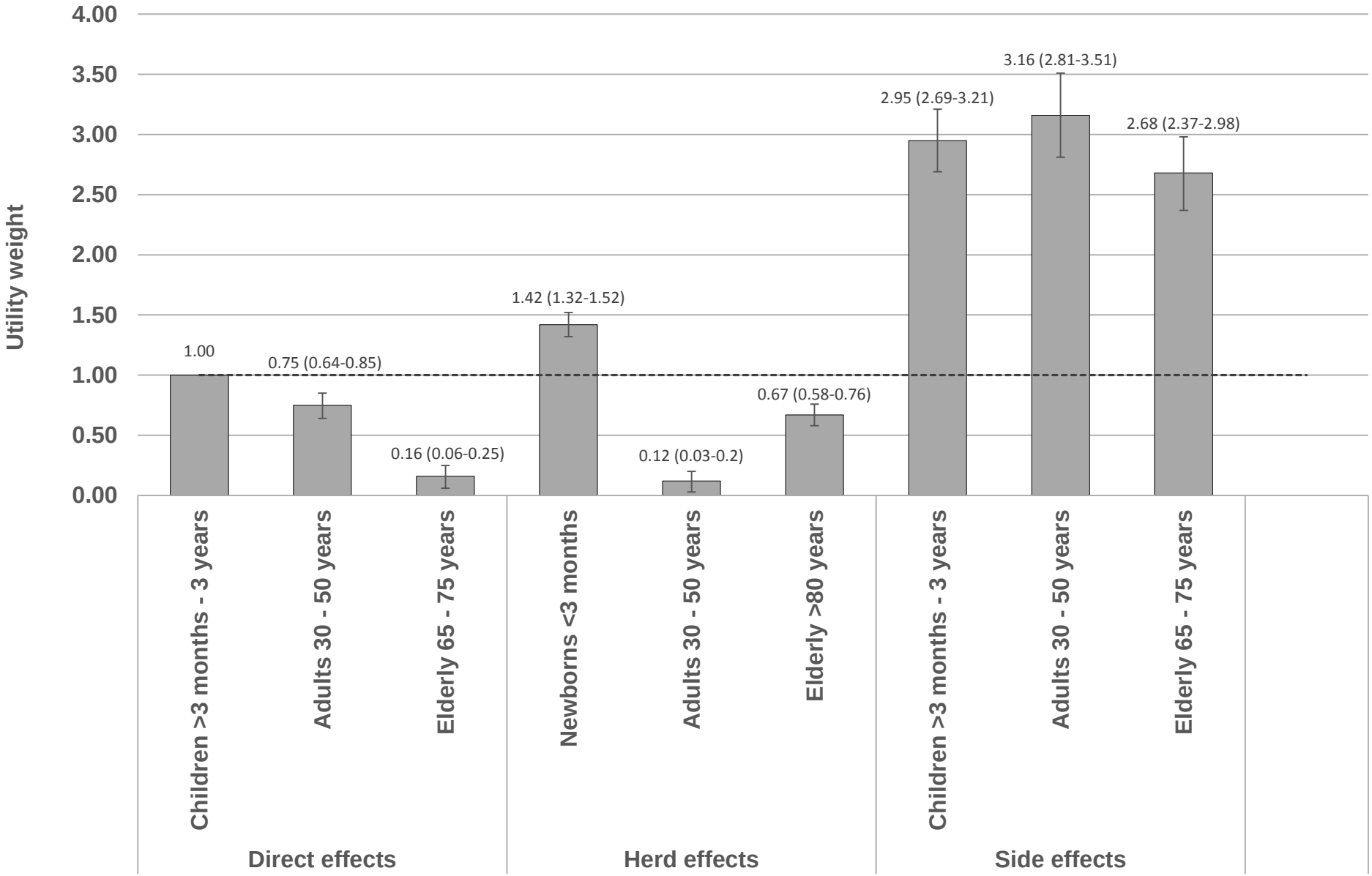
Figure 3. Utility weights representing public preferences for identical health outcomes with different attributes, with 95% confidence intervals.

Figure 4. Intergenerational preferences: interaction effects between the age group vaccinated and the age group receiving herd protection effects. Marginal utility values consist of main effects of the attributes involved and their interaction effect..

	PROGRAM A	PROGRAM B
TOTAL NUMBER OF PREVENTED CASES (per 100,000)	7500	7700
Direct effects		
How old are the 100,000 people who will become vaccinated?	**Adults (30-50 years)**	**Adults (30-50 years)**
*How many cases of disease will be **prevented** in the 100,000 who become vaccinated?*	**5000 cases prevented** 	**3000 cases prevented** 
Side-effects		
*How many of the 100,000 vaccinated persons will get the disease through **side effects** of vaccination?*	**500 cases occurring**	**300 cases occurring**
Indirect effects		
*How old are those who will benefit from the **indirect protection** but are not vaccinated themselves?*	**Infants (Under 3 months)** 	**Infants (Under 3 months)**
*How many cases of disease will be **prevented** via indirect protection in those who will not be vaccinated?*	**3000 cases prevented** 	**5000 cases prevented** 


Disease description
Mild / 9 days
Mild / 160 days
Severe / 9 days
Severe / 160 days
DCE survey 1
DCE survey 2
DCE survey 3
125
125
125
125
125
125
125
125
125
125
125
125
500 participants
500 participants
500 participants
375 participants
375 participants
375 participants
375 participants
Total 1500 participants

Figures (NO AUTHOR DETAILS)



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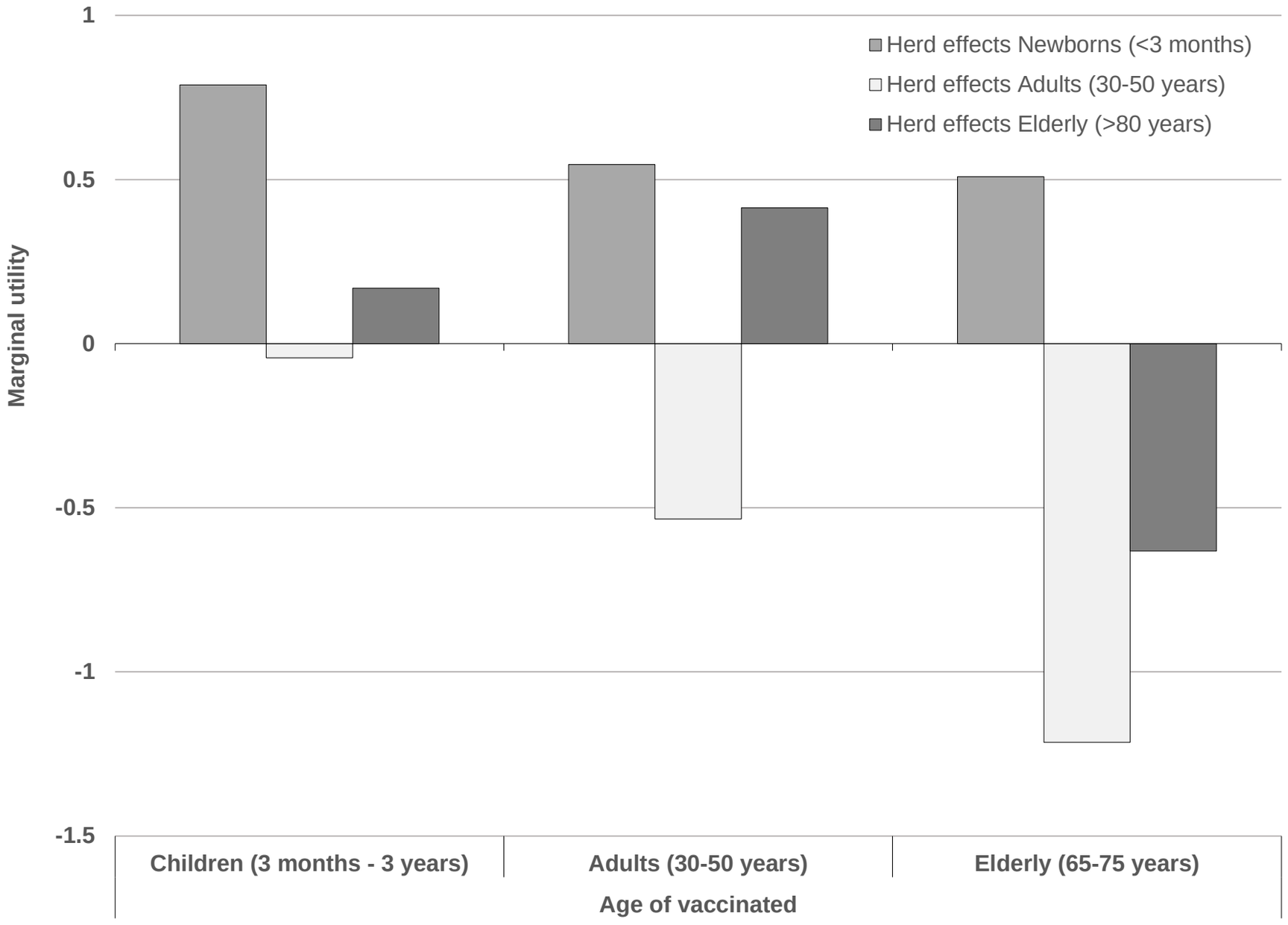

Electronic Supplementary Material (online publication only - NO AUTHOR DETAILS)

Click here to download Electronic Supplementary Material (online publication only - NO AUTHOR DETAILS): Appendix 20180315

***Ethics approval/Statement EA not required**

Ethical approval

We obtained informed consent from all respondents and ethical approval of the study from the Ethics Committee of the London School of Hygiene & Tropical Medicine (Ref 10335). We conducted the research in accordance with the Code of Conduct of the Market Research Society, which ensured that information is collected for research purposes only, is kept confidential, and respondent anonymity is guaranteed.

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