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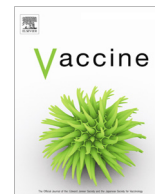
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Motors of influenza vaccination uptake and vaccination advocacy in healthcare workers: Development and validation of two short scales

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ABSTRACT

Healthcare workers (HCWs) are an important priority group for vaccination against influenza, yet, flu vaccine uptake remains low among them. Psychosocial studies of HCWs' decisions to get vaccinated have commonly drawn on subjective expected utility models to assess predictors of vaccination, assuming HCWs' choices result from a rational information-weighting process. By contrast, we recast those decisions as a commitment to vaccination and we aimed to understand why HCWs may *want to* (rather than believe they need to) get vaccinated against the flu. This article outlines the development and validation of a 9-item measure of cognitive empowerment towards flu vaccination (MoVac-flu scale) and an 11-item measure of cognitive empowerment towards vaccination advocacy. Both scales were administered to 784 frontline NHS HCWs with direct patient contact between June 2014 and July 2015. The scales exhibited excellent reliability and a clear unidimensional factor structure. An examination of the nomological network of the cognitive empowerment construct in relation to HCWs' vaccination against the flu revealed that this construct was distinct from traditional measures of risk perception and the strongest predictor of HCWs' decisions to vaccinate. Similarly, cognitive empowerment in relation to vaccination advocacy was a strong predictor of HCWs' engagement with vaccination advocacy. These findings suggest that the cognitive empowerment construct has important implications for advancing our understanding of HCWs' decisions to vaccinate as well as their advocacy behavior.

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1. Introduction

Infections from the Influenza virus, commonly known as “the flu”, represent a hazard for healthcare facilities where sudden outbreaks of illness can lead to high morbidity and mortality in vulnerable patients [1,2]. Because they work in close proximity to these patients, healthcare workers (HCWs) are at risk of becoming infected themselves and of infecting other patients. Annual vaccination remains the most effective means to manage the spread of the flu and prevent nosocomial influenza [3]. HCWs are therefore considered an important priority group for vaccination against the flu by health organisations and government bodies [4–6]. In England, the national 2016/2017 Flu plan aims to achieve flu vaccination for 75% of HCWs with direct patient contact and primary care providers [7]. Despite this emphasis, flu vaccine uptake

remains low among HCWs. In Europe, few countries actively monitored HCWs' uptake of the flu vaccination between 2010 and 2012. Those who did generally reported less than 50% uptake [8]. In England, only 50.8% of all HCWs with direct patient care were vaccinated against the flu during the 2015/2016 flu season, with wide variations in uptake between NHS Trusts from as low as 10.9% to as high as 83.5% [9].

Increasingly, focus has shifted towards a better understanding of the psychosocial determinants of HCWs' personal decision to receive the flu vaccine or not [10]. A number of studies have thus drawn on decision-making models to assess predictors of vaccination [11]. These models are derived from the concept of ‘subjective expected utility’ [12], and assume that HCWs' choices result from a rational analysis of risks and benefits associated with all possible choice alternatives. Among the most commonly used theories within this overarching approach, we find the Health Belief Model (HBM) [13] and the Theory of Planned Behavior (TPB, [14]). According to these models, uptake is driven by HCWs' belief that their susceptibility to contamination by the flu is high, and the

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belief that the flu is a severe disease while non-uptake is driven by HCWs' belief that vaccination comes with severe side effects (high costs) coupled with the belief that it is not effective (low benefits). Both the TPB and HBM models have been “augmented” over the years with socio-cognitive variables (e.g., perceived attitudes of significant others towards vaccination) and perceived control (e.g., confidence in one's ability to get vaccinated).

A limitation of such models is that they conceive decision-making as deliberate and rational information processing. They highlight why HCWs may feel they *need* to be vaccinated given their beliefs associated with vaccination, with a balance of benefits and costs. As such, they implicitly assume that HCWs who decline the flu vaccination do so because they hold “inaccurate” beliefs about the flu and its vaccine. This in turn, calls for interventions aimed at “debiasing” HCWs through educational interventions seeking to reestablish scientific facts. Yet, education aiming to reassure can be surprisingly unhelpful for those who are already doubting or challenging vaccination, leading instead to greater negativity towards vaccination [15,16].

In the present study, we propose and test a complementary theoretical framework, namely the cognitive model of empowerment (CME) [17] to study HCW flu vaccination behaviors. The CME conceives empowerment as an intrinsic motivation to engage in a purposeful behavior. These positive experiences are assumed to arise from four distinct cognitive assessments of the behavior:

- (1) the feeling of *value*, or how much one cares about the purpose of the behavior;
- (2) the feeling of *impact*, or the belief that the behavior makes a difference in achieving its purpose;
- (3) the feeling of *knowledge*, or the belief that one has the skills and knowledge to perform the behavior when he or she tries; and
- (4) the feeling of *autonomy*, or the belief that the initiation of the purposeful behavior is self-determined.

We recast the decision to get vaccinated as a commitment to vaccination (rather than a rational information-weighting process) as we aim to understand why HCWs may *want* to get vaccinated. To our knowledge, this is the first attempt to apply and empirically evaluate the CME in the context of HCWs flu vaccination. Our primary aim was to develop a reliable measure of levels of empowerment towards flu vaccination for HCWs. A secondary aim was to examine whether this framework could also be extended to vaccination advocacy. Finally, a third, conceptual aim was to test whether the CME could be successfully applied to both vaccination decisions and vaccination advocacy.

2. Methods

2.1. Overview

The project involved the development of an online questionnaire to gather information on HCWs views on the flu vaccination. The questionnaire measured their intrinsic motivation to get vaccinated against the flu through four components: the extent to which they felt vaccination was (a) important, (b) impactful, and the extent to which they felt (c) knowledgeable about vaccination and (d) autonomous in their decision to get vaccinated.

2.2. Measures

2.2.1. Motors of influenza vaccination acceptance (MoVac-flu) and motors of engagement with vaccination advocacy (MovAd)

We measured each of the four dimensions of cognitive empowerment based on the CME (value, impact, knowledge, and autonomy) with three survey items, resulting in a 12-item scale for flu

vaccination (MoVac-flu) and a 12-item scale for vaccination advocacy (MovAd) (see [Supplemental materials](#)). Items were initially generated by the first author and reviewed by the research team as well as two subject matter experts (one medical doctor and one industry specialist) for clarity and sound language structure. The content validity of the items was initially confirmed by a pilot study with a small sample of HCWs [18].

2.2.2. Other predictors of vaccination behavior

Participants' perceptions of the threat posed by the flu virus were measured using three items: the perceived severity of the flu, the susceptibility to be negatively affected by the flu, and the subjective likelihood of contracting the flu without the flu vaccine. Subjective perceptions of the threat posed by the flu vaccine were measured using three items: the perceived (lack of) safety of the flu vaccine, the fear of vaccination, and concerns for side-effects (see [Supplemental materials](#) for item wordings).

2.2.3. Behavioral measures

Participants were asked whether they had been vaccinated against the flu in the 2013/2014 flu season, the extent to which they agreed they had encouraged their patients to get vaccinated against the flu, measured on a 7-point Likert scale ranging from 1 (Strongly disagree) to 7 (Strongly agree), and whether they knew if their line manager within the hospital was vaccinated against the flu.

2.3. Procedure

Data collection took place between 19th June 2014 and 11th July 2014 at a single metropolitan hospital group. The study was introduced as aiming to find out healthcare professionals' thoughts about vaccination, emphasizing there were no right or wrong answers to the survey. Participation was voluntary and participants were free to withdraw at any time, without giving any reason. Duration to complete the questionnaire was estimated to be about 5–7 min. Participants were invited to take part in the study through emails, hospital newsletters, and posters. The questionnaire included a brief introduction and 40 survey questions. Participants could answer questions in their own time. Upon answering all questions, they were offered a voucher for a free coffee from a nearby coffee shop or 1 in 200 chances to win an £80 gift voucher. The study protocol was submitted to a research ethics committee and approved prior to the data collection.

2.4. Statistical analyses

Statistical analyses were undertaken using SPSS for Mac Version 23 Release 23.0.0.2. Parallel analyses were used to determine the number of components to retain in an Exploratory Factor Analysis for both the MoVac and MovAd scales. Principal Component Analysis with oblimin rotation was used to examine item loadings and reliability analyses based on Cohen's alpha were used to explore the dimensionality and internal consistency of the scales.

The incremental validity of the MoVac-flu scale was assessed using hierarchical binary logistic regression analysis to determine odds ratios and 95 per cent confidence intervals with 2013–14 influenza vaccination status (1 = vaccinated, 0 = not vaccinated) as a discrete outcome measure. Demographics were entered in the first step, risk perception measures of the flu and the flu vaccine were entered in the second step, and knowledge of line manager's vaccination against the flu in the third step of the analysis as per standard practice. Finally, the MoVac-flu score, computed as the average across the individual MoVac-flu items, was entered in the fourth and final step. To allow comparison of coefficient

across variables, all continuous predictors were rescaled on a scale from 0 to 1 [19].

The incremental validity of the MovAd scale was assessed using a hierarchical regression analysis with advocacy behavior as a continuous outcome to determine regression coefficients and confidence intervals. We only included demographics in the first step as we had no specific hypothesis about other predictors of vaccination advocacy. We entered the MovAd scores, computed as the average of the MovAd item scores, in the second and final step.

3. Results

3.1. Participants

A total of 1015 frontline NHS HCWs with direct patient contact completed the online questionnaire. Responses were screened for careless responding (see [Supplemental materials](#) for details). Altogether, 23% of questionnaires were discarded and the final sample included data from 784 individual respondents with no missing data (representing about 10% of the HCWs with direct patient care in this NHS Trust). [Table 1](#) summarizes the demographic data.

Table 1
Demographic characteristics of the sample.

Variable	Job					Total
	Doctor	Nurse or midwife	Allied health professional	Healthcare assistant	Student	
N	88	283	233	132	48	784
Age						
M	35.2	40.0	34.8	35.8	24.9	36.26
SD	11.2	10.1	9.4	11.2	5.1	10.63
18–29 years (%)	38.6	21.2	45.5	40.2	89.6	37.8
30–49 years (%)	52.3	65.4	46.8	47.0	10.4	51.9
50–65 years (%)	6.8	12.7	7.3	12.9	–	9.7
Over 65 years (%)	2.3	0.7	0.4	–	–	0.6
Gender						
Female (n)	41	242	178	83	34	578
Male (n)	47	41	55	49	14	206

Table 2
List of final items, means, standard deviations, and factor loadings sorted by standardized loadings for the MoVac-flu and the MovAd scales.

Dimension	Item	M	SD	Standardized loadings
<i>MoVac-flu scale</i>				
1. Value	It is important that I get the flu jab. (VacVal1)	5.08	1.63	0.91
	The contribution of the flu jab to my health and well-being is very important. (VacVal2)	4.90	1.67	0.86
	The flu jab plays an important role in protecting my life and that of others. (VacVal3)	4.98	1.73	0.93
2. Impact	Vaccination is a very effective way to protect me against the flu. (VacImp1)	4.95	1.71	0.90
	Vaccination greatly reduces my risk of catching the flu. (VacImp2)	4.92	1.66	0.87
	Getting the flu jab has a positive influence on my health. (VacImp3)	4.71	1.63	0.81
3. Knowledge	I know very well how vaccination protects me from the flu. (VacKno1)	5.10	1.55	0.87
	I understand how the flu jab helps my body fight the flu virus. (VacKno3)	5.22	1.52	0.87
4. Autonomy	I can choose whether to get a flu jab or not. (VacAut1)	5.46	1.64	0.49
<i>MovAd scale</i>				
1. Value	Vaccination is an important topic I want to discuss with others. (AdvVal1)	4.99	1.6	0.84
	It is important that I mention the topic of vaccination to others. (AdvVal2)	4.96	1.51	0.85
	It matters that I talk openly about vaccination with other people. (AdvVal3)	5.05	1.47	0.85
2. Impact	When I talk openly about vaccination, it has a positive impact on people's beliefs. (AdvImp1)	4.85	1.66	0.77
	If I discuss vaccination, it will very much change others' views on this topic. (AdvImp2)	4.79	1.41	0.79
	People's opinions of vaccination can really be influenced by the conversations I have with them. (AdvImp3)	4.87	1.47	0.84
3. Knowledge	I am confident I can answer questions that others could ask me about vaccination. (AdvKno1)	4.76	1.47	0.79
	I know exactly how to talk about vaccination with others. (AdvKno2)	4.66	1.52	0.75
	I feel able to discuss vaccination. (AdvKno3)	5.02	1.44	0.79
4. Autonomy	I decide whether to have conversations on vaccination with others. (AdvAut1)	4.93	1.51	0.70
	Discussing vaccination with others is entirely my choice. (AdvAut3)	5.17	1.49	0.62

Note. The range of individual item scores was [1,7] on all items for both MoVac-flu and MovAd scales.

3.2. Exploratory factor analysis (EFA) and reliability analysis

3.2.1. MoVac-flu

Preliminary analyses revealed that the second and third items from the Autonomy subscale as well as the second item from the Knowledge subscale were outliers and were therefore eliminated (see [Supplemental Materials](#) for details). A parallel analysis with all 9 remaining items suggested one component. The exploratory factor analysis revealed this component had an eigenvalue of 6.40 and accounted for 71% of the variance. The upper half of [Table 2](#) lists the items and factor loadings for the MoVac-flu items. The MoVac-flu scale exhibited excellent internal consistency with a Cronbach's α of 0.946.

3.2.2. MovAd

Preliminary analyses revealed that the second item from the Autonomy subscale was an outlier and was therefore eliminated (see [Supplemental Materials](#) for further details). A parallel analysis with the 11 remaining items suggested one component. The exploratory factor analysis revealed this component had an eigenvalue of 6.74 and accounted for 61% of the variance. The lower half

of Table 2 lists the items and factor loadings for the MovAd items. Finally, a reliability analysis revealed the MovAd scale exhibited excellent internal consistency with a Cronbach's α of 0.935.

3.3. Incremental validity of the MoVac-flu scale

Next, we examined whether the MoVac-flu scale accounted for vaccination behavior over and above demographic statistics, risk perception beliefs, and social cues. Table S1 in the Supplemental materials presents the mean values, standard deviations and observed frequencies for the predictor variables as a function of HCWs' flu vaccination behavior. Table 3 provides a summary of the analysis. Taken together, demographics variables did not provide insight into flu vaccination behavior, LR $\chi^2(3) = 6.17$, $p = 0.104$. The risk perception variables significantly predicted vaccination behavior over and above the demographic variables, LR $\chi^2(6) = 88.2$, $p < 0.001$. The strongest predictor was the perceived risk of getting the flu without the vaccine: a 1-point increase on the 7-point Likert scale used to measure perceived risks resulted in an increase of HCWs' odds of being vaccinated by a factor of 4.56, 95% CI [2.68, 7.75], Wald $\chi^2(1) = 31.4$, $p < 0.001$. Conversely, the biggest detractor was concern about safety of the vaccine, a 1-point increase on the 7-point Likert scale resulted in a decrease of the odds of vaccination by a factor of 3.58, 95% CI [1.70, 7.58], Wald $\chi^2(1) = 11.2$, $p < 0.001$. At Step 3, knowledge of the line manager's vaccination further improved predictability, Step LR $\chi^2(1) = 38.3$, $p < 0.001$. It was the second most influential predictor after the perception of the likelihood of contracting the flu without the flu vaccine, OR = 4.76, 95% CI [2.87, 7.91], Wald $\chi^2(1) = 36.2$, $p < 0.001$. More importantly for our present purpose, adding the MoVac-flu score in Step 4 made a further significant contribution to predictability, Step LR $\chi^2(1) = 32.6$, $p < 0.001$. In fact, the MoVac-flu score was the strongest predictor of all: a 1-point increase on the cognitive empowerment measure resulted in increased odds of vaccination by a factor of 9.74, 95% CI [4.35, 21.78]. The overall model contributed to predict vaccination behavior above and beyond the baseline model including only

the intercept, Model LR $\chi^2(11) = 165.3$, $p < 0.001$ and provided a good fit to the observed data, Hosmer and Lemeshow's $\chi^2(8) = 10.3$, $p = 0.24$.

3.4. Incremental validity of the MovAd scale

A secondary objective was to examine whether the MovAd scale contributed to explain advocacy behavior above and beyond demographics. Fig. S5 in the Supplemental materials presents the scatterplot of advocacy behavior and MovAd scores. Table 4 provides a summary of the analysis. Age was a significant predictor of advocacy behavior at Step 1 and was positively related to advocacy: older HCWs were more likely to advocate vaccination, $B = 0.02$, 95% CI [0.01, 0.03], $t(771) = 3.11$, $p = 0.002$. This variable was no longer a significant predictor ($p = 0.07$) when controlling for the MoVad scores at Step 2. The MoVad score, however, was a significant and strong predictor of vaccination advocacy behavior, $B = 0.75$, 95% CI [0.67, 0.82], $t(770) = 19.07$, $p < 0.001$.

4. Discussion

4.1. Main findings

In this study, we sought to apply the Cognitive Model of Empowerment model (CME) [17] to flu vaccination behavior. To empirically evaluate the potential of this model, we developed a new short scale, the 9-item MoVac-flu scale, which measures cognitive empowerment towards vaccination against the flu. We also extended this framework to account for vaccination advocacy behaviors in this professional group. To this end, the 11-item MovAd scale was developed to measure cognitive empowerment towards vaccination advocacy. Results indicated that both scales had excellent internal validity and contributed to predicting behavior above and beyond standard psychosocial variables. The MoVac-flu scores made a distinct contribution to the understanding flu vaccination behavior among HCWs while the MovAd scale was a better predictor of advocacy behavior than age and gender

Table 3
Summary of the binary logistic regression analysis predicting flu vaccination behavior.

Predictors	<i>b</i>			
	Step 1	Step 2	Step 3	Step 4
Step 1: Demographic variables				
Gender ^a	-0.13	-0.23	-0.20	-0.11
Age	1.28 [*]	0.49	0.47	0.40
Qualification level ^b	0.10	0.18	0.07	0.10
Step 2: Risk perception variables				
Flu likelihood		1.52 ^{***}	1.60 ^{***}	1.41 ^{***}
Flu susceptibility		1.02 ^{**}	1.08 ^{**}	0.72
Flu severity		0.78 [*]	0.63 [*]	0.15
Vaccine (lack of) safety		-1.28 ^{***}	-1.16 ^{**}	-0.89 [*]
Vaccine side effects		-1.04 ^{**}	-1.08 ^{**}	-1.02 ^{**}
Vaccine fear		0.31	0.38	0.59
Step 3: Social variable				
Line manager vaccination ^c			1.56 ^{***}	1.51 ^{***}
Step 4: Cognitive empowerment				
MoVac-flu score				2.28 ^{***}

Note. All variables were rescaled on a [0, 1] scale to allow comparing weights across predictors. For Step 1, $R^2 = 0.01$ (Nagelkerke), Step LR $\chi^2(3) = 6.17$, $p = 0.10$, $-2LL = 1049.4$. Percent correct = 57.6%. For Step 2, $R^2 = 0.154$ (Nagelkerke), Step LR $\chi^2(6) = 88.2$, $p < 0.001$, $-2LL = 961.1$, Percent correct = 65%. For Step 3, $R^2 = 0.212$ (Nagelkerke), Step LR $\chi^2(1) = 38.3$, $p < 0.001$, $-2LL = 922.8$, Percent correct = 65.8%. For Step 4, $R^2 = 0.258$ (Nagelkerke), Step LR $\chi^2(1) = 32.61$, $p < 0.001$, $-2LL = 890.2$, Percent correct = 70.3%.

^a 1 = Female, 0 = Male.

^b 1 = Doctor, 0.75 = Nurse or Midwife, 0.50 = Allied health professionals, 0.25 = Healthcare assistant, 0 = Student.

^c 1 = Yes, 0.5 = Don't know, 0 = No.

^{*} $p < 0.05$.

^{**} $p < 0.01$.

^{***} $p < 0.001$.

Table 4
Summary of the linear regression analysis predicting flu vaccination advocacy behavior.

Predictors	β	
	Step 1	Step 2
Step 1: Demographic variables		
Gender ^a	−0.03	−0.02
Age	0.11**	0.05
Step 2: Cognitive empowerment		
MovAd score		0.57***
Multiple R	0.11	0.57
Delta R ²	0.01**	0.32***
Adjusted R ²	0.01	0.33

Note. For Step 1, Model $F(3, 770) = 5.15, p = 0.002$. For Step 2, Step $F(1, 769) = 356.86, p < 0.001$, Model $F(4, 769) = 94.86, p < 0.001$.

^a 1 = Female, 0 = Male.

* $p < 0.05$.

*** $p < 0.001$.

alone. Taken together, these preliminary results suggest that the CME could be successfully applied to better account for both vaccination decisions and vaccination advocacy behaviors.

4.2. Strengths and limitations

This is, to our knowledge, the first attempt to model HCWs' flu vaccination uptake based on a framework of motivational factors, namely the Cognitive Model of Empowerment model (CME). Testing the applicability and elements of the validity of the CME allowed us to reframe the decision to get vaccinated against the flu as a motivated commitment, rather than a choice driven by a rational evaluation of costs/benefits. This preliminary study, however, is not without limitations. First, since our purpose was exploratory, we chose to rely on a self-selected sample: participation was voluntary and participants were compensated for their time. Although this resulted in a large sample, we cannot be certain that the views expressed are representative of the general population of HCWs. Future research may use probability sampling to address this shortcoming. Second, since HCWs are difficult to access, we chose to use a limited number of pretested items to assess each component of the CME so that the survey completion would be swift. While this may have increased participation rate, it may also have limited our ability to validate the four-dimensional factor structure suggested by the CME in the current sample. Still, future research may address this shortcoming by using a larger set of items to measure each of the four components of the CME construct (perceived value, impact, knowledge, and autonomy). Third, the Cronbach's alphas for the MoVac and MovAd scales were above the recommended maximum alpha value of 0.90 [20] (but see also [21]), possibly suggesting that cognitive empowerment may be measured with a smaller number of items without a significant loss of internal consistency. However, since Cronbach's alpha is a property of the scores on a test in a particular sample of participants, future research will need to establish that the high value observed is a property of the scale rather than a characteristic of the particular sample used in this study [20]. Fourth, as we could not access objective measures of flu vaccination and advocacy behavior, our analyses of the incremental validity relied on self-reported measures of vaccination and advocacy behaviors. Although possibly biased, self-report measures are generally viewed as an acceptable proxy for actual past behavior (as opposed to future behavioral intentions) [22]. Finally, the study was introduced as aiming to finding out HCWs' thoughts about vaccination. While being open about the purpose of the survey is good practice to ensure informed consent, this could have resulted in selection

bias. A total of 56.7% participants reported receiving the flu shot in our sample, approximately 10% more than the official record of doses distributed in the site population during this season.

5. Implications for policy and practice

Our findings highlight the promise of including considerations of cognitive empowerment above and beyond perceptions of risk and benefits in better understanding vaccine hesitancy issues. The MoVac-flu and MovAd short scales developed can also form a useful toolkit to address vaccine hesitancy among HCWs. For example, Kassianos, et al. (submitted, this issue) used these scales to explore and profile HCWs' level of engagement towards flu vaccination and vaccination advocacy across six European countries. Their results showed that hesitancy was mostly driven by neutral (rather than negative) empowerment towards flu vaccination and advocacy. Thus, the MoVac-flu and MovAd short scales can be used as tools to spot the presence and prevalence of HCWs with lower levels of motivation to vaccinate. Such an increase in the granularity of our understanding the motors of vaccination could pave the way for designing more bespoke, and therefore potentially more effective, interventions to target vaccine hesitancy. For example, the identification of the main driver(s) of hesitancy among the four CME assessments of vaccination behavior (value, impact, knowledge, or autonomy) could provide useful insights for hospital administrators in charge of designing communication campaigns or staff development strategies.

6. Conclusions

We found that the CME, operationalised through the MoVac-flu and MovAd scales, offers a promising way to capture HCWs' motivations to get vaccinated against the flu and their ability to advocate towards this behavior and in a useful and psychometrically robust manner. Our data offer some reassurance that these short scales can be used effectively with this sample. We propose that further research be conducted within this large and important professional group – so we can better understand the determinants of these motivations and also what interventions may positively impact on them.

Conflict of interest

GV-T received financial support from Sanofi Pasteur. MP was employed as a postdoctoral research fellow for this project. NS is the director of London Safety and Training Solutions Ltd, which provides team and safety interventions on assessment and training and behavioral science methods advisory services on a consultancy basis to universities, hospitals, industry (including pharmaceutical) and other organisations in the UK and internationally on a consultancy basis. Sevdalis has been a paid consultant on the ZOOM project to Sanofi Pasteur MSD (until December 2016) and to MSD Ltd (ongoing until December 2017). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2017.08.025>.

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