nature human behaviour

LETTERS

https://doi.org/10.1038/s41562-018-0432-2

Letters designed with behavioural science increase influenza vaccination in Medicare beneficiaries

David Yokum[1], Julie C. Lauffenburger[2], Roya Ghazinouri[2] and Niteesh K. Choudhry[2*]

The influenza ('flu') vaccination is low cost[1] and effective, typically reducing the likelihood of infection by 50–60%[2]. It is recommended for nearly everyone older than 6 months of age[3]; yet, only 40% of Americans are immunized each year. Vaccination rates are higher among at-risk groups, such as those ≥65 years of age, but still only 6 in 10 receive it[4]. There have been numerous attempts to improve vaccination rates using strategies such as school-based programmes, financial incentives and reminders, but these have generally had limited success[5–7]. Of the attempts that are successful, most are expensive—limiting scalability—and have not been evaluated in the elderly[8]. Conversely, lower-cost interventions, such as mailed information, hold promise for a scalable solution, but their limited effectiveness may result from how they have been designed. We randomly assigned 228,000 individuals ≥66 years of age to one of five versions of letters intended to motivate vaccination, including versions with an implementation intention prompt and an enhanced active choice implementation prompt. We found that a single mailed letter significantly increased influenza vaccination rates compared with no letter. However, there was no difference in vaccination rates across the four different letters tailored with behavioural science techniques.

A growing body of research in the psychological sciences has found that subtle changes in the layout and framing of a message, as well as components such as tone and the sender, can meaningfully affect whether a reader understands and is motivated by a message[9]. Such insights are beginning to be applied in the vaccination context and may offer novel strategies to increase the effectiveness of low-cost public health outreach efforts.

In a study by Milkman et al.[10], for example, about 9,000 employees at a large utility company were randomly assigned to receive one of three mailings about workplace vaccination clinics. All letters provided information on the hours and location of clinic availability, but some also prompted recipients to write in either (1) the date they planned to get their vaccination or (2) the date and time they planned to get their vaccination (for example, Monday 26 October at 15:00). These write-in additions were designed to prompt the recipient to form an 'implementation intention'—a concrete plan of action in response to a particular situation—a psychological intervention that has been shown to increase action in various contexts[11]. This strategy was effective: vaccination rates increased from 33% to 36% when the date was written in and increased further still to 37% with both the date and time included.

A different line of work explores the influence of how choices are presented to patients. In the case of vaccinations, individuals can be asked to make an active choice between getting vaccinated and not, and this choice set can be 'enhanced' with language that makes certain consequences salient (for example, 'I will not get a flu shot this fall even if it means I may increase my risk of getting the flu'). Keller et al.[12] tested this approach with employees at an educational institution. They were asked to imagine receiving one of several messages, in which they indicated whether they would vaccinate. Compared to an opt-in checkbox, enhanced active choice increased the intention to get vaccinated from 62% to 75%[12].

Yet another line of research emphasizes how the perceived credibility of the person sending a communication affects the listener's receptivity to the message[13]. Features such an expert's advertised credentials or whether the listener believes that the communicator shares similar values may increase the likelihood that information is believed and acted on. For example, patients are 10% more likely to trust diet advice from overweight than from normal-weight physicians[14].

Thus, we launched the Mail Outreach To Increase Vaccination Acceptance Through Engagement (MOTIVATE) trial with the goal of evaluating different psychological approaches in mailed communications on vaccination rates among a large, national Medicare population. We also designed and evaluated the effectiveness of implementation intention and enhanced active choice dynamics compared to traditional letters. This large field experiment estimates the effectiveness of a letter reminder to promote vaccination as well as two specific behavioural strategies: an implementation intention prompt and enhanced active choice.

In this investigator-initiated, 5-arm randomized controlled trial, 228,000 Medicare beneficiaries were randomized to 1 of 5 arms, as follows: (1) no letter (that is, control) (N=114,000 beneficiaries), (2) an informational letter from the National Vaccine Program Office (N=23,000 beneficiaries), (3) an informational letter from the acting US Surgeon General (N=23,000 beneficiaries), (4) a letter with an implementation intention prompt from the acting US Surgeon General (N=34,000 beneficiaries), and (5) a letter with an active-choice-enhanced implementation prompt from the acting US Surgeon General (N=34,000 beneficiaries) (see Fig. 1).

The baseline characteristics of the study participants are presented in Table 1. Subjects were a mean (s.d.) of 76 (8) years of age, 56% were female, 84% white and 38% had been vaccinated in the previous season. Within study arms, patient characteristics

[1]The Lab @ DC, Washington DC, USA. [2]Center for Healthcare Delivery Sciences (C4HDS) and Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.
*e-mail: nkchoudhry@bwh.harvard.edu

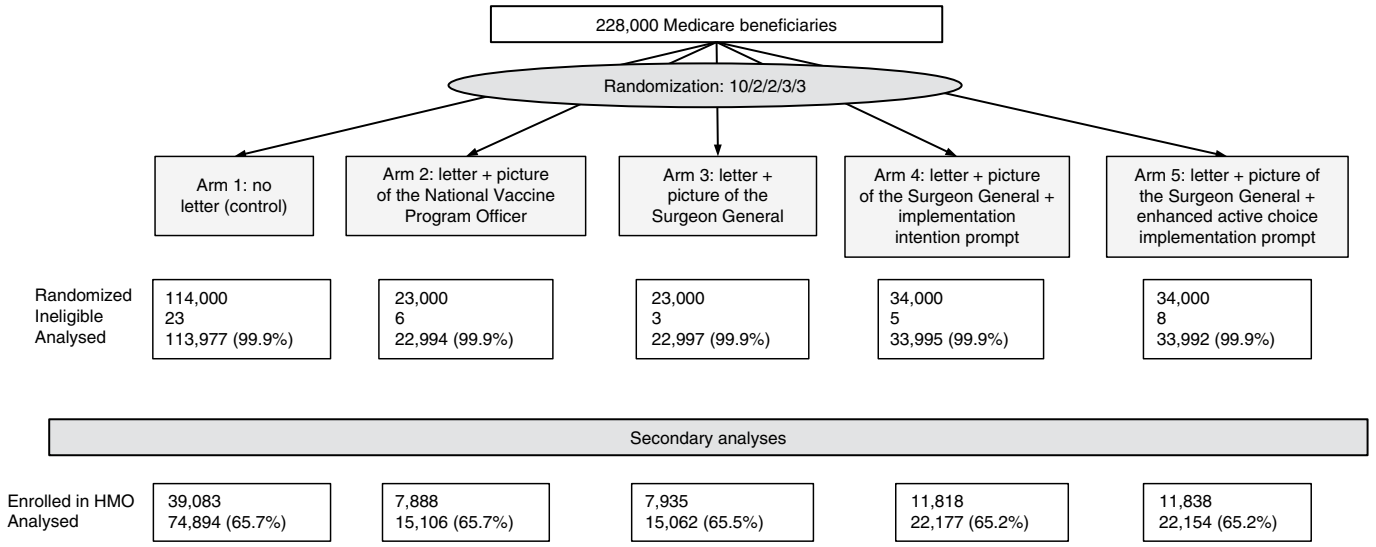

Fig. 1 | Study participants and randomization scheme. .

were well balanced. The only baseline covariate that was unbalanced prior to randomization was influenza vaccination in the previous season.

Table 2 shows the vaccination rates for the five study arms and the differences between the control group and the intervention arms. The vaccination rate in the control group was 25.9% and was 0.4–0.7 percentage points higher in each of the intervention arms. In analyses adjusted for sex, age, comorbidity score and receipt of a flu vaccination in the previous season, patients who received a letter were significantly more likely to receive a flu vaccine than patients who did not (hazard ratios (HRs): 1.04–1.05, $P<0.001$).

When comparing letters to each other, the magnitude of the effect was largest for the informational letters (0.7% and 0.9%) compared to the letters using the implementation prompts (0.5% and 0.4%); however, these differences were not significant (Supplementary Table 1). The numbers needed to treat (NNTs) for vaccination receipt was 143 for arm 2 (information-only letter from the National Vaccine Program Officer), 111 for arm 3 (informational letter from the Surgeon General), 200 for arm 4 (implementation intention prompt letter) and 250 for arm 5 (enhanced active choice implementation prompt letter; Fig. 2).

The baseline characteristics of the study cohort after excluding those participants concomitantly enrolled in both Medicare fee-for-service (FFS) and a Health Maintenance Organization (HMO) plan, and therefore for whom vaccination information may not be complete (see Methods), are shown in Supplementary Table 2. The only unbalanced pre-randomization characteristic was age, although the magnitude of these differences was small. In this cohort, all letters led to a significant increase in vaccination rate relative to control. The absolute magnitude of the effect was somewhat larger than in the primary analyses (ranging from 0.8 to 1.4 percentage points), although the relative effect sizes remained unchanged (see Table 2).

The effect of letters on vaccination rates were similar in sensitivity analyses that extended the follow-up period to 31 May 2015 and in which patients who already received the flu vaccination prior to randomization or who did not maintain continuous eligibility for the 2014–2015 flu season were excluded (Supplementary Table 3). Sensitivity analyses in which we altered the covariate adjustment set were also similar, except for a fully unadjusted analysis (excluding unbalanced baseline covariates) in which the implementation intention prompt letter (HR: 1.02, 95% CI: 1.00–1.05, $P=0.08$) and the enhanced active choice implementation prompt letter (HR: 1.02, 95% CI: 0.99–1.04, $P=0.15$) were no longer significant compared to no letter. Other sensitivity analyses, including the logistic regression analysis, also yielded similar findings (Supplementary Table 3).

Results of our subgroup analyses of sex, previous vaccination, and age are presented in Supplementary Table 4. There were no substantial differences in the subgroups with one exception. We observed a greater effectiveness of the implementation intention prompt letter (arm 4) among men than among women ($P=0.03$) compared with control.

As seen in Supplementary Table 5, the increased vaccination rates were not associated with changes in all-cause hospitalizations or hospitalizations for respiratory or infectious conditions.

In this large field experiment, we found that numerous versions of a single mailed letter increased vaccination rates relative to no letter by a small but significant amount. Although the magnitudes of effects that we observed were modest and not associated with changes in rates of hospitalization, we believe that they still have the potential to be meaningful when applied at scale. For example, if an informational letter, such as that sent to subjects in arm 3, was sent to the approximately 35 million individuals enrolled in Medicare Parts A and B, the effect we observed would translate into more than 500,000 additional beneficiaries receiving their essential flu vaccination. As a result, consistent with previous trials evaluating the effect of letters on rates of vaccination, we suggest that letters are a potentially effective tool (at less than US$1 per letter) that policymakers should consider deploying in vaccination campaigns.

Unlike previous studies that suggest added effects of implementation intention prompts and active choice dynamics on patient behaviour, we did not observe meaningful effects of using these strategies compared to informational letters alone. This is despite the substantial power of our study, in which differences as small as 1 percentage point would be detectable with 80% power at $P<0.05$. Our findings may deviate from previous research for several reasons—and these deviations suggest ways that the behavioural constructs may be optimized in the future. We studied a Medicare population who are substantially older than the working utility firm population in the implementation intention prompt study by Milkman et al. (means of 76 versus 51 years of age, respectively). Among other differences, older populations tend to have more experience with health-related difficulties and treatments. Physicians, aware of the increased influenza risk when ≥65 years of age, might advocate for vaccination more aggressively with the Medicare population, such

Table 1 | Characteristics of study sample

Characteristic	Arm 1: no letter (control)	Arm 2: letter + picture of the National Vaccine Program Officer	Arm 3: letter + picture of the Surgeon General	Arm 4: letter + picture of the Surgeon General + implementation intention prompt	Arm 5: letter + picture of the Surgeon General + enhanced active choice implementation prompt	*P* value for differences across arms
	N = 113,977	*N* = 22,994	*N* = 22,997	*N* = 33,995	*N* = 33,992	
Demographic (%)						
Age (yr), mean (s.d.)	75.7 (7.6)	75.6 (7.6)	75.7 (7.6)	75.7 (7.6)	75.6 (7.6)	0.20
Female sex	57.0	57.1	57.4	57.0	56.9	0.83
Race/ethnicity						0.48
White	84.0	84.2	84.1	84.2	84.4	
Black	8.5	8.4	8.6	8.5	8.5	
Other/unknown	7.5	7.4	7.3	7.3	7.1	
Vaccine related (%)						
Flu vaccine in the previous season	37.7	37.9	37.8	37.1	37.0	0.01
Flu vaccine for current season before randomization	11.2	11.2	11.1	10.9	11.1	0.63
Potential contraindication	0.2	0.2	0.2	0.2	0.2	0.56
Clinical (%)						
Comorbidity score, mean (s.d.)	1.1 (2.3)	1.0 (2.3)	1.1 (2.3)	1.0 (2.3)	1.0 (2.3)	0.44
Asthma/COPD	14.4	14.5	14.5	14.2	14.5	0.77
Coronary artery disease	19.0	18.8	19.1	18.7	18.4	0.06
Congestive heart failure	8.7	8.6	8.5	8.3	8.4	0.24
Dementia	6.0	6.0	6.1	6.0	6.0	0.97
Diabetes	21.6	21.7	21.4	21.0	21.5	0.17
Hypertension	52.3	52.0	52.3	51.5	51.8	0.07
Kidney disease	10.6	10.4	10.7	10.2	10.4	0.19
Stroke	5.9	5.9	5.7	6.0	5.9	0.61
Resource utilization (%)						
Emergency room visits, mean (s.d.)	0.5 (2.0)	0.5 (2.4)	0.5 (2.0)	0.5 (2.0)	0.5 (2.5)	0.95
Hospitalizations, mean (s.d.)	0.2 (0.7)	0.2 (0.7)	0.2 (0.7)	0.2 (0.7)	0.2 (0.7)	0.34
Office visits, mean (s.d.)	5.2 (6.9)	5.2 (7.0)	5.3 (7.1)	5.3 (7.1)	5.2 (7.0)	0.07

Differences tested with ANOVA for continuous variables and chi-square tests for binary variables. COPD, chronic obstructive pulmonary disease.

that those marginal patients who would have been moved by a letter are already moved elsewise. Behavioural interventions of the nudge variety tend to work on the margins; if that margin does not exist, there is less room for effect-size movement. Our findings are probably an illustration of how context-specific effects can be and therefore could also prompt further redesign of letter content or adjustment to the timing or method of delivery.

A more subtle difference, with more importance for theorizing, is that the implementation intention prompts here did not include as precise logistic information as in previous studies. Their letters included the location of available clinics as well as precise hours of operation. Such details were practically impossible in our study. It would have involved generating and linking information on hundreds of thousands of health providers across the entire country and then personalizing those details for each letter recipient. Even specifically directing patients to their own primary care providers would have required that such information be readily available in administrative claims data for Medicare FFS beneficiaries. Unfortunately, it is not.

Practical or not, one implication was that the letter recipient was left to imagine those clinic details on their own. They could not pick and choose from a menu of options on the same page as the write-in space for their plan. As such, it is possible that some people failed to create an implementation intention because they stumbled on the step of imaging where they would go for the vaccination or whether the location would be open at their preferred time. If this is the case, then an important lesson is as follows: when considering whether and how to operationalize an implementation intention prompt, special attention must be given to what action steps are critical to the plan and also whether the recipient of the prompt already knows or could infer knowledge about those steps from their memory. Where lacking, such information should be explicitly provided. An invitation to plan will otherwise fall flat if the person lacks the ability to construct their intended course of action.

Keller et al.'s studies of enhanced active choice for flu vaccination also had notable differences from our study. Again, the population was quite different—they studied employees from an educational institution—but more fundamentally, the vaccination choice studies

Table 2 | Influenza vaccination rates by experimental condition

	Arm 1: no letter (control)	Arm 2: letter + picture of the National Vaccine Program Officer	Arm 3: letter + picture of the Surgeon General	Arm 4: letter + picture of the Surgeon General + implementation intention prompt	Arm 5: letter + picture of the Surgeon General + enhanced active choice implementation prompt
Full study population	*N* = 113,977	*N* = 22,994	*N* = 22,997	*N* = 33,995	*N* = 33,992
Flu vaccination (%)	25.9	26.6	26.8	26.4	26.3
Difference versus control (%)	-	0.7	0.9	0.5	0.4
Adjusted HR[a] (95% CI)	-	1.04 (1.01–1.07)	1.05 (1.02–1.08)	1.04 (1.02–1.07)	1.04 (1.02–1.07)
P value	-	0.01	<0.001	<0.001	<0.001
Excluding HMO patients	*N* = 74,894	*N* = 15,106	*N* = 15,062	*N* = 22,177	*N* = 22,154
Flu vaccination (%)	38.5	39.6	39.9	39.4	39.3
Difference versus control (%)	-	1.1	1.4	0.9	0.8
Adjusted HR[a] (95% CI)	-	1.04 (1.01–1.07)	1.05 (1.03–1.08)	1.04 (1.02–1.07)	1.04 (1.02–1.07)
P value	-	<0.001	<0.001	<0.001	<0.001

[a]Adjusted for sex, age, comorbidity score and receipt of a flu vaccination in the previous season.

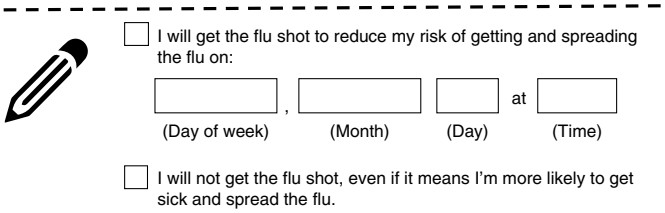

Fig. 2 | Enhanced active choice implementation intention prompt included in the arm 5 letter. See Supplementary Information for additional details.

were hypothetical. Although intentions predict actual behaviour, in many contexts, the size of the correlation can be surprisingly small. A strength of our study is the reliance on administrative records that objectively capture whether the vaccination occurred, rather than potentially subjective patient self-report. The effectiveness of enhanced active choice prompts may be restricted to situations where the choice action is immediate, thereby avoiding the possibility of a growing intention–behaviour gap over time. Keller et al. conducted two additional field studies, in which CVS/Caremark customers were presented with either an opt-in or an enhanced active choice prompt regarding whether they would participate in an automatic refill programme for their prescriptions. The enhanced active choice prompt outperformed the opt-in approach in both studies: 32% versus 16% enrolment (prompt by recorded phone message) and 22% versus 12% (prompt by webpage). In both, the action needed—affirmation to enrol—was immediate. Perhaps our letters would have been more effective if, for example, they were instead brochures in a physician's office, timed to more closely tether in time the moment of intention formation with the moment of needed behavioural action.

There were competing intuitions as to which sender might outperform (the Surgeon General or the Director of the National Vaccine Program Office), related to theories of persuasion. These include the elaboration-likelihood model, which posits that a person will more closely scrutinize information when motivated and capable of engaging the information[13]. One fountain of motivation (or lack thereof) relates to the source of such information. With a trusted 'sender', a listener will more likely accept an argument or suggestion without scrutiny. By contrast, a listener will more actively parse and criticize propositions coming from a distrusted source.

In the case of our study, there were several reasonable speculations for why either position may engender more trust and credibility. For example, the Surgeon General is a more recognizable name, but compared to the Director of the National Vaccine Program Office, they may seem more removed than a typical physician. Conversely, the Surgeon General's military status (for example, he wears a uniform in official photos) may bestow credibility or it may trigger concerns of 'big government'. A second ambiguity is whether enhanced scrutiny of the letter would increase or decrease the likelihood of vaccination. On the one hand, less scrutiny could cause faster acceptance of the suggestion to vaccinate. On the other hand, less scrutiny may actually undermine the mechanisms by which implementation intentions and enhanced active choices are meant to operate, namely, to prompt more thinking about the action steps that are needed and the consequences under consideration. In particular, if most people already accept that vaccination is medically indicated, there may be more value in triggering a closer reading of the details of the letter. Note also that even if the Surgeon General performed better, the effect size matters. It is operationally complex to coordinate a letter through the nation's senior medical official, and it would not be repeated unless the benefit was notable. Rather than speculating, we put the letters to a head-to-head test.

At the end of the day, we found no notable differences as a function of sender. However, we do not conclude that the sender is irrelevant. Recipients may not have perceived as much of a difference between the two sources as we originally hypothesized. Both senders are highly credentialled physicians, who also look physically similar. Future iterations could strive to be even more personalized, such as orchestrating for a representative from the recipient's provider or even his or her primary-care physician to send the letter.

More generally, as a result of the differences between the approach we evaluated and those of previous investigators, we do not interpret the results of this trial as necessarily undermining the promise of behavioural insights to improve communication, including implementation intentions and enhanced active choice in particular. Our lesson is instead that researchers, policymakers and other communicators applying these methods should think carefully about how and when to apply behavioural insights, rather than wielding them as a blunt instrument. Experimental testing is likely to be a required step in refining a communication strategy, especially when generalizing to new settings and behaviours.

Several other patient-facing interventions have been tested for their effectiveness in improving adult influenza vaccination rates, including text messages, telephonic outreach in the form of voicemails or electronic messages within patient portals from provider offices[15–17]. These studies have had mixed results and

may not necessarily apply as potential strategies within the general Medicare population, as these were primarily delivered within the outpatient provider office setting. Although not focused solely on influenza vaccination, a recent *Cochrane* systematic review found stronger evidence of effectiveness on vaccination for letters (relative risk (RR): 1.29, 95% CI: 1.21–1.38) and personal telephone calls (RR: 1.75, 95% CI: 1.20–2.54) than for postcards (RR: 1.18, 95% CI: 1.08–1.30) and auto-dialer calls (RR: 1.17, 95% CI: 1.03–1.32)[18].

It is worth emphasizing that even without a perfectly tuned behavioural design, these simple letters may represent a highly efficient strategy to improve vaccination rates. A Markov model study of hypothetical vaccination programmes among the elderly in the United States found that all types of strategies (with costs for five strategies ranging between ~US$1 and US$42 per person) would be cost-effective at reducing the cases of influenza versus no programme[19]. That said, the US Centers for Disease Control and Prevention has stated that cost-effectiveness on vaccination rates requires additional research[20]. Contextualized with the NNT analyses, assuming each letter costs US$0.80, approximately US$90 would need to be spent to vaccinate one additional older adult (that is, arm 3 NNT of 111 × US$0.80 = US$89), which is in line with other strategies that were found to be cost-effective[21,22]. A recent systematic review of 29 different interventions[23] aimed at improving influenza vaccinations observed a median programme cost of US$51 (interquartile range: $28–125) per additional enrollee vaccination. The costs differed substantially depending on the population and country that were studied; adding in fixed costs would almost certainly increase these cost estimates further.

Notably, few of these interventions were conducted as patient-facing interventions in older adults in the United States, and most were provider-facing interventions or among a defined population that would not apply to an older adult population (for example, health care workers). Although text messages (SMS) could be a particularly cost-effective direct-to-consumer strategy[16], regulatory restrictions mean that they can only be delivered to those individuals who have provided a cellphone number and opted in to receive them[24]. Furthermore, not all populations may be receptive to electronic communication and elderly individuals, in particular, may be less likely to respond to SMS[25,26]. The length and format limitations of SMS also restrict the design possibilities: pictures, personalized signatures, and fill-in spaces for an implementation prompt, among others, are simply not possible via SMS. Accordingly, the comparatively simple mailed strategies that we evaluate provide intervention options that are economically and practically attractive relative to the set of other interventions that have been evaluated.

Our study, like all studies, involved several methodological trade-offs. First, the use of claims data ensured an objective measure of vaccination rate and avoided costly survey data collection. However, even though we measured vaccination rates using the specific HCPCS (Healthcare Common Procedure Coding System) and ICD-9 (International Classification of Diseases, ninth revision) codes recommended by CMS, it does mean that vaccinations paid for out-of-pocket or by any other method, such as a workplace-sponsored vaccination programme, that does not generate a reimbursement claim would not be captured in our analyses[27]. Second, we focused on FFS Medicare beneficiaries as they are a particularly vulnerable population who have not been studied as much. Thoughtfulness should be applied in generalizing to other, non-FFS Medicare beneficiaries. We also note that the effectiveness of a simple letter is probably underestimated by our study. Third, it is possible that not all of the intervention patients received and opened the letters; this would bias the results towards the null of no effect. Fourth, the randomization of patients with some HMO enrolment and for whom we may not have had full capture could have reduced power, although we did not observe any substantial differences in the relative estimates in the full population and in secondary analyses. Fifth, although reviewed extensively by government officials, we did not formally pre-test the letters with patients. Last, we did not conduct a formal cost-effectiveness analysis of the interventions.

In conclusion, in this large pragmatic randomized trial of 228,000 Medicare beneficiaries, we observed that a single mailed letter significantly increased influenza vaccination rates compared with no letter. There was no difference in vaccination rates across four different letters that were tailored with different behavioural science techniques. These findings have meaningful implications for health care organizations and payers when considering different potential levers for improving vaccination rates among older adults.

Methods

The MOTIVATE trial was an investigator-initiated, 5-arm randomized controlled trial that evaluated the effectiveness of letters to increase vaccination rates among 228,000 Medicare recipients. The trial protocol was designed and written by the academic investigators and conducted in collaboration with the National Vaccine Program Office, which implemented the study mailing. We analysed the trial data using an independent copy of the study database and vouch for analytic accuracy and completeness, as well as the fidelity of the report to the study protocol.

This study was approved by the Department of Health and Human Services Office for Human Research Protections and by the institutional review board of the Brigham and Women's Hospital (Boston, MA, USA). The trial is registered with ClinicalTrials.gov (NCT02243774). Study enrolment began in September 2014, and follow-up of all trial participants ended in May 2015. The data for outcome evaluation became available in July 2017.

Patients were eligible for inclusion if they were Medicare FFS beneficiaries ≥66 years of age. We focused on elderly adults as they are at particular risk of the morbidity and mortality resulting from influenza virus infection with resultant economic consequences for public health spending[28]. We included subjects ≥66 years of age so that we would have at least 1 year of baseline data after patients gained Medicare eligibility and prior to randomization to assess previous receipt of vaccination and subject comorbidity.

On 30 September 2014, we randomized 228,000 randomly selected Medicare beneficiaries in a 10/2/2/3/3 ratio to 1 of 5 arms, as follows: (1) no letter (control) (N = 114,000 beneficiaries), (2) an informational letter from the National Vaccine Program Office (N = 23,000 beneficiaries), (3) an informational letter from the acting US Surgeon General (N = 23,000 beneficiaries), (4) a letter with an implementation intention prompt from the acting US Surgeon General (N = 34,000 beneficiaries), and (5) a letter with an active-choice-enhanced implementation prompt from the acting US Surgeon General (N = 34,000 beneficiaries). The randomization sequence was generated using PROC SURVEY SELECT with a fixed seed in SAS Enterprise Guide 5.1 (SAS Institute Inc.).

All of the letters were printed on US Department of Health and Human Services letterhead, addressed to the recipient's first name and included the bolded first sentence 'Protect yourself and those you love—get your free flu shot!' The active-choice-enhanced implementation prompt from the letter in arm 5 is shown in Fig. 2, and Supplementary Fig. 1 depicts all the letters mailed in arms 2–5. The subsequent four, brief paragraphs describe the risks associated with the influenza virus (for example, '36,000 Americans die every year'; 'more than 200,000 hospitalizations annually'), that adults ≥65 years of age are at special risk, how yearly vaccination mitigates that risk, and that the flu shot is freely covered by Medicare and widely available at 'your local pharmacy, senior centre, hospital or doctor's office'.

The four letters varied along two dimensions. The first dimension was whether the sender was the Director of the National Vaccine Program Office or the Surgeon General of the United States. This manipulation is reflected in typical letter components indicating sender, namely, a top letterhead of the office and a bottom signature line (hand-written name together with position title); in addition, a photo headshot is included. The second dimension was whether the letter included an implementation intention prompt or an enhanced active choice implementation intention prompt. With the implementation intention prompt, the bottom of the letter stated, 'Many people find it helpful to make a plan for getting their flu shot. Write yours below, and stick it on your refrigerator so you don't forget!'; it provided space for subjects to write down their intended plan. In the enhanced active choice implementation prompt condition, the bottom of the letter stated, 'Many people find it helpful to decide now on a plan for getting their flu shot. Mark your decided plan below, and stick it on your refrigerator so you don't forget!' and asked subjects to select one of two option boxes designed to make more salient that receiving the vaccine reduces the risk of getting and spreading the flu to their friends and family members. The options were: 'I will get the flu shot to reduce my risk of getting and spreading the flu on: [space to answer]'; and 'I will not get the flu shot, even if it means I'm more likely to get sick and spread the flu'. These sections were below the signature line, in a 'P.S.' section, which also included a dotted line and scissors icon for participants to cut off the section and place it somewhere as a physical reminder. All of the specific letters are included in the Supplementary Materials.

Study participants were not blinded to group assignment. Study investigators and data analysts remained blinded until all follow-up data were obtained and the primary analytic strategies were finalized. Letters to subjects randomized to arms 2–5 were mailed within 1 week after randomization. Each letter cost less than US$1 to send.

Our primary outcome was influenza vaccination receipt in the 4-month period after randomization (that is, between 1 October 2014 and 31 January 2015). This period was chosen because it reflects the critical period when there is the greatest potential benefit of vaccination on preventing morbidity and mortality before influenza rates typically peak each season. Vaccination receipt was assessed on the individual level using a Health Insurance Portability and Accountability Act (HIPAA)-limited data set that contained administrative claims data from Medicare Parts A, B and D from the Research Data Assistance Center at the Centers for Medicare and Medicaid Services, containing patient-level information on beneficiary enrolment and claims for all procedures, physician encounters, hospitalizations and outpatient prescriptions.

In particular, we measured vaccination rates using the specific HCPCS and ICD-9 codes recommended by CMS for payers and providers in their preventive and screening services guidelines published in collaboration with the American Medical Association and the American Hospital Association, which are estimated to have approximately 65% sensitivity compared to self-report. Our pre-specified secondary outcomes were: (1) respiratory hospitalization, including hospitalizations that met any of the outcome definitions for severe sepsis, acute respiratory failure, influenza virus infection, acute respiratory infections or in-hospital death; and (2) all-cause hospitalizations between 1 October 2014 and 31 May 2015. These outcomes were measured using validated or commonly used ICD-9 codes in the inpatient Medicare claims data.

We randomized 228,000 patients in a 10/2/2/3/3 ratio to achieve more than 80% power to detect a 1% difference in the proportion of patients who were vaccinated between each of the intervention arms and control, as well as between each of the intervention arms assuming that 66% of patients in the control group would get vaccinated, based on the national vaccination rate among adults ≥65 years of age of 66% in 2013, and a two-tailed $\alpha = 5\%$. Our sample size calculations were based on previous research, which has suggested that we might expect an informational letter to increase vaccine uptake up to 10% relative to no letter. We hypothesized that the addition of an implementation intention prompt would increase vaccination update by another 1–5% and that an enhanced active choice implementation intention prompt, which has never been formally tested, would be even more effective.

We first calculated the means and frequencies of pre-randomization variables separately by study arm and compared them using analysis of variance (ANOVA) for continuous variables and chi-square tests for binary variables (two-tailed $P < 0.05$ was considered to be significant). In our primary analyses, we analysed outcomes based on intention-to-treat principles and included all patients randomized using Cox proportional hazards modelling to estimate the relationship between study arm and receipt of vaccination, respiratory hospitalization and all-cause hospitalization. In brief, Cox proportional hazards modelling is a type of survival analysis that models time until a certain event occurs (for example, influenza vaccination). In this approach, subjects were censored at the time of death, disenrollment from the health plan and at the end of follow-up, which accounts for competing risks. The data for these tests met the assumptions of the statistical tests used. To increase precision, our models were adjusted for sex, age, the receipt of a flu vaccination in the previous season and comorbidity score—a validated marker of patient morbidity calculated based on Medicare claims data. We chose to adjust our primary models for these covariates because they were judged in advance to be associated with the outcome[29,30].

Although we included only Medicare beneficiaries enrolled in FFS plans (that is, those with Medicare Part A and B benefits), approximately 35% of the study population also had supplemental HMO coverage (Fig. 2) and therefore these individuals lacked individual Medicare-processed claims-level information on vaccination receipt. As shown in Table 1, there was an approximately equal distribution of patients enrolled in HMOs across the experimental groups. Thus, this 'missing' data should not have influenced the internal validity of our primary intention-to-treat analyses. Nevertheless, we conducted secondary analyses by excluding patients who were enrolled in an HMO at the time of randomization so as to ensure complete outcome capture in the follow-up period.

We conducted sensitivity analyses of the primary outcome in which the follow-up period was extended to 31 May 2015, in patients who already received the flu vaccination prior to randomization, or who did not maintain continuous enrolment for the 2014–2015 influenza season (that is, from 1 August 2014 to 31 May 2015). We also conducted sensitivity analyses of the covariate adjustment set. In addition, we conducted a sensitivity analysis in which we used logistic regression and a binary outcome for influenza vaccination receipt in the 4-month follow-up period. Subgroup analyses were also performed according to sex, vaccination in the previous flu season (that is, 2012–2013) and age, in which we formally tested interactions with the main effect. Of note, we chose not to formally adjust for multiple testing for several reasons. First, although the chance of finding at least one false positive among several tests is >5%, a Bonferroni correction would be much too conservative in this case, because the multiple comparisons among the treatment arms share the same five exposure groups[31]. Second, a recent systematic review of multiple arm trials showed that more than half of all randomized trials with multiple exposure groups do not adjust for multiple comparisons, reasoning that if each exposure was compared with control in a separate trial, no adjustment would be necessary[32].

Finally, we also calculated the NNTs for influenza vaccination receipt for the four different interventions based on the absolute difference between the intervention arms and the control arm. NNT is 'an aggregate measure of clinical benefit that represents the number of patients who would need to be treated to prevent one additional adverse event'[33] and is calculated as the reciprocal of the absolute risk difference between two treatment arms. In the case of our study, the NNT is the average number of people who need to receive a letter for one additional person to get vaccinated, over the duration of our study.

For all evaluations, significance was evaluated at the $P = 0.05$ level; all tests were two tailed. All analyses were conducted using SAS 9.4.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Code availability. The statistical code used is available from the corresponding author.

Data availability

Restrictions apply to the availability of the raw data, which were used under data use agreements for the current study and therefore cannot be shared publicly. However, data may be available upon reasonable request and permission of the vendor.

Received: 28 January 2018; Accepted: 15 August 2018;
Published online: 1 October 2018

References

1. *CDC Vaccine Price List* (CDC, 2018); https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html
2. *Vaccine Effectiveness—How Well Does the Flu Vaccine Work?* (CDC, 2017); https://www.cdc.gov/flu/about/qa/vaccineeffect.html
3. Advisory Committee on Immunization Practices (ACIP) *Recommendations and Immunization Schedules* (CDC, 2012); http://www.cdc.gov/vaccines/acip/recs/index.html
4. *Flu Vaccination Coverage, United States, 2015–16 Influenza Season* (CDC, 2016); https://www.cdc.gov/flu/fluvaxview/coverage-1516estimates.html
5. Briss, P. A. et al. Reviews of evidence regarding interventions to improve vaccination coverage in children, adolescents, and adults. The task force on community preventive services. *Am. J. Prev. Med.* **18**, 97–140 (2000).
6. Jacob, V. et al. Increasing coverage of appropriate vaccinations: a community guide systematic economic review. *Am. J. Prev. Med.* **50**, 797–808 (2016).
7. Stinchfield, P. K. Practice-proven interventions to increase vaccination rates and broaden the immunization season. *Am. J. Med.* **121**, S11–S21 (2008).
8. Arthur, A. J. et al. Improving uptake of influenza vaccination among older people: a randomised controlled trial. *Br. J. Gen. Pract.* **52**, 717–722 (2002).
9. Social and Behavioral Sciences Team *Social and Behavioral Sciences Team Annual Report* (Office of Science and Technology Policy, 2015); https://sbst.gov/download/2015%20SBST%20Annual%20Report.pdf
10. Milkman, K. L., Beshears, J., Choi, J. J., Laibson, D. & Madrian, B. C. Using implementation intentions prompts to enhance influenza vaccination rates. *Proc. Natl Acad. Sci. USA* **108**, 10415–10420 (2011).
11. Gollwitzer, P. Implementation intentions: strong effects of simple plans. *Am. Psychol.* **54**, 493–503 (1999).
12. Keller, P., Harlam, B., Loewenstein, G. & Volpp, K. Enhanced active choice: a new method to motivate behavior change. *J. Consum. Psychol.* **21**, 376–383 (2011).
13. O'Keefe, D. J. in *The International Encyclopedia of Communication* (ed. Donsbach, W.) https://doi.org/10.1002/9781405186407.wbiece011.pub2 (John Wiley and Sons, 2013).
14. Bleich, S. N., Gudzune, K. A., Bennett, W. L., Jarlenski, M. P. & Cooper, L. A. How does physician BMI impact patient trust and perceived stigma? *Prev. Med.* **57**, 120–124 (2013).
15. Herrett, E. et al. Text messaging reminders for influenza vaccine in primary care: a cluster randomised controlled trial (TXT4FLUJAB). *BMJ Open* **6**, e010069 (2016).
16. Regan, A. K., Bloomfield, L., Peters, I. & Effler, P. V. Randomized controlled trial of text message reminders for increasing influenza vaccination. *Ann. Fam. Med.* **15**, 507–514 (2017).
17. Cutrona, S. L. et al. Improving rates of outpatient influenza vaccination through ehr portal messages and interactive automated calls: a randomized controlled trial. *J. Gen. Intern. Med.* **33**, 659–667 (2018).
18. Jacobson Vann, J. C., Jacobson, R. M., Coyne-Beasley, T., Asafu-Adjei, J. K. & Szilagyi, P. G. Patient reminder and recall interventions to improve immunization rates. *Cochrane Database Syst. Rev.* **1**, CD003941 (2018).

19. Michaelidis, C. I., Zimmerman, R. K., Nowalk, M. P. & Smith, K. J. Cost-effectiveness of programs to eliminate disparities in elderly vaccination rates in the United States. *BMC Public Health* **14**, 718 (2014).
20. *Reminder Systems and Strategies for Increasing Childhood Vaccination Rates* (CDC, 2017); https://www.cdc.gov/vaccines/hcp/admin/reminder-sys.html
21. Kim, M. & Yoo, B. K. Cost-effectiveness analysis of a television campaign to promote seasonal influenza vaccination among the elderly. *Value Health* **18**, 622–630 (2015).
22. Shoup, J. A. et al. Effectiveness and cost of influenza vaccine reminders for adults with asthma or chronic obstructive pulmonary disease. *Am. J. Manag. Care* **21**, e405–e413 (2015).
23. Anderson, L. J. et al. The cost of interventions to increase influenza vaccination: a systematic review. *Am. J. Prev. Med.* **54**, 299–315 (2018).
24. *VIII. Privacy—Telephone Consumer Protection Act. FDIC Compliance Examination Manual* (Federal Deposit Insurance Corporation, 2016); https://www.fdic.gov/regulations/compliance/manual/index.html
25. Kuerbis, A., van Stolk-Cooke, K. & Muench, F. An exploratory study of mobile messaging preferences by age: middle-aged and older adults compared to younger adults. *J. Rehabil. Assist. Technol. Eng.* **4**, 1–10 (2017).
26. *Mobile Fact Sheet* (Pew Research Center, 2018); http://www.pewinternet.org/fact-sheet/mobile/
27. Lochner, K. A., Wynne, M. A., Wheatcroft, G. H., Worrall, C. M. & Kelman, J. A. Medicare claims versus beneficiary self-report for influenza vaccination surveillance. *Am. J. Prev. Med.* **48**, 384–391 (2015).
28. Alemayehu, B. & Warner, K. E. The lifetime distribution of health care costs. *Health Serv. Res.* **39**, 627–642 (2004).
29. Kahan, B. C., Jairath, V., Doré, C. J. & Morris, T. P. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. *Trials* **15**, 139 (2014).
30. Lee, P. H. Covariate adjustments in randomized controlled trials increased study power and reduced biasedness of effect size estimation. *J. Clin. Epidemiol.* **76**, 137–146 (2016).
31. Rothman, K. J. No adjustments are needed for multiple comparisons. *Epidemiology* **1**, 43–46 (1990).
32. Wason, J. M. S., Stecher, L. & Mander, A. P. Correcting for multiple-testing in multi-arm trials: is it necessary and is it done? *Trials* **15**, 364 (2014).
33. McAlister, F. A. The "number needed to treat" turns 20—and continues to be used and misused. *CMAJ* **179**, 549–553 (2008).

Acknowledgements

This project would not have been possible without the collaboration of the White House's Social and Behavioral Sciences Team (SBST), the General Service Administration's Office of Evaluation Sciences, the National Vaccine Program Office and the Centers for Medicare and Medicaid Services (CMS) at the US Department of Health and Human Services. We especially thank G. Brill, M. Donneyong, B. Gellin, T. A. Johnson, B. Luca and B. Sivak. We also thank The Laura and John Arnold Foundation for generous financial support. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. This work was supported by an unrestricted grant from the Laura and John Arnold Foundation.

Author contributions

D.Y. and N.K.C. contributed to the study conception and design and interpretation of the results. J.C.L. prepared and analysed the data. D.Y. and J.C.L. contributed to manuscript drafting. N.K.C. and R.G. provided interpretation of the results and critical manuscript revisions.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41562-018-0432-2.

Reprints and permissions information is available at www.nature.com/reprints.

Correspondence and requests for materials should be addressed to N.K.C.

nature research

Corresponding author(s): Niteesh Choudhry

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Statistical code are available from the corresponding author at nkchoudhry@bwh.harvard.edu. Restrictions apply to the availability of the raw data, which were used under data use agreements for the current study and therefore cannot be shared publicly. Data may be available, however, upon reasonable request and permission of the vendor.
Data analysis	Statistical code are available from the corresponding author at nkchoudhry@bwh.harvard.edu. Restrictions apply to the availability of the raw data, which were used under data use agreements for the current study and therefore cannot be shared publicly. Data may be available, however, upon reasonable request and permission of the vendor.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Technical appendix and statistical code are available from the corresponding author at nkchoudhry@bwh.harvard.edu. Restrictions apply to the availability of the raw data, which were used under data use agreements for the current study and therefore cannot be shared publicly. Data may be available, however, upon reasonable request and permission of the vendor.

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	In the "Mail Outreach To Increase Vaccination Acceptance Through Engagement" (MOTIVATE) trial, we randomly assigned 228,000 Medicare fee-for-service (FFS) beneficiaries (aged 66 and older) to one of five arms: (1) no letter (i.e. control); (2) an informational letter from the National Vaccine Program Office; (3) an information letter from the acting U.S. Surgeon General; (4) a letter with implementation intention prompt; and (5) a letter with an enhanced active choice implementation prompt.
Research sample	228,000 Medicare fee-for-service (FFS) beneficiaries (aged 66 and older)
Sampling strategy	On September 30, 2014, we randomly selected 228,000 Medicare beneficiaries from the list of all Medicare beneficiaries.
Data collection	The data relied on already existent Medicare administrative data.
Timing	The data sampling was conducted on September 30, 2014.
Data exclusions	No data were excluded from primary analyses.
Non-participation	Not applicable, as we measure intention-to-treat.
Randomization	On September 30, 2014, we randomized 228,000 randomly selected Medicare beneficiaries in a 10:3:3:2:2 ratio to one of 5 arms, as follows: (1) no letter (i.e. control) (n=114,000 beneficiaries), (2) an informational letter from National Vaccine Program Office (n=23,000 beneficiaries), (3) an information letter from the acting U.S. Surgeon General (n=23,000 beneficiaries), (4) a letter with implementation intention prompt from the acting U.S. Surgeon General (n=34,000 beneficiaries), and (5) a letter with an enhanced implementation prompt from the acting U.S. Surgeon General (n=34,000 beneficiaries) (see Figure 1). The randomization sequence was generated using PROC SURVEY SELECT with a fixed seed in SAS Enterprise Guide 5.1 (SAS Institute Inc, Cary, NC).

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	Subjects were a mean (SD) of 76 (8) years of age, 56% were female, 84% white, and 38% had been vaccinated in the prior season.
Recruitment	On September 30, 2014, we randomized 228,000 randomly selected Medicare beneficiaries in a 10:3:3:2:2 ratio to one of 5 arms, as follows: (1) no letter (i.e. control) (n=114,000 beneficiaries), (2) an informational letter from the National Vaccine Program Office (n=23,000 beneficiaries), (3) an informational letter from the acting U.S. Surgeon General (n=23,000 beneficiaries), (4) a letter with an implementation intention prompt from the acting U.S. Surgeon General (n=34,000 beneficiaries), and (5) a letter with an active choice enhanced implementation prompt from the acting U.S. Surgeon General (n=34,000 beneficiaries). All analyses were conducted using intention-to-treat principles; any bias in would likely be towards the null.