Brief Education to Promote Maternal Influenza Vaccine Uptake: A Randomized Controlled Trial

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1. Introduction

Pregnant women have higher rates of influenza-related hospitalizations [1], complications [2, 3], and mortality [2, 4] during pandemic and non-pandemic years. Influenza vaccination is beneficial and safe for pregnant women throughout pregnancy [5-8] and provides protection for the newborn in the first 6 months of life [9]. Although the World Health Organization (WHO) has identified pregnant women as having highest priority for seasonal influenza vaccination [10], maternal influenza vaccination rates are often lower than in other high-risk groups and the general population [11-13]. A recent review of influenza vaccination rates in pregnant women across 11 countries found vaccination rates ranged from 1.7%–88%, but were most often less than 50% [14].

Pregnant women who have more knowledge about the potential complications of influenza and the safety of the influenza vaccine are more likely to be vaccinated [15-17]. To date, the majority of interventions aimed at improving maternal influenza vaccination rates have targeted healthcare providers, primarily obstetricians, and encouraged them to discuss influenza vaccination with pregnant women [18-22]. Among pregnant woman-focused interventions, one trial showed that an education pamphlet, with or without a verbalized benefits statement, increased vaccination rates [23]. In other studies, one found that 5 weekly text messages to pregnant women about the importance of maternal influenza vaccination significantly increased vaccine uptake [24] while another found that 12 weekly text messages had no effect on maternal vaccination rates [25]. Chamberlain et al. [26] found that a multi-component vaccination promotion intervention consisting of provider to patient education, educational brochures, and an electronic patient-centred tutorial did not improve vaccine uptake. Frew et al. [27] evaluated the effect of two types of vaccination messages (i.e., information about the benefits of vaccination vs. information about the risks of not vaccinating) and found that neither of the two message types significantly improved vaccination uptake.

The low rate of vaccine uptake in this target group and the conflicting evidence from evaluated interventions indicate a need to further develop interventions to improve maternal influenza vaccine rates. Although the Hong Kong government has endorsed the WHO recommendation for prioritizing pregnant women in seasonal and pandemic influenza vaccination programs, there is no free or subsidized vaccination program for this target group and publicly-funded antenatal clinics do not provide influenza vaccination as part of routine care to pregnant women. Pregnant women must get vaccinated in private clinics, primarily general practice clinics dispersed throughout the city. In public antenatal clinics, pregnant women do not have a dedicated provider and at each visit are assessed by a midwife or physician, depending on their stage of pregnancy and any complicating conditions. Thus, provider-focused interventions would likely be ineffective in such settings and interventions targeting pregnant women may be more appropriate to improve influenza vaccination coverage. The objective of the present study was to assess the effect of a brief education intervention targeting pregnant women on the uptake of influenza vaccination.

2. Materials and Methods

2.1 Design, setting, and participants

We designed a randomized controlled trial to evaluate the efficacy of a brief, one-to-one education session on the influenza vaccination rate during pregnancy and the proportion of participants seeking out influenza vaccination. A more detailed study protocol is reported elsewhere [28]. During two consecutive influenza seasons (2013-14 and 2014-15), pregnant women attending the antenatal clinics at four geographically-dispersed public hospitals in Hong Kong were screened for eligibility and recruited into the study by a research nurse. These hospitals were selected based on geographical representativeness and the large populations of eligible pregnant women from a wide range of socioeconomic backgrounds they served. Hong Kong has eight public and ten private hospitals that offer obstetric services.

Public health care, including high-quality antenatal, postnatal and well-child health care, is available free of charge to all Hong Kong residents. Private health care is available on a fee for service basis. In 2011, two-thirds of all Hong Kong women gave birth in public hospitals [29]. Although women giving birth in private hospitals are usually of higher socioeconomic status, many high-income families chose to access public maternity services because it is free, high quality and comprehensive.

Inclusion criteria were pregnant women: (a) with a singleton pregnancy; (b) at least 18 years of age; (c) in at least the second trimester of pregnancy; (d) who spoke Cantonese; (e) were Hong Kong residents; (f) without serious medical conditions (i.e., cancers, rheumatoid arthritis, major psychiatric illnesses) or obstetrical complications (i.e., full placenta previa or diagnosed birth defects); (g) who had not yet received the influenza vaccination during this pregnancy; and (h) who would be staying in Hong Kong for at least 2 weeks after birth. Non-residents who are not entitled to health benefits in Hong Kong were excluded. Although influenza vaccine is safe in any trimester of pregnancy, we recruited pregnant women after the first trimester to avoid any perceived association between vaccination and early pregnancy complications.

2.2 Randomization and concealment

Participating pregnant women were randomized into either a standard care group or an intervention group at a 1:1 ratio, using block randomization with random block sizes of 2–8. An independent researcher who did not participate in the study generated an allocation sequence using Stata 13.1 statistical software (StataCorp 2013, *Stata Statistical Software: Release 13*, College Station, TX; StataCorp LP). Treatment assignments were placed in sequentially numbered, sealed, opaque envelopes. The research nurse selected the next envelope in the sequence to determine treatment allocation, after the eligible pregnant women

were given information about the study and had signed a written consent form. Blinding of the research nurse and participants was not possible given the nature of the intervention.

2.3 Intervention

Standard antenatal care consists of routine checking of maternal and fetal health by either obstetricians or midwives, along with health education to promote a healthy pregnancy. Childbirth preparation classes were available to all women attending the clinics for no additional cost. Recommendations and education about influenza vaccination in pregnancy are not normally included in routine antenatal care. However, participants allocated to the standard care group were provided with an education pamphlet on influenza vaccination in pregnancy, developed by the Hong Kong Centre for Health Protection (CHP) [30] and freely available in the antenatal clinics during the study.

The intervention group received standard care plus brief one-to-one education lasting 10 minutes that focused on four key recommendations identified from the literature: (i) informing the participants about vaccination recommendations; (ii) encouraging them to discuss vaccination with their antenatal care provider or general practitioner (GP); (iii) increasing accessibility of the vaccine by referral to clinics where vaccination could be obtained; and (iv) providing influenza-related information from the official government website and the website uniform resource locator [14]. Specifically, participants in the intervention group were informed about: (i) the WHO [10] and Hong Kong CHP recommendations [31] regarding influenza vaccine during pregnancy; (ii) potential complications associated with influenza infection during pregnancy and for young infants; (iii) the safety of influenza vaccination for pregnant women; (iv) potential benefits of influenza vaccination for pregnant women and infants; and (v) where and how to get the influenza vaccination in Hong Kong. Almost all participants had a personal GP who provided

influenza vaccine and for the few that did not, we provided information on nearby clinics that could provide vaccination.

Immediately after randomization, the intervention was delivered in a private room in the antenatal clinics so that participants in the standard care group were unable to overhear the education intervention and to ensure that all participants were unaware of the intervention other participants received. A digital flip chart was used to present the education content and participants were encouraged to express concerns and ask questions. To ensure consistency of intervention delivery, one research nurse carried out the education intervention across the four sites.

2.4 Data collection

All participants completed a standard baseline questionnaire collecting: (i) key background data (i.e., age, marital status, education level, family income, and employment status); (ii) maternal health status (i.e., pre-existing health conditions, pregnancy-related health problems, gravidity and parity, and expected date of confinement); and (iii) influenza and influenza vaccine knowledge. Participants were subsequently followed up by telephone at 2–3 weeks after their expected delivery date by a study research assistant who had not been involved in participant recruitment and was blinded to participants' treatment allocation. During the follow-up telephone interviews, participants reported their influenza vaccination status during the pregnancy, reasons for receiving or not receiving influenza vaccination, discussion of influenza vaccination with antenatal care providers or GPs, attempts to receive the vaccination (i.e., participant went to their GP and requested the vaccine but were unable to receive it), and anti-vaccination advice from any healthcare professional.

127 *2.5 Outcome measures*

128 The primary study outcome was the self-reported influenza vaccination rate during pregnancy.
129 The secondary outcomes were the proportion of participants who initiated discussion about
130 influenza vaccination with a healthcare professional and the proportion of participants who
131 attempted to get vaccinated.

132

133 *2.6 Sample size calculation*

134 Previous Hong Kong studies showed that seasonal influenza vaccination uptake among
135 pregnant women ranged from 1.7%–5% [15, 32, 33]. Other studies also showed that in
136 pregnant woman-focused interventions, the risk difference of influenza vaccination uptake
137 among pregnant women before and after implementing the intervention ranged from 2% to
138 39% [23-25, 27]. Therefore, an estimate of the "normal" influenza vaccination uptake rate
139 among pregnant women in Hong Kong would be 5.0%, and an increase to 20% would be
140 conservative but clinically meaningful. With a power of 0.80 and significance level of 0.05
141 and using a chi-square test in the G-power statistical analysis program [34], we calculated that
142 76 participants would be required for each group (152 participants in total). After accounting
143 for a loss to follow-up and dropout rate of around 20%, approximately 92 participants per
144 group were required, giving a total of 184 participants.

145

146 *2.7 Data analysis*

147 Baseline sociodemographic characteristics of the two groups were compared using a χ^2 test or
148 a Fisher's Exact Test for categorical variables and Student's t-test for continuous variables.
149 The proportion of participants in the two study groups who received influenza vaccination
150 during pregnancy was compared using χ^2 tests. We further computed the odds ratios of
151 vaccination using logistic regression, while adjusting for one baseline variable that was
152 significantly different between the two groups. The intention-to-treat principle was used, with

missing values taken as no vaccination while the per-protocol analysis, with missing values removed, was reported as a comparison. We used χ^2 tests to compare the proportion of participants in the two groups who discussed influenza vaccination with a healthcare professional and the proportion of participants who attempted to receive influenza vaccination. Each estimate was accompanied by a 95% confidence interval (CI); a 5% level of significance was considered statistically significant in all statistical tests. Data analyses were performed using Stata statistical software (StataCorp 2015, *Stata Statistical Software: Release 14.1*, College Station, TX; StataCorp LP) [35].

2.8 Ethical approval

Ethical approval for the study was obtained from: (1) the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster; (2) the Kowloon West Cluster Research Ethics Committee (KWC-REC); and (3) the Ethics Committee of Hong Kong East Cluster (EC-HKEC). Informed written consent was obtained from all study participants before any personal data were collected and the intervention delivered. The research nurse informed each eligible pregnant woman about the purpose and nature of the study, the potential benefits and risks of participation, and their right to refuse to participate or withdraw at any time during the study without affecting the antenatal care they received.

3. Results

Data were collected from October 7, 2013, to February 4, 2014 (Year 1), and from October 20, 2014, to December 23, 2014 (Year 2) (Figure 1). Data collection was interrupted in the first year when several cases of H7N9 avian influenza were admitted to Hong Kong public hospitals. Because of the raised influenza threat level, non-essential clinical duties were suspended in all public hospitals from December 7, 2013, through January 19, 2014.

Therefore, to achieve the required sample size, recruitment was resumed in the next influenza season. In total, 489 pregnant women were assessed for eligibility across all sites (Figure 1). Of these, 6% (n=29) did not meet the eligibility criteria, and 29% (n=140) declined to participate. Of the 321 who consented to participate, 160 were randomized to the standard care group and 161 to the intervention group; 305 (95%) participants completed follow-up. Nine participants were lost to follow-up, and seven were contacted but refused to complete follow-up. The treatment fidelity rate was 100%, because the intervention was delivered immediately after randomization.

An overview of participants' characteristics is presented in Table 1. The two groups were similar, except for a significantly higher proportion of participants with a pre-existing chronic illness in the intervention group (p=0.006). The reported pre-existing chronic illnesses were Hepatitis B carrier status (n=14), respiratory disease (n=6), thyroid disease (n=6), and others (n=13). The influenza vaccination rate for all participants was 15.6% (n=50) with a higher proportion of vaccinated participants in the intervention group (21.1%, n=34) than the standard care group (10%, n=16) (risk difference [RD] 11.1; 95% CI 3.3–19.0; p=0.006) (see Table 2). The number needed to treat was 9 (95% CI 5.3–30.4). After excluding those lost to follow-up, 22.5% (n=34) of participants in the intervention group received vaccination compared with 10.4% (n=16) in the standard care group (RD 12.1%; 95% CI 3.9–20.3; p=0.004). The logistic regression analysis showed that after adjusting for pre-existing chronic disease status, the intervention group was still significantly more likely to be vaccinated in the intention-to-treat analysis (odds ratio [OR] 2.45; 95% CI 1.28–4.68; p=0.007) and the per-protocol analysis (OR 2.52; 95% CI 1.32–4.82; p=0.005). There were no substantive differences in the vaccination uptake rates of participants between the two study years (see Supplementary Table).

The proportion of participants who initiated discussion about influenza vaccination with a healthcare professional was higher among participants in the intervention group

(19.9%; n=32) than in the standard care group (13.1%; n=21), but the difference was not statistically significant (p=0.10). Of participants who did not receive influenza vaccination during pregnancy (n=271), 45 reported that they had attempted to get vaccinated. A significantly higher proportion of participants who attempted to get vaccinated were in the intervention group (82.2%; n=37) than in the standard care group (17.8%; n=8) (p<0.001). If participants who made the attempt had received the vaccination, the vaccination rate would have been 44.1% (n=71) in the intervention group and 15% (n=24) in the standard care group (RD 29.1%, 95% CI 19.6%–38.6%, p<0.001) (Table 3). At baseline, only 6.2% (n=20) of participants reported that a healthcare professional had discussed influenza vaccination with them. At follow-up, 8.5% (n=26) of participants reported that they were advised against influenza vaccine by a healthcare professional, which included obstetricians (n=11), general practitioners (n=8), and nurses (n=7).

4.0 Discussion

The results of this study show that a brief, one-to-one education intervention for pregnant women significantly increased maternal influenza vaccination. However, the vaccination rate in the intervention group (21.1%) was still substantially below the Healthy People 2020 target vaccination rate of 80% [36]. This may be because other supportive vaccination practices (e.g., on-site vaccine availability and positive recommendations from their obstetric healthcare provider) were not in place. Pregnant women needed to obtain the vaccination from a private provider, which increased vaccination barriers. In obstetric settings where vaccination is readily available however, the effectiveness of brief education may be greater as the barriers that exist in our setting would be removed. Furthermore, when our participants did attempt to get vaccinated, many were advised against vaccination by a healthcare professional or were unable to receive the vaccine. If these participants had received vaccination, the vaccination rate in the intervention group would have been approximately twice as high.

The relationship between healthcare professionals, pregnant women and influenza vaccination is complex. Studies show that doctors and nurses frequently recommend influenza vaccination to elderly or chronically ill clients or people perceived to be at highest risk from influenza morbidity and mortality [37-39]. However, healthcare professionals are less likely to recommend vaccination for young healthy populations [40-42]. Furthermore, rates of influenza vaccination among healthcare professionals, an identified risk group, are consistently low [43-45]. Studies of US obstetric healthcare providers have found that over 85% report that they routinely recommend influenza vaccine to their pregnant patients [20, 46, 47]. Other studies however, suggest that many obstetric healthcare providers are unaware of vaccine recommendations for pregnant women and even if aware, are reluctant to recommend vaccination [40, 42, 48, 49]. In addition, surveys of pregnant women have found that only 7–40% report receiving such a recommendation [32, 33, 50-52]. Although pregnant women who receive a vaccination recommendation from their healthcare provider are substantially more likely to receive influenza vaccination [14], only 30–70% of pregnant women receiving the recommendation get vaccinated [33, 50-52]. This suggests that even with knowledge of the benefits of vaccination, many pregnant women remain reluctant to get vaccinated. This reluctance is likely due to an long-held belief system that pregnant women should minimize exposing the fetus to any unknown or potentially adverse substances [46], especially those injected into the body. Evidence has shown that interventions targeting healthcare professionals improved maternal influenza vaccination rates [18, 21, 53]. In our study a nurse delivered the education intervention and recommended the vaccination to participants, and although vaccine uptake was significantly improved, rates were still suboptimal. Pregnant women may be more willing to follow recommendations from their regular GP or obstetric healthcare provider but some women may still be reticent to receive the vaccination during pregnancy [54]. In addition to maternal education, enthusiastic vaccination recommendations,

and on-site vaccine access, vaccine promotion through mass media and social media may help to further overcome these barriers [46].

In this study the vaccination coverage in the standard care group (~10%) was somewhat higher than in previous Hong Kong studies among pregnant women, where rates ranged from 1.7–6.2% [15, 32, 33]. The influenza vaccination pamphlet provided to participants in the standard care group was widely available in antenatal clinics. However, it is not given directly to pregnant women, and it is likely that few read the pamphlet. Therefore, it is possible that simply being given the influenza vaccination pamphlet by a nurse increased the women's risk perceptions and perceived importance of vaccination. Other studies have shown significant increases in maternal influenza vaccination coverage following the distribution of education pamphlets by healthcare professionals [23, 55]. In addition, pregnant women may perceive healthcare staff-delivered information as more personally relevant and important [56]. Although the effect may be small, actively distributing pamphlets is a simple action, easily implemented in clinical settings at a minimal cost.

4.1 Strengths and limitations

This study provides high-quality evidence of the effectiveness of brief education in improving maternal influenza vaccination rates. First, random allocation and allocation concealment minimized treatment assignment bias. Second, there was a high participation rate. This might have been because the study involved only a brief onsite intervention, requiring less than 10 minutes of participants' time, and a short follow-up telephone interview. Evidence shows that people are more likely to participate in studies with a low participation burden such as in-person or telephone interviews [57]. Third, as the intervention was delivered immediately after randomization, we achieved 100% treatment fidelity. Finally, the loss to follow-up rate was <5%, meaning the risk of attrition bias was minimal.

This study also has some limitations that need to be considered when interpreting the findings. First, participants were recruited from the antenatal clinics at four public hospitals; therefore, the demographic and socioeconomic characteristics might not be representative of all pregnant women in Hong Kong. When compared with the 2014 Hong Kong female population from 20-49 years of age, our sample had fewer participants in the lowest education category (7.2% vs. 17.9%) and more participants in the higher education category (42.4% vs. 30.7%) [58]. Second, the higher-than-expected vaccination rate in the standard care group might indicate that study participants were more receptive to the influenza vaccination information than other pregnant women. As the study information sheet, the consent form, and the education pamphlet all identified that the study was on influenza vaccination, the standard care group may have also received some priming regarding the importance of influenza vaccine in pregnancy. Third, although we took measures to minimize potential contamination between the two treatment groups, we did not assess whether there was contamination or sharing of information between the participants. Fourth, the H7N9 avian influenza outbreak may also explain the higher-than-expected vaccination rate in the standard care group. However, outbreaks of avian influenza are not uncommon in Hong Kong [59] and these outbreaks have had minimal impact on influenza vaccination rates in various population and at risk groups [60, 61]. Fifth, it is also possible, as the assessment of the primary outcome relied on self-reported data, reporting or recall bias may have affected the study results. It was not possible to verify participants' vaccination status as most primary care providers work in solo practices that do not have centralized vaccination reporting systems. However, existing studies have shown that recall of vaccination status is accurate, and maternal recall is particularly reliable for pregnancy-related events [62-64]. In addition, the unavailability of influenza vaccine in the antenatal clinics may have limited the effect of antenatal education as other barriers such as employment or lack of childcare may have prevented pregnant women from being vaccinated. Finally, due to the nature of the intervention, participants and the

research nurse could not be blinded to the treatment allocation and this may have biased the study in some unmeasurable way.

4.2 Conclusion

Although our study supports the effectiveness of brief education in improving maternal influenza vaccination rates, coverage remained low. It is possible that in populations with higher baseline vaccination rates, brief education may be sufficient to achieve target vaccination rates. However, in populations such as Hong Kong, where baseline vaccination rates are low, multi-component interventions are likely required. In addition to education about influenza vaccination, other supportive practices such as a direct healthcare professional recommendation, onsite vaccination, and promotion campaigns that specifically address maternal concerns and fears about vaccination may need to be implemented to reduce barriers and achieve optimal vaccination coverage.

Full text of the trial protocol is available at www.biomedcentral.com/1471-2393/14/19 [28].

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Conflict of Interest Statement

The authors have no potential conflicts of interest to report.

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Figure Caption

Figure 1: Flow diagram of participants through each stage of the study

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Tables

Table 1. Baseline Characteristics of Participants by Intervention Group

Demographic variable	Standard care (n=160), No. (%)	Intervention (n=161), No. (%)	Total (n=321)	*P*
Maternal age, year M(SD)	33.8 ± 4.3	33.2 ± 4.0	33.5 ± 4.2	.21
Parity				
0	99 (61.9)	92 (57.1)	191 (59.5)	.69
1	53 (33.1)	60 (37.3)	113 (35.2)	
>=2	8 (5.0)	9 (5.6)	17 (5.3)	
Maternal education				
Compulsory secondary or below	12 (7.5)	11 (6.8)	23 (7.2)	.21
Upper secondary	64 (40.0)	68 (42.2)	53 (41.1)	
Some post-secondary	10 (6.3)	20 (12.4)	30 (9.4)	
University degree or above	74 (46.3)	62 (38.5)	136 (42.4)	
Place of birth				
Hong Kong SAR	116 (72.5)	112 (69.6)	228 (71.0)	.71
Mainland China	41 (25.6)	47 (29.2)	88 (27.4)	
Others	3 (1.9)	2 (1.2)	5 (1.6)	
Length of residency in Hong Kong				
<10 years	20 (12.5)	21 (13.0)	41 (12.8)	.75
10-15 years	26 (16.3)	31 (19.3)	57 (17.8)	
Since birth	114 (71.3)	109 (67.7)	223 (69.5)	
Family income[1]				
Below median	44 (27.5)	49 (30.4)	93 (29.0)	.56
Above median	116 (72.5)	112 (69.6)	228 (71.0)	
Smoked during pregnancy				
No	158 (98.8)	157 (97.5)	315 (98.1)	.69
Yes	2 (1.3)	4 (2.5)	6 (1.9)	
Pre-existing chronic illness				
No	149 (93.1)	134 (83.2)	283 (88.2)	.006
Yes	11 (6.9)	27 (16.8)	38 (11.8)	
Types: (some participants had >1 illness)				--
Hepatitis B carrier status	3 (27.3)	11 (40.7)	14 (36.8)	
Respiratory disease	1 (9.1)	5 (18.5)	6 (15.8)	
Thyroid disease	1 (9.1)	5 (18.5)	6 (15.8)	
Others	6 (54.5)	7 (25.9)	13 (34.2)	
Pregnancy related health problem				
No	125 (78.1)	126 (78.3)	251 (78.2)	.98
Yes	35 (21.9)	35 (21.7)	70 (21.8)	
Types: (some participants had >1 health problem)				--
Gestational diabetes	13 (37.1)	19 (54.3)	32 (45.7)	
Anaemia	15 (42.9)	13 (37.1)	28 (40.0)	
Hypertension	2 (5.7)	4 (11.4)	6 (8.6)	
Others	5 (14.3)	2 (5.7)	7 (10.0)	

[1]Median household income in HK in 2011 was $20,000 to $24,999 HKD per month (1USD=7.7HKD)

Tables

Table 2. Observed Influenza Vaccine Uptake During Pregnancy by Treatment Group[1]

	Treatment group, n (%)			
	Standard care	Intervention	RD, % (95% CI)	*P*
Intention-to-treat analysis[2]				
Vaccinated	16 (10.0)	34 (21.1)		
Non-vaccinated	144 (90.0)	127 (78.9)	11.1 (3.3–19.0)	0.006
Per-protocol analysis[3]				
Vaccinated	16 (10.4)	34 (22.5)		
Non-vaccinated	138 (89.6)	117 (77.5)	12.1 (3.9–20.3)	0.004

RD=Risk Difference; CI=Confidence Interval

[1]The actual influenza vaccine uptake rate among pregnant women

[2]In the standard care group, n=160. In the intervention group, n=161.

[3]In the standard care group, n=154. In the intervention group, n=151

Tables

Table 3. Expected Influenza Vaccine Uptake During Pregnancy by Treatment Groups[1]

	Treatment group, n (%)			
	Standard care	Intervention	RD, % (95% CI)	*P*
Intention-to-treat analysis[2]				
Vaccinated	24 (15.0)	71 (44.1)		
Non-vaccinated	136 (85.0)	90 (55.9)	29.1 (19.6–38.6)	<0.001
Per-protocol analysis[3]				
Vaccinated	24 (15.6)	71 (47.0)		
Non-vaccinated	130 (84.4)	80 (53.0)	31.4 (21.6–41.2)	<0.001

RD=Risk Difference; CI=Confidence Interval

[1]The estimated influenza vaccination rate if participants who attempted to be vaccinated had received the vaccine

[2]In the standard care group, n=160. In the intervention group, n=161.

[3]In the standard care group, n=154. In the intervention group, n=151

Figures

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