Influenza vaccination of health care workers

Riphagen-Dalhuisen, Josien

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STELLINGEN

behorende bij het proefschrift

Influenza Vaccination of Health Care Workers

1. In ziekenhuizen dient het personeel beter te worden voorgelicht over de gevaren van influenza voor henzelf en hun patiënten. (dit proefschrift)

2. De vaccinatiegraad onder ziekenhuispersoneel zal stijgen als de influenza vaccinatiecampagne wordt toegespitst op determinanten die voor hen bevorderend of belemmerend zijn om het vaccin te nemen. (dit proefschrift)

3. Een gestructureerde influenza vaccinatiecampagne gericht op ziekenhuispersoneel kan bijdragen aan een hogere vaccinatiegraad, mits er voldoende blootstelling aan de componenten is. (dit proefschrift)

4. Hoewel verplichte vaccinatie een oplossing zou kunnen zijn voor de lage influenza vaccinatiegraad onder ziekenhuispersoneel, bestaat hier op dit moment nog geen draagvlak voor onder ziekenhuismanagements. (dit proefschrift)

5. Een hogere influenza vaccinatiegraad onder ziekenhuispersoneel is gerelateerd aan een lagere morbiditeit door influenza en/of een longontsteking onder opgenomen patiënten. (dit proefschrift)

6. Het implementeren van een gestructureerde influenza vaccinatiecampagne is kostenbesparend voor ziekenhuizen. (dit proefschrift)

7. Maak van een ziekenhuis geen ziekmaakhuis.

8. Studying a deadly virus is risky, not studying it is riskier. (The Economist, 2013)

9. Hij die weet dat hij niets weet, weet meer dan hij die niet weet dat hij niets weet. (onbekend)

10. Een promotietraject is vergelijkbaar met een zwangerschap; naar het einde toe wordt het steeds zwaarder maar je houdt vol met het oog op het uiteindelijke resultaat.

Josien Riphagen-Dalhuisen
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Prof. dr. K. Taxis
Prof. dr. J.C. Wilschut

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CHAPTER 1

General Introduction

GENERAL INTRODUCTION

Influenza is one of the major respiratory person-to-person transmittable viral infections in humans. The disease itself comes in two distinct forms: (1) *seasonal epidemics* which occur every year in the winter period, and (2) *(global) pandemics* that occur with unpredictable frequency and which can occur in any season. Influenza signs and symptoms are characterized by sudden onset of fever, cough, headache, myalgia, sore throat, runny nose and overall malaise/general discomfort.[1] Influenza-like illness (ILI) ("flu") has the same symptoms but can be caused by other viruses, like adenovirus, respiratory syncytial virus or para-influenza virus. Influenza occurs among persons of all ages, though transmission is highest among (school) children.[2] The incubation period varies from a short one day to three days during which signs and symptoms are developing. Almost half of the infected patients remain asymptomatic but carry the virus and can transmit the virus.[3] Most symptomatic patients recover within a week from influenza without seeking medical attention. However, influenza can cause severe illness and even death in risk groups like elderly patients and patients with underlying cardiovascular and respiratory disorders. Patients who are immunocompromised, for instance because of cancer or diabetes, are also more prone to complications from viral pneumonia or viral myocarditis, or secondary bacterial infections like pneumonia or acute otitis media. Deaths occur especially in vulnerable populations, such as the elderly and chronically ill patients.[4]

Although *seasonal influenza* is commonly a self-limiting disease among healthy persons, there are only very few other diseases that annually have such a massive impact on society because of the large numbers of medical consultations in primary and secondary care and associated productivity loss which both come with a high economic burden.[5] Over the past decade *seasonal influenza* in Europe has resulted in an estimated 80,000 to 500,000 deaths per year, depending on the severity of the flu outbreak. Direct influenza-associated health care costs for Europe are estimated at more than €50 million per million of population per year (i.e. for the whole of Europe €2.5 billion/yr), and costs are likely to increase further due to an ageing of the population.[6]

Pandemic influenza arises when new influenza strains enter the human population by transmission from farm animal species. These viruses are antigenically very different from seasonal influenza strains and are therefore not or very poorly contained by pre-existing immunity. For this reason they can spread very easily in the entire population. In fact, recent epidemiological data show that during the last pandemic, the 2009 Mexican Flu, about 24% of the entire world population and nearly 50% of children between 5 and 19 years of age had been infected.[7] Fortunately, the Mexican Flu virus caused relatively mild symptoms. Nevertheless, an estimated 31,000 Europeans died during the pandemic from respiratory disease or associated cardiovascular failure.[8] The costs associated with pandemics are estimated to double or triple those of seasonal influenza and would thus be €5-€7.5 billion for Europe.

Vaccination has proven to be an effective measure against influenza in reducing morbidity among adults both during seasonal epidemics and pandemics.[9-11] Osterholm et al. demonstrated in a meta-analysis among 31 eligible studies during *seasonal influenza* a pooled efficacy for trivalent inactivated influenza vaccine of 59% (95% CI 51 – 67%) in adults aged 18 to 65 years.[9] Jefferson et al. also conducted a large review and found that when matched with circulating strains, vaccination is effective in preventing symptoms of influenza in healthy adults and has a modest positive effect on work absenteeism.[12] Importantly, despite some methodological constraints Thomas et al. showed in a meta-analysis that vaccinating HCWs in long-term care is beneficial for both patient morbidity and mortality.[13] During the 2009 influenza newH1N1 pandemic, several studies determined the efficacy of the pandemic vaccines.[11]

In the Netherlands, like in most European countries, general practitioners (GPs) are the main distribution channel for delivering influenza vaccination to risk groups. Among risk persons the highest influenza vaccine coverage in Europe has been achieved because of the GP-based national influenza vaccination program;[14] vaccine coverage is currently around 80% among the elderly, 90% among patients with cardiovascular disease and 70% among patients with chronic respiratory disorders.[15]

Following recommendations by the WHO, since 2007, the Dutch Health Council has been recommending influenza vaccination of risk groups like adults aged over 60 years and younger persons with risk-elevating conditions as well as of health care workers (HCWs) to indirectly protect their patients.[16] HCWs serve as an important vector in transmitting the influenza virus to their patients, and literature has shown that up to 75% of HCWs continue their work while being symptomatic, resulting in an even higher risk of transmission.[17] Despite the fact that the majority of risk patients who are hospitalized during an influenza epidemic have been vaccinated against influenza, there are two main reasons why indirect protection remains important: (1) hospitalized patients are already more prone to infections because of their underlying illness and are at greater risk of dying from influenza as a result of exacerbation of underlying conditions, and (2) because of immunosenescence the influenza vaccine is less efficacious in older persons and immunocompromised patients, which limits the development of a proper immune response to vaccination and affects their ability to resist influenza.[18,19] Since the world population is aging, the numbers of persons with inadequate protection to the influenza virus will also increase. Therefore it is most important for HCWs to be immunized, not only to protect themselves but especially to protect their patients.

However, despite recommendations from the WHO and the Dutch Health Council, vaccine uptake among HCWs remains low in the Netherlands as in other European countries. In 2011, Maltezou et al. demonstrated that all 27 European Union Member States and three additional European countries (Norway, Switzerland and Russia) have been recommending HCWs to get vaccinated against influenza.[20] Kroneman et al. showed that vaccine uptake rates among HCWs remain low, varying from a low 15% in the UK and Germany to the highest coverage of 25% of HCWs in Romania.[21] Dutch guidelines for vaccinating staff in nursing homes (2004) and hospitals (2007) may have created more awareness among HCWs that annual influenza vaccination is important, but so far have failed to reach the objective of the majority of HCWs being vaccinated each year.

AIM AND OBJECTIVES OF THIS THESIS

This thesis aims to assess the factors associated with influenza vaccine uptake among HCWs, how to increase vaccine coverage and to determine the impact of a targeted multi-faceted hospital-based intervention program to raise immunization rates among HCWs.

The following research questions will be addressed:

1. Which factors are reported by administrators of Dutch general hospitals regarding influenza vaccine uptake among HCWs?
2. How do administrators of Dutch general hospitals and nursing homes perceive *seasonal influenza* and vaccination and what is the vaccine coverage in both settings?
3. Which predictors are most important in *seasonal influenza* vaccine acceptance among hospital HCWs?

4. Which factors determine influenza vaccine uptake among hospitals-based HCWs in the Netherlands?
5. How can we develop a structured influenza vaccination program targeted at changing behaviour in hospital staff, and is such a program successful?
6. What is the effect of a multi-faceted influenza vaccination program on vaccine coverage among HCWs, and what are the effects on patient morbidity?
7. Is the implementation of a multi-faceted influenza vaccination program among Dutch HCWs cost-effective?

OUTLINE OF THIS THESIS

In this thesis we focus on factors associated with increasing influenza vaccine uptake among HCWs, and on the impact of such a program. In chapter 2 we first describe the factors associated with influenza vaccine uptake among HCWs according to administrators of Dutch general hospitals. Chapter 3 combines these outcomes with the factors mentioned by the administrators of nursing homes, and compares these factors between both health settings. In chapter 4 a meta-analysis on the predictors of seasonal influenza vaccination among hospital HCWs is presented. Chapter 5 describes the factors associated with influenza vaccine uptake among HCWs in the Dutch university medical centers. Chapter 6 demonstrates the development of a multi-faceted program in order to change vaccination behaviour and its evaluation. Chapter 7 describes the effects of this multi-faceted program on HCWs' influenza vaccine coverage and on patient morbidity. In chapter 8 we performed a cost-effectiveness analysis of the implemented vaccination program, and finally we concluded with a general discussion of our findings and future perspectives in chapter 9.

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CHAPTER 2

Contributing factors to influenza vaccine uptake in general hospitals: an explorative management questionnaire study from the Netherlands

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Josien Riphagen-Dalhuisen
Joep Kuiphuis
Arjen Procé
Willem Luytjes
Maarten Postma
Eelko Hak

ABSTRACT

Background The influenza vaccination rate in hospitals among health care workers in Europe remains low. As there is a lack of research about management factors we assessed factors reported by administrators of general hospitals that are associated with the influenza vaccine uptake among health care workers.

Methods All 81 general hospitals in the Netherlands were approached to participate in a self-administered questionnaire study. The questionnaire was directed at the hospital administrators. The following factors were addressed: beliefs about the effectiveness of the influenza vaccine, whether the hospital had a written policy on influenza vaccination and how the hospital informed their staff about influenza vaccination. The questionnaire also included questions about mandatory vaccination, whether it was free of charge and how delivered as well as the vaccination campaign costs. The outcome of this one-season survey is the self-reported overall influenza vaccination rate of health care workers.

Results In all, 79 of 81 hospitals that were approached were willing to participate and therefore received a questionnaire. Of these, 42 were returned (response rate 52%). Overall influenza vaccination rate among health care workers in our sample was 17.7% (95% confidence interval: 14.6% to 20.8%). Hospitals in which the administrators agreed with positive statements concerning the influenza vaccination had a slightly higher, but non-significant, vaccine uptake. There was a 9% higher vaccine uptake in hospitals that spent more than €1250,- on the vaccination campaign (24.0% versus 15.0%; 95% confidence interval from 0.7% to 17.3%).

Conclusions Agreement with positive statements about management factors with regard to influenza vaccination were not associated with the uptake. More economic investments were related with a higher vaccine uptake; the reasons for this should be explored further.

BACKGROUND

A large number of studies from different regions and among different healthy adult populations have demonstrated that seasonal influenza vaccination is effective in preventing influenza infection.[1-5] In acute health care settings it is essential to protect patients against influenza because most of them are vulnerable at admission for infections and its complications. Because of person-to-person transmission and intensive contacts with patients, vaccination of health care workers has been suggested to indirectly benefit patients.[6] There is also some evidence that vaccinating health care workers against influenza reduces costs in health care by reducing the length of hospitalization and reducing absenteeism of health care workers, though some did not find an effect on absenteeism rates.[1,7,8] Lastly, there are ethical arguments in favour of vaccination, like health care workers' primary duty not to harm their patients.

Despite the potential benefits of vaccination, its uptake in hospitals among health care workers in Europe remains low. In 2003 Kroneman et al. showed vaccine uptake rates among health care workers of five European countries ranging from 15% in the UK and Germany to 25% in Romania.[9] More recently, the survey of Blank et al. also demonstrated low overall influenza vaccine coverage rates among health care workers in eleven European countries which ranged from 6.4% in Poland to 26.3% in Czech Republic in the 2007/2008 influenza season.[10] Vaccination rates exceeding 50% are difficult to reach.[11,12]

To improve vaccine uptake, several behavioural factors are essential to be targeted and different methods should be applied to increase vaccine uptake.[13] For example, in most studies a positive relation with knowledge about the vaccine's efficacy and side effects and the importance not to harm patients is found. Several interventions targeting these determinants can influence the uptake such as educational materials, interactive sessions, role models, facilitating access like the use of mobile carts and the dedication of a person to coordinate the campaign. Some hospitals in the Netherlands have already implemented a vaccination campaign, but the relevant management factors have been under-explored in the worldwide literature. In this study a questionnaire was used to assess and quantify the factors reported by administrators of the general hospitals in the Netherlands regarding influenza vaccine uptake among health care workers.

METHODS

All 81 Dutch general hospitals were approached for this study in December 2010. University hospitals were excluded because there was already an intervention program implemented in these hospitals as part of an ongoing trial [registration no. NCT01481467]. These 81 hospitals were contacted by telephone for participation and 79 out of 81 hospitals were willing to participate. The questionnaire was sent on December 6th 2010 to the participating 79 hospitals and, if necessary, after two weeks a reminder was sent. In the beginning/mid January the hospital managements that did not return the questionnaire were contacted again by telephone as a reminder.

The hospitals in the Netherlands are all publicly funded, not private nor specialty clinics, and we did not contact university medical centers, since they were part of a trial on influenza vaccination uptake. In the Netherlands all persons with risk-elevating conditions can get the vaccine via their general practitioner. Among HCWs this proportion is less than 5%.[6]

The following items were assessed in the self-administered questionnaire: the overall influenza vaccination rate of health care workers in the hospital, the opinion about the effectiveness of the influenza vaccine, whether the hospital had a written policy on influenza vaccination and how the hospital informed their staff about influenza vaccine, e.g. personal by mail or letter, through general written information by posters or the intranet, or in the form of group meetings. The questionnaire also included questions about mandatory vaccination and, whether it was free of charge and how it was organized and about the program costs.

The study was part of a trial [registration no. NCT01481467] and the protocol of the trial was waived by the medical ethical committee of the University Medical Center Groningen for ethical approval according to the Dutch Law of Research with Humans (No. 2009.267). The study was conducted in accordance with the Dutch Law for the Protection of Personal Data (Wet Bescherming Persoonsgegevens) and the Declaration of Helsinki [http://www.wma.net/e/policy/b3.htm].

Statistical analysis

Data were analyzed using SPSS version 18.0. To determine which predictors were associated with mean influenza vaccination rates independent t-tests were used.

95% confidence intervals (95% CI) were calculated to determine statistical significance at a p-level of 5%.

RESULTS

A questionnaire was sent to 79 of a total of 81 hospitals. Eventually, the questionnaire was returned by 42 hospitals (52% response rate). The size of the hospitals ranged from 600 to 5,500 health care workers. The average vaccination rate for influenza in this sample was 17.7% (median value 16.0%, minimum 0.5% and maximum 45.4%, 95% CI 14.6% to 20.8%).

Health care workers were invited for influenza vaccination personally by mail in 26% of hospitals, and 100% used general written information for all health care workers. Only 3% organized information meetings about influenza vaccination. In all, 100% of the hospitals supplied their health care workers with influenza vaccination free of charge. Vaccines were administered at the departments in 58% of hospitals, 84% had mobile carts, 97% had a central location to administer vaccines and only 4% vaccinated at special request.

As shown in Table 1, the majority of management of hospitals agreed with the first three items (vaccination effects mortality and both health care workers and hospital managements have a special responsibility in protecting patients and offering vaccination). Thirty of the 42 hospital administrators (71.4%) believed that vaccinating against influenza has an effect on mortality of patients in the hospital. However, when vaccination rates remain too low only three hospitals (7.1%) would consider implementing a mandatory vaccination program.

Table 1 Agreement of hospital management on questions concerning influenza vaccination (n=42)

Question/statement	Management of hospital that agrees, n (%)
Vaccinating against influenza has effect on mortality of patients in the hospital.	30 (71.4)
Health care workers with patient contact have a special responsibility in preventing infection of their patients.	38 (90.5)
The management of the hospital has a moral responsibility of offering influenza vaccination to their health care workers.	35 (83.3)
An intervention program with the purpose to stimulate vaccination has a positive effect on vaccination rate.	19 (45.2)
The management of the hospital would implement such an intervention program to raise vaccination rate.	22 (52.3)
The management of the hospital considers mandatory vaccination when vaccination rate remains too low.	3 (7.1)
A mandatory vaccination against influenza will reduce costs in the hospital.	12 (28.6)
The vaccine against influenza is effective.	29 (69.0)

Half of the hospital managements thought that an intervention program could raise the vaccination rate. Further, 19 administrators (45.2%) believed that an intervention program would have a positive effect on vaccination rate. Management of 29 hospitals (69.0%) believed that the vaccine is effective against influenza.

In Table 2 is shown how the factors were related to the average vaccination rate. When health care workers are personally informed about influenza vaccination, the average vaccination rate is somewhat higher than any other form of providing information (18.9% compared to 15.6%, 95%CI −2.97% to 9.70%). The managements' positive beliefs about the effect of vaccination on mortality of patients was associated with an average vaccination rate of 19.0% compared to 16.7% when there were negative beliefs about this effect.

Table 2 Agreement of management of hospitals (n=42) with possible predictors of vaccination rate and mean vaccination rate

Predictor	Agreement Yes n (%)	Agreement No n (%)	Mean difference (95% CI)
Health care workers are personally informed about influenza vaccination	24/38 (18.9)	14/38 (15.6)	3.36 (−2.97 to 9.70)
Agreement with the effect of vaccination on mortality of patients	27/33 (19.0)	6/33 (16.7)	2.24 (−6.50 to 10.98)
Agreement of management with the statement that they are responsible for offering the vaccine to health care workers	32/35 (18.8)	3/35 (10.0)	8.78 (−2.75 to 20.32)
Believing that an intervention program to stimulate vaccination has a positive effect on vaccination rate	18/26 (16.5)	8/26 (17.3)	−0.85 (−8.15 to 6.46)
Hospitals willing to implement an intervention program	20/25 (17.4)	5/25 (12.7)	4.70 (−2.66 to 12.06)
Hospitals willing to implement mandatory vaccination	3/33 (18.0)	30/33 (17.5)	0.51 (−11.49 to 12.51)
Believing that mandatory vaccination will reduce costs	11/24 (16.7)	13/24 (15.6)	1.08 (−5.23 to 7.38)
Believing that the vaccine against influenza is effective	27/32 (18.7)	5/32 (14.2)	4.48 (−5.20 to 14.16)

CI, confidence interval

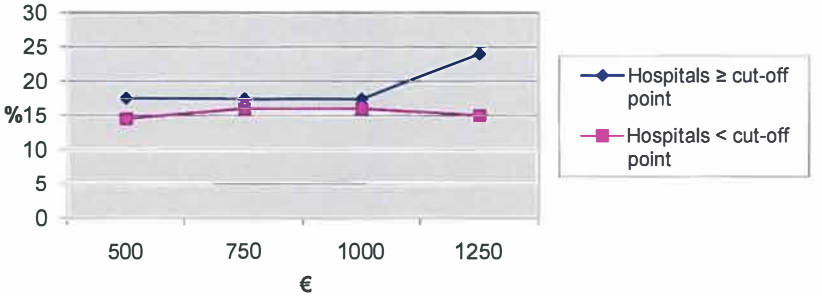
In hospitals where management agreed to be responsible for offering the vaccine to health care workers an average vaccination rate of 18.8% was observed opposed to 10.0% in hospitals in which management disagreed with being responsible.

In all, 11 out of 42 hospital management believed mandatory vaccination will reduce costs. Of these hospitals, the ones that agreed had an average vaccination rate of 16.7% and the ones that disagreed had an average vaccination rate of 15.6%. When asked if they wanted to implement a mandatory vaccination only three hospitals were willing to do so.

The costs of the annual flu campaign and the actual vaccination differed a lot between general hospitals. The average costs for the annual influenza vaccination campaign in 2010 were €640.38 per hospital with a minimum of €0.00 and a maximum of €2000.00 (standard deviation 563.21). The average costs for vaccination were €4198.54 per hospital with a minimum of €0.00 and a maximum of €14262.50 (standard deviation 3643.61).

In Figure 1 the costs of the vaccination campaigns are compared to the vaccination rate, showing a higher vaccine uptake among HCWs in hospitals which spent more money on their vaccination campaign. To assess if a more expensive influenza campaign is correlated with a higher vaccination rate an independent t-test was performed. Only four hospitals spent more than €1250 on the influenza campaign. The average vaccination rate of these hospitals was 24.0% compared to 15.0% of hospitals that spent less than €1250 (mean difference 8.97; $p<0.05$), demonstrating a higher vaccine uptake among HCWs in hospitals which spent more than €1250 on their vaccination campaign. These differences remained if analyzed according to size of the hospital (25% versus 18% in hospitals with less than 2,000 health care workers and 23% and 14% in hospitals with more than 2000 health care workers).

Figure 1 Average vaccination rate at different cut-off points of influenza campaign costs in Euros. n=25 (vaccination rate in %)



For €1250 the mean difference is statistically significant with $p<0.05$.

DISCUSSION

In this study we found that agreement of hospital management with positive statements about influenza vaccination was not associated with influenza vaccine uptake. The average influenza vaccination rate among health care workers in our sample of Dutch hospitals was low; less than one in five received the vaccine. However, this is similar to the European situation.[9-11] In theory, one would expect that health care workers that are better informed about influenza vaccination, e.g. by personal information, have a higher vaccination rate because of a better understanding of the need to be vaccinated. As can be seen in Table 2 there is no significant difference in mean vaccine uptake between hospitals that personally inform their health care workers and hospitals that do not. This could be explained by the fact that hospitals invest only marginal in informing their health care workers in the proper way or they fail to deliver the personal messages to their staff.

The total response rate in the general hospitals was 52% which is quite high for a questionnaire study. However, response bias might have influenced the results. Since it is unknown what the actual current characteristics are of the non-responder hospitals, we were not able to compare them with the responders. We do believe however that the potential for selection bias is not large and more depending on the time and availability of the contact person (which is highly unlikely to be associated with the type of hospital). Importantly, there was a large variation in size of hospitals and agreements with statements, hence the associations between factors and vaccine uptake are most likely not influenced by this type of bias. Also, the average vaccination rate in our sample could not be weighted by the size of the hospitals to obtain a national estimate, so the 17% as observed in this study should not be directly accepted as a national estimate. However, as mentioned above, the sample may be assumed as rather representative of the total hospital population. Further, we asked about the percentage of health care workers being vaccinated and did not actually count vaccinees and total number of health care workers. Since it is important for quality management and for financial reasons, most hospitals do have accurate figures on this preventive method. In addition, another limitation of this study is that we have not taken into account other potential confounders in our analyses, like age structure of the hospital and hospital size. Lastly, it is unknown how many HCWs in these hospitals were already vaccinated against influenza by their general practitioner.

Most of the factors contributing to a slightly higher vaccination rate were only marginally related to a higher vaccine uptake. The questionnaires were directed at management of the hospital – for this reason the statements are the statements of the management and not necessarily of the whole hospital. Although in general it appeared that the studied beliefs of the administrators were not essential in raising the vaccine uptake, it may be that there are elements of these beliefs that may well be important. Detailed factors on how exactly HCWs were informed or motivated for vaccination could be of relevance and we therefore would advocate to study these in more detail using qualitative techniques such as focus groups in addition to what we already know from questionnaire studies.[14] The difference in vaccination costs can be explained by the fact that some hospitals have more health care workers than others. The correlation between investing in educational campaigns apparently leads to higher vaccination rates, even if results were obtained from small or larger hospitals. Therefore, when hospitals invest in educational materials to inform their health care workers that vaccination against influenza will protect their patients, vaccination rates are expected to be higher.

The fact that 11 hospitals think mandatory vaccination reduces costs but only three hospitals would want to implement mandatory vaccination is a bit contradictory. This contrast could be caused by the fact that hospital managements think the ethical concerns outweigh the health benefits, or the hospitals do not want to take away the freedom of choice from their medical staff. The lack of legal permission for mandatory vaccination will probably also play a big role in this matter. However, the ethical discussion about this subject is increasingly being raised. Such mandatory vaccination programs are more likely to reach a high vaccination rate (>90%) and these rates will probably be sustained for a long period of time.[12,15,16] Van Delden et al. showed the pros and cons of mandatory vaccination, and concluded that the advantages of mandatory vaccination outweigh the burdens and risks.[12] However, in the Netherlands as in many European countries there is no legal basis for implementing mandatory vaccination in health care workers yet. Ethical discussions are currently ongoing but preferably vaccine uptake should be raised voluntarily.

CONCLUSION

In conclusion, agreement of hospital management with positive statements about influenza vaccination was not associated with the uptake. Economic investments were low and more economic investments were related with a higher vaccine uptake. Reasons for the higher uptake should be explored further preferably by more qualitative methods. When vaccine uptake remains too low, only a minority of the general hospital administrators would consider implementing a mandatory vaccination program, and such a policy may take some time and efforts before is generally accepted.

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CHAPTER 3

Contributing factors to staff influenza vaccination in hospitals versus nursing homes: a management questionnaire study

Submitted

Josien Riphagen-Dalhuisen
Joep Kuiphuis
Arjen Procé
Johannes van Delden
Eelko Hak

ABSTRACT

Background Patients who receive acute or long-term health care in general hospitals or nursing homes need to be protected against influenza infection. Despite recommendations by the World Health Organization, influenza vaccine uptake among health care workers (HCWs) remains low. Management beliefs associated with this preventive measure have not been extensively explored.

Methods We conducted a self-administered questionnaire study among administrators of all 81 Dutch hospitals and 310 nursing homes to assess and compare specific beliefs associated with influenza vaccine coverage among HCWs.

Results In all, 185/310 (59.7%) nursing home questionnaires and 42/85 hospital questionnaires (49.2%) were returned. The reported mean vaccination rate among HCWs in nursing homes was 18.8% versus 17.7% in general hospitals. In 69.2% of nursing homes there was a written policy for influenza vaccination versus 23.8% of general hospitals ($p<.001$). In 24.3% of nursing homes mandatory vaccination would be accepted when vaccine coverage remains low versus 8.6% of management in general hospitals ($p=0.04$). All other beliefs were not statistically significant different.

Conclusion Despite recommendations, influenza vaccine coverage among HCWs remains low in both nursing homes and hospitals, and mandatory vaccination is not accepted. To increase vaccine coverage in both health care settings, written policies are needed and vaccine behaviour among HCWs needs to be targeted through well-developed, structured, implementation programs.

INTRODUCTION

Annually, influenza causes outbreaks in health care institutions. Patients who receive acute or long-term care need to be protected against this respiratory virus, because they are already more prone to infections and associated risk of complications. Evidence from trials and observational studies clearly showed that the seasonal influenza vaccination is effective in preventing infection with the influenza virus among adults.[1] To reduce transmission of the virus to patients and the spread of the virus within institutions it is therefore recommended to immunize health care workers (HCWs).[2,3] Despite scientific limitations,[4] some four large trials showed considerable reductions in morbidity and mortality during influenza seasons in long-term care institutions with high uptake of the vaccine compared with controls.[5-8] There is also evidence that vaccinating health care workers against influenza may reduce costs in health care by reducing the length of hospitalization and reducing absenteeism of health care workers.[9,10] Further, because of herd immunity in health care institutions can not be reached, it is very important for all HCWs to be vaccinated.[11]

In the Netherlands, influenza vaccine coverage of risk groups is among the highest in the world.[12] Interestingly, vaccine uptake among HCWs remains low.[13] In 2004, the Dutch association of nursing homes physicians (Verenso) developed a guideline on influenza vaccination in which they recommend influenza vaccination for HCWs in nursing homes.[14] The association's goal was to prevent influenza and to limit any complications from such infection among residents. Residents often have an impaired immune system and immunization does not fully protect them.[15] In the Netherlands ageing has led to more than 1.9 million people who are aged 65 years or older and two percent of them resides in nursing homes. Because of these large numbers of risk patients and the expectation that the Dutch population will age further, it is of high importance to achieve effective protection in this group.[16,17]

In 2007, the Dutch Health Council recommended influenza vaccination for HCWs in contact with high-risk patients, i.e. elderly and the chronically ill, in all health care institutions such as nursing homes and hospitals. Despite this recommendation, anecdotal reports indicate that vaccine uptake remains low among HCWs in both general hospitals (GH) and nursing homes (NH), and management factors have not been extensively studied. We therefore aimed to assess the influenza vaccine uptake among HCWs in both health care settings, and we also determined the possible effects of the recommendations in both groups. Further, because of a lack of studies among managements of general hospitals, we aimed to compare the beliefs about influenza and vaccination among management staff of both GH and NH.

METHODS

Setting

This self-administered questionnaire study was conducted in both nursing homes and general hospitals in the Netherlands. In 2011, there were 85 general hospitals in the Netherlands providing secondary care, and eight university medical centers (UMCs) where tertiary care was taken care of. In total, the general hospitals had 176,000 employees and the university medical centers had 60,500 HCWs. The total number of beds was 38,792 for the general hospitals and 7,723 for the UMCs.[18] In 2004 there were 342 nursing homes in the Netherlands with a total capacity of 63,027 beds. The total number of Dutch nursing homes was 310 in 2008 because of merging.[19] Nursing homes provide long-term care for frail, mainly elderly people with somatic and/or psychogeriatric disorders. Within nursing homes care is provided by registered nurses as well as care workers. In 2011, 264,460 certified nurses were working in both hospitals and long-term care facilities.[20] In 2010, 4,000 care workers were working in hospitals versus 77,700 care workers in nursing homes.[21]

Participants and methods

In October and November 2008, a questionnaire was sent to the administrators of all 310 Dutch NH.[22] The following items were assessed: influenza vaccination rates in NH HCWs and residents in the preceding flu-season, whether there was a written policy about vaccinating HCWs against influenza, how they offered the influenza vaccination to their HCWs, whether the HCWs received information about the influenza vaccination, beliefs about effectiveness of the vaccine in reducing morbidity and mortality, beliefs about effectiveness of vaccinating HCWs in reducing costs, beliefs about the moral responsibility to offer the vaccine to HCWs, beliefs about the HCWs' special responsibility to prevent transmission of influenza to their patients and beliefs about mandatory vaccination. Respondents were asked to state to which extent they agreed or disagreed with the statements by means of a 5-point Likert scale. Reminders were sent after two and four weeks.

In December 2010, all 81 organizations of the 85 Dutch general hospitals were approached for participation in a similar questionnaire study. Items relevant to this study were identical to the NH study. 79 out of 81 hospitals were willing to participate and they received the questionnaire. Respondents were asked to state to which extent they agreed or disagreed with the statements by means of a 5-point Likert scale. After two and four weeks a reminder was sent.

Statistical analysis

Data were analyzed using SPSS (version 16.0). Questions on the 5-point Likert scale were dichotomized. The comparison between the hospitals and the nursing homes[22] was made by merging the datasheets. Chi-square tests were used to test for statistically significant differences among comparison groups for binomial variables and t-tests were used for continuous variables.

RESULTS

Of the 310 distributed NH questionnaires, 185 were returned (59.7% response rate). The average vaccination rate was 18.8% (median value 15%, 95% confidence interval (CI) 16.5 to 21.1%).The GH questionnaire was sent to 79 hospitals. Eventually, the questionnaire was returned by 42 hospitals (49.2% response rate). The average vaccination rate for influenza was 17.7% (median value 16.0%, 95% CI = 14.6% to 20.8%). There was no significant difference between the vaccination rate in hospitals and nursing homes (95% CI -4.9 to 2.7%). There was a large and significant difference between NH and GH in having a written policy (see Table 1). In ten (23.8%) of 42 hospitals there was a written policy for influenza vaccination, as is in 126 (69.2%) of the 182 nursing homes ($p<.001$). Another statistically significant difference was the administrators' belief that the GH or NH will accept mandatory vaccination if vaccination rate remains low. Only 8.6% of the GH administrators agreed on this statement versus 24.3% of the NH administrators ($p=0.04$). Also, believing that mandatory vaccination is cost-effective was more common in NH than in GH (69.2% versus 46.2%, $p=0.02$).

There was little difference in providing personal written information to HCWs in both health institutes which occurred in approximately 60% of both types of institutions. On the statement about the vaccine's effectiveness of both hospitals and nursing homes over 80% agreed. There was a slight difference regarding the view that HCWs have a special responsibility. Of the general hospitals 95.0% of administrators agreed with this statement against 86.5% in the nursing homes (p=0.13). Administrators' beliefs about moral responsibility showed no difference between GH (89.7%) and NH (83.2%) (p=0.31).

Table 1 Comparison of administrators' beliefs about vaccination in general hospitals and nursing homes

Factor	Hospital		Nursing home		*p*-value
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	
1. Written policy for vaccination	10 (23.8)	32 (76.2)	126 (69.2)	56 (30.8)	**<.001**
2. Personal written information	25 (59.5)	17 (40.5)	112 (60.9)	72 (39.1)	0.87
3. Vaccine is effective	30 (81.1)	7 (18.9)	153 (82.7)	32 (17.3)	0.81
4. Special responsibility of the HCW to protect patients.	38 (95.0)	2 (5.0)	160 (86.5)	25 (13.5)	0.13
5. Moral responsibility of the management to offer vaccination	35 (89.7)	4 (10.3)	154 (83.2)	31 (16.8)	0.31
6. Mandatory vaccination if vaccination rate remains low	3 (8.6)	32 (91.4)	45 (24.3)	140 (75.7)	**0.04**
7. Mandatory vaccination is cost-effective	12 (46.2)	14 (53.8)	128 (69.2)	57 (30.8)	**0.02**

In Bold p<0.05
HCW, health care worker

DISCUSSION

In all, in both nursing homes and general hospitals influenza vaccine coverage among health care workers remained far below the health objective exceeding 50%.[23] Despite that both types of health care institutions did not differ in vaccine uptake rates, there were few remarkable differences in management views. Having a written policy was more common in nursing homes than in general hospitals, as NH already developed their influenza vaccination guideline in 2004. However, this did not affect vaccine uptake. A possible reason for the absence of an effect from having a policy is that the actual procedures to promote the vaccine uptake may not differ. A well designed policy, as we have already implemented in an earlier phase in nursing homes,[24] may be more effective.

With mandatory vaccination it is possible to reach a vaccination rate of 90% or more. For example, Rakita et al. showed a vaccine coverage of more than 98% after implementing mandatory vaccination.[25] However, in our study only three (8.6%) out of 35 hospitals agreed with the statement that mandatory vaccination should be implemented against 45 (24.3%) out of 185 nursing homes. This could be caused by the fact that hospitals and nursing homes believe that ethical objections in favour of autonomy outweigh the possible benefits of higher vaccination rates for their patients. Currently, there are ongoing ethical discussions about mandatory vaccination. Van Delden et al. showed that there are several arguments in favour of mandatory vaccination. For example the duty to do no harm to your patients and the moral responsibility of HCWs. However, it may be helpful to emphasize these arguments in the program.[23] Another issue of course is that mandatory vaccination should have a legal basis which is not the case in the Netherlands at present. However, a recent study performed by Hakim et al. demonstrated that implementing mandatory vaccination was not always without problems.[26] One hospital was even sued by its health care workers who were against it. The court however, favoured the continuation of mandatory vaccination because they argued that the need to protect patients and co-workers against influenza outweighed the objections.

The statement on the cost-effectiveness also shows a difference between GH and NH. A majority of the nursing homes agreed with this statement whereas only a small minority of the hospitals agreed. The reason for this difference can be the size and organizational structure which is mostly larger and more complex in GH compared to NH. Further research should be done to find out what the exact costs and benefits are.[9]

The GH response rate of 53.2% was not substantially lower than the 59.7% in the study performed by Looijmans-van den Akker.[22] Hence we do not expect response bias to have influenced our results considerably. The average influenza vaccination rate in GH and NH is respectively 17.7% and 18.8% (95% CI -4.9 to 2.7). This is relatively low and can possibly be explained by the fact that GH and NH don't inform their HCWs in an optimal way. Looijmans-van den Akker et al showed that organizational determinants like HCWs receiving information through an information meeting and from a nursing home physician were associated with a higher influenza vaccine uptake among HCWs.[27] So in theory, health care workers that are better informed about influenza vaccination, e.g. by personal information, can be expected to have a higher vaccination rate.

Lastly, in order to increase vaccine uptake, it is important to focus on the GH and NH management staff first. Only if they are fully convinced of the need and importance for HCWs to get vaccinated against influenza, a change in vaccine uptake might be possible. Behavioural change at the level of HCWs is needed to achieve this.

In order to achieve such a behavioural change a structured and multi-faceted communication program should be developed and implemented in general hospitals to change the beliefs of HCWs and to create awareness of the risks and the consequences of not getting vaccinated. This study was not aimed at assessing determinants of vaccine uptake. However Hopman et al. and Riphagen-Dalhuisen et al. conducted studies to determine the predictors of influenza vaccination compliance in hospital-based HCWs.[28,29] Hopman et al. demonstrated a prediction model that proved to determine vaccine uptake among HCWs for over 95%. In future programs, these predictors should be taken into account.

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CHAPTER 4

Predictors of seasonal influenza vaccination among health care workers in hospitals: a descriptive meta-analysis

Occupational and Environmental Medicine 2012;69:230-235.

Josien Riphagen-Dalhuisen
Giedre Gefenaite
Eelko Hak

ABSTRACT

Objective Vaccinating health care workers (HCWs) against influenza is one of the most important methods of decreasing influenza transmission among at-risk patients in health care facilities. However, despite recommendations, the rate of uptake of influenza vaccine among HCWs remains low. The objective of this meta-analysis was to determine the most important predictors of seasonal influenza vaccine acceptance among HCWs in hospitals.

Method A literature search of PubMed and Embase resulted in 4586 hits. Screening of the titles, abstracts and full text identified 13 studies eligible for inclusion in the meta-analysis. Based on the crude data, pooled risk ratios (Mantel-Haenszel risk ratios, mhRR) and their 95% CIs were calculated using Mantel-Haenszel analysis to estimate the associations of predictors with influenza vaccination status.

Results and conclusion Knowing that the vaccine is effective (mhRR 2.22; 95% CI 1.93 to 2.54), being willing to prevent influenza transmission (mhRR 2.31; 95% CI 1.97 to 2.70), believing that influenza is highly contagious (RR 2.25; 95% CI 1.66 to 3.05), believing that influenza prevention is important (mhRR 3.63; 95% CI 2.87 to 4.59) and having a family that is usually vaccinated (RR 2.32; 95% CI 1.64 to 3.28) were statistically significantly associated with a twofold higher vaccine uptake. We therefore recommend targeting these predictors when developing new influenza vaccination implementation strategies for hospital HCWs.

INTRODUCTION

Health care workers (HCWs) with influenza can transmit the virus to patients who are at increased risk of developing serious complications. Seasonal influenza vaccination reduces influenza-confirmed episodes among healthy adults by approximately 75% when matched with circulating strains[1] and there is evidence that vaccinating HCWs against influenza reduces the number of respiratory tract infections among these workers.[2,3] The main reason for vaccinating against influenza, however, is to prevent severe morbidity and mortality among patients, as shown by Hayward et al.[4] In a recent Cochrane review,[5] an overall reduction in all-cause mortality of 32% (95% CI 16% to 45%) was found in long-term care facilities in which some of the HCWs were vaccinated versus control homes. Although the included studies were heavily criticized by the authors, in most countries the evidence so far is still perceived as favouring vaccination. One of the studies from that review[6] revealed that in the control homes 20% of a sample of 30 deaths were caused by influenza, while in the intervention homes none of the sampled deaths had evidence of influenza infection, giving a 100% reduction in deaths caused by influenza. In addition, Thomas et al. estimated a 29% reduction (95% CI 10% to 45%) in influenza-like illness in intervention homes compared with control homes.[5] It is well established that during influenza epidemics, the aetiological fraction of culture or PCR-confirmed influenza virus in elderly patients is high at between 55% and 67%.[7] Recently, Van den Dool et al.[8] developed a mathematical model to predict the effects of increasing vaccine uptake among HCWs in hospitals. Assuming a 73% vaccine efficacy among HCWs, it was estimated that only seven of the workers needed to be vaccinated to prevent one influenza infection in a hospital patient. Another of their conclusions was that due to stochastic variations, more than 184 homes would be needed in each intervention arm to detect a statistically significant reduction in influenza episodes among patients between homes with zero and 50% vaccine uptake by HCWs. Therefore, a huge trial would be needed to confirm this assumption which in itself is less relevant from a clinical perspective. Meanwhile, current evidence supports the provision of large investments to improve vaccine uptake among HCWs, so waiting for more evidence is simply unethical.

Despite evidence in favour of vaccinating HCWs, the uptake rate of seasonal influenza vaccine among HCWs remains far below target. For example, the vaccination rates in the studies included in our meta-analysis ranged from as low as 2.1%9 to 62%.[10] Many studies have examined possible predictors of influenza vaccination acceptance by HCWs, but due to small sample sizes, different study designs, settings, populations and assessed predictors, it is difficult to get an overall picture. Although current reviews provide some evidence regarding the most important predictors of acceptance of influenza vaccination in HCWs,[11,12] systematic or pooled data analysis is missing. Additionally, no distinction has been made between evidence from intervention and evidence from non-intervention studies.

We therefore conducted a meta-analysis to assess the predictors of seasonal influenza vaccination in HCWs working in hospitals by pooling the crude data from non-intervention studies.

METHODS

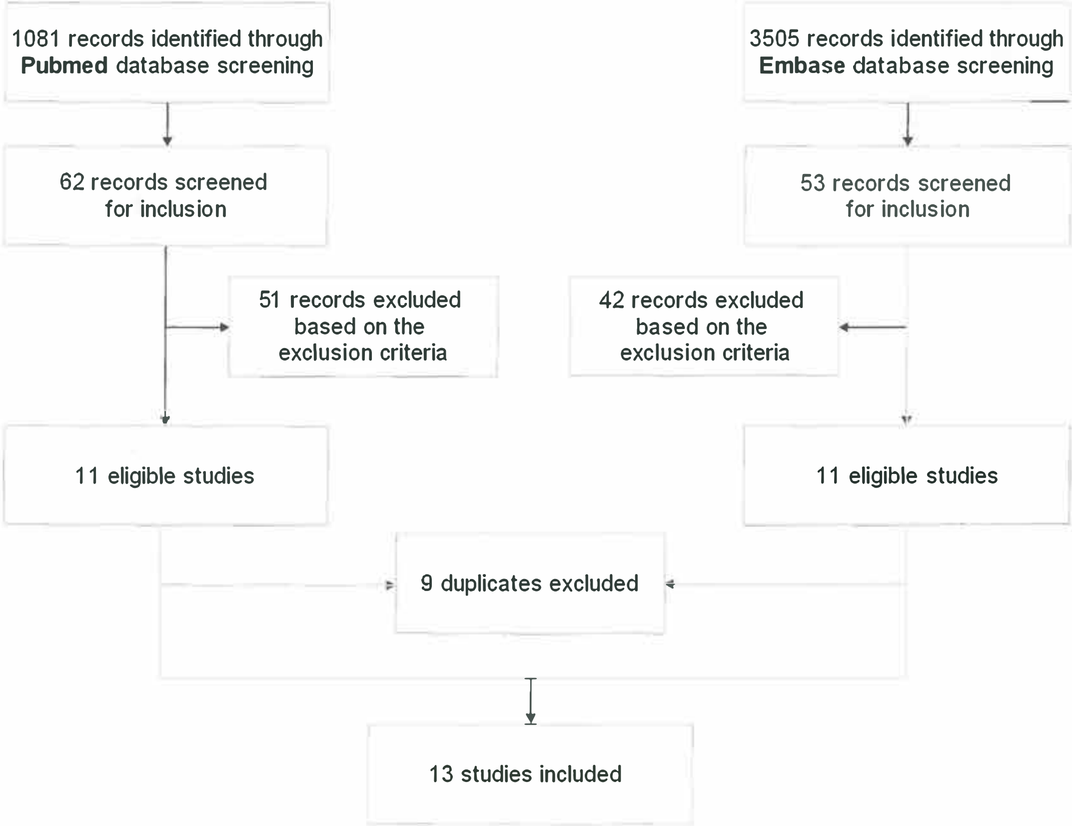
Search strategy

A literature search was performed using PubMed and Embase on 9 December 2009 using the following search strategy: ('Vaccines' (MeSH) OR 'Vaccination' (MeSH) OR 'Immunization' (MeSH) OR 'vaccination' (TIAB) OR 'vaccin*' (TIAB)) AND ('influenza' (TIAB) OR 'influenza virus' (TIAB) OR 'influ*' (TIAB) OR 'flu' (TIAB) OR 'Influenza, Human' (MeSH) OR 'Influenza Vaccines' (MeSH)) AND ('HCWs' (TIAB) OR 'healthcare worker' (TIAB) OR 'hospital personnel' (TIAB) OR 'hospital staff ' (TIAB) OR 'staff ' (TIAB) OR 'personnel' (TIAB) OR 'Hospitals' (MeSH) OR 'Long- Term Care' (MeSH) OR 'Nursing Homes' (MeSH) OR 'Patient Care' (MeSH) OR 'Health Personnel' (MeSH)) AND (English (LA) OR Dutch (LA)) NOT 'child' (MeSH Terms) NOT review(pt).

We used MeSH terms for the PubMed search and Emtree terms for the Embase search. We limited our search to articles in the English or Dutch language. The studies were included in the meta-analysis if they were non-pandemic, non-intervention studies performed among HCWs working in hospitals, reported current influenza vaccination status and had available crude data on at least one predictor of interest for this study. Reference lists were scrutinized to identify other relevant studies, but none were found (Figure 1).

During the selection procedure, articles were also independently judged on their quality according to several quality criteria by two reviewers (JRD, GG), and discussed with EH in case of disagreement. The main quality criteria were response rate, sample size, number of included determinants, data collection methods, study design and vaccine uptake measures.

Figure 1 Flowchart of literature search.



Predictors and outcome

We classified the predictors for influenza vaccination into several groups according to behavioural and implementation models (see Table 1).

Current influenza vaccination status was chosen as the outcome.

Table 1 Predictors of influenza vaccination

Predictors	Characteristics of the predictors
Demographic characteristics	Gender (male vs. female)
	Age (40 years and older versus younger than 40 years)
	Occupation (being a physician versus other HCWs[a] or being a nurse versus other HCWs[a])
Knowledge	Vaccine effectiveness
	Current recommendations
	Symptoms of disease
Perceived benefits influenza vaccination	Willingness to prevent transmission
	Willingness to protect patients
Perceived risks and severity	Influenza complications
	Influenza vaccine
	Influenza disease
Perceived barriers to get vaccinated	Fear related to vaccination
	Availability of the vaccine
Previous influenza and influenza vaccination	Previous influenza vaccination
	History of influenza
Other predictors	
- Smoking	
- Vaccination status of relatives	
- Direct patient contact	
- Prevention of influenza is important	

[a]Health care workers

Statistical analysis

We calculated the average response rates (%) of the included studies and their 95% CIs using SPSS V.16.0. After the raw data were pooled, the risk ratios (RR) and Mantel-Haenszel risk ratios (mhRR) and their 95% CIs were calculated using K. Rothman's Episheet.[13,14] When information about a predictor was available from only one study, RR instead of mhRR were calculated.

Statistical heterogeneity between the studies was examined visually by comparing mhRR and 95% CIs in the forest plot across studies.

RESULTS

Description of the studies

Our search resulted in 4586 hits. Abstracts, titles and full texts were screened and duplicates excluded, resulting in 13 eligible studies.[9,10,15-25] All 13 studies included in the meta-analysis were cross-sectional. The total sample included 84 880 HCWs and the average response rate was 56.9% (see Table 2 for more details). Vaccination status was determined by questionnaire in 10 studies, and was known from clinical records in three studies.[20,24,25] Twelve studies used a questionnaire during the same season that the vaccine was administered[9,10,16-25] and one study used a questionnaire one season later.[15] All studies included at least one demographic predictor (gender, age or occupation), eight studies included at least one behavioural predictor, and two studies included an organisational predictor. All studies were carried out in developed countries: six were performed in the USA,[9,10,17,18,21,22] three in Europe,[16,20,25] two in Canada[19,23] and one in Australia,[24] and one study was a multi-nationality survey.15 In most of the studies, influenza vaccines were provided for free by the hospitals on an annual, voluntary basis.

Table 2 Characteristics of included studies

Study	Location and year of the study	Response rate (%)	Study sample (n)	Provision of the vaccine
Al-Tawfiq	Multi-national[a], 2007	54.2	450	Unknown
Beguin	Belgium, 1996	37.2	4,109	Free of charge to HCW who wish to be vaccinated
Bull	Australia, 2005	69.7	63,330	Coordinated by the infection control department during autumn
Christian	USA, 1990	63.3	379	Offered to all employees annually, $2 administration fee.
Christini	USA, 2005	42.2	2,467	Free of charge, through advertised clinics and mobile carts, fact sheet is provided
Lester	Canada, 2000	58.0	1,195	Unknown
Maltezou	Greece, 2006	8.9	8,062	Unknown
Nichol	USA, 1994	38.0	1,031	Annual influenza vaccination program, walk-in clinic, mobile carts
Piccirillo	USA, 2004	87.0	230	Unknown
Saluja	Canada, 2000	80.5	426	Unknown
Steiner	USA, 1999	84.2	2,200	Free influenza vaccination is offered during mandatory tuberculosis screening of all employees
Tapiainen	Switzerland, 2004	75.5	538	Free of charge for all HCWs
Weingarten	USA, 1987	41.1	463	Available to hospital employees at a $5 charge
Total		56.9 (43.1 – 70.7) Average (95% CI)	84,880	

[a] Multi-nationality survey among HCWs from the UK, USA, South Africa and Saudi Arabia.
[b] University Medical Hospital or Teaching Hospital.

Type of secondary care	Predictors per study		
	Demographic	Behavioural	Organisational
Hospital	x	x	x
UMC[b]	x	x	
Hospital	x		
Hospital	x	x	
UMC[b]	x		
UMC[b]	x		
Public Hospital	x	x	
UMC[b]	x	x	
Community hospital	x	x	x
UMC[b] emergency departments	x	x	
Tertiary care hospital	x	x	
University children' s hospital	x		
Acute care UMC[b]	x		
	13	8	2

Predictors of influenza vaccination in HCWs

The results from the pooled analyses of the associations between influenza vaccination status and different predictors are shown in Table 3. The forest plot in Figure 2 presents the results graphically.

Male gender, being aged 40 years and older and being a physician were the demographic predictors that were positively associated with being vaccinated, while being a nurse was negatively associated with vaccine uptake. Statistically significant factors resulting in a twofold higher vaccine uptake were knowing that the vaccine is effective, being willing to prevent influenza transmission, believing that influenza is highly contagious, believing that influenza prevention is important and having a family that is usually vaccinated.

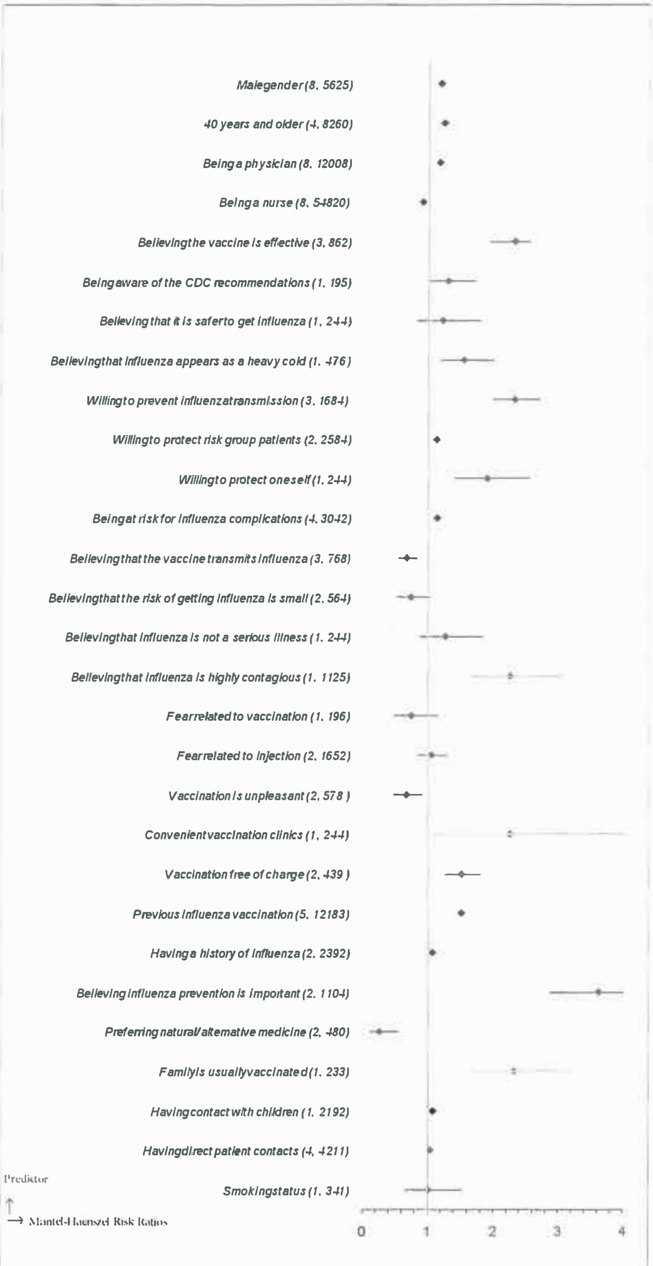
Table 3 Results

Type of predictor	Predictor	Number of studies that included the predictor	mhRR	95% Confidence Interval
Demographic	Male gender	8[10,15-17,19,21-23]	1.18	1.13 – 1.23
	40 years and older	4[15,16,20,23]	1.23	1.17 – 1.28
	Being a physician	8[9,15,16,18,20,21,23,24]	1.16	1.13 – 1.20
	Being a nurse	8[9,15,16,18,20,23-25]	0.90	0.88 – 0.91
Knowledge	The vaccine is effective	3[15,16,21]	2.22	1.93 – 2.54
	Being aware of the CDC recommendations	1[*22]	1.29	0.98 – 1.70
	Getting influenza is safer	1[*15]	0.83	0.56 – 1.23
	Influenza appears as a heavy cold	1[*16]	1.53	1.18 – 1.98
Perceived benefits	Willing to prevent influenza transmission	3[15,16,21]	2.31	1.97 – 2.70
	Willing to protect risk group patients	2[10,21]	1.12	1.06 – 1.18
	Willing to protect oneself	1[*15]	1.89	1.40 – 2.54
Perceived risks and severity	Being at risk for influenza complications	4[10,15,16,23]	1.13	1.08 – 1.19
	Believing that the vaccine transmits influenza	3[15,16,22]	0.67	0.55 – 0.83
	Believing that the risk of getting influenza is small	3[15,16,22]	0.73	0.52 – 1.03
	Believing that influenza is not a serious illness	1[*15]	1.26	0.87 – 1.83
	Believing that influenza is highly contagious	1[*16]	2.25	1.66 – 3.05

Perceived barriers	Fear related to vaccination	1[*15]	0.74	0.49 – 1.15
	Fear related to injection	2[15,16]	1.05	0.84 – 1.29
	Vaccination is unpleasant	2[15,16]	0.68	0.49 – 0.92
	Convenient vaccination clinics	1[*15]	2.25	0.95 – 5.34
	Vaccination free of charge	2[15,22]	1.52	1.27 – 1.81
Previous influenza and influenza vaccination	Previous influenza vaccination	5[10,16,20-22]	1.51	1.47 – 1.55
	Having a history of influenza	2[10,22]	1.07	1.02 – 1.13
Other predictors	Believing influenza prevention is important	2[15,16]	3.63	2.87 – 4.59
	Preferring natural/ alternative medicine	2[15,16]	0.26	0.12 – 0.55
	Family is usually vaccinated	1[*16]	2.32	1.64 – 3.28
	Having contact with children	1[*10]	1.08	1.04 – 1.13
	Having direct patient contacts	4[10,16,17,21]	1.04	0.99 – 1.08
	Smoking status	1[*23]	1.01	0.66 – 1.53

*When the information about a predictor was available from only one study, risk ratios (RR) and not Mantel-Haenszel risk ratios (mhRR) were calculated.

Figure 2 Forest plot (number of studies with this specific predictor, total number of persons per predictor). CDC, Centers for Disease Control and Prevention.



DISCUSSION

With this meta-analysis we aimed to determine the most important predictors of acceptance of seasonal influenza vaccination by HCWs in hospitals. Our results showed that the strongest predictors were knowing that the vaccine is effective, being willing to prevent influenza transmission, believing that influenza is highly contagious, believing that it is important to prevent influenza and having a family that is usually vaccinated.

Other predictors had a weaker association but might be helpful in developing future influenza vaccination campaigns. Our findings are consistent with the results of previous reviews which also suggested that raising awareness about vaccine effectiveness and the risks of influenza makes vaccination more likely to be accepted.[11,12]

Although it seemed that there were many more predictors of influenza vaccination acceptance in HCWs, the risk ratios of many predictors were close to 1. This suggests that interventions focusing on these predictors most likely would not achieve a significant increase in vaccination uptake rates in HCWs as these predictors have little impact on vaccine acceptance.

We also looked at demographic characteristics to determine if they predicted vaccination status. We found that being male, being older than 40 years and being a physician increased the chances of being vaccinated, while being a nurse was associated with less vaccination. However, the risk ratios only differed very slightly from 1 for these predictors. Nevertheless, these population characteristics could be used in implementation programs to define specific target groups according to age, gender and occupation.

In addition, in our study we assessed the predictors of influenza vaccination in non-intervention studies performed in similar settings, namely (teaching) hospitals. We deliberately excluded intervention studies because merging the results from intervention and non-intervention studies might have introduced bias: knowledge derived from an educational campaign used in an intervention study could have influenced a particular predictor, which would not have occurred in a non-intervention study.

Regarding heterogeneity, most predictors point in the same direction with overlapping risk ratios. Therefore, these predictors are fairly homogeneous.

The fact that our study was unsuitable for multivariate analysis should be taken into account when interpreting the results. It might be that some predictors contain other information. For example, male gender was found to be a predictor of influenza vaccine acceptance. However, it is likely that there are more male than female physicians, and therefore the relative risks might be overestimated. We were not able to address the issue of how the predictors interacted with one another.

Finally, this meta-analysis was performed with the underlying purpose of providing evidence for use in future influenza vaccination campaigns among HCWs in hospitals during common epidemics, so we described the factors that were associated with seasonal influenza vaccine uptake. Pandemic influenza is different from seasonal influenza in many ways, but some of the described factors might also be important in a pandemic. Some reports on pandemic influenza vaccination have shown predictors similar to those described here, although other predictors also might play a role in vaccine uptake.[26,27] Influenza vaccination will only be successful in HCWs if they are properly educated and if the vaccine is easily accessible. Therefore, we recommend targeting these predictors when developing new influenza vaccination implementation strategies for hospital HCWs.

CONCLUSIONS

Our main aim was to assess the predictors for seasonal influenza vaccination in HCWs in hospitals. Our meta-analysis provided information on the strength of the predictors of current influenza vaccination status. Future studies could use this information for their interventions and target the predictors that seem to have the most influence on vaccine uptake, and also focus on educating HCWs in order to prevent misinformation.

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CHAPTER 5

Determination of factors required to increase uptake of influenza vaccination among hospital-based health care workers

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Conny Hopman
Josien Riphagen-Dalhuisen
Ingrid Looijmans-van den Akker
Gerard Frijstein
Nannet van der Geest-Blankert
Marita Danhof-Pont
Herbert de Jager
Nita Bos
Ed Smeets
Marjan de Vries
Pieter Gallee
Annet Lenderink
Eelko Hak

ABSTRACT

A questionnaire study was performed in all eight University Medical Centers in the Netherlands to determine the predictors of influenza vaccination compliance in hospital-based health care workers (HCWs). Demographical, behavioural and organizational determinants were assessed based on behavioural and implementation models. Multivariable regression analysis was applied to assess the independent predictors for influenza vaccine uptake. Age >40 years, the presence of a chronic illness, awareness of personal risk and awareness of risk of infecting patients, trust in the effectiveness of the vaccine to reduce the risk of infecting patients, the HCWs' duty to do no harm and their duty to ensure continuity of care, finding vaccination useful despite the constant flow of visitors and having knowledge of the Health Council's advice, social influence and convenient time for vaccination were all independently associated with vaccine uptake. The accuracy of the prediction model was very high (area under the receiver operating curve: 0.95). Intervention programs to increase influenza vaccine uptake among HCWs should target the relevant determinants identified in this study.

INTRODUCTION

Influenza is a highly contagious respiratory tract infection causing significant morbidity and mortality in high risk groups, especially when antigenic drift has occurred as in the case of swine-like H1N1 influenza. While the overall uptake of influenza vaccines is high, uptake among health care workers (HCWs) is sometimes incomplete. Since 30–50% of influenza cases are asymptomatic, HCWs have substantial rates of both clinical and subclinical influenza during influenza seasons when they often continue to work.[1-3] Indirect protection of patients by immunisation of HCWs has therefore been proposed. Significant decreases in mortality in care home patients have been observed even though their vaccination coverage was only 50%.[4-6] Other advantages of such a vaccine strategy include the personal benefit to HCWs of a decreased risk of influenza and less disruption of services through staff absences. Burls et al. and Demicheli et al. reviewed the literature and observed reductions of influenza-like illness in vaccinated HCWs ranging from 68% to 90% with about 40% fewer days of absence.[7,8] Since uptake among HCWs remains low, more information is needed about barriers to HCWs' uptake of influenza vaccine. So far, research that has already been performed among HCWs in hospitals shows that there are a number of different determinants responsible for low vaccine uptake. To our knowledge these studies are less comprehensive than the study reported here. Several studies did not use sufficient determinants in all relevant fields. For example, neither Walker et al. nor Maltezou et al. investigated behavioural determinants.[9,10] Also, there are studies that have only investigated the primary reason for refusing or accepting influenza vaccination.[11] The purpose of this study is to identify the factors which determine influenza vaccine uptake among hospital-based HCWs which may help to plan future influenza vaccination campaigns.

METHODS

Study population

In November and December 2008, all eight University Medical Centers (UMCs) in the Netherlands took part in a questionnaire study. Four or five wards per hospital were selected to participate. The selected wards included patients at medium and high risk for influenza including intensive care units, internal medicine, neonatology and paediatric wards. Self-administered paper questionnaires were distributed on these wards among all HCWs (mainly physicians, nurses, and nursing assistants) in November – December 2008.

Outcome measure

The primary outcome measure was self-reported compliance with influenza vaccination prior to the influenza season 2008/2009. The question to divide study subjects into compliant or not was the following: 'Did you receive influenza vaccination this year (2008)?' The possible answers were: 'No', 'No, but I still intend to' or 'Yes'. Those who responded positive were regarded as compliant with influenza vaccination; those who responded negative were regarded non-compliant. Since it is impossible to predict how many of the 'No, but I still intend to' respondents actually would have taken the vaccine, those HCWs (N = 42, 3.2%) were excluded from the final analysis.

Determinants of influenza vaccination compliance

An anonymous, self-administered, 52-item paper questionnaire was used to assess determinants of influenza vaccination compliance. This questionnaire was based on a review of the literature and a questionnaire previously developed by our research group to determine the factors influencing influenza vaccination compliance among HCWs in care homes.[12] The aim was to assess demographic, behavioural and organizational determinants.

Determinants

Demographical determinants included sex, age and the presence of a chronic illness for which influenza vaccination is indicated. Also, the profession, number of years working in health care, type of shift working, type of ward and occurrence of an influenza outbreak in the last three years were assessed (Table 1 and Table 2). The Health Belief Model contains five domains: perceived susceptibility, perceived severity, perceived benefits, perceived barriers and cues to action, and 25 questions focused on these domains.[13] The Behavioural Intention Model comprises two more domains: attitude and social influences. A further 12 questions were posed to assess these domains.[14] The ASE Model adds self-efficacy to attitude and social influences.[15] Four questions addressing self-efficacy were included in the questionnaire. Respondents were asked to answer most propositions on a five-point Likert scale ranging from 'strongly agree' to 'strongly disagree'. Organizational determinants were assessed by six questions. The current situation concerning available information about influenza vaccination and the organization around the administration of influenza vaccination were studied. The respondents were asked if the information provided was sufficient and if the organization of the administration of influenza vaccination was adequate.

Table 1 Baseline characteristics of study and target population

Characteristic	Study subjects	Target population[a]
Personal data		
Male gender	19.2%	19.4%
Mean age (years)	40.4	40.7
Profession		
Physician	154 (12.1%)	(10.8%)

[a] Based on statistics from the medical officers of the participating hospitals.

Statistical analysis

Data were analysed using SPSS (Version 14.0; SPSS, Inc., Chicago, IL, USA). Questions on the five-point Likert scale were dichotomized [agree (number 1–2 of the scale) versus uncertain and disagree (number 3–5 of the scale)] in agreement with previous studies. Because clustering effects at a hospital level could have been been present, we performed Generalized Estimation Equation analysis with the UMCs as the clustering variable to obtain odds ratios and 95% confidence intervals (CIs). The area under the receiver operating characteristic (ROC) curve (AUC) was estimated after correction of regression coefficients for statistical overoptimism using the heuristic shrinkage factor

$$C_{heur}=X^2_{model}-(df-1)/X^2_{model}$$

by Van Houwelingen et al. where df is based on the number of candidate variables (df = 65).[16] The ROC indicates how well the prediction model is able to discriminate between those who did not take the vaccine versus those who took the vaccine. An ROC area of 0.5 indicates no discrimination (or tossing of a coin) and an area of 1.0 indicates perfect discrimination.

Table 2 Univariate analysis: demographic determinants associated with influenza vaccination compliance among health care workers

Determinants	Vaccinated (n=466)	Unvaccinated (n = 772)	Odds ratio (95% CI)	*P*-value
Demographic				
Male gender	343/465 (73.8%)	648/759 (85.4%)	2.08 (1.56-2.77)	<0.001
Age > 40 years	295/457 (64.6%)	368/748 (49.2%)	1.88 (1.48-2.39)	<0.001
Chronic illness	60/464 (12.9%)	100/772 (13.9%)	3.94 (2.77-5.59)	NS
Professional data				
Working >20 years in health care	255/459 (55.6%)	336/751 (44.7%)	1.54 (1.22-1.95)	<0.001
Working no evening or night shifts	171/466 (36.7%)	162/772 (21.0%)	2.18 (1.69-2.82)	<0.001
Influenza outbreak in last three years	70/462 (15.2%)	65/769 (8.5%)	1.93 (1.35-2.77)	<0.001
Profession				
Nursing assistant vs. nurse	35/295 (11.9%)	14/631 (2.2%)	5.93 (3.14-11.21)	<0.001
Physician vs. nurse	97/357 (27.2%)	42/659 (6.4%)	5.48 (3.71-8.10)	<0.001
Type of ward				
Internal medicine vs ICU	129/293 (44.0%)	170/491 (34.6%)	1.49 (1.10-2.00)	0.010
Neonatology vs ICU	70/234 (29.9%)	106/427 (24.8%)	1.29 (0.91-1.85)	NS
Paediatrics vs ICU	73/237 (30.8%)	89/410 (21.7%)	1.61 (1.12-2.31)	0.011

CI, confidence interval; ICU, intensive care unit; NS, non-significant

RESULTS

Study population

The response rate was 39% (1295/3324 distributed questionnaires). The mean age of respondents was 40.4 years (range 19–69 years; SD: 10.7) and 80.8% were female (Table 1). In all Dutch hospitals in 2005, the mean age of HCWs was 40.7 years and 80.6% were female. Profession was distributed as 12.1% physicians, 71.5% nurses and 4.1% nursing assistants.

Outcome measure

Of all respondents, 37.6% (N = 466) were vaccinated against influenza. Influenza uptake was 69.8% among physicians, 29.6% among nurses and 71.4% among nursing assistants. In the preceding 2007–2008 influenza season 29.2% of respondents (N = 370) received influenza vaccination (respectively 47.4%, 23.6% and 59.6%).

Determinants univariately associated with influenza vaccination uptake

Nearly all demographic determinants were univariately associated with influenza vaccine uptake (Table 2). In the domain 'perceived susceptibility' the determinant that most strongly predicted vaccine uptake was 'awareness of risk to infect patients' (Table 4). Concerning 'perceived severity', the danger to patients was the most strongly associated determinant. Reduction of work pressure was appreciated as an important benefit of influenza vaccination. In the domain 'perceived barriers', 'vaccination is useful despite the constant flow of visitors' was important. Among the cues to action 'having knowledge of the content of the advice of the Dutch Health Council' was most important. Furthermore, 'ensuring continuity of care and all HCWs should get vaccinated' were attitudes univariately associated with vaccine uptake. The head of department and the people surrounding the HCW also influence uptake. Respondents reported that they would definitely get influenza vaccination if it was available at a convenient time, if it could be administered on their own ward, if they would be rewarded, and if they would get a reminder (Table 3). Available information, especially from the internet, from the medical officer and sufficient information were all univariately associated with vaccine uptake. Finally, flexible day and time of execution were important in vaccine uptake.

Table 3 Univariate analysis: organizational determinants associated with influenza vaccination compliance among health care workers

Determinants	Vaccinated (n=466)	Unvaccinated (n=772)	Odds ratio (95% CI)	*P*-value
Information				
Information received	436/464 (94.0%)	693/771 (89.9%)	1.75 (1.12-2.74)	0.015
Information received….				
- by poster/leaflet	254/464 (54.7%)	386/771 (50.1%)	1.21 (0.96-1.52)	NS
- by letter	210/464 (45.3%)	363/771 (47.1%)	0.93 (0.74-1.17)	NS
- through an information meeting	5/464 (1.1%)	10/771 (1.3%)	0.83 (0.28-2.44)	NS
- through the media	53/464 (11.4%)	119/771 (15.4%)	0.71 (0.50-1.00)	NS
- by internet	99/464 (21.3%)	128/771 (16.6%)	1.36 (1.02-1.83)	0.041
- from the clinical officer	49/464 (10.6%)	43/771 (5.6%)	2.00 (1.30-3.06)	0.002
Received information is sufficient	406/455 (89.2%)	560/725 (77.2%)	2.44 (1.73-3.44)	<0.001
Important to receive information by poster/leaflet	335/444 (75.5%)	350/728 (48.1%)	3.32 (2.56-4.31)	<0.001
Important to receive information by letter	389/453 (85.9%)	458/734 (62.4%)	3.66 (2.70-4.96)	<0.001
Important to receive information through an information meeting	49/412 (12.3%)	88/702 (12.5%)	0.94 (0.65-1.37)	NS
Important to receive information from the clinical officer	136/442 (32.2%)	141/701 (20.1%)	1.89 (1.43-2.49)	<0.001
Important to receive information by internet	215/424 (50.7%)	248/707 (35.1%)	1.90 (1.49-2.43)	<0.001
Important to receive information through the media	182/425 (42.8%)	199/710 (28.0%)	1.92 (1.49-2.48)	<0.001
Execution				
Execution of vaccination is organised	458/461 (99.3%)	742/747 (99.3%)	1.03 (0.25-4.33)	NS
Execution of vaccination is organised				
- at a fixed day and time	73/461 (15.8%)	129/747 (17.3%)	0.90 (0.66-1.23)	NS
- at a fixed day, but at a flexible time	17/461 (3.7%)	57/747 (7.6%)	0.46 (0.27-0.81)	0.006
- at a flexible day and time	320/461 (69.4%)	378/747 (50.6%)	2.22 (1.74-2.83)	<0.001
Execution is at an adequate number of moments	412/459 (89.8%)	620/716 (86.6%)	1.36 (0.94-1.97)	NS

CI, confidence interval; NS, non-significant.

Table 4 Univariate analysis: behavioural determinants associated with influenza vaccination compliance among health care workers (HCWs)

Determinants	Vaccinated (n=466)	Unvaccinated (n=772)	Odds ratio (95% CI)	*P*-value
Perceived susceptibility				
High personal risk for influenza infection	159/466 (34.1%)	55/772 (7.1%)	6.75 (4.83-9.43)	<0.001
Aware of risk to infect patients	400/466 (85.8%)	346/771 (44.9%)	7.44 (5.53-10.01)	<0.001
During an epidemic HCWs are more likely to get influenza infection	387/463 (83.6%)	503/762 (66.0%)	2.62 (1.97-3.50)	<0.001
Perceived severity				
Influenza is dangerous for me	201/465 (43.2%)	140/772 (18.1%)	3.44 (2.65-4.45)	<0.001
Influenza is dangerous for my patients	465/466 (99.8%)	23/770 (2.9%)	14.32 (1.93-106.37)	<0.001
Perceived benefits				
Vaccination reduces the personal risk of influenza	118/464 (25.4%)	94/765 (12.3%)	2.43 (1.80-3.29)	<0.001
Vaccination reduces the risk to infect patients	81/464 (17.5%)	24/764 (3.1%)	6.52 (4.07-10.45)	<0.001
Vaccination reduces the risk to infect family members	84/463 (18.1%)	27/766 (3.5%)	6.07 (3.86-9.52)	<0.001
Vaccination can reduce work pressure	405/463 (87.5%)	286/764 (37.4%)	11.67 (8.55-15.94)	<0.001
Perceived barriers				
Vaccination is useful despite the constant flow of visitors	314/463 (67.8%)	152/767 (19.8%)	8.53 (6.55-11.10)	<0.001
Not against vaccination in general	450/462 (97.4%)	716/766 (93.5%)	2.62 (1.38-4.97)	0.002
Vaccination is not only offered to reduce costs	368/463 (79.5%)	509/768 (66.3%)	1.97 (1.50-2.58)	<0.001
Vaccination is not only offered to reduce sick leave	352/463 (76.0%)	481/767 (62.7%)	1.89 (1.46-2.44)	<0.001
Experienced side-effects in the past	61/459 (13.3%)	64/755 (8.5%)	1.66 (1.14-2.40)	0.009
Side-effects in the past are no reason for not getting vaccinated this year	279/454 (61.5%)	103/751 (13.7%)	10.03 (7.57-13.28)	<0.001
Expecting no side-effects after vaccination	256/463 (55.3%)	304/764 (39.8%)	1.87 (1.48-2.36)	<0.001
Expecting no allergic reactions or autoimmune disease after vaccination	436/461 (94.6%)	697/765 (91.1%)	1.70 (1.06-2.73)	0.026

After getting vaccinated once you do not have to get vaccinated every year	422/463 (91.1%)	699/765 (91.4)	0.97 (0.65-1.46)	NS
Vaccinations do not reduce resistance	347/347 (100.0%)	532/532 (100.0%)	[a]	[a]
Vaccination do not cause influenza infection	392/392 (100.0%)	609/609 (100.0%)	[a]	[a]
Vaccination is necessary, even though patients are protected by their own vaccination already	450/460 (97.8%)	703/750 (93.7%)	3.01 (1.51-6.02)	0.001
Cues to action				
Knowing there is an advice from the Dutch Health Council	301/465 (64.7%)	466/768 (60.7%)	1.19 (0.94-1.51)	NS
Having knowledge on the contents of this advice	312/465 (67.1%)	433/770 (56.2%)	1.59 (1.25-2.02)	<0.001
Attitudes				
Finding it important that HCWs do not infect patients	441/464 (95.0%)	588/760 (77.4%)	5.61 (3.57-8.82)	<0.001
HCWs should get vaccinated to ensure continuity of care	280/462 (60.6%)	63/765 (8.2%)	17.14 (12.47-23.57)	<0.001
All HCWs should get vaccination	407/463 (87.9%)	265/766 (34.6%)	13.74 (10.01-18.86)	<0.001
Not finding it important that HCWs have freedom of choice concerning influenza vaccination	60/464 (12.9%)	31/764 (4.1%)	3.51 (2.24-5.51)	<0.001
In case of influenza outbreak unvaccinated HCWs should be banned from work	96/463 (20.7%)	147/764 (19.2%)	1.10 (0.82-1.46)	NS
In case of influenza outbreak unvaccinated HCWs should be banned from work without payment	59/462 (12.8%)	25/759 (3.3%)	4.30 (2.65-6.97)	<0.001
HCWs should get vaccination because of their duty not to harm	389/462 (84.2%)	262/761 (34.4%)	10.15 (7.58-13.58)	<0.001
Influenza vaccination should become mandatory for HCWs in hospitals	229/462 (49.6%)	116/764 (15.2%)	5.49 (4.20-7.18)	<0.001
Social influences				
People close to me think it is important for me to get vaccination	263/461 (57.0%)	137/765 (17.9%)	6.09 (4.69-7.91)	<0.001
My colleagues think it is important for me to get vaccination	272/463 (58.7%)	195/765 (25.5%)	4.16 (3.25-5.33)	<0.001
The chief of department should recommend vaccination	359/463 (77.5%)	261/766 (34.1%)	6.68 (5.13-8.70)	<0.001
Finding it important to do what people close to me think	316/463 (68.3%)	330/763 (43.3%)	2.82 (2.21-3.60)	<0.001

Self efficacy				
I would definitely get influenza vaccination, if...				
- It would be at convenient time	425/443 (95.9%)	179/751 (23.8%)	75.45 (45.73-124.47)	<0.001
- I could get it on my own ward	411/442 (93.0%)	197/748 (26.3%)	37.08 (24.87-55.30)	<0.001
- It would be rewarded	259/433 (59.8%)	134/745 (18.0%)	6.79 (5.19-8.87)	<0.001
- I would get a reminder	357/441 (81.0%)	142/751 (18.9%)	18.23 (13.51-24.60)	<0.001

CI, confidence interval; NS, non-significant; [a] Odds ratios cannot be estimated.

Determinants multivariately associated with influenza vaccination uptake

The multivariate analysis resulted in an 11-item final prediction model with two demographic and nine behavioural determinants (Table 5). Age >40 years, the presence of a chronic illness, awareness of personal risk and awareness of risk of infecting patients, trust in the effectiveness of the vaccine to reduce the risk of infecting patients, the HCWs' duty to do no harm and their duty to ensure continuity of care, finding vaccination useful despite the constant flow of visitors and having knowledge of the Health Council's advice, social influence and convenient time for vaccination were all independently associated with vaccine uptake. The ROC AUC corrected for overoptimism for the final model ($C_{heur} = 892 - 65/892 = 0.92$) including all 11 determinants was 0.95 (95% CI: 0.94–0.96). When only demographic factors were included in the model, the AUC was 0.63 (0.60–0.67). Adding behavioural determinants lifted the AUC to 0.95 (0.94–0.96).

Table 5 Multivariate logistic regression analysis: determinants associated with influenza vaccination compliance in hospital-based health care workers (HCWs) (n = 1120)

Determinants	Vaccinated (n= 431)	Unvaccinated (n= 714)	Odds ratio (95% CI)	*P*-value
Demographic				
Age > 40 years	273/431 (63.3%)	344/714 (48.2%)	2.65 (1.76-4.00)	<0.001
Chronic illness	93/431 (21.6%)	49/714 (6.9%)	3.37 (1.82-6.22)	<0.001
Behavioural				
Aware of personal risk for influenza infection	141/431 (32.7%)	47/714 (6.6%)	2.80 (1.62-4.84)	<0.001
Aware of risk of infecting patients	369/431 (85.6%)	323/714 (45.2%)	2.54 (1.59-4.05)	<0.001
Vaccination reduces risk of infecting patients	76/431 (17.6%)	22/714 (3.1%)	3.68 (1.71-7.93)	0.001
Vaccination is useful despite the constant flow of visitors	292/431 (67.7%)	143/714 (20.0%)	1.88 (1.24-2.84)	0.003
Having knowledge on the contents of the Health Council's advice	290/431 (67.3%)	398/714 (55.7%)	2.41 (1.58-3.69)	<0.001
HCWs should get vaccinated to ensure continuity of care	260/431 (60.3%)	60/714 (8.4%)	2.15 (1.37-3.39)	0.001
HCWs should get vaccinated because of their duty not to harm	361/431 (83.8%)	246/714 (34.5%)	2.22 (1.41-3.50)	0.001
People around me think it is important for me to get vaccination	248/431 (57.5%)	130/714 (18.2%)	1.74 (1.14-2.65)	0.010
I would definitely get influenza vaccination if it would be at a convenient time	413/431 (95.8%)	174/714 (24.4%)	28.91 (15.90-52.58)	<0.001

CI, confidence interval.

DISCUSSION

This questionnaire study suggested that a multivariate model containing a combination of two demographic and nine behavioural determinants was accurate in the prediction of influenza vaccine uptake among HCWs in Dutch hospitals. These determinants can be used to develop effective implementation programs in health care settings and may be of use in the planning for immunisation during a pandemic.

This study has several strengths. First, an extensive questionnaire based on a literature search was used. This questionnaire addressed demographic, behavioural, organizational and self-efficacy determinants, making it very unlikely to have missed predictors of influenza vaccination. Second, this is one of few studies using multivariate analysis to assess the independent value of the determinants. Third, this is one of the first studies on this subject conducted in hospitals rather than long term care homes. There are several differences between hospitals and care homes, for example, hospitals tend to be larger, making their organization a lot more complicated, and the average level of education of employees is more diverse. Fourth, a relatively large number of HCWs was included, contributing to the study's power. Fifth, the determinants were largely in accordance with findings from previous studies.[11,12,17-20] For example, as in our study, Quigley and Hayes also observed increasing vaccine uptake with age and reductions of uptake when respondents perceived the vaccine as ineffective.[19]

Potential limitations of this study are the response rate and the possibility of response bias. The response rate was 39% which is within the expected range, and mean age and sex were similar for all HCWs of the UMCs. Also, in these study departments, physicians and nurses are relatively overrepresented as compared with total hospital personnel. Since most determinants confirm other studies, we believe that the developed model is representative for the HCW population.

How can these determinants be used to develop an intervention programme? The process of intervention design can be divided into six steps: (1) a needs assessment, (2) specification of proximal programme objectives, (3) selection of theory-based methods and practical strategies for inducing change, (4) planning the programme, (5) planning of programme adoption and implementation, and (6) planning for evaluation. The data from this study are part of the needs assessment and may be used to specify the programme objectives. For example, sex and presence of illness are associated with uptake, but cannot be changed. However, these determinants might be of use to define specific subgroups for the intervention. Perceived risk and potential reduction by vaccination can be changed by effective educational methods that focus on increasing knowledge such as information leaflets, websites, group presentations and videos with role models. Ethical issues such as 'do no harm' need to be targeted with more intensive activities such as small group discussions and role models in health care management. Social influence also requires a more comprehensive approach including discussions at department level and discussion evoking items such as buttons indicating that personnel took the vaccine. Finally, logistics need to be worked out to reduce efforts to get the vaccine such as the introduction of mobile carts for the distribution of vaccine.

Due to the disappointing vaccination rates so far, the ethics of mandatory vaccination for HCWs are being explored. Arguments in favour of this measure are the professional responsibility of HCWs and their duty to do no harm. An important counter-argument is the personal autonomy of HCWs. While this debate continues, research should continue to identify interventions to optimise vaccine uptake. In conclusion, an influenza vaccination implementation programme targeting the determinants identified in this study may be effective in increasing vaccine uptake. Further evidence for the impact of such a programme is needed.

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CHAPTER 6

Planning and process evaluation of a multi-faceted influenza vaccination implementation strategy for health care workers in acute health care settings

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Josien Riphagen-Dalhuisen
Gerard Frijstein
Nannet van der Geest-Blankert
Marita Danhof-Pont
Herbert de Jager
Nita Bos
Ed Smeets
Marjan de Vries
Pieter Gallee
Eelko Hak

ABSTRACT

Background Influenza transmitted by health care workers (HCWs) is a potential threat to frail patients in acute health care settings. Therefore, immunizing HCWs against influenza should receive high priority. Despite recommendations of the World Health Organization, vaccine coverage of HCWs remains low in all European countries. This study explores the use of intervention strategies and methods to improve influenza vaccination rates among HCWs in an acute care setting.

Methods The Intervention Mapping (IM) method was used to systematically develop and implement an intervention strategy aimed at changing influenza vaccination behaviour among HCWs in Dutch University Medical Centers (UMCs). Carried out during the influenza seasons 2009/2010 and 2010/2011, the interventions were then qualitatively and quantitatively evaluated by way of feedback from participating UMCs and the completion of a web-based staff questionnaire in the following spring of each season.

Results The IM method resulted in the development of a transparent influenza vaccination intervention implementation strategy. The intervention strategy was offered to six Dutch UMCs in a clustered Randomized Controlled Trial (RCT), where three UMCs were randomized for intervention, and three UMCs acted as controls. A further two UMCs elected to have the intervention. The qualitative process evaluation showed that HCWs at four of the five intervention UMCs were responsive to the majority of the 11 relevant behavioural determinants resulting from the needs assessment in their intervention strategy compared with only one of three control UMCs. The quantitative evaluation among a sample of HCWs revealed that of all the developed communication materials, HCWs reported the posters as the most noticeable.

Conclusions Our study demonstrates that it is possible to develop a structured implementation strategy for increasing the rate of influenza vaccination by HCWs in acute health care settings. The evaluation also showed that it is impossible to expose all HCWs to all intervention methods (which would have been the best case scenario). Further study is needed to (1) improve HCW exposure to intervention methods; (2) determine the effect of such interventions on vaccine uptake among HCWs; and (3) assess the impact on clinical outcomes among patients when such interventions are enacted.

BACKGROUND

Influenza is an annual respiratory infection which has the capacity to cause severe morbidity and mortality, particularly among frail hospitalized patients. The influenza attack rate among health care workers (HCWs) can be considerable,[1] with studies showing that more than 75% continue to work after infection.[2,3] As HCWs can transmit influenza to their patients, immunizing them against influenza is an extremely important measure to protect patients from the viral infection.[4,5] Such vaccination has proven to be effective in preventing influenza infection among HCWs themselves since they are generally young and able to mount a more effective immune response when compared to frail patients.[6] In a recent systematic review, Osterholm et al. found a significant pooled influenza vaccine efficacy with an estimated reduction in influenza of 59% among young adults.[7] Whilst the number of available studies is limited, influenza vaccination has also been shown to reduce influenza-like illness-related absenteeism of HCWs,[8] which is essential to preserve continuity of care. Using a micro-simulation hospital department model, Van den Dool et al. demonstrated that, although no herd immunity can be achieved, there is an inverse linear relationship between the number of vaccinated HCWs and the number of infected hospital patients, meaning that each additional HCW who is immunized against influenza adds to the preventive effect.[9] These clinical trial studies demonstrating the effects of immunizing HCWs against influenza on patient outcomes were all conducted in long-term care facilities,[10] and it should be noted that acute care hospital settings are very different compared to long-term care as they have a higher patient turnover, which hampers the applicability of findings from long-term care settings to acute care settings.[9]

Following guidelines set by the World Health Organization, the Dutch Health Council has (as of 2007) recommended influenza vaccination for HCWs in contact with high-risk patients in the Netherlands, but vaccine coverage of HCWs has been low. For example, in 2006 and 2008 in all eight Dutch University Medical Centers (UMCs) vaccination uptake among HCWs ranged from 0% to 28%, with an average uptake of 13%. Such low vaccine coverage appeared to be consistent with European figures reported in a study by Blank et al., which showed low influenza vaccine coverage of HCWs in 11 European countries, with a maximum coverage of a low 26% in the Czech Republic.[11]

Using special interventions, it is possible to increase influenza vaccine coverage of HCWs in acute health care settings. In a before-after trial from Spain, Llupia et al. demonstrated an increase in vaccine coverage of HCWs from 23% in 2007/2008 to 37% in 2008/2009 by means of a promotional and educational strategy,[12] but they did not report a systematic method for developing their strategy. In the Netherlands, Looijmans-van den Akker et al. developed a systematic program to increase vaccine uptake among HCWs in nursing homes. After the intervention, the influenza vaccine uptake in the intervention group was on average 9% higher than in the control group (p=0.02). However, it should be noted that the applicability of these findings to acute care settings is likely to be limited.[13] To extract the full value of an influenza vaccination strategy in hospitals, a theoretical framework that underpins the development of such a strategy is essential, especially for future applications. For the study reported in this paper, we have used the Intervention Mapping (IM) method to systematically plan, develop and evaluate the process of an influenza vaccination implementation strategy.[14] To the best of our knowledge, our study is the first report on the development of an implementation strategy that targets influenza vaccine uptake among HCWs in acute care settings which includes a process evaluation. The effects of the developed intervention program on actual behaviour, and the clinical outcomes, will be separately reported as part of a cluster randomized controlled trial.

METHODS

SETTING AND TRIAL DESIGN

This report outlines the development of the intervention and process evaluation as part of an intervention trial conducted in the Netherlands during the seasons 2009/2010 and 2010/2011 [trial number NCT01481467]. With the permission from the Board of Directors, and with permission from the Dutch Association of UMCs (Nederlandse Federatie van Universitair Medische Centra), all eight Dutch UMCs participated in the study. Six UMCs agreed to be randomized to receive either the intervention (3 UMCs) or act as controls (3 UMCs), and two UMCs chose to implement the developed intervention program (the 'external intervention UMCs'). Formal ethical approval to conduct the implementation trial, according to the Dutch Law of Research with Humans, was not required (Medical Ethical Committee, University Medical Center Groningen, Netherlands, No. 2009.267). The study was conducted in accordance with the Dutch Law for the

Protection of Personal Data (Wet Bescherming Persoonsgegevens), and the Declaration of Helsinki [http://www.wma.net/e/policy/b3.htm].

The Intervention Mapping (IM) method[14] was used to develop, implement and evaluate the process of the intervention strategy for HCWs. The IM method is a framework for systematically developing health education interventions, and can be used as part of the dynamic process of planning intervention strategies in health education. The process of developing and evaluating an implementation strategy is composed of six steps: 1) a needs assessment; 2) establishment of proximal program objectives; 3) development of theory-based methods and practical strategies; 4) program planning; 5) adoption and implementation of the program; and 6) program evaluation (see Figure 1).

DEVELOPING THE PROGRAM ACCORDING TO THE IM METHOD

Step one: Needs assessment

To gain insight into how to improve the influenza vaccine coverage of HCWs, we first assessed the relevant determinants of influenza vaccination behaviour. In 2008, prior to the onset of the 2009 trial, a questionnaire-based study was performed among HCWs of five selected departments from the group of eight participating University Medical Centers (UMCs).[15] Based on the Health Belief Model and the Behavioural Intention Model demographical, behavioural and organizational determinants were assessed.[16,17] Multivariate analysis of the responses resulted in an 11-item prediction model, with two relevant demographic and nine behavioural determinants (the results of which are presented in Table 1). The final prediction model showed a high discriminative value (area under the receiver operating curve: 0.95), meaning that on the basis of the presence or absence of these determinants, vaccination behaviour of 95% of HCWs can be accurately predicted.

Table 1 Determinants associated with influenza vaccination uptake among health care workers (HCWs) resulting from the needs assessment

Determinants	Odds Ratio	Changeability[a]	Category	Target Group[b]
Demographic				
Age >40 years	2.65	-	Not applicable	Not applicable
Chronic illness	3.37	-	Not applicable	Not applicable
Behavioural				
Aware of personal risk for influenza infection	2.80	+	Knowledge	2
Aware of risk of infecting patients	2.54	+	Knowledge	2
'Vaccination reduces risk of infecting patients'	3.68	+	Knowledge	2
'Vaccination is useful despite the constant flow of visitors'	1.88	+	Knowledge	2
Aware of the contents of the Health Council's Advice	2.41	+	Knowledge	2
'HCWs[c] should get vaccinated to ensure continuity of care'	2.15	+	Common interest	3
'HCWs should get vaccinated because of their duty to do no harm'	2.22	+	Common interest	3
'People around me think it is important for me to get vaccinated'	1.74	+/-	Social impact	3
'I would definitively get vaccinated if it was available at a convenient time'	28.91	+	Organizational	1,2,3

[a] - : not changeable, + : changeable as discussed in our 10-person research team under supervision of a communication expert.
[b] Target group 1: HCWs who deliberately comply with vaccination.
Target group 2: HCWs who deliberately do not comply with vaccination.
Target group 3: HCWs who unintentionally do not comply with vaccination.
[c] HCWs: health care workers.

Step two: Proximal program objectives

Each of the 11 determinants associated with influenza vaccination compliance were discussed by our 10-person research team (the principal researchers/authors of this study) in order to determine which behavioural determinants could reasonably be changed through an implementation strategy. Decisions were taken by consensus, using an independent facilitator with expertise in the area of influenza vaccination from the National Institute of Health and the Environment (Bilthoven, the Netherlands). For these discussions, the core research team of the ten principal researchers was expanded by inclusion of the UMC research contacts (physicians from the departments of Occupational Health and Environment, or from the departments of Microbiology) who were in charge of the planning and implementation of the annual influenza vaccination strategy in their hospitals. Based on the measures of association (odds ratios) obtained from the 2008 questionnaire study,[15] and in order to demonstrate the independent relevance of the determinants for potential change in behaviour (Table 1), the discussion group divided the determinants into different categories so as to target the use of methods/materials. The following categories were identified: knowledge; common interest; social impact; and organizational (see Table 1).

One of the critical assessments in developing an implementation strategy for changing behaviour is exploring whether the person's behaviour is intentional or not. The research team identified three different target groups among HCWs: (1) HCWs who deliberately choose to comply; (2) HCWs who deliberately choose not to comply; and (3) those HCWs who unintentionally do not comply with vaccination. The varying methods/materials are separated according to target groups in the IM matrix, but in best practice all three target groups were exposed to all developed methods in line with the proximal objectives (see Table 2).

Table 2 Proximal program objectives and methods

Determinants	Proximal Program Objectives	Methods/materials
Demographic		
Age >40 years	Not applicable due to limited changeability	- Not applicable
Chronic illness	Not applicable due to limited changeability	- Not applicable
Behavioural		
Aware of personal risk for influenza infection	Create awareness among HCWs[a] of the risk to get infected with influenza and it's consequences	- Provide information on influenza, transmission and risks through an information stand at the UMC restaurants, a website, a folder and plenary meetings - Polls and a quiz on the intranet - Video testimonials with role models
Aware of risk of infecting patients	Create awareness among HCWs of the risk to transmit influenza to patients and how vaccinating HCWs can prevent this	- Provide information on influenza and the risk of transmission to patients through an information stand at the UMC restaurants, a website, a folder and plenary meetings - Polls and a quiz on the intranet - Video testimonials with role models
'Vaccination reduces risk of infecting patients'	HCWs being convinced that vaccinating HCWs against influenza will reduce the risk of transmission to patients	- Provide information on influenza and the effectiveness of vaccination through an information stand at the UMC restaurants, a website, a folder and plenary meetings - Polls and a quiz on the intranet - Video testimonials with role models
'Vaccination is useful despite the constant flow of visitors'	HCWs being convinced that vaccinating HCWs is useful despite the constant flow of visitors	- Provide information on influenza and the effectiveness of vaccination through an information stand at the UMC restaurants, a website, a folder and plenary meetings - Polls and a quiz on the intranet - Video testimonials with role models

Aware of the contents of the Health Council's Advice	Create awareness among HCWs on the existence and contents of the guideline developed by the Dutch Health Council	- Provide and explain contents of the advice on the intranet or website - Explain and discuss in a plenary meeting
'HCWs should get vaccinated to ensure continuity of care'	HCWs understand the ethical aspects of this matter and the need to ensure continuity of care	- Explain and discuss ethical aspects (plenary meeting, website) - Video testimonials with role models - Involve Board of Directors (e.g. first vaccination, be present at vaccination, column) - Distribute badges to vaccinated HCWs saying 'deliberately vaccinated for you' to start the discussion
'HCWs should get vaccinated because of their duty to do no harm'	HCWs understand the ethical aspects of vaccinating HCWs and that this is part of their duty of care	- Explain and discuss ethical aspects (plenary meeting, website) - Video testimonials with role models - Involve Board of Directors (e.g. first vaccination, be present at vaccination, column) - Distribute badges to vaccinated HCWs saying 'deliberately vaccinated for you' to start the discussion
'People around me think it is important for me to get vaccinated'	Create awareness of the importance of vaccination among those close to the HCWs	- Personal invitation letter with information folder and a link to the website at the home address
'I would definitively get vaccinated if it was available at a convenient time'	Create a more convenient approach	- Poster with clear practical information on location and time - Personal invitation at home address with location and time - Extended vaccination hours which take changing shifts into account

[a] HCWs: health care workers.

Step three: Theory-based methods and practical strategies

To influence the behaviour of a target group, a wide range of intervention methods/materials is required and these need be propagated through different channels and means.[14] Bartholomew et al., for example, provides theoretical methods for major behavioural determinants as well as for all higher environmental levels.[14] After reviewing the literature pertaining to vaccine studies[2,18-21] the research team agreed on the methods to be implemented. As no simple practical strategies or methods exist that guarantee success,[22] we took the different target groups into account when developing the tools. Examples of methods at the individual level included: participation in information meetings; consciousness raising by way of letters of invitation for vaccination; persuasive communication (such as a dedicated website with clear messages); interactive learning through 'frequently asked questions' or polls on a website; tailored to different target groups. HCWs who intentionally do not comply with influenza vaccination, need to be provided with clear information in order to eliminate any possible misconceptions or misunderstandings (e.g. on absence of vaccine effects or risk of serious adverse effects) so that they may change their views. In contrast, for HCWs who unintentionally remain unvaccinated it is more important to increase their awareness of their behaviour and its possible consequences. Testimonials from role models (e.g. members of the Board of Directors or Heads of Departments), where the reasons to comply with the vaccination program are provided, can play an important role in this awareness change. Thus, by actively promoting the vaccination campaign, and by demonstrating the importance of vaccination in a variety of ways, vaccine coverage of HCWs was expected to be improved.

Step four: Program planning

The topics and channels of the strategy methods were discussed individually by the lead investigator with members of the research team. After a number of meetings, consensus was reached in each UMC about the program methods to be used, and the best way to design and produce them. Common formats and sample materials were developed and pre-tested by the research team, which were subsequently adapted by the communication departments of the individual UMCs. A dedicated website, www.bewustgepriktvooru.nl (in Dutch), was developed by a web designer using the structure and contents produced by the research team. The Dutch Federation of UMCs (the NFU) and the Dutch association of nurses and nursing assistants (the V&VN) indicated their support by their approval for their logos to be displayed on the website. In order to stimulate discussion among HCWs, badges were developed with the tagline "bewust geprikt voor u" (Dutch for 'deliberately vaccinated for you'), to be handed out to HCWs after vaccination. The badges were designed by an external designer in two forms, one for HCWs working on regular wards, and a child-friendly badge for HCWs working on the paediatric ward (showing a hedgehog). In support of the intervention, the research team also provided written information about the relevance of influenza vaccination for HCWs and about the time and location of vaccination, for use on individual hospital intranet websites and/or in folders and leaflets. To engage HCW staff in the project, a quiz was also developed that was made available on the project website. The effective exchange and availability of these developed materials to members of the research team, and the contact persons of the intervention UMCs was facilitated by making them accessible on a secured section of the project website.

Step five: Adoption and implementation of the program

To achieve the highest impact, the implementation of the developed strategy needed to be arranged in a programmatic and structured fashion. As a first step, the intervention UMC contacts and relevant communication staff were visited by the communication expert to explain and discuss the timelines and program of the implementation strategy before and during the vaccination campaign. For further assistance, all UMC contact persons were able to pose questions, or to initiate discussions on the secured section of the central project website. During the vaccination campaign members of the research team were also available for questions and advice. The team also developed news items for use by UMC communication officers to raise awareness among HCWs. In line with current practice, all intervention UMCs were free to choose the methods that were most appropriate to them. The three control UMCs were asked to carry out their own annual influenza vaccination program as planned, without putting more efforts into their strategy than normal, and without using any of the intervention program materials and/or strategies that were developed by the research team.

Step six: Program evaluation

Both a qualitative and quantitative process evaluation was carried out. Part of the qualitative process evaluation was conducted through the completion of set checklists by the contact person from each intervention UMC. In addition, annual communication reports on the influenza vaccination campaign were compiled by the communication offices of all UMCs, providing summaries of the evaluation of the intervention program by the teams involved in the organization of the influenza vaccination program. In addition, UMC contacts were invited to comment on the methods/materials used in the intervention campaign. The checklists and reports were then reviewed for the number of behavioural determinants that the actual implementation strategy at each of the UMCs targeted. These are presented as a 'yes/no' per determinant (see Table 3).

Table 3 Evaluation of the use of behavioural determinants in vaccination campaign by implementers of the intervention UMCs (n is given)

Determinants	Intervention UMCs n = 3	External intervention UMCs n = 2	Control UMCs n = 3
Aware of personal risk for influenza infection	2/3	2/2	2/3
Aware of risk of infecting patients	3/3	2/2	3/3
'Vaccination reduces risk of infecting patients'	2/3	2/2	2/3
'Vaccination is useful despite the constant flow of visitors'	2/3	1/2	1/3
Aware of the contents of the Health Council's Advice	3/3	2/2	1/3
'HCWs[a] should get vaccinated to ensure continuity of care'	2/3	2/2	1/3
'HCWs should get vaccinated because of their duty to do no harm'	2/3	2/2	2/3
'People around me think it is important for me to get vaccinated'	1/3	1/2	1/3
'I would definitively get vaccinated if it was available at a convenient time'	3/3	2/2	1/3

[a] HCWs: health care workers.

To obtain more detailed quantitative information on the process variables, in both intervention and control UMCs, we developed a web-based questionnaire for HCWs of the five selected departments that were also involved in the 2008 questionnaire study by Hopman et al. (two intensive care units, internal medicine, paediatric ward and neonatology).[15] An email invitation with a link to the web-based questionnaire was sent to the heads of the five departments after both influenza study seasons, requesting them to invite their HCW staff to complete the questionnaire. The study participants included nurses, physicians and support staff. The questionnaire assessed vaccination determinants as well as possible exposure to the developed materials, e.g. folders, posters, the website and testimonials, and how these were rated (e.g. 'have you noticed posters in your UMC'; 'did you like them'; rated on a 5-point Likert scale).

RESULTS OF THE PROCESS EVALUATION

Qualitative process evaluation in the intervention and control UMCs

Table 3 shows the qualitative evaluation of the methods that were applied in both intervention and control UMCs. Though the intervention program focused on the specific determinants according to the study of Hopman et al,[15] the control UMCs might independently also have focused their program on one or more of these determinants. With the exception of the determinants "Vaccination is useful despite the constant flow of visitors" and "People around me think it is important for me to get vaccinated", the determinants (c.f. Table 1) were targeted by four or all five intervention UMCs, compared with fewer by the control UMCs. Both intervention and control UMCs targeted the determinant "awareness of risk".

From the communication reports derived from the intervention UMCs, it became evident that (1) longer opening hours for administration of the vaccine, (2) more vaccination locations, and (3) the use of mobile carts appeared to be associated with an increased vaccine uptake among HCWs. Providing information on influenza and vaccination by different means (intranet, posters, magazine and letters) was found to be very useful. Although there was not much difference in the level of involvement of the Boards of Directors of the intervention UMCs compared with the control UMCs, the self-reported impression by the UMC evaluation teams was that such involvement led to positive intentions among HCWs. Two intervention UMCs organized plenary and interactive meetings for HCWs where information on influenza, the influenza vaccination and the determinants was provided, and where HCWs were given the opportunity to ask questions. In contrast, in the communication reports of the control UMCs it was stated that the information provided to staff was too limited, and with only one control UMC organizing a plenary information meeting.

Quantitative evaluation of the implementation process in the intervention group

In the quantitative evaluation, a sample of HCWs from five selected departments of the participating UMCs was asked to complete an anonymous web-based questionnaire. In the spring of 2010, 2,255 HCWs were approached, of whom 678 (249 from intervention UMCs) completed the questionnaire (response rate of 30.1%). In the spring of 2011, 4,885 HCWs were invited to participate in the questionnaire with 908 (303 from intervention UMCs) responses (response rate of 18.6%). Baseline data of participants were similar across study seasons and UMCs. Respondents were predominantly female (in 2009/2010 88.9% in the 'external intervention group' and 86.7% in the 'intervention group', p= 0.554). The proportion of HCWs older than 45 years was similar across seasons and groups, ranging from 37.8% to 42.7%. More nursing staff than physicians participated in the questionnaire (nursing staff ranging from 86.4% to 99.2%), and overall response rates varied by department, with the highest response rates in the paediatric ward and the lowest response rates in the internal medicine department.

Table 4 summarizes the questionnaire results from the intervention UMCs across study seasons concerning the usage of the developed tools in their UMC. As the findings for the three 'intervention UMCs' and the two 'external intervention UMCs' were similar, the results for both sets of UMCs were combined. In the pandemic influenza season of 2009/2010, approximately 25% of HCWs attended an information meeting on influenza. One year later, approximately 10% of HCWs attended such an information meeting. In the pandemic season (2009/2010) the badges were handed out to around 32.9% of HCWs, while in the 2010/2011 season this number was almost halved (16.6%). In addition, a higher proportion of the handed-out badges was worn in the pandemic season than in the 2010/2011 influenza season. Of all the developed communication materials, HCWs reported the posters as the most noticeable.

Table 4 Quantitative evaluation: percentage of health care workers (HCWs) within intervention UMCS during study year 2009/2010 and 2010/2011 that used and appreciated the methods/ materials

Methods/materials	Intervention UMCs 2009/2010 n = 249 HCWs (%)	Intervention UMCs 2010/2011 n = 303 HCWs (%)
Visited the website	9.6	19.7
Attended information meeting	4.1	9.0
Badge was handed out	32.9	16.6
Wore the badge	20.5	14.3
Rated the badge as appealing	3.2	7.4
Rated the poster(s) as appealing	9.6	7.9[a]
Rated the folder as appealing	9.2	3.3[a]
Rated the video(s) as appealing	2.8	1.3

[a]$p < 0.05$.

DISCUSSION

In this study we have demonstrated how the IM method by Bartholomew et al.[14] can be applied to develop a structured immunization strategy to increase the influenza vaccine coverage of HCWs in acute care settings. According to the process evaluation we were able to implement such a strategy in participating hospitals. Compared with the Dutch study performed by Looijmans-van den Akker et al. in nursing homes, our IM-based intervention achieved an increased attendance rate of HCWs at information meetings of 24% in the 'pandemic' 2009/2010 influenza season, and 9% in the 'normal' 2010/2011 influenza season, when compared with the observed 7% participation rate in the nursing home study.[13] Our evaluation showed that posters were an efficient tool for use in acute care settings as these were most commonly noticed by the HCWs. However, it appeared to be impossible to achieve a 100% exposure of every HCW to all materials, which would be the best case scenario.

At the core of this implementation study was the systematic planning of the program and the selection of methods according to the IM method, in consultation with a communication expert. Using a number of discussion sessions the team agreed upon and developed different methods/materials to be directed at the different target groups. The inclusion of an assessment of the needs of each intervention UMC enhanced the program's applicability. The diversity of backgrounds of the research team members (ranging from physicians to hospital hygienists) was considered an advantage since this led to a wider perspective during the development of the different implementation tools.

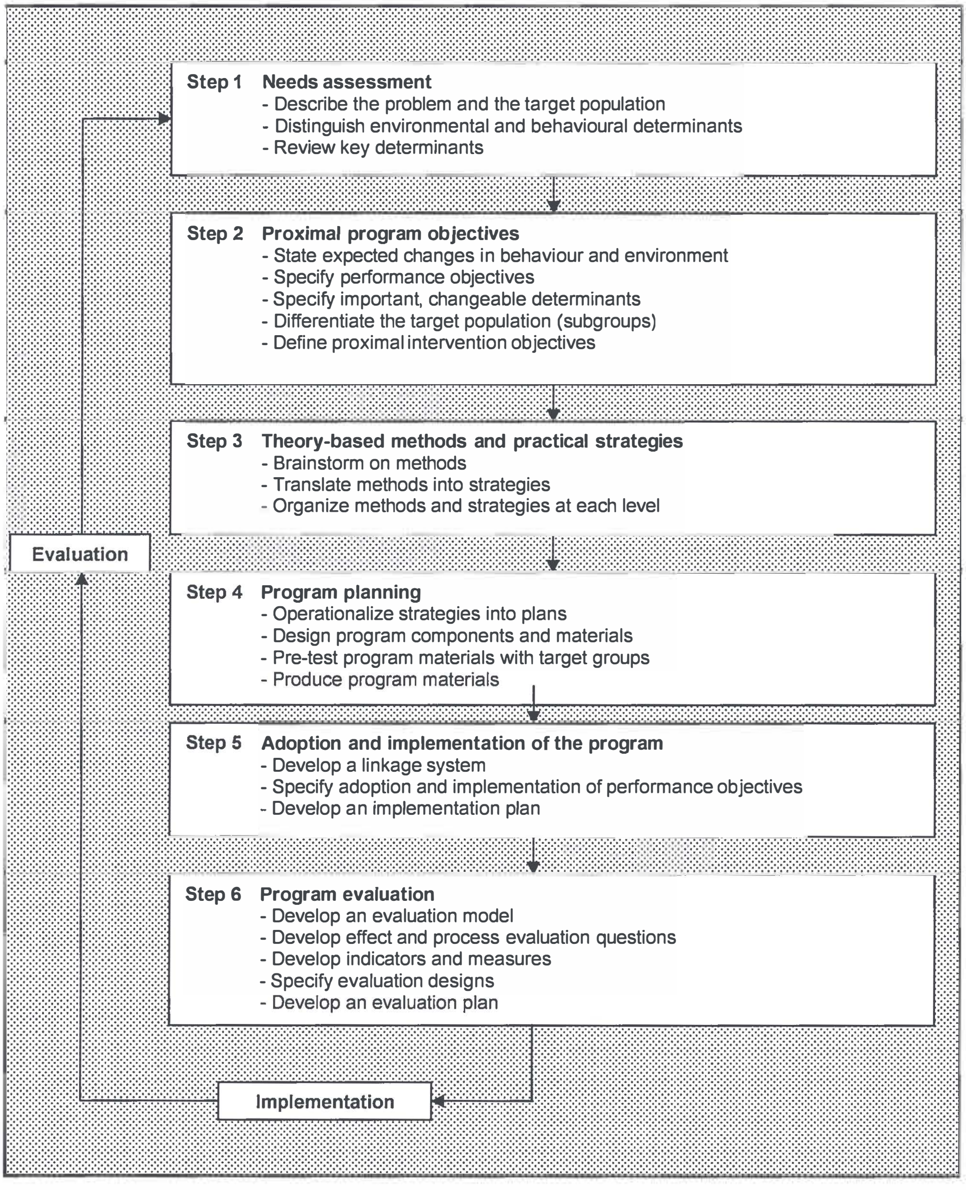
A possible limitation to the current study may be the observed discrepancy between the findings of the qualitative and quantitative evaluation. In the qualitative evaluation, most of the three 'intervention' and the two 'external intervention' UMCs reported that the majority of the nine behavioural determinants were taken into account, and that most of the proposed methods were implemented. However, the quantitative questionnaire results showed that the actual exposure of HCWs to these developed tools appeared suboptimal. This discrepancy may in part be due to the lower response rates to the web-based questionnaire, notably during the second study season. Although the response rate in the first season was rated 'quite high' for such evaluations and 'acceptable' during the second season, bias may have occurred such that respondents were more negative (or positive) regarding the program than the average HCW. Since we did not pursue a non-responder study, the direction of such potential bias remains undetermined. In the nursing home study by Looijmans et al,[13] a clear trend towards higher vaccine coverage of HCWs was observed when nursing homes implemented more components of the intervention program. Therefore, whilst it is clearly difficult to achieve full exposure to the different program elements, future programs should consider exposure to all intervention program elements as part of their aim of achieving optimal influenza vaccine coverage.[22]

Another possible limitation of this study was the widespread pandemic of new influenza A(H1N1) that occurred during the study period. Our evaluation showed that during an influenza pandemic methods/materials were used and rated differently when compared with the normal (seasonal) influenza period. For instance, more HCWs attended information meetings on influenza and vaccination in the pandemic season than during the normal season. It should also be noted that the influenza pandemic caused a lot of anxiety and media attention in the Netherlands and in the participating hospitals. In particular, it was predicted that many hospital admissions could be expected as well as understaffing of hospitals by HCWs' absenteeism. As a consequence, extra efforts were made towards vaccinating HCWs against new influenza A(H1N1). Although this external effect will have interfered with the purpose and conduct of the randomized intervention trial in the pandemic year, the increased attention was national and can be assumed to have been similar for both intervention and control UMCs. Therefore the conclusions from our study based on relative performance of the intervention and control UMCs should still be valid.

CONCLUSIONS

A structured implementation strategy for promoting influenza vaccination amongst HCWs was developed using the IM method and trialled over two influenza seasons in 5 UMCs. A process evaluation showed that the intervention could be successfully implemented in acute health care settings. Whilst the evaluation showed increased vaccination uptake by HCW staff of the participating UMCs, it also showed that it was impossible to expose all HCWs to all intervention methods (which would be the best case scenario). Further study is needed to (1) improve HCW exposure to intervention methods; (2) evaluate the effect of such interventions on vaccine uptake among HCWs; and (3) assess the impact on clinical outcomes among patients in hospitals where such interventions are enacted.

Figure 1 Intervention mapping method (adapted from Bartholomew et al).[14]



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CHAPTER 7

Hospital-based cluster randomised controlled trial to assess effects of a multi-faceted programme on influenza vaccine coverage among hospital health care workers and nosocomial influenza in the Netherlands, 2009 to 2011

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Josien Riphagen-Dalhuisen
Hans Burgerhof
Gerard Frijstein
Nannet van der Geest-Blankert
Marita Danhof-Pont
Herbert de Jager
Nita Bos
Ed Smeets
Marjan de Vries
Pieter Gallee
Eelko Hak

ABSTRACT

Nosocomial influenza is a large burden in hospitals. Despite recommendations from the World Health Organization to vaccinate health care workers against influenza, vaccine uptake remains low in most European countries. We performed a pragmatic cluster randomised controlled trial in order to assess the effects of implementing a multi-faceted influenza immunisation programme on vaccine coverage in hospital health care workers (HCWs) and on in-patient morbidity. We included hospital HCWs of three intervention and three control University Medical Centers (UMCs), and 3,367 patients. An implementation programme was offered to the intervention UMCs to assess the effects on both vaccine uptake among hospital staff and patient morbidity. In 2009/10, the coverage of seasonal, the first and second dose of pandemic influenza vaccine as well as seasonal vaccine in 2010/11 was higher in intervention UMCs than control UMCs (all $p<0.05$). At the internal medicine departments of the intervention group with higher vaccine coverage compared to the control group, nosocomial influenza and/or pneumonia was recorded in 3.9% and 9.7% of patients of intervention and control UMCs, respectively ($p=0.015$). Though potential bias could not be completely ruled out, an increase in vaccine coverage was associated with decreased patient in-hospital morbidity from influenza and/or pneumonia.

Trial registration number NCT01481467 (www.clinicaltrials.gov)

INTRODUCTION

The value of vaccinating health care workers (HCWs) against influenza has been subject of debate over decades. In the United States (US), despite respective immunisation recommendations since 1981, vaccine coverage among HCWs was only 63.5% in 2010/11.[1] In the United Kingdom (UK), the Netherlands and other European countries, coverage is even lower.[2,3] Several arguments support influenza vaccination of HCWs. First, each year, influenza causes substantial morbidity and mortality among vulnerable patients in hospitals and nursing homes.[4-6] Since contacts between patients, visitors and HCWs are frequent in such settings, and HCWs who are infected with mild symptoms often continue to work,[7] epidemics can easily develop and can be large.[8] Second, prophylaxis with neuraminidase inhibitors can be effective, but viral resistance may develop rendering these drugs less effective during influenza infections and such a strategy has not been routinely implemented in health care settings. Third, immunisation with the inactivated influenza vaccine has been shown in a large meta-analysis of randomised controlled trials among healthy adults representative of the HCWs population to be 59% effective in preventing laboratory-confirmed influenza infection.[9] Fourth, a mathematical model for a 30-bed hospital predicted that seven HCWs need to be vaccinated to prevent one influenza infection in a patient.[10] Finally, despite some methodological constraints, a meta-analysis of four large randomised controlled trials in long-term care institutions showed significant reductions in patients presenting influenza-like illness and patient mortality in settings with high vaccine coverage among HCWs versus control settings with low coverage.[11]

In the Netherlands, a high influenza vaccine uptake is reached among those belonging to risk groups for influenza. Each year, in October/November, general practitioners immunise patients aged 60 years or older and patients with risk-elevating diseases with stable high vaccination uptake rates above 71% across most parts of the Netherlands.[12] However, if younger than 60 years and admitted for the first time with a high-risk diagnosis, patients are mostly not immunised since they did not belong to a risk group before. Also they are infrequently vaccinated in the hospital since there is no vaccination programme for hospitalised patients in the Netherlands.

In contrast, in both the Netherlands and most other European countries, vaccine uptake among HCWs remains low and influenza vaccination programmes have been voluntary. To be effective in reaching high vaccine coverage against influenza, a large variety of behavioural and organisational factors has to be targeted[13] and a setting- and culture- specific quantitative need assessment is essential to focus the programme on the most influential factors.[14]

We applied the Intervention Mapping (IM) method[15] to structure the development of an influenza vaccination programme targeted at hospital staff. We here report the results of an evaluation of this programme. In the study, University Medical Centers (UMCs) from the Netherlands participated during the 2009/10 and 2010/11 influenza seasons. We primarily set out to determine the effects of the programme on vaccine coverage among HCWs using a pragmatic cluster randomised controlled trial. As clinical assessments from hospital settings are lacking, we also set out to determine the effects on patient outcomes during the studied influenza seasons.

METHODS

Design, setting and participants

We aimed to assess the clustered effects of a multi-faceted influenza vaccination programme on influenza vaccine coverage in HCWs as well as the effect on influenza morbidity in hospitalised patients in UMCs in the Netherlands. In our trial, a cluster is the unit of randomisation defined as one UMC. In this study, we consider HCWs to be all employees working in the hospital. The study period included the influenza seasons 2009/10 and 2010/11.

To reach the objectives we conducted a pragmatic cluster randomised trial because the developed influenza vaccine implementation programme was best applied at hospital level rather than at individual level. All eight UMCs (Erasmus Medical Center, Rotterdam; Academic Medical Center, Amsterdam; University Medical Center, Groningen; University Medical Center, Utrecht; University Medical Center, Maastricht; Free University Medical Center, Amsterdam; University Medical Center, Nijmegen; Leiden University Medical Center, Leiden) were invited to participate in the trial. After permission from the Dutch Federation of UMCs, the board of directors of six of the eight UMCs agreed to randomisation at cluster level. The board of directors of the two remaining UMCs refused to be randomised because their institutions had already undertaken considerable efforts to raise influenza vaccine coverage among staff, but they agreed to act as external controls. Unfortunately, the two UMCs did not give permission to collect patient data.

At baseline, policies for the randomised UMCs were either to offer influenza vaccination to selected health care workers or not to vaccinate at all, and the highest vaccine coverage in any UMC was estimated at just below 27%. The baseline vaccine coverage in the external UMCs was somewhat higher reaching levels as high as estimated at 37%, and there was more experience with immunistion campaigns.

UMCs are tertiary referral centers each taking care of special hospitalised patient populations in the eight geographical regions of the Netherlands where they are placed. Acute care is delivered for a large number of patients who are admitted for a wide variety of indications.

In May 2009, prior to the upcoming 2009/10 influenza season, six UMCs were randomly allocated by computer (using the procedure Random in SPSS version 18.0) into two clusters, either the intervention or the control group, by a researcher blinded to the identity of the UMCs. Since the UMCs were about similar in size, number of HCWs and annual number of hospitalisations, we did not match before randomisation. Since we conducted a pragmatic study, the outcome of randomisation was neither blinded for the research group nor for the lead contacts of the UMCs. Although most HCWs were aware that they were targeted for vaccination, they did not know to which arm their UMC was randomly allocated. The study period covered the period from the first influenza vaccination campaign in September/October 2009 to the end of the influenza season 2010/11. The protocol of the trial was waived by the medical ethical committee of the University Medical Center Groningen for ethical approval according to the Dutch Law of Research with Humans (No. 2009.267). The study was conducted in accordance with the Dutch Law for the Protection of Personal Data (Wet Bescherming Persoonsgegevens) and the Declaration of Helsinki.[16]

Intervention

In November and December 2008, prior to the trial start in 2009, we conducted a survey to assess which behavioural and organisational factors were associated with vaccine uptake among hospital staff of the UMCs.[17] An 11-item prediction model with nine behavioural and two demographic predictors could be developed that was highly accurate in discriminating vaccinated from non-vaccinated staff in approximately 95% of the study population. Subsequently, we used the Intervention Mapping (IM) method to thoroughly plan, develop and evaluate a programme that was directed at HCWs in order to influence their behaviour towards immunisation.[15,18] This IM method is a theoretical framework to systematically develop health education interventions and can be used as part of the dynamic process of planning intervention strategies in health education. It contains six consecutive steps: (i) a needs assessment, (ii) creating a matrix of proximal programme objectives, (iii) selecting theory-based intervention methods and practical strategies, (iv) programme planning, (v) adopting and implementing the programme, and (vi) monitoring and programme evaluation.

Various educational tools were developed following the proximal objectives based on the needs assessment (Box). Prior to the immunisation campaign in September 2009 and 2010, the programme educational tools were offered to the lead contact persons from the departments of occupational health of each UMC in the intervention and external group. These departments, in close collaboration with the communication units, are responsible for the influenza vaccination campaign. Information on the methods was provided to them by communication experts within the research group and they were encouraged to communicate the methods at various levels including the board of directors, heads of departments and staff members. The intervention and external group were allowed to make their own choices and decisions regarding the implementation of programme elements. An evaluation of the process showed that intervention and external UMCs targeted most of the behavioural determinants and choose to implement a variety of the developed methods, whereas the control UMCs targeted less determinants (Figure).[18] However, actual exposure of HCWs to these methods was variable and in 2009 largely affected by the pandemic preparedness plans. Lead contacts from the control group did not receive the developed methods and were encouraged to follow their usual influenza vaccination policy. We did not seek to influence vaccine coverage among patients.

Box Behavioural determinants associated with vaccine uptake and developed health education methods to increase influenza vaccine uptake, the Netherlands, 2009

Behavioural determinants	Developed health education methods
Awareness of personal risk for influenza infection	- Provision of information on influenza, transmission and risks through an information stand at the UMC restaurants, a website, a folder and plenary meetings - Polls and a quiz on the intranet - Video testimonials with role models
Awareness of risk of infecting patients	- Provision of information on influenza and the risk of transmission to patients through an information stand at the UMC restaurants, a website, a folder and plenary meetings - Polls and a quiz on the intranet - Video testimonials with role models
Belief that vaccination reduces the risk of infecting patients	- Provision of information on influenza and the effectiveness of vaccination through an information stand at the UMC restaurants, a website, a folder and plenary meetings - Polls and a quiz on the intranet - Video testimonials with role models
Usefulness of vaccination despite the constant flow of visitors	- Provision of information on influenza and the effectiveness of vaccination through an information stand at the UMC restaurants, a website, a folder and plenary meetings - Polls and a quiz on the intranet - Video testimonials with role models
Knowledge on the contents of the Health Council's Advice	- Provide and explain contents of the advice on the intranet or website - Explain and discuss in a plenary meeting
Vaccination of HCWs to ensure continuity of care	- Explain and discuss ethical aspects (plenary meeting, website) - Video testimonials with role models - Involve board of directors (e.g. first vaccination, be present at vaccination, column) - Distribute pins to vaccinated HCWs saying 'deliberately vaccinated for you' to start the discussion
Vaccination of HCWs because of their duty to do no harm	- Explain and discuss ethical aspects (plenary meeting, website) - Video testimonials with role models - Involve board of directors (e.g. first vaccination, be present at vaccination, column) - Distribute pins to vaccinated HCWs saying 'deliberately vaccinated for you' to start the discussion
Belief that people around me think it is important for me to get vaccinated	- Personal invitation letter with information folder and a link to the website at the home address
Willingness to get vaccinated if the vaccine was available at a convenient time	- Poster with practical information on location and time - Personal invitation at home address with location and time - Extended vaccination hours which take changing shifts into account

HCW, health care worker; UMC, University Medical Center.

Outcomes

The primary outcome measure of this trial was the influenza vaccine uptake among all HCWs at UMC level. Vaccine uptake was expressed as percentage calculated through dividing the number of all vaccinated HCWs by the total number of HCWs multiplied by 100. For financial administrative reasons all immunisations are accurately recorded at the hospital level, hence this information was regarded most valid.

Secondary outcome measures were absenteeism rates among HCWs during December of each study year as this is normally the month in which influenza circulates at epidemic levels.[19] The cumulative absenteeism rates for the month December were provided by each department of occupational health of all UMCs after the influenza seasons. Vaccine uptake and absenteeism among HCWs were both analysed at cluster level.

As further secondary outcome, patient outcome data from two selected high risk departments i.e. paediatrics and internal medicine, were collected retrospectively for all patients hospitalised three days or more, to ensure nosocomial exposure during both study seasons. In the 2009/10 influenza season, a lower number of patients could be included after vaccination of HCWs, since the campaign had begun late in the epidemic, whereas we could observe a high number of patients during the complete season of 2010/11. The outcomes collected were laboratory-confirmed influenza and/or pneumonia, length of hospital stay in days, admittance to intensive care and duration. They were compiled by scrutinising computerised discharge letters from the patients' medical files and information from the microbiology laboratories by two reviewers. Influenza was defined as laboratory-confirmed influenza A (all subtypes) or influenza B during hospital stay. Pneumonia was defined as any pneumonia which was clinically diagnosed during hospital stay. Since vaccination coverage was different between departments, patient data were analysed at department level. Since pneumonia is a common complication following influenza, influenza remains often undiagnosed and the combined outcome is regarded most accurate and specific. In accordance with previous studies among seniors we combined this outcome.[11]

We were able to obtain patient outcome data on a large number of patients in two departments during the influenza seasons.

Sample size

We aimed to include all HCWs from the eight UMCs prior to conducting the study. Sample size calculations for cluster randomised studies were applied. Based on the high vaccine uptake among patients (around 70%) we expected that we could raise the vaccine coverage of staff in the intervention group from 37%, the highest vaccination rate in all UMCs as estimated by questionnaire[17] to at least 70% and that the control group would remain at 37% coverage. We assumed that all eight UMCs would participate. A minimum of 32 participants per UMC (128 per cluster) were needed to provide more than 80% power if the intra-class correlation (ICC) was estimated at 10% and significance level was set at 5%. Given the much higher numbers of HCWs per UMC, smaller effects could be detected with adequate power.

Statistical methods

Data were analysed using SPSS for Windows, version 18.0 and SAS statistical package 9.1. All outcomes were analysed at cluster level. In addition, patient outcomes were analysed at departmental level. For the primary outcome influenza vaccine coverage and absenteeism rates, we calculated risk differences (RD) and relative risks (RR) with their corresponding 95% confidence intervals (95% CI) and the levels of statistical significance in the different clusters for both influenza seasons combined. This was done by a specifically designed bootstrap program in R statistical software[20] to account for clustering. To account for dependencies of individual observations within hospitals and possible heterogeneity between hospitals we addressed our research questions within the generalised linear mixed model framework. To estimate RR, the binomial distribution was used employing the logarithmic function as link between the mean of the response and the linear part of the model using SAS statistical package. RD were obtained using the identity link function and the normal distribution. We calculated RR and corresponding 95% CI as well as levels of statistical significance for the patient outcomes pooled over both years after adjustments for small baseline differences of sex (see results). We chose to pool the data to obtain a more precise estimate of the effect because both seasons were dominated by influenza A(H1N1)pdm09 and vaccines matched the circulating strain in both seasons. Adjusted differences in duration of hospitalisation and intensive care admission between clusters were compared after transformation of extreme values to a clinically relevant maximum (30 days for hospital and seven days for intensive care stay). Results were similar as for the non-transformed values.

RESULTS

Baseline characteristics

At the beginning of the measurements in 2009, the baseline characteristics at the level of the whole UMC were determined per group (Table 1). On average, the intervention UMCs were somewhat larger than control and external UMCs with more staff full time equivalents and a higher number of clinical admissions each year. However, the mean HCW/patient ratio was comparable for all three groups. The age and sex distribution of staff as estimated from a web-based survey in 2009 was similar as well (response rate 30.1%) (data not presented). The pooled baseline characteristics of patients from the selected departments of the intervention and control groups showed similar mean age and percentage of men in the intervention and control group (Table 2). The percentage of patients from the internal medicine department and study year 2010/11 was also similar between both groups.

Table 1 Baseline characteristics of University Medical Centers, randomised controlled trial in the Netherlands, 2009 (n=8)

	Intervention UMCs (n=3)	Control UMCs (n=3)	External UMCs (n=2)
Mean number of HCWs' full time equivalents	8,065	5,765	6,584
Mean number of clinical admissions	34,395	28,841	25,999
Mean HCW/patient ratio	0.23	0.20	0.25
Mean percentage of HCWs older than 40 years[a]	37.8 (SD 48.6)	42.6 (SD 49.6)	42.1 (SD 49.6%)
Mean percentage of female HCWs[a]	86.7 (SD 34.0)	75.6 (SD 43.0)	88.9 (SD 31.6)

HCW, health care worker; UMC, University Medical Center.
[a] Data derived from web-based questionnaire in 2009.

Table 2 Baseline characteristics of patients in eight University Medical Centers by intervention/ control and department, randomised controlled trial in the Netherlands, 2009–2011 (n=3,367)

Baseline characteristics	**Intervention UMCs n=1,387**	Intervention UMCs Department of Internal Medicine n=769/1,804	Intervention UMCs Department of Paediatrics n=618/1563	**Control UMCs n=1,980**	Control UMCs Department of Internal Medicine n=1,035/1,804	Control UMCs Department of Paediatrics n=945/1,563
Mean age (years)	35.3 (range 0-101, SD 31.0)	59.8 (range 18-101, SD 18.8)	4.7 (range 0-19, SD 5.5)	34.1 (range 0-104, SD 30.4)	60.0 (range 17-104, SD 18.3)	5.8 (range 0-23, SD 5.6)
Male (%)	54.2 752/1,387	51.2 394/769	57.9 358/618	51.1 1,012/1,980	50.6 524/1,035	51.6 488/945

SD, standard deviation; UMC, University Medical Center.
None of the outcomes were statistically significant.

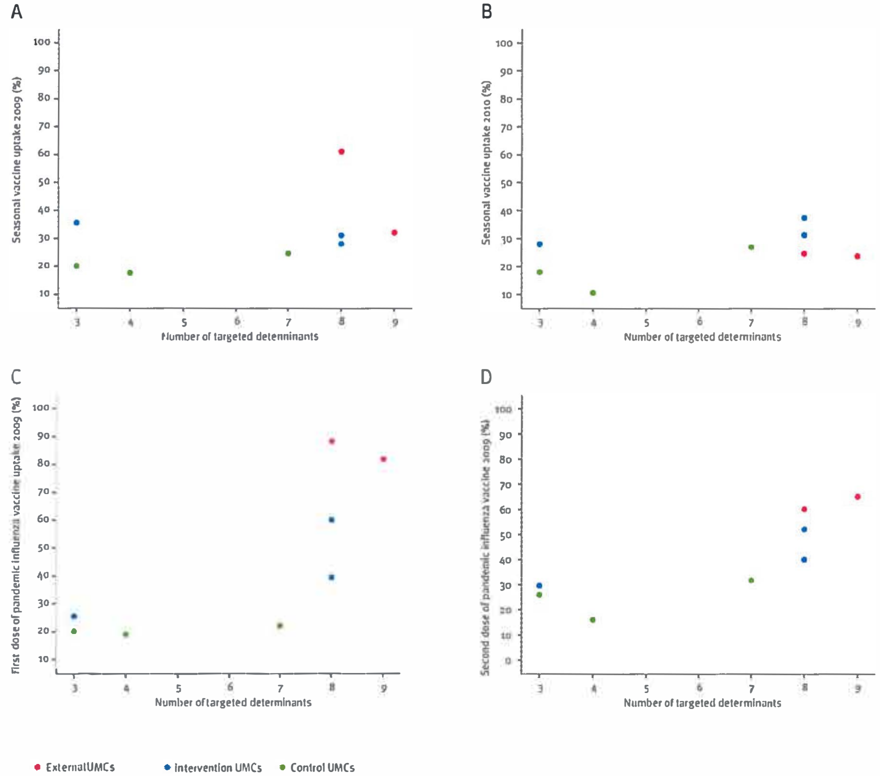
Influenza vaccine uptake

In both study seasons, influenza vaccine coverage among HCWs was significantly higher in the intervention group compared with the control group (Table 2). In 2009 three influenza vaccination rounds were offered because of the emergence of the influenza A(H1N1)pdm09 pandemic virus. In all three groups coverage was highest for the first dose of the pandemic vaccine. In the intervention group the absolute difference in vaccine coverage compared with the control group, for the first dose of the pandemic vaccine was 23.7% (95% CI 4.3% to 47.8%, p<0.05). For the second pandemic vaccine dose, coverage was lower in all groups than for the first one, but still 21.4% higher in the intervention than in the control group (95% CI: 3.6% to 40.3%; p<0.05). The external UMCs, which were already more active in their vaccination campaign prior to the study than the randomised UMCs, reached even higher influenza vaccine uptake rates compared to the control UMCs in all vaccination rounds with an outstanding 44.0% absolute higher uptake of the first pandemic vaccine dose from 38.0% to 82.0% (95% CI: 30.0% to 53.7%; p<0.05). In 2010/11, when the pandemic threat was no longer an issue, coverage of the seasonal influenza vaccine was much lower than the pandemic vaccine coverage in the year before for each group. The absolute RD was the intervention and external group, respectively, compared with the control group (both p-levels <0.05).

To obtain more insights into exposure to different programme methods and the vaccine uptake, we related the number of targeted determinants to vaccine uptake

(Figure). There was a clear trend towards increased vaccine coverage if more methods were applied. There was a significant correlation between the number of applied methods and vaccine coverage for both pandemic vaccines (first pandemic vaccine dose Spearman r=0.79, P=0.021; second pandemic vaccine dose Spearman r=0.90, P=0.003). Correlation estimates were not significant for the seasonal vaccines (2009/10: Spearman r=0.41, P=0.317; 2010/11: Spearman r=0.27, P=0.51).

Figure Number of targeted behavioural determinants in the influenza vaccination programme and vaccine uptake in healthcare workers in University Medical Centers by vaccine, randomised controlled trial in the Netherlands, 2009-2011



UMC: University Medical Center.

Absenteeism

Work absenteeism rates among HCWs were recorded for December 2009 and December 2010 (Table 3). For both seasons, absenteeism rates were 0.7% to 1.2% higher (absolute RD) on average in both the intervention and external cluster compared with the control group (all $p<0.05$ except for comparison between external and control UMCs in 2010 where $p>0.05$).

Table 3 Influenza vaccine uptake rates and work absenteeism rates for the month of December among health care workers in eight University Medical Centers, randomised controlled trial in the Netherlands, 2009–2011

	Intervention UMCs	Control UMCs	External UMCs	RD Intervention vs Control	(95% Confidence interval)	RD External vs Control	(95% Confidence interval)
Year 2009							
Seasonal influenza vaccine uptake	32.3% (9,022/27,900)	20.4% (4,572/22,451)	48.7% (8,231/16,893)	11.9%[a]	(7.5 – 15.5)	28.3%[a]	(8.6 – 42.3)
Pandemic influenza vaccine uptake (first dose)	61.7% (17,212/27,900)	38.0% (8,541/22,451)	82.0% (13,852/16,893)	23.7%[a]	(4.3 – 47.8)	44.0%[a]	(30.0 – 53.7)
Pandemic influenza vaccine uptake (second dose)	45.8% (12,772/27,900)	24.4% (5,480/22,451)	56.7% (9,582/16,893)	21.4%[a]	(3.6 – 40.3)	32.3%[a]	(23.4 – 40.5)
Work absenteeism (December 2009)	4.6% (1,297/27,900)	3.4% (579/17,229)[a]	4.1% (701/16,893)	1.2%[a]	(0.9 – 1.7)	0.7%[a]	(0.2 – 1.3)
Year 2010							
Seasonal influenza vaccine uptake	28.6% (8,176/28,621)	17.8% (4,345/24,459)	27.2% (4,555/16,717)	10.8%[a]	(2.0 – 19.9)	9.4%[a]	(1.0 – 17.2)
Work absenteeism (December 2010)	4.6% (1,318/28,621)	3.9% (745/19,267)[b]	4.6% (765/16,717)	0.7%[a]	(0.1 – 1.3)	0.7%	(-0.2 to 1.4)

RD, risk difference; UMC, University Medical Center.
[a] These results are statistically significant.
[b] For this variable no data could be obtained from one control UMC.

Patient outcomes

Self-reported vaccine coverage in 2009/10 and 2010/11 influenza seasons among HCWs differed between the two studied departments. In 2009/10 coverage of a pandemic vaccine in the internal medicine and pediatric departments of intervention UMCs was 100% and 50%, and 92% and 81% in control UMCs, respectively. In 2010/11, corresponding vaccine coverage were 57% and 50%, and 51% and 44%, respectively. Over the two study years, the probability of being tested for the presence of influenza virus during the influenza epidemics was nearly twice as high in the intervention cluster compared with the control group, though not statistically significant

(Table 4). Despite higher diagnostic testing rates, a diagnosis of influenza and/or pneumonia during hospitalisation was made in half as many cases in the internal medicine department of intervention UMCs compared with the control UMCs (RR=0.5; 95% CI: 0.3-0.9; p=0.015). Nosocomial pneumonia was reduced by a relative reduction of 76% (p=0.028). Other characteristics did not significantly differ between groups and no statistically significant differences were observed in the paediatric departments.

Table 4 Pooled analysis of patient outcomes by department for intervention and control of eight University Medical Centers, randomised controlled trial in the Netherlands, 2009-2011 (n=3,367)

	Intervention UMCs Department of Internal Medicine n=769/1,804	Intervention UMCs Department of Paediatrics n=618/1,563	Control UMCs Department of Internal Medicine n=1,035/1,804	Control UMCs Department of Paediatrics n=945/1,563	RR (95% Confidence interval) p value Department of Internal Medicine	RR (95% Confidence interval) p value Department of Paediatrics
Outcomes						
Tested for influenza during hospitalisation	17.6% 121/688[a]	10.4% 46/441[a]	7.2% 75/1,035	7.6% 72/945	2.1 (0.5 – 8.4) p=0.29	2.0 (0.7 – 6.1) p=0.22
Influenza and/or pneumonia during hospitalisation	3.9% 30/769	3.6% 22/618	9.7% 100/1,035	1.9% 18/945	0.47 (0.3 – 0.9) p=0.015	2.1 (0.7 – 6.7) p=0.19
Pneumonia during hospitalisation	1.4% 11/769	1.3% 8/618	8.5% 88/1,035	1.1% 10/945	0.24 (0.1 – 0.9) P= 0.03	1.5 (0.3 – 7.3) p=0.65
Use of intensive care during hospitalisation	5.5% 42/769	8.3% 51/618	7.4% 77/1,035	8.5% 80/945	0.7 (0.4 – 1.3) p=0.29	0.6 (0.1 – 3.5) p=0.56
Mean duration of hospitalisation (in days, risk difference is given)[b]	10.2 (SD 8.1)	8.7 (SD 7.6)	10.7 (SD 8.4)	8.1 (SD 7.1)	0.96 (-11.82 to 13.73) p=0.85	0.60 (-3.32 to 4.52) p=0.69
Mean duration of intensive care use (in days, risk difference is given)[c]	3.5 (SD 2.3) n=42	3.2 (SD 2.0) n=51	4.4 (SD 2.5) n=77	4.3 (SD 2.3) n=80	-0.91 (-1.83 to 0.009) p=0.12	-1.14 (-1.92 to -0.36) p=0.06

RR, relative risk; SD, standard deviation; UMC, University Medical Center.
[a] For this variable no data could be obtained from one intervention UMC.
[b] Until 30 days.
[c] Until 7 days.

DISCUSSION

In a 2008 publication, Nicoll et al. stated that there is strong evidence for immunising HCWs against influenza that take care of the elderly and the chronically ill in long-term care facilities. However, they did not find strong data on whether or not to vaccinate HCWs in other health care settings, such as hospitals.[21]

Our study is the first hospital-based trial that showed that adopting a multi-faceted influenza vaccination programme was associated with improved vaccine coverage among HCWs. We also observed a lower risk for nosocomial influenza and/or pneumonia in hospitalised patients at the internal medicine departments during two consecutive influenza seasons, but we did not observe this effect in the studied paediatric departments.

It is surprising that only a small self-reported higher vaccine uptake in the departments of internal medicine led to our observation of a 50% reduction of the RR in patient outcomes. There may be several explanations for this finding. Actual vaccine coverage differences might have been higher than our self-reported estimates given that we observed an absolute higher difference of 23.7% (from 38.0% to 61.7%) and 11.9% (from 20.4% to 32.3%) respectively at group level in both seasons. Other explanations might be that not only vaccine uptake was higher in the intervention UMCs but that the programme led to more hygienic measures such as earlier diagnosis of influenza and isolation or better compliance with hand hygiene. This agrees with the fact that the number of influenza tests was twice higher in the intervention clusters than in the control clusters. Alternatively, baseline risks of patient outcomes might by chance have been different between the departments. For example, we did not have pre-intervention patient outcome prevalences of nosocomial influenza for both clusters. Potential of confounding bias cannot be completely ruled out, but is unlikely given similar age and sex distributions between the two groups.

Further, vaccine uptake was measured at the level of the UMCs and could not be obtained from all individual departments because of the centralisation of the immunisation in most UMCs. Of note, at baseline prior to the trial start, vaccine coverage might have been higher in departments of intervention UMCs than in control UMCs. Self-reported data from HCWs showed, however, that the seasonal influenza vaccine coverage in 2008/09 was 44% and 14% among HCWs of the internal medicine and paediatric departments in intervention UMCs and 54% and 58% in control UMCs, respectively, hence baseline differences cannot explain the improved coverage. The uptake at UMC level most probably accurately reflects the coverage in most but not all departments as observed for the departments of paediatrics and internal medicine. The self-reported coverage was almost twice higher than the overall UMC level data because of the high-risk residents of these departments and longer tradition of taking hygienic preventive measures against infectious diseases in internal medicine and paediatric departments, as compared with most other departments.

The lead contacts and researchers were not blinded for the allocated strategy; hence this may have caused information bias. However, since the numbers of administered vaccines is a marker of quality of care in the UMCs and administration has financial consequences, it is highly unlikely that such bias has occurred.

A major strength of the study includes the randomised design which resulted in largely comparable HCWs and patient populations over the study years. Also, the presence of a control group accounted for natural fluctuation in vaccine coverage as well as external factors at a national level, and the presence of an external group confirming the positive correlation between a targeted campaign and influenza vaccine uptake among HCWs was a major strength. Moreover, the size of the trial HCWs population and patient population was more than adequate to obtain highly precise estimates of the main effects. Finally, in day-to-day practice swabbing is not routinely done and can therefore not have affected differentially the intervention and control UMCs.

The work absenteeism rate was 1.2 HCWs per 100 HCWs higher in the whole month of December 2009 in the intervention than in control clusters. Since testing for influenza appeared to be more frequent in intervention than control UMCs, if anything, it is likely a marker of stricter working rules applied during influenza seasons in the intervention compared with control UMCs. Obviously, routine swabbing of all patients suspected of influenza would have been the ideal study outcome. Because the pandemic threat was over in 2010,[22] the absolute risk difference for the trial population was down to 0.7 per 100 HCWs during the latter study season. One participating UMC from the control group could not reliably obtain absenteeism data at their UMC level. However, department specific data that could be obtained showed similar rates as within similar departments of the other control UMCs.

The participating hospitals were tertiary centers and the observed effects may not necessarily be applicable to all types of hospitals. In a survey among administrators of all hospitals in the Netherlands in 2010 with a response rate of over 53%, we observed that the average vaccine coverage of staff reported by the administrators was comparable with the coverage in control UMCs (17.7% versus 17.8% in our study).[23] Interestingly, in that survey we observed a clear association between economic spending on the immunisation programme in these hospitals and vaccine coverage, with higher programme spending (>1,250 Euro versus ≤1,250 Euro) leading to 9% improved coverage (24% versus 15%; 95% CI for the difference: 0.7% to 17%). We also observed in our trial that the higher the number of determinants targeted, the higher vaccine uptake in both study seasons (Figure). Although evidence is scarce, the introduction of a thoroughly developed programme likely leads to improved coverage in any type of hospital.

In 2009, the influenza A(H1N1)pdm09 pandemic also affected the Netherlands, starting in early October and ending in December 2009. Following the advice from the World Health Organization and the Dutch Health Council, the Ministry of Health decided that risk patient groups should be prioritized for pandemic vaccination against this new influenza variant. HCWs were considered both as an important potential transmitter of influenza to risk patients and essential in the care of patients during a pandemic and were considered a target group for pandemic vaccination. As in most other countries, the pandemic was associated with enormous media attention and fear in the community. Therefore, in summer of 2009, all UMCs installed their pandemic response team and prepared for a worst case scenario.[24] The installed preventive measures were very costly, reaching hundred thousands of Euros per UMC, and led to pressure on both management and HCWs. It was therefore unexpected to see that despite general circumstances, both the intervention and external cluster reached higher vaccine coverage than the controls.

After the pandemic was declared over and it appeared to be much less severe than had initially been feared,[24] we hypothesized that many HCWs were displeased about the pressure on them and the measures taken. In 2010/11, therefore, seasonal vaccine coverage was half the coverage of the first dose of pandemic vaccine, and despite higher coverage in the intervention than the control cluster, it remained below a staggering low of 30%.

In conclusion, our results suggest that a multi-faceted influenza vaccination programme for hospital HCWs is effective in raising vaccine uptake among HCWs. Although bias cannot be completely ruled out, an increase in vaccine coverage was associated with a decrease in influenza and/or pneumonia among patients during hospitalisation. Given the current evidence for annual risks of influenza complications in hospital and benefits of vaccination, and the low voluntary coverage, mandatory programmes should be seriously considered.

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CHAPTER 8

Cost-effectiveness of a multi-faceted program to increase influenza vaccine coverage among health care workers alongside a hospital-based cluster randomized controlled trial.

Submitted

Josien Riphagen-Dalhuisen
Marjan Meijboom
Eelko Hak

ABSTRACT

Objective To determine the cost-effectiveness of implementing a hospital-based multi-faceted influenza immunization program among health care workers (HCWs) in the Netherlands.

Design Cost-effectiveness analysis from a societal perspective alongside a cluster randomized controlled trial.

Setting University Medical Centers (UMC) in the Netherlands during the influenza seasons of 2009/2010 and 2010/2011.

Participants Hospital staff of three intervention (n=27,900 in 2009), three control (n=22,451) and two external non-randomized intervention UMCs (n=16,893), and 3,367 patients admitted to the departments of pediatrics and internal medicine during both influenza epidemics.

Intervention Vaccination implementation program offered to staff of intervention and external UMCs, but not to control UMCs.

Outcome measures Primary clinical outcome measures were influenza vaccine coverage among health care workers (HCWs), work absenteeism and patient morbidity. Primary economical outcome measure was the cost-benefit of the program.

Results In both seasons, the vaccine coverage among HCWs improved in the intervention compared with the control cluster with risk differences ranging from 11.9 per 100 HCWs for the seasonal vaccine in 2010 to 23.7 per 100 HCWs for the first pandemic vaccine in 2009 (all $p<0.05$). When comparing patients from intervention with control UMCs, influenza and/or pneumonia was reduced by 2.7 per 100 patients ($p<0.05$) across both departments (i.e. pediatrics and internal medicine). In a base-case scenario with no vaccine coverage, annual costs of influenza were estimated at €389,264 for an average UMC of 8,000 HCWs and 6,000 patients hospitalized during an epidemic. If the vaccine coverage was increased to 23.7% as observed for the intervention cluster, the program's savings were estimated at €2,993.

Conclusions Adoption of the program improved the influenza vaccine coverage among hospital staff and was associated with decreased patient morbidity from influenza and/or pneumonia. The hospital immunization program resulted in cost-savings and more efforts to increase vaccination coverage among HCWs should be considered.

Trial registration number NCT01481467

INTRODUCTION

Despite the available clinical evidence, influenza vaccination coverage among health care workers remains very low. It has been widely recognized that immunizing health care workers against influenza has a direct and an indirect medical effect.[1-6] It decreases influenza infection among healthy adults, reduces the probability of viral transmission in health care settings, and indirectly benefits vulnerable patients by reducing the probability of becoming infected. In the United States in 2010/2011, only 63.5% of staff accepted the vaccine.[7] In Europe, health care workers are even more noncompliant with reported vaccine coverage's lower than 30%.[8,9]

Despite methodological shortcomings, in four trials conducted in long-term care settings,[1-4] a decrease in patient morbidity or mortality was observed after vaccine coverage was increased. For acute care settings where patients are being treated during epidemics such data are still not available. And, while influenza immunization is safe and relatively cheap, evidence on the economic benefits is virtually absent[10], but crucial for hospital managers and policy makers to support such a program.

The Intervention Mapping method has been used to structure the development of an influenza vaccination program targeted at hospital staff. University medical centers from the Netherlands participated during the 2009/2010 and 2010/2011 influenza season in a cluster-randomized controlled trial. This paper reports the economic results of this program for an average hospital with 8.000 staff members and 6.000 patients hospitalized during an epidemic from a societal perspective.

METHODS

Trial design, setting and participants

The trial study design has been reported earlier.[11] In brief, the aim was to assess the clustered effects and cost-effectiveness of a multi-faceted influenza vaccination program in University Medical Centers (UMCs) in the Netherlands. The study period included two influenza seasons (2009/2010 and 2010/2011). A cluster randomized trial was conducted because the developed influenza vaccine implementation program was best applied at the level of the hospital rather than individuals. The board of directors of six of eight UMCs agreed on randomization at the cluster level. Two UMCs refused to be randomized because of the effort already put into the vaccination program. UMCs are regarded tertiary referral centers each taking care of specialized patient populations in approximately one-eighth of the Netherlands, but acute care is delivered for large numbers of patients who are admitted for a wide variety of indications. General practitioners immunize patients 60 years or older and patients with risk-elevating diseases in October/November of each year with stable high vaccination uptake rates above 71% across most parts of the Netherlands.[9,12] However, if younger than 60 and admitted for the first time with a high-risk diagnosis, patients are either not immunized or they infrequently receive their vaccine in the hospital.

Intervention

The Intervention Mapping (IM) method was used to thoroughly plan, develop and evaluate an intervention program that was directed at HCWs in order to influence their behaviour towards immunization.[13] The method contains six consecutive steps: a needs assessment, creating a matrix of proximal program objectives, selecting theory-based intervention methods and practical strategies, planning the program, adopting and implementing the program, and monitoring and program evaluation. Prior to the immunization campaign in the month September 2009 and 2010, the developed educational tools were offered to the lead contact persons from the departments of occupational health of each UMC in the intervention and external group. These departments are, together with the communication units responsible for the influenza vaccination campaign. Lead contacts from the control group did not receive the developed methods and were encouraged to follow their usual influenza vaccination policy. No attempts were made to increase vaccine coverage among patients.

Clinical Outcomes

The primary outcome measure of this trial was the influenza vaccine uptake among all HCWs at UMC level. Vaccine uptake was measured by means of actual count data of all vaccinated persons and divided by the total HCW population as provided by the lead contacts of the departments of occupational health of each UMC. Secondary outcome measures were absenteeism rates among HCWs during the month December of each study year as this was the month in which influenza circulated at epidemic levels.[14] Further, as secondary outcome patient outcome data from two selected high risk department (i.e. Pediatrics and Internal Medicine) were collected retrospectively for all patients who were hospitalized three days or more to ensure nosocomial exposure during both study epidemic seasons. The outcomes were laboratory-confirmed influenza and/or pneumonia, length of hospital stay, use and duration of intensive care and were collected by scrutinizing computerized discharge letters and laboratory outcome data from the microbiology laboratories by two reviewers. Influenza was defined as laboratory-confirmed influenza A (all subtypes) or influenza B during hospital stay. Pneumonia was defined as any pneumonia which was clinically diagnosed during hospital stay.

Cost estimates

The cost estimates associated with the immunization program were based on Dutch guidelines for cost-effectiveness research.[15] The cost prices were indexed to the 2011 level use price-index figures per year. For example, if the cost price in 2009 for hospitalization in an academic hospital was estimated at € 575, the used cost price for 2011 was calculated as €575+ (€ 575*0.013) = € 582.48 (year 2010); € 582.45+(€ 582.45*0.023) = € 595.87 (year 2011).

Direct medical costs, direct non-medical costs and indirect non-medical costs related to the study objective have been taken into account. For an overview of the model parameters used, see Table 1.

Table 1 Model parameters

Parameter	Value	Reference	Remarks
Employees (number)	8,000	Riphagen 2013[11]	Average of UMCs
Patients (total number of patients per UMC)	6,000	Riphagen 2013[11]	Average of UMCs during influenza season (2 months)
Patients (number of patients in hospital who are exposed to the same risk as patients in the departments where the clinical trial was performed)	600	Assumption	Average of UMCs
Vaccination coverage old (%)	0%		Base case
Vaccination coverage new (%)	23.7%	Riphagen 2013[11]	Trial data
Work absence due to ILI (%)	4.6%		Work absence registration control UMCs
GP visit following ILI	24%	Postma 2005[16]	
Use of OTC with ILI	80%	Postma 2005[16]	
GP visit due to side effects of vaccination (%)	1%	Assumption & Postma 2005[16]	Proportion of persons vaccinated and experiencing side effects following vaccination
Antibiotic use following GP visit (%)	20%	Postma 2005[16]	
Decrease of productivity because of ILI (in days)	4	Palmer 2010[17]; Saxen 1999[19]; Wilde 1999[21]	
Vaccine effectiveness in reducing ILI	20%	Jefferson 2010[6]	
Probability of attracting influenza/ pneumonia in hospital	11.74%	Riphagen 2013[11]	In case of 0% vaccination coverage of HCWs; proportion tested positive in hospitals
Cost			
GP visit	€ 29.01	CVZ 2010[15]; Riphagen 2013[11]	
Treatment hospital acquired influenza/ Pneumonia	€1,013.00	Rozenbaum 2010[22]; CVZ 2010[15]	Based on longer hospital stay of 1.7 day (Rozenbaum) Cost per day in academic hospital is € 596 euro in 2011 (CVZ). Total cost per treatment of hospital aquired pneumonia is therefore 1.7*596 euro
OTC medicine	€6.62	Postma 2005[16]	
Productivity loss per day	€212.81	CVZ 2010[15]; Riphagen 2013[11]	Average number of working hours per day is 7.2 (36 contracthours per week/5=7.2). Weighted average productivity costs are calculated using age and sex distribution of trial data and productivity costs from guidelines healtheconomic research (CVZ) and corrected for inflation. Costs per hour are 29.56 euro
Antibiotics	€7.18	Postma 2005[16]	
Vaccination related costs	€15.00	Assumption	Costs for vaccine, administration, vaccination campagne

UMCs, University Medical Centers; ILI, influenza like illness; GP, general practitioner; OTC, over the counter.

Costs associated with the immunization program

The cost estimates of the influenza vaccination program were estimated at €15.00 per staff member and include the costs for the vaccine, the communication and implementation of the program.[10] In the study by Hak et al., the potential cost-savings were determined using plausible, but theoretical, effects in a UMC setting using the data from the University Medical Center Groningen. For the administration, a nurse gross salary (scale 9) per month was assumed with 5 minutes for vaccination of one staff member and another 5 minutes for correction of inefficiency (waiting time). The assumed costs currently assume a linear relationship between the number of persons vaccinated and the total cost for the vaccination campaign. Indirect costs due to productivity loss for administration of the vaccine were assumed to be virtually absent because of the elasticity in working hours. The vaccine efficacy for preventing ILI was assumed to be 20%.[6]

Direct medical effect cost estimates

The direct medical effects of immunizing staff members against influenza are associated with seeking medical care for influenza. Direct medical costs associated with influenza were based on Dutch estimates from Postma et al.[16] and Hak et al.[10] in combination with data from a web-based questionnaire carried out in 2009 and 2010 as part of the trial. The questionnaire was sent to all staff members of internal medicine and pediatrics as well as three other departments (two intensive care departments and neonatology). The response rate was 31% in 2009 and 18% in 2010, and the data were pooled to increase statistical power on the outcome variables. The proportion of people seeking primary care at the general practice was estimated at 24% with an average of one GP consultation (€29.01). Of all persons with ILI it was assumed that 80% used over-the-counter (OTC) medications (€6.62) and 20% received an antibiotic (€7.18). It was assumed that vaccination in this healthy group would not lead to adverse events leading to hospital admission. It was assumed that the vaccine caused side effects only in 10% of staff members, and that associated GP consultations occurred in 10% of them.[16]

Working days lost due to influenza-like illness

To calculate the productivity loss, the friction costs method was applied. Studies reviewing the impact of influenza or influenza like illness on working days lost are very heterogeneous in terms of methodology used.[17-19] Based on the available literature, four days working loss was taking into account for influenza like illness. No differentiation has been made between work absence and presenteeism. Based on the work absence registration from the university hospitals it was possible to calculate a gender and age weighted productivity costs per hour.[11,15] The average cost for one day of work loss was estimated at € 212.81 per day.

Indirect effect cost estimates

The indirect medical effect costs estimates were largely based on the costs associated with occurrence of morbidity among patients and associated hospital care as observed in the trial. Since information on mortality could not be obtained, no effect on patient mortality was conservatively assumed. The main outcome was influenza and/or pneumonia during hospital stay. The average costs for this diagnosis was based on the estimated increased difference in duration in hospital of 1.7 days extra at €1,013 for these patients compared with the other patients without nosocomial influenza and/or pneumonia.

To estimate the effects on the reduction in the incidence of influenza and/or pneumonia for different vaccine coverage rates, a linear relationship between vaccine coverage rates of HCWs and the proportion of patients with outcomes was assumed according to the mathematical model by Van den Dool et al.[20] In the estimates, an average of 23.7 per 100 additionally vaccinated HCWs in the intervention cluster as compared with the control cluster was assumed. The increase in coverage resulted in 2.7 per 100 less patients to develop influenza and/or pneumonia. Thus, if the coverage would be 100 per 100 HCWs (full coverage), 11.74 per 100 fewer patients would develop influenza and/or pneumonia. This results in a 0.1174% decrease in the outcomes per 1% increase in vaccine coverage of HCWs.

Cost-effectiveness analysis

The model was developed using Excel for Windows, version 2007. The basis for the analysis is a decision tree in which the direct effect of the influenza immunization for staff members is modeled as well as the indirect effects it has on the hospitalized patients. The basis for the probability input is in large part based on the trial input data (see above) and in part on the existing literature. A univariate sensitivity analysis was conducted to obtain the most influential factors in the cost-effectiveness estimates on the outcome measure using plausible ranges. For the sensitivity analysis for the base case scenario the values presented in Table 1 have been taken into account. For all cost items, a range of 10% was taken into account.

For patients already hospitalized only the excess days of hospitalization which were related to the influenza acquired in the hospital have been taken into account in the model. Also mortality and short term and long term complications following for example pneumonia have not been taken into account. The same applies to the effect the program potentially has on the quality of life for patients.

RESULTS

In the base-case scenario assuming no vaccination of staff members in an average UMC of 8.000 staff members and 6.000 patients, 368 staff members were absent from work because of influenza like illness resulting in 1,472 days of productivity loss, 88 persons visited a general practitioner, 294 used OTC medications and 18 persons an antibiotic treatment. The costs associated with illness in staff members was estimated at €4,638 for medical care and € 313,256 for reduced productivity. In addition, 70 patients developed influenza and/or pneumonia while hospitalized. The cost associated with the extended hospitalization period was estimated at €71,370. Vaccinating 23.7% of the HCWs with a vaccine efficacy of 20% on ILI resulted in a reduction of work absenteeism for 17 HCWs and a reduction in the associated nr of persons visiting a GP (four persons), OTC use (14 persons) and persons using antibiotic treatment (one person) but resulted in an increase in the number of persons visiting the GP due to the side effects of the vaccination. The costs associated with the vaccination and the direct medical costs of the staff members increased with € 33,408 and the costs for reduced productivity decreased with € 14,848. In total 17 patients were prevented from contracting influenza in the hospital and this resulted in a reduction of the extended hospitalization period with € 16,915. Taking into account the effect of vaccination on both HCWs and patients would therefore lead to a cost saving of € 2,993 (for an overview of the results see Tables 2a and 2b).

Table 2a Vaccination coverage 23.7% versus 0%.

	Vaccination coverage (new)	Vaccination coverage (old)	Difference
Health care workers			
Employees (number)	8,000	8,000	0
Number of employees vaccinated	1,896	-	1,896
Number of persons who were absent from work	351	368	-17
Total number of days absent from work	1,402	1,472	-70
GP visit following ILI	84	88	4-
GP visits due to side effects from vaccination	19	0	19
Number of persons who used OTC medication	280	294	14-
Number of persons who used antibiotics	17	18	1-
Costs			
Vaccination	€ 28,440	€ -	€ 28,440
GP visits following ILI	€ 2,441	€ 2,562	€ 121-
GP visits due to side effects vaccination	€ 550	€ -	€ 550
OTC use	€ 1,857	€ 1,949	€ 92-
Antibiotic use	€ 121	€ 127	€ 6-
Productivity loss	€ 298,408	€ 313,256	€ 14,848-
Total costs health care workers	**€ 331,816**	€ 317,894	€ 13,922
Patients			
Number of extended hospitalizations	54	70	17-
Costs of extended hospitalizations	€ 54,455	€ 71,370	€ 16,915-
Total costs patients	**€ 54,455**	**€ 71,370**	**€ 16,915-**
Total costs (health care workers + patients)	€ 386,271	€ 389,264	€ 2.993-

GP, general practitioner; ILI, influenza like illness; OTC, over the counter.

Table 2b Vaccination coverage 70% versus 0%.

	Vaccination coverage (new)	Vaccination coverage (old)	Difference
Health care workers			
Employees (number)	8,000	8,000	0
Number of employees vaccinated	5600	-	5600
Number of persons who were absent from work	316	368	-52
Total number of days absent from work	1,266	1,472	-206
GP visit following ILI	76	88	12-
GP visits due to side effects from vaccination	56	0	56
Number of persons who used OTC medication	253	294	41-
Number of persons who used antibiotics	15	18	2-
Costs			
Vaccination	€ 84,000	€ -	€ 84,000
GP visits following ILI	€ 2,203	€ 2,562	€ 359-
GP visits due to side effects vaccination	€ 1625	€ -	€ 1625
OTC use	€ 1,676	€ 1,949	€ 273-
Antibiotic use	€ 109	€ 127	€ 18-
Productivity loss	€ 269,400	€ 313,256	€ 43,856-
Total costs health care workers	**€ 359,014**	€ 317,894	€ 41,119
Patients			
Number of extended hospitalizations	21	70	49-
Costs of extended hospitalizations	€ 21,411	€ 71,370	€ 49,959-
Total costs patients	**€ 21,411**	**€ 71,370**	**€ 49,959-**
Total costs (health care workers + patients)	€ 380,425	€ 389,264	€ 8,839-

GP, general practitioner; ILI, influenza like illness; OTC, over the counter.

In the univariate sensitivity analyses individual parameters have been adjusted to understand the effect it has on the outcomes of the study. The results show that when health care costs increase, the savings increase following a vaccination program and this is also true when the probability of attracting influenza/pneumonia in the hospital. In case the work absence is lower and the decrease in productivity is also lower, the potential savings of a program are lower than might be expected following our results.

Two scenarios have been reviewed. In the first scenario where the vaccination coverage is very high but the disease burden which can be reduced is not significant and the efficacy of the vaccine is low and the costs are lower than expected, a vaccination program will not be cost-effective. In such a scenario, total net costs can increase up tot € 16,000. In the reverse situation, a vaccination program is more cost-effective than presented in the results.

The results show that investing in higher vaccination coverage among HCWs leads to a reduction in the disease burden among hospitalized patients which leads to a cost saving related to the prevented extended hospitalizations. It also shows that the scope of the analyses influences the advice that will be provided to the hospital.

Because of the linear relationship that is assumed in the model for the vaccination costs, an increase in the vaccination coverage to 70% would lead to a reduction in the number of HCWs with work absenteeism. It would also result in an increase in the costs, mainly due to the vaccination costs of €84,000 but also to a much lower number of patients that will be infected and therefore require extended hospitalization (49 persons) which reduces the hospitalization costs substantially with € 49,959. With this coverage rate, a cost saving of € 8,839 can be expected (see Table 3). With a vaccination coverage of 23.7% and a higher vaccine efficacy more HCWs would be protected against influenza which also translates to a lower transmission rate to hospitalized patients. Both effects would lead to a reduction in the direct medical costs for HCWs and lower productivity losses as well as lower costs related to the extended hospitalization that is required for patients following hospital acquired influenza.

DISCUSSION

This cost-effectiveness study alongside a trial clearly showed potential cost savings from the introduction of an influenza vaccination program among hospital staff. Savings were both derived from reduced productivity loss and decreased extended hospitalization of patients already admitted to the hospital.

The input for the analysis was largely based on the established effects of the trial, and potential limitations and strengths have been discussed earlier. The most important parameters were the proportion of staff members absent from work and the percentage reduction in nosocomial influenza and/or pneumonia in patients. The absenteeism rate (4.6%) was estimated using the work absence registration from the hospitals participating in the trial. In the trial a slight increase in absenteeism rates was reported in intervention as compared with control UMCs. It is likely a proxy for more strict regulations regarding working when staff has influenza, and is not a result of the vaccination program. Therefore it was decided to use the 4.6% for the situation where no vaccination was available. Comparing the situation where no vaccination program is offered to a vaccination coverage of 23.7% and taking into account work absenteeism of 4.6% following ILI makes the vaccination program cost saving. Higher work absenteeism rates increase the effect the vaccination program has on the total savings.

The proportion of patients with nosocomial influenza and/or pneumonia was also an important cost-driver. We observed considerable reduction in the intervention versus control UMCs with an estimated 11.74% being infected during an epidemic. This figure agrees with the modeled 13% of nosocomial infection during an epidemic in a mathematical model developed by Van den Dool et al.[20]

When only taking into account the effect vaccination has on HCWs the business case would not be positive and investing in vaccination campaigns for HCWs would not be favorable for a hospital. Taking into account the effect it has on patients however makes it different because of the health gains that can be reached.

Vaccinating HCWs has a direct and an indirect effect whereby the indirect effect is more significant because it affects mainly frail persons. Would it be considered ethical to offer vaccination to a group of persons whereby the benefit of the vaccination program lies with another person? From a cost-effectiveness perspective it would be reasonable to offer vaccination to HCWs but it remains unclear whether they are willing to receive the vaccination which thus leads to a higher vaccination coverage. The results presented show that vaccinating HCWs is favorable for patients but does it also legitimate the discussion of mandatory vaccination of health care workers in the Netherlands? For the authors, more research is needed in different health care settings before this can be considered but programs to voluntary increase the vaccination coverage among HCWs should definitely be considered.

The study was performed in academic hospitals in a number of departments and the question therefore is whether the results can also be applied to other departments and also to for example general hospitals in the Netherlands. However, when applying the results of the study to other health care settings it should be taken into account that the turnover of patients in different settings can be an important parameter for the effectiveness of the vaccination program.

To conclude, the vaccination program is likely cost-saving from a societal perspective but from the hospital perspective this is not the case. The investments for the influenza vaccination program made by hospital management result in higher productivity costs and lower direct medical costs related to patients. Within the current financial system these investments are not supported by financial incentives. However, hospitals might use the vaccination program in their communication strategy to patients. Studies are warranted that focus on peripheral hospitals and to focus on translational research in order to understand how to increase the vaccine uptake in different settings during consecutive years and might become a subject for negotiation between health care insurers and hospitals.

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CHAPTER 9

General discussion

GENERAL DISCUSSION

In this thesis we presented studies that focused on the issue how to increase influenza vaccination coverage among Health Care Workers (HCWs) in hospital settings. In **chapter 2** we showed which factors reported by administrators of Dutch general hospitals were associated with influenza vaccine uptake among HCWs. Hospitals in which the administrators agreed with positive statements concerning influenza vaccination of HCWs had slightly higher vaccine coverage, though not statistically significant. Importantly, in hospitals that economically invested more in their vaccination campaign in comparison with their counterparts, statistically significantly higher vaccine coverage was recorded. In **chapter 3** we assessed potential differences in management beliefs on influenza vaccination of HCWs between administrators from general hospitals and nursing homes, and we concluded that in both health care settings behavioural changes are urgently needed in order to increase influenza vaccine coverage, possibly through well-developed, structured, implementation programs. In **chapter 4** we performed a systematic literature search and meta-analysis to determine the most important predictors of seasonal influenza vaccine acceptance among HCWs in hospitals. After examining 13 studies, we found five determinants that were associated with a relevant two-fold higher influenza vaccine coverage. In **chapter 5** we focused our study on health care settings in the Netherlands and assessed which determinants predicted influenza vaccination behaviour among HCWs in all Dutch University Medical Centers (UMCs). The questionnaire study revealed an accurate and discriminative prediction model with two demographic and nine behavioural determinants. In **chapter 6** we described how a multi-faceted influenza vaccination implementation strategy was developed based on the need assessment of chapters 4 and 5, using the Intervention Mapping method, and how it was applied and evaluated in the intervention UMCs (see also chapter 7). The process evaluation showed that more exposure to the intervention program elements was associated with higher vaccine coverage among HCWs. In **chapter 7** we assessed the effects of the developed intervention strategy on both influenza vaccine uptake among hospital staff in the UMCs and on patient morbidity using a cluster-randomized controlled clinical trial design. The trial study showed that vaccine coverage of HCWs increased after implementation of the intervention strategy and we also demonstrated that the increase in vaccine coverage among HCWs was associated with decreased patient in-hospital morbidity from influenza and/or pneumonia. Finally, in **chapter 8** a cost-effectiveness analysis is reported that showed that the developed implementation program resulted in cost-savings and is likely cost-effective. Therefore, hospital managements should advocate the influenza vaccination to their HCWs.

Rationale for immunizing HCWs against influenza

Influenza is one of the leading causes of epidemic respiratory infections,[1,2] causing severe morbidity and mortality among older persons and persons with acute or chronic risk-elevating medical conditions.[3-6] There are several arguments *in favour* of immunizing HCWs working in hospitals against influenza:

1. Indirect protection of patients

Some four clinical trial studies demonstrated that immunizing HCWs of nursing homes or long-term care facilities against influenza is effective in protecting patients against influenza and its possible complications.[7-10] The indirect protection of patients is hypothesized to be possible as HCWs serve as one of the main vectors for transmitting the influenza virus to their patients after infection. In a cohort study Elder et al. showed that during a mild influenza epidemic 23% of non-vaccinated HCWs in acute care had serological evidence of influenza and up to 59% remained asymptomatic.[11] This increases the chance to continue to work and infect patients. Importantly, studies from the US showed that up to 75% of HCWs continue their work while being symptomatic.[12]

Carman et al. who studied the effects of increasing the coverage of influenza vaccination among HCWs on mortality among seniors in a long-term care setting in the US, reported that higher vaccine coverage of HCWs was associated with a substantial decrease in mortality among patients.[7] A similar effect was observed by Hayward et al who used a cluster randomized controlled trial to demonstrate a significant decrease in mortality and influenza-like illness among residents in homes where influenza vaccination was offered to staff compared to homes where the vaccine was not offered to their caregivers.[8] Potter et al. demonstrated a significant reduction in total patient mortality from 17% to 10% (OR 0.56; 95% CI 0.40 – 0.80) and an adjusted 43% reduction in influenza-like illness in 12 geriatric medical long-term-care sites that increased the vaccine coverage compared with sites with low vaccine coverage.[9] Finally, Lemaitre et al. performed a cluster-randomized controlled trial in 40 nursing homes showing that the effect of staff influenza vaccination resulted in a 20% reduction in resident all-cause mortality.[10] Hence, Thomas et al. who performed a meta-analysis of existing trial studies demonstrated in their Cochrane review that all trials showed benefits in both patient morbidity and mortality.[13] However, they also reported that there are some methodological limitations in that bias cannot be excluded. Several outcomes used in the four studies were not specific enough, for instance death from pneumonia is less specific than death from pneumonia due to influenza. Further, all studies had inadequate HCW vaccine coverage which underestimates the effect that would occur if full coverage was achieved. Importantly, the evidence for these effects is mainly observed in nursing homes and long-term care facilities, which limits the applicability to HCWs working in hospitals. The data of our multicenter controlled trial adds evidence to previous studies in favour of vaccinating hospital HCWs against influenza. We showed that an increase in vaccine coverage is associated with a decrease in patient in-hospital morbidity from influenza and/or pneumonia.

2. Indirect protection of relatives

A 2009 review showed that HCWs mainly get immunized against influenza for self-protection. However, a second self-reported reason to accept the vaccine was to protect patients, or family members or colleagues.[14] In chapter 5 we showed that HCWs who are aware of their own personal risk of getting influenza are more likely to get vaccinated than HCWs who are not (OR 2.8, $p<0.001$). Other studies showed the same effects and also concluded that when HCWs were aware of the risk of infecting family members like their children they are more likely to get vaccinated.[15]

3. Individual protection

Seasonal influenza vaccination reduces influenza-confirmed episodes among healthy adults by approximately 75% when matched with circulating strains.[16] In 2010 Jefferson et al. reviewed 50 reports to assess the effect of vaccination on influenza in healthy adults.[17] They concluded that when the vaccine matched the circulating viral strains, 4% of unvaccinated persons versus 1% of vaccinated persons developed symptoms of influenza (95% CI 2-5%). Also, vaccination had a modest positive effect on work absenteeism, but an effect on hospital admissions or complication rates could not be detected, possibly because of inadequate statistical power. So, if healthy people are vaccinated against influenza they are less likely to become infected. Recently, Osterholm et al. showed in a large meta-analysis of randomized controlled trials among healthy adults that immunization with the inactivated influenza vaccine leads to a 59% efficacy (95% CI 51-67%) in preventing laboratory-confirmed influenza infection.[18] As healthy adults can be considered representative for HCWs this evidence shows that HCWs can be protected against influenza by vaccination. Our observation in internal medicine departments that increased influenza vaccine coverage among HCWs was associated with reduced influenza morbidity in patients confirms these trial findings.

4. Productivity loss and continuity of care

Two double-blind randomized controlled trials demonstrated that influenza vaccination can reduce work absenteeism caused by respiratory infections.[19,20] Saxen et al. showed a statistically significant reduction of 28% in total sick leave days (because of respiratory infections), thereby indicating that vaccinating HCWs is very important for the continuity of care.[20] In our trial, we did not find an association between increased vaccination coverage and a reduction of productivity loss in HCWs. However, in our trial HCWs were instructed during the peak of the influenza season not to start working if they were not feeling well or if they had flu-like symptoms. It is known from literature that even when HCWs are feeling ill, they continue to work in around 76% which poses a major risk for patients to get infected.[12] Because of potential additional reduction in infected working personnel in the intervention group this might be the reason we were not able to demonstrate a reduction in productivity loss.

5. Cost-effectiveness

In 2010 Hak et al. performed a cost-benefit analysis to assess the annual productivity loss among HCWs attributable to influenza, and to estimate the costs and benefits of a vaccination program from the employers' perspective.[21] They showed in this modelling study that the costs due to productivity loss among HCWs are considerably high. Therefore, reaching higher vaccine coverage among staff through a vaccination program can be cost-saving. As demonstrated in chapter 8, we show similar results in that it is cost-saving to vaccinate HCWs, which makes it also more appealing for the hospitals' managements to advocate vaccination among HCWs.

6. Moral duty not to harm and professional responsibility

Lastly, there are also several ethical arguments *in favour* of vaccination. One of the most important ethical arguments is the moral duty of all HCWs to do no harm to their patients.[22] In addition, HCWs serve as a role model for patients in showing that they are willing to provide the best possible care to their patients resulting from their professional responsibility.

The pre-pandemic situation in Europe and the Netherlands.

Since infected HCWs may transmit the influenza virus to individuals at risk of severe disease, the WHO has been recommending influenza vaccination for HCWs. Such a strategy should also be part of a broader infection control policy in health care settings.[23] The United States Centers for Disease Control and Prevention (CDC) has recommended influenza vaccination for HCWs who take care of patients at high risk for significant morbidity following an influenza infection already since 1981.[24] Despite the available evidence and these recommendations, influenza vaccine uptake among HCWs still remains low. Maltezou et al. showed that all 27 European Union Member States and three additional European countries (Norway, Switzerland and Russia) has been recommending HCWs to be vaccinated against influenza, except for Sweden that only recommended vaccination during the 2009/2010 H1N1 pandemic.[25] However, vaccine uptake rates among HCWs vary considerably between these countries, from 15% in the UK and Germany to 25% in Romania and in all these vaccine uptake rates still remain very low.[26]

As is shown in chapter 4 of this thesis, the vaccine coverage rates of HCWs studied in the meta-analysis ranged from as low as 2.1%[12] to 62% in a more recent study from 1999-2000.[27] The low vaccine coverage is currently still a problem in the Netherlands as we have shown in chapter 7. To further improve vaccine coverage in the Netherlands, a guideline for preventing influenza in nursing homes was developed in 2004,[28] while a guideline for hospitals was not developed until 2007 when the Dutch Health Council recommended vaccination for HCWs following guidelines from the WHO and CDC. The fact that after several years the vaccine coverage is still this low can be explained by various arguments *against* immunizing HCWs working in hospitals against influenza.

Reasons for HCWs not to get immunized against influenza

1. Perception of the vaccine's effectiveness

There are several reasons for the low vaccine coverage as there exist many barriers among HCWs against vaccination. The arguments for non-acceptance of the vaccine can be divided into two main categories: (1) knowledge, beliefs and attitudes or (2) accessibility. As expected, vaccinated HCWs believe that the vaccine is more effective (in reducing influenza-like illness and vaccine-strain specific illness) than non-vaccinated HCWs.[29] We showed in the chapters 2 and 5 that the determinant 'knowing that the vaccine is effective in preventing influenza transmission' is significantly associated with at least a two-times higher vaccine uptake. Unfortunately, most HCWs appear to be unaware of these effects or are apparently not able or willing to reconsider their arguments once they have made the decision to be immunized or not.

2. Perception of side effects associated with vaccination

One of the reasons for refusing vaccination is the fear of side effects. A study assessing the attitudes of HCWs towards pandemic influenza A (H1N1) vaccination showed that concern about the long-term side effects was the main reason for non-vaccination among refusers (37%).[30] Nurses are more likely to refuse the vaccine because of possible side effects than doctors as shown by Smedley et al.[31] They also conclude that in a group of 214 healthy HCWs 74% had no side effects and that 13% of HCWs experienced a local reaction. Further, Saxen et al. demonstrated in a randomized placebo-controlled double blind trial that vaccination against influenza caused no severe side effects.[20] The only statistically significant symptom associated with the influenza vaccine was local tenderness of the arm. A Dutch study assessing the attitudes of general practitioners towards vaccination showed that 6% refused because of the fear of side effects.[32] Following these results we found similar evidence in chapter 5 where we concluded that the expectation not to have side effects after vaccination was statistically significantly associated with influenza vaccination compliance among HCWs (OR 1.87, 95% CI 1.48 – 2.36).

3. Perception of management/colleagues regarding vaccination is negative

Looijmans-van den Akker et al. pointed out that the opinions of people close to HCWs working in nursing homes are of significant importance.[33] The investigators found an odds ratio of 5.33 ($p<0.001$) for the determinant to get vaccinated if people close to the HCW thought that it was important to be vaccinated. In chapter 2 we found an odds ratio of 1.74 for the same determinant in hospitals ($p=0.010$). This means that the people surrounding HCWs, like co-workers, managers and relatives, should also be targeted with the right information in the most ideal situation, so that HCWs can make up their own decision based on the proper knowledge and are not led by other people's misconceptions.

4. It is difficult to receive the vaccine

Smedley et al. assessed the possible reasons for poor influenza vaccine uptake among HCWs in a survey in the UK.[31] They showed that the main perceived barriers for uptake were problems with access to vaccine and lack of time to attend. In chapter 5 similar results are shown, as the determinant 'I would get vaccinated if vaccination was available at a convenient time' was highly associated with vaccine uptake resulting in an odds ratio of 28.9 (95% CI 15.90 – 52.58).

To conclude, with the new emerging evidence that has been published over the past decade, it is important to educate HCWs and their social surroundings, and to expand their level of knowledge on influenza as a disease, on their own role as possible vectors and on the effects of vaccination. Further, since accessibility of vaccination has proven to be a problem this should be one of the most important factors in increasing influenza vaccine coverage among HCWs as will be discussed later.

The effect of the Influenza A (H1N1) pandemic on influenza vaccine uptake.

In 2009, the worldwide pandemic with new influenza A (H1N1) caused a lot of distress and public concerns. In an attempt to restrict the spread of infection and to get as many risk groups vaccinated as possible, vaccines were rapidly produced and disseminated throughout many countries worldwide. Overall, hospitals were very active in encouraging HCWs to get their influenza vaccine in order to prevent understaffing due to sick leave and in order to prevent morbidity and mortality among patients. Most studies assessing that particular period of time showed that vaccine uptake increased in this pandemic season, even up to 92% (see also chapter 7).[30,34] However, the influenza season following the pandemic showed a decrease in influenza vaccine uptake among HCWs (see also chapter 7).[34] This could suggest that anxiety among HCWs caused by the fact that young people were actually dying from this new variant of influenza played an important role in getting vaccinated. This situation is different from the regular seasonal influenza in that HCWs often feel that they don't need a flu shot because they are not afraid to get ill themselves, and even if they do get ill, there are normally few complications. This is also demonstrated by Kraut et al.,[35] who assessed the attitudes of HCWs that were vaccinated against H1N1 in two groups: those that were routinely vaccinated against seasonal influenza and those that were not. They showed that the main motivators for getting vaccinated against H1N1 in both groups were concerns about personal or family safety. That is consistent with this thesis as we showed in chapter 2 that being aware of the personal risk to get infected with influenza is associated with an almost three-time higher probability to get vaccinated yourself. HCWs that were routinely not being vaccinated against seasonal influenza reported lower levels of concern on the seriousness of influenza, their sense of exposure risk and had less confidence in the effectiveness of the vaccine compared to the HCWs that were routinely vaccinated against seasonal influenza.[35]

How to further improve influenza vaccine coverage among HCWs without mandate

We studied multiple ways in which we could influence the behaviour and attitudes of HCWs so that HCWs could make a deliberate choice in accepting the influenza vaccine or not. Our aim was to increase vaccine coverage in this group in order to achieve protection not only for the HCWs but mainly for their patients, as we showed in chapter 7. However, we did not succeed in achieving full vaccine coverage among HCWs.

In chapter 6 we showed the results of the process evaluation of our vaccine implementation strategy. The nine behavioural determinants that resulted from our needs assessment in chapter 2 were targeted in the influenza vaccination strategy that we developed, in order to raise vaccination behaviour in HCWs. These determinants largely cover both the arguments *in favour* and *against* influenza vaccination. Tools were developed by our research team to target the determinants and to disseminate these. However, in the actual implementation these determinants were not all applied by the intervention UMCs, as shown in chapter 6. To have highest impact, all determinants need to be targeted in order to achieve the most effective vaccination campaign possible. Unfortunately, the communication tools that we have developed were not used in an optimal way or noticed by the majority of HCWs. For example, the research team developed badges that could be handed out after a HCW was vaccinated, showing that that HCW had received the vaccine. They were meant as an item that would raise discussion among HCWs so that they would debate about it on the work floor. However, these badges were handed out to only 32.9% of HCWs in the intervention UMCs in the season 2009/2010. One year later this number was even halved when only 16.6% of HCWs were provided with a badge. One explanation for this was resistance from the Board of Directors of some UMCs, as some members of the Board of Directors did not support this idea. Another tool that was developed by the research team was a website providing information about influenza and the vaccination. This website was visited by less than 10% of HCWs the first trial season, and one year later by almost 20%. Despite this increase, the potential impact of the program might have been increased if all UMCs had put the link to the website on their intranet.

Another reason for differential use of the communication tools is that in the UMCs different departments were responsible for the annual vaccination campaign. In some UMCs, the communication staff was the main responsible for the influenza vaccination campaign, while in other UMCs the department of occupational health was responsible. This caused differences in usage of the communication tools. Also, in the intervention UMCs, these departments were asked to change their own routine which hampers effective implementation.

In chapter 7 we demonstrated a significant correlation between the number of applied methods and vaccine coverage; showing a clear trend towards increased vaccine coverage if more methods were applied. Therefore it is very important for future implementation that the intervention strategy is applied with maximal exposure of all tools.

Potential new tools that may prove to be effective

One of the latest studies demonstrated a positive effect of text messaging on influenza vaccine uptake in a low-income, urban population, taking into account the society that is connecting increasingly via cellular telephones and the internet.[36] Public reporting of institutional influenza vaccine uptake rates among HCWs is another element that might be effective in raising vaccine coverage.[37] In this way, HCWs can be informed about the way their department and/or their hospital reaches their vaccination goals compared to other hospitals. Llupia et al. showed that their intervention increased vaccine coverage among HCWs significantly from 23% before the intervention to 37% after the intervention.[38] They used 3 lines of activity: (1) a high level of institutional support, (2) raising awareness in the campaign by weekly educational e-mails, prize drawings and a website with photographs of vaccinated HCWs, and (3) enhancing accessibility by means of mobile vaccination units which routes were spread in advance.

In conclusion, we can say that there are several possibilities for further improvements in the implementation of the vaccination program. Despite all the efforts made during the implementation of our strategy, full influenza vaccine coverage among HCWs could not be reached since the UMCs did not achieve maximum exposure to the determinants.

Dissemination of the vaccination program in non-academic hospitals

ZONMW has granted a dissemination project in which it is planned to implement the developed intervention strategy in non-academic hospitals in the Northern part of the Netherlands. In this project we will take into account the abovementioned drawbacks of the UMC project. The tools will be adjusted following the evaluation in chapter 6. The new methods used by Llupia et al., Stockwell et al. and Johnson et al. are also worth to take into account.[36-38] Only when the tools are brought under the attention of HCWs, they can achieve their maximum effect in increasing influenza vaccine coverage among HCWs.

Should influenza vaccination of HCWs be mandatory or not?

In the Netherlands influenza vaccination is a voluntary measure taken by HCWs which may be the reason for such low uptake rates. Therefore, to reach maximal vaccine coverage among HCWs mandatory vaccination is an option that should be considered, as we will discuss below.

With mandatory vaccination we do not mean forced vaccination against one's will. Mandatory vaccination is conditional, in that people who refuse vaccination, e.g. for religious or philosophic reasons, are refused from their work for a certain period of time. There are several arguments in favour of mandatory influenza vaccination.[22,39] The most important argument is the moral duty of HCWs not to harm their patients. This is especially important in the case of influenza where it is known that infecting patients with influenza is easily preventable by a once a year single flu shot preceding every influenza season.

Further, the professional responsibility of HCWs also comprises that in order to deliver the best possible care for their patients, they adhere to hygienic protocols and are also vaccinated against hepatitis B and tested on tuberculosis. In the Netherlands, every

HCW is required to be properly vaccinated against hepatitis B when working with patients and also must be excluded to have tuberculosis before starting with patient care. This is a mandatory measure following the advice of the Dutch Health Council that is taken in order to protect HCWs and their patients from these infectious diseases.

Lastly, despite the fact that influenza vaccination in HCWs has proven to be effective in protecting patients from influenza,[7-9,13,19] is cost-effective[40] and reduces absenteeism,[19,20] voluntary vaccination is not sufficient in raising the influenza vaccine uptake rates as these remain low (see also chapter 5).[26,41,42]

Arguments against mandatory vaccination are taking away the freedom of choice and autonomy of staff, possible damage of morale, possible side-effects from the vaccine and the view that vaccination of HCWs is only in the interest of the employers.[22,43] Taking away the freedom of choice is a major issue among HCWs. Also, many HCWs feel that the distance between HCWs on the work floor and the board of directors/managers of the hospitals is too large. The feeling that mandatory vaccination is appealing for employers from a financial perspective adds to HCWs' resistance. Therefore HCWs disapprove of being forced into mandatory vaccination which, in their point of view, interferes with their autonomy. The possible side-effects from the influenza vaccine can be considered as minor,[20] with certain exceptions like Guillain-Barré syndrome.[17,44] However, considering all arguments together we believe that the benefits of protecting patients against influenza outweigh the possible objections of HCWs.

Of course, the most ideal situation would be a voluntarily based influenza vaccination campaign that results in high vaccination coverage rates. However, this thesis and several other studies[26,41,42,45] show that in the case of voluntary vaccination vaccine uptake remains too low. Studies performed in the United States however show that mandatory vaccination is associated with influenza vaccine coverage up to 100% as demonstrated by Kidd et al.[46] They managed to increase their vaccine uptake rate among Universital Hospital HCWs from 51% to a staggering 100% after mandating the flu shot. They created a program with an exemption committee where employees could admit applications for refusing the vaccine for medical or religious reasons. The committee reviewed each application and approved or denied it. Employees who were denied were required to receive the vaccine otherwise they were ineligible to report to work during the flu-season. A Greek study performed by Maltezou et al. showed that there is a higher rate of accepting a mandatory vaccination policy among physicians compared to nurses or other medical professions.[47] Over 50% of HCWs would accept mandatory influenza vaccination for all HCWs, and over 66% favoured HCWs to be mandatory vaccinated against influenza for HCWs who take care for immunocompromised patients. They also demonstrated that physicians and nurses working in the internal medicine departments had higher acceptance rates towards mandatory vaccination than HCWs working in other departments.

Feemster et al. described their experience with implementing mandatory influenza vaccination for HCWs at a tertiary children's hospital in Philadelphia.[48] They first implemented a mandatory program in targeted groups of HCWs, before expanding it to the entire hospital. The concluded that the majority of HCWs (72%) found mandatory vaccination to be coercive, but also a vast majority of HCWs (>90%) felt that mandatory influenza vaccination was important for protecting patients as well as staff and was part of their professional and ethical responsibility.

Considering all these arguments, the implementation of mandatory vaccination in Dutch hospitals should be considered and should ideally be a part of the multi-faceted implementation strategy described in chapter 6. However, there is a long way to go before HCWs will fully accept this. A future study assessing the attitudes of Dutch hospital HCWs towards mandatory influenza vaccination will be helpful in finding the proper way to implement it in the Netherlands.

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CHAPTER 10

Summary

Samenvatting

Dankwoord

Curriculum Vitae

Research Institute for Health Research SHARE

SUMMARY

Influenza is a potential life-threatening viral infection which can be easily prevented by vaccination. Health care workers are recommended to be vaccinated against influenza, not only to protect them selves but mainly to protect their vulnerable patients. However, despite recommendations, vaccine coverage among health care workers is disappointingly low since many years. The pandemic with new influenza A (H1N1) temporarily raised vaccine coverage among health care workers, showing that if the threat is evident, high vaccine coverage is possible. However, after the 2009/2010 pandemic season, vaccine coverage has been returned to lower levels.

This thesis starts in **chapter 2 and 3** with two studies exploring the contributing factors to influenza vaccine uptake among hospital staff and nursing home staff from the management's point of view. Both studies were questionnaire studies where the managements of hospitals and nursing homes were questioned about the reasons they believed were important for vaccination according to their staff. The first study, among 42 Dutch general hospitals, showed a low influenza vaccination rate among health care workers; only 17.7% of them was vaccinated against influenza. Hospitals in which the administrators agreed with positive statements concerning the influenza vaccination had a slightly higher, but non-significant, vaccine uptake. However, it was demonstrated that more economic investments in the vaccination campaign were related with a higher vaccine uptake. The second study compared the results from the general hospitals with those from Dutch nursing homes. Significant differences between both care institutions were amongst others the presence of a written policy on the influenza vaccination; this was the case in almost three times as many nursing homes than general hospitals. Also, almost three times as many nursing homes administrators compared to general hospital administrators believed that mandatory vaccination of staff against influenza would be accepted in their institution.

In **chapter 4**, a meta-analysis was performed in order to determine which factors were associated with seasonal influenza vaccine acceptance among hospital health care workers. An extensive literature search in Pubmed and Embase eventually resulted in 13 studies eligible for inclusion in the meta-analysis. We calculated pooled risk ratios and identified five determinants that were statistically significant associated with a twofold higher vaccine uptake. These determinants were: knowing that the vaccine is effective; being willing to prevent influenza transmission; believing that influenza is a highly

contagious disease, believing that the prevention of influenza is important and having a family member that is usually vaccinated. After this meta-analysis was performed we knew which factors were important in international literature for developing new vaccination strategies.

We also wanted to know which factors were associated with influenza vaccine uptake among health care workers at a national level. We therefore performed a questionnaire study among Dutch health care workers in **chapter 5**. In 2008, we selected five departments from all eight Dutch university medical centers (UMCs) where patients were at medium and high risk for influenza: internal medicine, neonatology, paediatrics and two intensive care units. Health care workers of these specific wards were provided with an anonymous, self-administered paper questionnaire and were asked to give their opinion on demographic, behavioural and organizational determinants that would predict their vaccination behaviour. In total, 1295 questionnaires were filled out (response rate 39%) and 37.6% of all respondents were vaccinated against influenza. In the univariate analysis, nine out of 11 demographical determinants were significantly related to influenza vaccine uptake. This was also the case for 11 out of 19 organizational determinants and for 34 out of 39 behavioural determinants. The final multivariate analysis resulted in an 11-item final prediction model with two demographical and nine behavioural determinants. The accuracy of this prediction model was very high with an area under the receiver operating curve of 0.95.

Chapter 6 describes the planning of a multi-faceted influenza vaccination implementation strategy for health care workers in acute health care settings. We used the Intervention Mapping method as a framework to systematically plan, develop and evaluate the process of an influenza vaccination implementation strategy. The Intervention Mapping method can be used as part of the dynamic process of planning intervention strategies in health education and is composed of six steps: 1) a needs assessment; 2) establishment of proximal program objectives; 3) development of theory-based methods and practical strategies; 4) program planning; 5) adoption and implementation of the program; and 6) program evaluation. Following these steps, the 11-item prediction model developed in chapter 5 was discussed in a 10-person research team to assess their changeability. Based on the measures of association and their level of changeability, the determinants were divided into four categories: knowledge; common interest; social impact; and organizational. The objectives of all determinants were set and methods and materials to achieve the objectives were developed. These program methods and materials were then drafted into common formats and sample materials, and were prepared for implementation. A communication expert supervised the whole process.

After implementation of the program both a qualitative and quantitative process evaluation was carried out. In the qualitative evaluation was assessed which parts of the implementation program were used by the university medical center. Communication reports were also requested, and the contact persons of the UMCs were asked to comment on the materials used. Intervention and external UMCs showed more use of targeted determinants than the control UMCs. In the quantitative evaluation, a sample of health care workers from the earlier mentioned five departments of the Dutch university medical centers was asked to complete an anonymous web-based questionnaire. This was done in the spring of 2010 and 2011, after both study seasons of 2009/2010 and 2010/2011. The questionnaire contained questions concerning the usage of the developed tools in their hospital. Of all the developed communication materials, health care workers reported the posters as most noticeable.

Chapter 7 describes the results of a hospital-based cluster randomized controlled trial to assess the effects of the earlier developed multi-faceted program on influenza vaccine coverage among health care workers and on patient morbidity. The study period included the influenza seasons of 2009/2010 and 2010/2011. All eight Dutch university medical centers were invited to participate in the trial. Six of them agreed to randomization at cluster level, and were randomized in an intervention group (three UMCs) and a control group (three UMCs). The remaining two UMCs (refused randomization and) acted as external controls. We included 3367 patients. The primary outcome was influenza vaccine uptake among health care workers. Secondary outcomes were absenteeism among health care workers in the month of December and patient morbidity.

In both study seasons, influenza vaccine uptake among health care workers was significantly higher in the intervention UMCs than in the control UMCs. In the pandemic season of 2009/2010, where three vaccination rounds were offered, the highest absolute risk difference was seen for the first dose of the pandemic vaccination, namely 23.7% (95% CI 4.3 – 47.8). At the internal medicine departments of the intervention group with higher vaccine coverage compared to the control group, nosocomial influenza and/or pneumonia was recorded in 3.9% and 9.7% of patients of intervention and control

UMCs, respectively (p=0.015). So an increase in vaccine coverage was associated with decreased patient in-hospital morbidity from influenza and/or pneumonia.

In **chapter 8** we assessed the cost-effectiveness of implementing a hospital-based multi-faceted influenza immunization program among Dutch health care workers. We showed that in a base-case scenario with no vaccine coverage, annual costs of influenza were estimated at €389.264 for an average UMC with 8000 health care workers and 6000 patients hospitalized during an epidemic. If the influenza vaccine coverage among HCWs was increased to 23.7%, as was observed in the intervention cluster in 2009, the program's savings were estimated at €2.993. Therefore we conclude that the implementation of this multi-faceted program results in cost-savings, and more efforts should be considered to increase vaccination coverage among HCWs in Dutch hospitals.

Finally, we conclude this thesis with a general discussion in **chapter 9**. First, the rationale for vaccinating health care workers against influenza is discussed. Several arguments are mentioned; the indirect protection of patients and relatives; individual protection of the health care worker; productivity loss because of absenteeism; the cost-effectiveness of vaccination and finally the moral duty not to harm your patients. Then the pre-pandemic situation in Europe and the Netherlands is summarized. In most European countries vaccine uptake among HCWs was low before the 2009 H1N1 pandemic, and during this pandemic vaccine coverage increased. Further, the reasons for HCWs not to get immunized against influenza are discussed. The general discussion ends with the question if mandatory vaccination against influenza is an option or not. Considering all arguments, mandatory vaccination in HCWs should be considered in the Netherlands and should ideally be part of the multi-faceted influenza vaccination implementation strategy. Future studies assessing the attitudes of Dutch hospital HCWs towards mandatory influenza vaccination will be helpful.

SAMENVATTING

Influenza is een potentieel levensbedreigende virale infectie die gemakkelijk kan worden voorkomen door vaccinatie. Gezondheidszorgwerkers wordt aangeraden zich te laten vaccineren tegen de griep, niet alleen om zichzelf te beschermen, maar vooral om hun kwetsbare patiënten voor infectie te behoeden. Echter, ondanks deze aanbeveling blijft de vaccinatiegraad onder gezondheidszorgwerkers al jaren teleurstellend laag. De Nieuwe Influenza A(H1N1) pandemie veroorzaakte een tijdelijke verhoging van de vaccinatiegraad onder gezondheidszorgwerkers, waaruit blijkt dat als de dreiging duidelijk is, een hoge vaccinatiegraad mogelijk is. Echter, na het pandemische seizoen van 2009/2010 is de influenza vaccinatiegraad wederom laag.

Dit proefschrift begint in **hoofdstuk 2 en 3** met twee onderzoeken waarin de factoren worden onderzocht die bijdragen aan de influenza vaccinatiegraad onder ziekenhuispersoneel en verpleeghuispersoneel, vanuit het oogpunt van het management. Beide onderzoeken zijn vragenlijstonderzoeken waarin de directies van ziekenhuizen en verpleeghuizen werd gevraagd naar de redenen die zij belangrijk achtten voor hun personeel om gevaccineerd te worden. Het eerste onderzoek, dat werd uitgevoerd in 42 Nederlandse algemene ziekenhuizen, liet een lage influenza vaccinatiegraad onder gezondheidszorgwerkers zien; slechts 17,7% van hen was gevaccineerd tegen influenza. Ziekenhuizen waarvan het management de influenza vaccinatie onder hun personeel meer positief beoordeelde, hadden een niet-significant hogere vaccinatiegraad. Ook werd in dit onderzoek aangetoond dat hogere economische investeringen in de vaccinatiecampagne leidden tot een hogere vaccinatiegraad. In het tweede onderzoek werden de resultaten van de algemene ziekenhuizen vergeleken met Nederlandse verpleeghuizen. Er werden enkele significante verschillen aangetoond tussen beide zorginstellingen; zo bleek dat in de verpleeghuizen drie keer zo vaak een schriftelijke richtlijn voor de influenza vaccinatie aanwezig was. Tevens waren bijna driemaal zoveel managements van verpleeghuizen ervan overtuigd dat hun personeel het verplicht stellen van de griepvaccinatie zou aanvaarden in vergelijking met de managements van algemene ziekenhuizen.

In **hoofdstuk 4** wordt een meta-analyse beschreven waarin werd onderzocht welke factoren geassocieerd zijn met de acceptatie van de seizoens griepprik onder gezondheidszorgwerkers in ziekenhuizen. Een uitgebreid literatuuronderzoek in Pubmed en Embase resulteerde uiteindelijk in 13 geschikte studies die in aanmerking kwamen voor inclusie in de meta-analyse. We berekenden gecombineerde risico ratio's (pooled risk ratios) en identificeerden vijf determinanten die statistisch significant geassocieerd zijn met een tweevoudig hogere vaccinatiegraad. Deze determinanten zijn: weten dat het vaccin effectief is; bereid zijn om de overdracht van influenza te voorkomen; geloven dat influenza een zeer besmettelijke ziekte is; ervan overtuigd zijn dat de preventie van influenza belangrijk is; en het hebben van een familielid dat gewoonlijk wordt gevaccineerd tegen influenza. Na het uitvoeren van deze meta-analyse wisten wij welke factoren belangrijk zijn in de internationale literatuur voor het ontwikkelen van nieuwe vaccinatiestrategieën.

Ook was het belangrijk om te weten welke factoren geassocieerd zijn met de influenza vaccinatiegraad onder gezondheidszorgwerkers op een nationaal niveau. We hebben daarom een vragenlijstonderzoek uitgezet onder Nederlandse gezondheidszorgwerkers, waarvan de resultaten beschreven staan in **hoofdstuk 5.** 2008 zijn er vijf afdelingen geselecteerd van alle Nederlandse universitair medisc centra (UMCs), waar patiënten een gemiddeld tot hoog risico liepen op het oplopen v influenza: de afdelingen interne geneeskunde, neonatologie, kindergeneeskunde twee intensive care afdelingen. Gezondheidszorgwerkers van deze afdelingen werd e anonieme vragenlijst aangeboden waarin hen werd gevraagd hun mening te geven ov demografische determinanten, gedragsdeterminanten en organisatorisch determinanten die hun vaccinatiegedrag voorspelden. In totaal werden 1295 vragenlijsten ingevuld (responspercentage 39%) en 37.6% van alle respondenten bleek gevaccineerd te zijn tegen influenza. Uit de univariate analyse bleek dat negen van de 11 demografische determinanten significant geassocieerd waren met de acceptatie van de influenza vaccinatie. Dit bleek ook het geval te zijn voor 11 van de 19 organisatorische determinanten en voor 34 van de 39 gedragsdeterminanten. De uiteindelijke multivariate analyse resulteerde in een predictiemodel met 11 determinanten; twee demografische determinanten en negen gedragsdeterminanten. De nauwkeurigheid van dit model was erg hoog met een oppervlakte onder de ‘receiver operating curve’ van 0.95.

Hoofdstuk 6 beschrijft de planning van een veelzijdige influenza vaccinatie implementatie strategie voor gezondheidszorgwerkers in de acute gezondheidszorg. We hebben gebruik gemaakt van de Intervention Mapping methode als kader om een influenza vaccinatie implementatie strategie systematisch te plannen, te ontwikkelen en het proces te evalueren. De Intervention Mapping methode kan worden gebruikt als deel van het dynamische proces voor het plannen van interventie strategieën in voorlichting in de gezondheidszorg en bestaat uit zes stappen: 1) een indicatie stelling; 2) het vaststellen van proximale programma doelstellingen; 3) de ontwikkeling van op theorie gebaseerde methoden en praktische strategieën; 4) programma planning; 5) acceptatie en implementatie van het programma; en 6) programma evaluatie.

In navolging van deze stappen werd het predictiemodel dat in hoofdstuk 5 was ontwikkeld besproken in een onderzoeksteam bestaande uit tien personen. Hierbij werd bekeken in welke mate de determinanten te beïnvloeden waren. Op basis van de effectmaten en de mate van beïnvloedbaarheid, werden de determinanten in vier categorieën verdeeld; kennis, gemeenschappelijk belang, sociale invloed en organisatorisch. De doelstellingen van alle determinanten werden bepaald en methodes en materialen werden ontwikkeld om deze doelstellingen te behalen. Deze methoden en materialen werden vervolgens aangepast tot halffabrikaten en klaargemaakt voor de implementatie. Dit proces werd gesuperviseerd door een communicatie deskundige. Na de implementatie van het programma werd zowel een kwalitatieve als een kwantitatieve evaluatie uitgevoerd. In de kwalitatieve evaluatie werd onderzocht welke elementen van het implementatie programma waren gebruikt door de universitair medische centra. Communicatie rapporten werden opgevraagd, en de contactpersonen van de UMCs werd gevraagd hun mening te geven over de gebruikte materialen. Interventie UMCs en externe UMCs lieten zien meer gebruik te hebben gemaakt van de bewuste determinanten dan de controle UMCs. Voor de kwantitatieve evaluatie werd opnieuw een anonieme vragenlijst verspreid onder gezondheidszorgwerkers van de eerder genoemde vijf afdelingen van de UMCs. Dit gebeurde in het voorjaar van 2010 en 2011, na beide studie seizoenen van 2009/2010 en 2010/2011. De vragenlijst bevatte vragen over het gebruik van de ontwikkelde materialen in hun ziekenhuis. Van alle materialen die zijn ontwikkeld, beoordeelden gezondheidszorgwerkers de posters als datgene wat hun het meest was opgevallen.

Hoofdstuk 7 beschrijft de resultaten van een geclusterde gerandomiseerde gecontroleerde studie (RCT) naar de effecten van het eerder ontwikkelde implementatie programma op de influenza vaccinatiegraad onder gezondheidszorgwerkers en naar de effecten op de morbiditeit van patiënten. De onderzoeksperiode besloeg de griepseizoenen van 2009/2010 en 2010/2011. Alle acht Nederlands universitair medische centra werden uitgenodigd om deel te nemen aan dit onderzoek. Zes UMCs stemden toe om gerandomiseerd te worden op cluster niveau. Zij werden gerandomiseerd in een interventie groep (drie UMCs) en een controle groep (drie

UMCs). De overige twee UMCs weigerden randomisatie en fungeerden als externe controles.

In totaal zijn 3367 patiënten geïncludeerd. De primaire uitkomst was de influenza vaccinatiegraad onder gezondheidszorgwerkers. Secundaire uitkomsten waren absentie onder gezondheidszorgwerkers in de maand december en morbiditeit onder patiënten.

In beide studie seizoenen bleek de influenza vaccinatiegraad onder gezondheidszorgwerkers significant hoger te zijn in de interventie UMCs vergeleken met de controle UMCs. In het pandemische griepseizoen 2009/2010, waar drie vaccinatierondes werden aangeboden, werd het hoogste absolute risicoverschil waargenomen voor de eerste pandemische vaccinatie, namelijk 23.7% (95% BI 4.3 – 47.8). Op de afdelingen interne geneeskunde van de interventie groep waar een hogere vaccinatiegraad bestond vergeleken met de controle groep, werd bij 3.9% van de patiënten nosocomiale influenza en/of een pneumonie geconstateerd in vergelijking met 9.7% van de patiënten in de controle groep (p=0.015). Een verhoging van de vaccinatiegraad is dus geassocieerd met een lagere morbiditeit door influenza en/of een pneumonie onder gehospitaliseerde patiënten.

In **hoofdstuk 8** is de kosten-effectiviteit van het implementeren van een influenza vaccinatie programma onder Nederlandse gezondheidszorgwerkers onderzocht. We lieten zien dat in een base-case scenario waarin geen gezondheidszorgwerkers zijn gevaccineerd, de jaarlijkse kosten voor influenza werden geschat op €389.264 voor een gemiddeld UMC met 8000 gezondheidszorgwerkers en 6000 patiënten die tijdens een griepepidemie zijn opgenomen. Als de influenza vaccinatiegraad onder gezondheidszorgwerkers werd verhoogd naar 23.7%, zoals in het interventie cluster werd gezien in 2009, liet het programma een kostenbesparing zien van €2.993. Wij stellen daarin dat de implementatie van een veelzijdig influenza vaccinatieprogramma resulteert in een kostenbesparing, en dat er meer pogingen zouden moeten worden ondernomen om de vaccinatiegraad onder gezondheidszorgwerkers in Nederlands ziekenhuizen te verhogen.

Deze thesis wordt afgesloten met een algemene discussie in **hoofdstuk 9**. Als eerste wordt de rationale voor het vaccineren van gezondheidszorgwerkers uiteengezet. Verschillende argumenten worden genoemd: de indirecte bescherming van patiënten en familieleden; de individuele bescherming van de gezondheidszorgwerker zelf; productiviteitsverlies door absentie; de kosteneffectiviteit van vaccinatie; en uiteindelijk de morele plicht om patiënten niet te schaden. Daarna wordt de pre-pandemische situatie in Europa en Nederland samengevat. In de meeste Europese landen was de vaccinatiegraad onder gezondheidszorgwerkers laag voor het uitbreken van de 2009 H1N1 pandemie, om tijdens deze pandemie te stijgen. Verder worden de redenen van gezondheidszorgwerkers om zich niet te vaccineren besproken.

De algemene discussie eindigt met de vraag of het verplicht stellen van de influenza vaccinatie een optie is of niet. Als alle argumenten worden beschouwd, zou het verplicht stellen van de griepprik in Nederland moeten worden overwogen. In het ideale geval zou dit een onderdeel zijn van de veelzijdige influenza vaccinatie implementatie strategie. Toekomstige onderzoeken naar de mening van gezondheidszorgwerkers in Nederlandse ziekenhuizen over verplichte vaccinatie tegen influenza kunnen hierbij van nut zijn.

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CURRICULUM VITAE

Josien Riphagen-Dalhuisen was born on the 6th of November 1984 in Oene, the Netherlands. After finishing secondary school at Christelijk College de Noordgouw in Heerde, she started her medical training in 2003 at Utrecht University. In 2009, her scientific internship was fulfilled at the RIVM in Bilthoven, where she studied the antibiotic treatment of Q fever. In Oktober 2009, after graduating as a Medical Doctor, she started working at the department of Epidemiology under the supervision of Prof. dr. Eelko Hak. As of March 2010, she combines this PhD project with a vocational training in general practice. She is currently living in Epe with her husband and son.

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