Original Article

Strategies for Improving Influenza Vaccination Rates in Patients with Chronic Renal Disease

Results from Two Randomized Controlled Trials and a Prospective Interventional Study

Kevin Schulte, Helen Schierke, Miguel Tamayo, Lutz Hager, Roland Engehausen, Matthias Raspe, Ralf-Harto Hübner, Georg Schlieper, Christoph Borzikowsky, Andreas Urbschat, Sven Auerswald, Ulrich Kunzendorf, Thorsten Feldkamp

Department of Nephrology and Hypertension. University Hospital Schleswig-Holstein: Dr. Kevin Schulte, Helen Schierke, Prof. Ulrich Kunzendorf, Prof. Thorsten Feldkamp

Department of Strategic Data Analysis and Health Policy North Rhine–Westphalia, North Rhine Association of Statutory Health Insurance Physicians, Düsseldorf: Miguel Tamayo

IKK Südwest, Saarbrücken: Dr. Lutz Hager, Roland Engehausen

Medical Department, Division of Infectiology and Pneumology, Faculty of Medicine, Charité Berlin: Dr. Matthias Raspe, PD Dr. Ralf-Harto Hübner

Center for Renal, Hypertensive, and Metabolic Diseases, Hanover: PD Dr. Georg Schlieper

Institute of Medical Informatics and Statistics, University of Kiel: Dr. Christoph Borzikowsky

Division of Information Technology—Analysis and Development, Schleswig-Holstein Association of Statutory Health Insurance Physicians, Bad Segeberg: Andreas Urbschat

Thuringia Association of Statutory Health Insurance Physicians, Weimar: Sven Auerswald

Summary

Background: The influenza vaccination rate among older and chronically ill patients in Germany has declined in the past decade in spite of vaccination campaigns.

Methods: The influenza vaccination rate among persons with chronic renal disease was studied with the aid of billing data from various Associations of Statutory Health Insurance Physicians (Kassenärztliche Vereinigungen, ASHIPs) in Germany. It was tested in a randomized controlled trial whether a written vaccination appeal, sent by physicians to patients, led to an increase in the vaccination rate. It was tested in a further such trial whether the vaccination rate among patients with renal disease could be improved by an appeal for vaccination that was sent by the ASHIPs to the treating nephrologists. Finally, it was also tested in a prospective interventional study whether the vaccination rate could be improved by an appeal for vaccination sent by a health-insurance carrier directly to the patients.

Results: In 2012–2017, the vaccination rate among persons with chronically impaired renal function ranged from 41.1% to 46.9%; it ranged from 31.7% to 33.7% in kidney transplant recipients and from 42.7% to 44.7% in dialysis patients. An appeal for vaccination that was sent from physicians to patients raised the vaccination rate by 8.3% in the intervention group compared to the control group ($p = 0.03$; number needed to treat [NNT]: 13). On the other hand, an appeal for vaccination that was sent to the nephrologists lowered the vaccination rate by 0.8% in the intervention group compared to the control group. Finally, an appeal for vaccination that was sent by the health-insurance fund to the patients raised the vaccination rate by 3.2% ($p < 0.001$; NNT: 32).

Conclusion: Fewer than half of all patients with chronic renal failure in Germany are vaccinated against influenza. The vaccination rate was found to be increased only after an appeal for vaccination that was sent directly to the patients. A letter sent to the treating physicians had no positive effect at all.

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In the winter of 2017/2018, there were 324 416 cases of laboratory-confirmed influenza infection among residents of Germany (1). Around 20% of these persons—principally the chronically ill and those over 60 years of age—required inpatient treatment (1). These figures underline the importance of vaccinating risk groups against seasonal influenza each year, as recommended by the German Standing Vaccination Committee and numerous professional societies (2–4). The value of this recommendation was shown by the results of a recently published benefit analysis in the USA: the authors concluded that vaccination against influenza avoided more than 100 000 admissions to hospital and

circa 8000 deaths in the influenza season 2017/2018 (5).

Nevertheless, the rate of vaccination of at-risk patients against influenza in Germany has decreased sharply in recent years. According to an analysis of billing data from the German Association of Statutory Health Insurance Physicians (ASHIP), the national average vaccination rate for persons over 60 was 49% in the season 2006/2007, but only 34.8% in 2016/2017 (6, 7). The situation is similar for the chronically ill, for whom the vaccination rate decreased from 46.2% in the season 2010/2011 to 40.4% in 2013/2014 (8, 9).

FIGURE 1

Flow chart of patient-centered, prospective controlled intervention study; UKSH, University Hospital Schleswig-Holstein, Kiel campus

This negative trend is worrying, particularly in light of the numerous campaigns to increase public awareness of the risk and acceptance of vaccination in recent years. These campaigns focused predominantly on direct persuasion of high-risk patients as to the importance of vaccination. Measures were also taken to encourage primary care physicians to recommend vaccination (10).

These figures clearly illustrate the urgency of effective preventive measures to avoid future epidemics of influenza. In the study presented here, we explored potential strategies specifically for application in patients with chronic renal disease, a group for whom vaccination against influenza is clearly indicated because of the particularly high risk associated with their pronounced multimorbidity (3, 11). After initial analysis of the current vaccination rates on the basis of billing data, we posed the following questions in three independent studies:

1. Does a recommendation in writing directly from physician to patient have a positive effect on the vaccination rate in patients with chronic renal disease?
2. Can a written appeal from a regional ASHIP persuade office-based nephrologists to increase their rate of vaccination of chronically ill patients?
3. Does a direct appeal from a health insurance fund to its members lead to an increase in the vaccination rate among those with chronic renal disease?

Methods

First, the billing data of three regional ASHIPs (North Rhine, Schleswig-Holstein, and Thuringia) were analyzed to ascertain the influenza vaccination rates among patients with chronic renal disease. To this end, data from about 12 million statutory health insurees were analyzed.

To answer the questions described above, we then carried out three separate studies:

FIGURE 2

Flow chart of physician-centered, prospective controlled intervention study; ASHIP, Association of Statutory Health Insurance Physicians

1. In a patient-centered randomized controlled intervention study, all patients who had undergone renal transplantation at the Kiel campus of the University Hospital of Schleswig-Holstein (UKSH) up to spring 2016 (n = 460) were randomized into two groups. Following determination of the patients' vaccination status and attitude to vaccination against influenza in an initial survey, we conducted a second survey to analyze the effect of an appeal from a physician on the vaccination rate and the patients' attitudes. The appeal came from physicians working in the renal transplantation clinic of the UKSH.
2. In a physician-centered randomized controlled intervention study, the office-based nephrologists of the North Rhine ASHIP (n = 141) were randomized into two groups. The intervention group were called upon by the ASHIP to recommend vaccination, and the effect was ascertained by evaluating the vaccination billing data for the following year.
3. In an insurree-centered prospective intervention study, the IKK Südwest health insurance fund sent a vaccination appeal directly to those of their members with chronic renal disease (n = 617). The effect of the intervention was established by analyzing the numbers of vaccinations billed.

Figures 1–3 are flow charts of the three intervention studies. The methods used are described in detail in the *eMethods*.

Results

Influenza vaccination rates in the observation period 2012–2017

During the observation period the influenza vaccination rate for patients with chronic impairment of renal function ranged from a minimum of 41.1% to a maximum of 46.9%. The vaccination rate for renal transplantation patients varied between 31.7% and 33.7%, that for dialysis patients between 42.7% and 44.7%. As well as these fluctuations over time, there were distinct differences among the ASHIP regions (Table, eTable 1). The groups differed considerably in number of physician–patient contacts. In Schleswig-Holstein, for example, the average of contacts with the patient's primary care physician or nephrologist was 12.6 for those with chronically impaired renal function, 12.1 for renal transplantation patients, and 35.5 for patients dependent on dialysis. In 79.5% of patients with chronically impaired renal function, influenza vaccination was additionally indicated on grounds of age (>60 years). This also applied to 43.1% of patients who had undergone renal transplantation and to 66.4% of dialysis patients (eTable 2).

Findings of the patient-centered intervention study

The patients' characteristics (age, sex, type of donation, and time since transplantation) did not differ significantly between the first and second surveys or between

Flow chart of insurree-centered prospective intervention study

the control and intervention groups (*eTable 3*). In the intention to treat (ITT) analysis, the influenza vaccination rate was 37.4% in the intervention group and 29.1% in the control group. Compared with the first survey (vaccination rate 35.2%), the rate rose by 2.2% in the intervention group and fell by 6.1% in the control group ($p = 0.03$), yielding an intervention effect of 8.2% (*Figure 4*). Therefore 13 intervention letters (= number needed to treat, NNT) had to be sent to achieve one additional vaccination against influenza. The proportion of participants who were of the opinion that an influenza vaccination could have severe adverse effects was 7.8% in the intervention group and 6.5% in the control group, decreasing from the figure in the initial survey (11.1%) by 3.3% and 4.6% respectively ($p = 0.29$). Influenza was believed to be a dangerous disease by 37% of participants in the intervention group and 36.1% of those in the control group ($p = 0.42$). In comparison with the initial value (40.7%), these figures represented decreases of 3.7% and 4.6% respectively. The flow chart in *Figure 1* shows the numbers of drop-outs after randomization. The results of per protocol analysis can be found in *eTable 4*.

Findings of the physician-centered intervention study

The characteristics of the office-based nephrologists did not differ between the intervention and control groups after randomization (*eTable 5*). There were no study drop-outs following randomization. The increase in influenza vaccination rate was lower in the intervention group than in the control group, at 0.3%

(2015/2016: 39.7%, 2016/2017: 40.0%) and 1.1% (2015/2016: 42.2%, 2016/2017: 43.3%) respectively. The intervention effect was therefore -0.8% (*Figure 4*). Restricting analysis to patients who were vaccinated by their nephrologist, the vaccination rate fell by 1.0% in the intervention group (2015/2016: 9.6%, 2016/2017: 8.6%) and rose by 1.0% in the control group (2015/2016: 11.9%, 2016/2017: 12.9%).

Findings of the insurree-centered intervention study

In the ITT analysis, the rate of vaccination against influenza climbed from 36.3% (2015/2016) to 39.5% (2016/2017), an increase of 3.2% (NNT 32, $p < 0.001$) (*Figure 4*). Including only those who lived to the end of the vaccination season (per protocol analysis), the vaccination rate rose by 3.8% from 36.3% (2015/2016) to 40.1% (2016/2017) (NNT 27; $p < 0.001$). None of the insurees used the hotline that had been set up to answer any queries. To uncover any general changes in influenza vaccination behavior in the same vaccination season, we investigated the vaccination rate among insurees with chronic pulmonary disease ($n = 79\ 411$) and found a decrease from 13.3% to 13.2%.

Discussion

The study presented here is the first to analyze the vaccination rate for chronically ill patients in Germany by means of billing data rather than telephone interviews. We found that less than half of our study population of patients with renal disease were vaccinated against influenza over the course of the observation period. Interestingly, the vaccination rate for patients with chronic impairment of renal function was only slightly lower than that for patients dependent on dialysis, although the latter had almost three times as many contacts with physicians per quarter. The vaccination rate is thus associated neither with the number of physician–patient contacts nor with the severity of the chronic illness. Rather, comparison of patients with chronically impaired renal function and those who had undergone renal transplantation shows that the vaccination rate tends to be determined by the proportion of patients for whom vaccination is also indicated on grounds of age. In daily practice, therefore, awareness of the importance of vaccination against influenza for the chronically ill seems lower than that of its significance in the elderly. This had already been indicated by previous investigations showing higher vaccination rates in chronically ill patients over 60 than in their younger counterparts (9).

In the first of the three approaches presented here, we evaluated whether an appeal in writing from a physician has the potential to increase the vaccination rate in patients with renal transplants or positively influence their attitude to influenza vaccination. The described intervention led to an increase of 8.3 percentage points in the vaccination rate compared with the control group. Thirteen intervention letters and circa €10 in printing and postage costs were thus required to achieve one additional vaccination. This

finding points in the same direction as several studies from other countries that also demonstrated a positive effect of a vaccination reminder from the treating physician (12–14). Assuming, as we did, that the selected intervention has no negative effect on the vaccination rate among the patients contacted (one-sided test, $p = 0.03$), the intervention exerted a significant influence on the vaccination rate. However, in interpreting the effect of the intervention one must take into account the wide confidence interval (Figure 4), which is largely determined by the sample size. For instance, it is quite feasible that a closer relationship between physician and patient than was the case in our study might positively influence the intervention effect.

With regard to the secondary endpoint of the study, the intervention had no positive effect on the patients' assessment of the risk of adverse effects or the severity of influenza as a disease. The increase in the vaccination rate of the intervention group was therefore not due to any modification of the patients' attitudes. This is a striking finding, because previous studies have presented convincing data to show that insufficiently or inaccurately informed patients have often not been vaccinated (9). Therefore many campaigns—like ours—are informative in nature. Our results show, however, that it is obviously not necessary to change patients' attitudes in order to increase the vaccination rate. It seems that thinking about vaccination, or just being reminded about it, is more important for the patients.

In the second approach we explored whether an appeal in writing from the regional ASHIP can influence the vaccination behavior of office-based physicians and thus indirectly help to increase the vaccination rate. This intervention showed no positive effect on the patients' vaccination rate. Since consistently correct coding and billing of the vaccinations given can be expected on financial grounds, this is unlikely to be a false-negative result. It is more likely that the information provided in our study was not conveyed with enough urgency to attract attention in daily practice, or that the appeal was not followed because of hitherto unknown barriers to implementation.

One of the most important vaccination campaigns of recent years in Germany is the “Let's Beat Flu to It” (“*Wir kommen der Grippe zuvor*”) campaign, jointly run by the Federal Centre for Health Education and the Robert Koch Institute since 2006 (10). Repeatedly, more than 50 000 primary care physicians have been sent letters urging them to vaccinate their patients against influenza. The effect has not yet been scientifically evaluated; however, our findings in the study presented here suggest that such a campaign does not result in an increased vaccination rate (10, 15). On the basis of our data it would seem appropriate to question the utility of this kind of approach.

In the third approach we tested whether a vaccination reminder from a health insurance fund has an effect comparable to a reminder from a physician. We

TABLE

Influenza vaccination rate in patients with chronic renal disease, 2012–2017*

Region	2012	2013	2014	2015	2016	2017
Indication: Chronic impairment of renal function (EBM 13600)						
Schleswig-Holstein	40.6	46.9	48.8	46.3	47.3	46.4
Thuringia	50.1	54.3	53.8	52.4	52.3	53.8
North Rhine	38.8	42.6	41.6	40.6	40.7	–
Overall	41.1	46.9	45.3	43.9	44.0	–
Indication: Renal transplantation (EBM 13601)						
Schleswig-Holstein	35.1	38.2	35.0	37.0	39.9	39.5
Thuringia	38.0	39.1	37.2	36.7	38.8	40.3
North Rhine	29.0	29.1	32.2	29.3	30.4	–
Overall	31.7	32.5	33.6	32.0	33.7	–
Indication: Dependence on dialysis (EBM 13602)						
Schleswig-Holstein	48.1	52.6	47.2	48.0	48.3	49.3
Thuringia	44.5	44.8	45.7	47.4	46.2	47.0
North Rhine	41.7	42.7	40.6	40.8	41.0	–
Overall	43.3	44.7	42.7	43.3	43.2	–

* EBM is the standard German Physicians' Fee Schedule. From 2013 the definition of EBM code number 13600 was changed (threshold for estimated glomerular filtration rate raised from ≤ 20 mL/min to ≤ 40 mL/min).

The corresponding absolute numbers are presented in eTable 1.

found that this intervention did indeed significantly increase the vaccination rate of patients with chronic renal disease, but not to the same extent as our patient-centered intervention. Overall, 32 letters had to be sent to achieve one additional vaccination against influenza. This result is in the same order of magnitude as the effect of a centralized reminder system recently tested in Colorado, USA (16). In that study the intervention raised the rate of vaccination against influenza by 3.4% (NNT: 30). Several studies have indicated that influenza vaccination is a cost-effective prophylactic measure, particularly in high-risk patients (17–19). It is estimated that US\$ 73 (circa € 65) in direct health-related costs can be saved by each vaccination (20). To what extent these figures are transferable to the German situation is unclear, but in view of the overall cost of an influenza vaccination (circa € 22) the expense generated by our intervention (circa € 25 for printing and postage to achieve one additional vaccination) does not seem excessively high.

Our study suggests that physicians could raise vaccination rates among their patients by adding written prompts to direct verbal reminders. To achieve a nationwide increase in vaccination rates, however, it would seem more pragmatic to establish vaccination reminder systems at the level of the health insurance funds. Such an approach has several potential advantages: An insurance fund covers far more patients than a physician's office, facilitating widespread implementation. Moreover, redundant establishment of

Effect of the intervention studies on the vaccination rate of patients with chronic renal disease. The 95% confidence intervals are shown as error bars.

Patient-centered study	(95% CI [-0.3; 16.8])
Physician-centered study	(95% CI [-0.9; -0.7])
Insuree-centered study	(95% CI [1.8; 4.7])

reminder systems would be ruled out. Furthermore, the principle could be extended, as and when required, to other indications, e.g., to combat low rates of vaccination against measles or HPV (21, 22). In the form tested here, the insurance fund approach offers scope for improvement: The wording and timing of the communications could be better adapted to the requirements of the target group, and insurees not vaccinated in the previous year could be prioritized. On grounds of data protection and costs, a key role could be played by digital reminder systems in which the insurees control the data. Any such system should be contained in the electronic medical record.

This approach would, for the first time, largely individualize the dissemination of information about vaccination. Rather than sending the same standard communications to everyone, information material could be tailored to the needs of the respective target group.

Limitations

- Direct comparison of our different studies is limited by the fact that the patient collectives are not uniform (kidney transplant patients versus patients with chronic renal disease).
- Because patients with other chronic illnesses might react differently to the same interventions, the findings cannot be generalized with any certainty.
- Despite the similarity of the patient characteristics between the initial and follow-up surveys of the

patient-centered intervention study, and despite the high response rate, the anonymization that was carried out means there is no guarantee that the same patients participated in both surveys.

- On data protection grounds, the ASHIP did not carry out any person-related data evaluation. The samples in this intervention study are therefore not strictly paired, so the possibility that the results are affected by patients who changed physician cannot be ruled out. However, the size of the sample means that a meaningful effect is very unlikely.
- With regard to the control group of the insuree-centered intervention study (insured persons with chronic pulmonary disease), it cannot be absolutely ruled out that factors external to the study (e.g., vaccination campaigns) affected only the behavior of patients with chronic renal disease.

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Data sharing

All of the data on participants in the patient-centered intervention study can be provided to interested researchers in anonymized form. The primary data from the physician-centered and insuree-centered intervention studies cannot be made available. All applicants should enclose a methodologically sound proposal for analysis of the data concerned and guarantee that the data will not be used for any other purpose. Applications should be sent to Dr. med. Kevin Schulte, Medizinische Klinik IV, Rosalind-Franklin-Str. 12, 24105 Kiel, Germany. The data will be available from 3 months to 5 years after publication of this article.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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Key messages

- Less than half of all patients with chronic kidney disease are vaccinated against influenza as recommended in the prevailing guidelines
- Calls for vaccination are effective only if addressed directly to the patient.
- The effect seems to be greater if the appeal comes from the treating physician rather than the patient's health insurance fund.
- A call for vaccination addressed to treating physicians has no positive effect on their vaccination behavior.

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Corresponding author

Dr. med. Kevin Schulte
Klinik für Nieren- und Hochdruckkrankheiten
Universitätsklinikum Schleswig-Holstein
Rosalind-Franklin-Str. 12
24105 Kiel, Germany
Kevin.Schulte@uksh.de

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► Supplementary material:

eMethods, eTables, eSupplement:
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Supplementary material to:

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eMETHODS

Analysis of vaccination rates

The influenza vaccination rates for the years 2012 to 2017 were investigated using billing data from the Associations of Statutory Health Insurance Physicians (ASHIPs) for the regions North Rhine, Schleswig-Holstein, and Thuringia. Patients with chronic impairment of renal function were identified from the EBM code 13600 (eGFR [estimated glomerular filtration rate] up to 2013, <20 mL/min; thereafter, eGFR <40 mL/min); renal transplant patients, from the EBM code 13601; and patients dependent on dialysis, from the EBM code 13602. (EBM is the standard Physicians' Fee Schedule used in Germany). To calculate the vaccination rates we ascertained the mean value for the four quarters of the year in question. Those persons who had been assigned the EBM codes 89111 or 89112 in a quarter of the year concerned were defined as having received a vaccination. Because the EBM code 13600 was redefined at the beginning of the third quarter of 2013 (eGFR threshold raised from ≤ 20 mL/min to ≤ 40 mL/min), we used only the third and fourth quarters of that year to calculate the case numbers in order to avoid overestimating the vaccination rate. The study population comprised all inhabitants of the above-mentioned ASHIP regions with statutory health insurance, i.e., over 90% of residents (ca. 12 million people). The patients' age structure and the average number of visits to physicians per quarter were established on the basis of the ASHIP Schleswig-Holstein data. The data were analyzed directly by ASHIP staff and provided to us in aggregated form.

Intervention studies

The intervention studies described here were funded from their own resources by the Department of Nephrology and Hypertension of the Kiel campus of University Hospital Schleswig-Holstein, the ASHIP concerned, and the IKK Südwest health insurance. All three of the intervention studies were submitted to the ethics committee of the University of Kiel and found to be legally and ethically acceptable or not requiring approval (D 465/16). Moreover, the studies were registered in the German Clinical Trials Register (DRKS 00016558).

Patient-centered prospective controlled intervention study

The goal of this intervention study was to explore whether a vaccination appeal from a physician, in the form of an letter with relevant information, could have a positive effect on the vaccination rate among patients with chronic renal disease or on their attitude to vaccination against influenza.

Study design and patients

This prospective controlled intervention study of two-arm parallel-group design included all patients who had undergone renal transplantation at the Kiel campus of University Hospital Schleswig-Holstein and were still being followed up in spring 2016 ($n = 460$). Equal numbers of patients were allocated to the intervention group and the control group.

Intervention

All patients were sent an initial questionnaire (*eQuestionnaire*; document in German) in spring 2016 to determine their vaccination status and their basic attitude to annual vaccination against

influenza. Two hundred fifty patients (54.3%) submitted evaluable responses to the study center. At the beginning of the vaccination season 2016/2017, the patients in the intervention group were sent a letter containing a flyer with information about influenza vaccination together with their physician's recommendation to have the vaccination (*eSupplement*; document in German). At the beginning of April 2017 the patients in both the intervention group and the control group received a second questionnaire to measure the intervention effect. All letters were signed and sent by physicians from the renal transplantation clinic of the Kiel campus of University Hospital Schleswig-Holstein. A total of 18 deaths reduced the intervention group to 222 patients and the control group to 220 patients, of whom 50% (n = 111) and 43.6% (n = 96), respectively, submitted evaluable responses.

Endpoints

The influenza vaccination rate of the renal transplant patients was defined as primary endpoint. Secondary endpoints were the patients' attitudes towards the risk of adverse effects of vaccination and the danger associated with influenza infection.

Randomization

Randomization of patients to the intervention or control group was simple with no limitations. Every second patient from the alphabetically ordered address list was allocated to the intervention group.

Blinding

Because the intervention comprised contact with the patient, no meaningful blinding of the patients was feasible. Nonetheless, to avoid any influence on their behavior, neither in the initial survey nor in the intervention letter were the patients told that they would be receiving a second questionnaire.

Statistical evaluation

The characteristics of the surveyed patients (first and second surveys; intervention and control groups) were compared by means of the χ^2 test (two-sided testing). Because there was no certainty that exactly the same patients had participated in the two surveys and the samples were therefore not strictly paired, the longitudinal data from this intervention study were analyzed descriptively. Both intention to treat analysis and per protocol analysis were carried out. To test whether the intervention had a positive effect on the defined endpoints, the intervention group and the control group were compared by means of the χ^2 test. Because a large number of previous studies suggested a positive influence of an intervention on the endpoints, one-sided testing was performed. The calculated measure of effect was the number needed to treat, i.e., the number of intervention letters required to achieve one additional vaccination. The result was always rounded up to the next whole number. The 95% confidence interval for the primary endpoint was given to enable estimation of the effect range.

Physician-centered prospective controlled intervention study

The goal of this intervention study was to find out whether a vaccination appeal directed at physicians leads to an increased vaccination rate among their patients with chronic renal disease.

Study design, probands, and patients

This prospective controlled intervention study of two-arm parallel-group design included all office-based nephrologists licensed to practice in the North Rhine region in 2016 (n = 141). Equal numbers of them were allocated to the intervention group and the control group. In the vaccination season 2015/2016, the nephrologists of the intervention group treated 16 693 patients and those in the control group treated 14 020 patients; in 2016/2017, the numbers treated were 18 959 and 17 038 respectively.

Intervention

At the beginning of the vaccination season 2016/2017, the office-based nephrologists in the intervention group received a letter written by the management team of the ASHIP North Rhine and the authors of this article urging them to vaccinate their patients with chronic renal disease against influenza (*eSupplement*; document in German).

Endpoint

The influenza vaccination rate of patients with chronic renal disease treated by the office-based nephrologists in the vaccination season concerned was defined as primary endpoint. The vaccination rate was determined from the number of vaccinations billed in the vaccination season 2016/2017 (1 October 2016 to 31 March 2017).

Randomization

The nephrologists were randomly allocated to the intervention or control group simply and with no limitations using the statistical software SPSS.

Blinding

Because the intervention comprised contact with each member of the intervention group, no meaningful blinding of the nephrologists was feasible. Nonetheless, to avoid any influence on their behavior they were not informed of the aim of the research.

Statistical evaluation

Following randomization the characteristics of the intervention group and the control group were compared by means of the χ^2 test (two-sided testing). Because there was no certainty that the nephrologists treated exactly the same patients in the vaccination seasons 2015/2016 and 2016/2017, and the samples were therefore not strictly paired, the longitudinal data from this intervention study were analyzed descriptively. The 95% confidence interval is given to enable estimation of the effect of the intervention.

Insuree-centered prospective intervention study

The aim of this intervention study was to investigate whether an appeal from a health insurance fund can lead to an increase in the vaccination rate of patients with chronic renal disease.

Study design and patients

This prospective intervention study included all persons insured by IKK Südwest for whom vaccination against influenza was indicated on grounds of chronic renal disease in the vaccination season 2015/2016 ($n = 617$; 0.1% of insurees). These patients were identified from the ICD codes Z49.1, N18.5, and Z94.0.

Intervention

On 1 October 2016 the IKK Südwest sent every person in the group defined above a letter with an information flyer (*eSupplement*; document in German). A telephone hotline was set up to answer any queries. Forty-one members of the group had died by the end of the vaccination season (31 March 2017).

Endpoint

The influenza vaccination rate in the intervention group was defined as primary endpoint. The vaccination rate was determined from the number of vaccinations billed in the vaccination season 2016/2017.

Randomization

There was no randomization.

Control group

To detect any general changes in influenza vaccination behavior in the vaccination season concerned, the influenza vaccination rate among IKK Südwest insurees with chronic lung disease (defined by ICD codes J40 to J47) was measured over the same period. The analysis was analogous to the intention to treat analysis in the intervention group.

Blinding

There was no blinding.

Statistical evaluation

Because the samples in this study were paired, the McNemar test was used for statistical evaluation. Because previous studies suggested a positive influence of an intervention on the endpoints, one-sided testing was performed. Both intention to treat analysis and per protocol analysis were performed. As measure of effect we have given the number needed to treat, i.e., the number of intervention letters required to achieve one additional vaccination. The result is always rounded up to the next whole number. The 95% confidence interval for the primary endpoint is given to enable estimation of the effect range.

Data sharing

All of the data on participants in the patient-centered intervention study can be provided to interested researchers in anonymized form. The primary data from the physician-centered and insuree-centered intervention studies cannot be made available. All applicants should enclose a methodologically sound proposal for analysis of the data concerned and guarantee that the data will not be used for any other purpose. Applications should be sent to Dr. med. Kevin Schulte, Medizinische Klinik IV, Rosalind-Franklin-Str. 12, 24105 Kiel, Germany. The data will be available from 3 months to 5 years after publication of this article.

eTABLE 1

Vaccinated and unvaccinated patients with chronic renal disease in the ASHIP areas Schleswig-Holstein, Thuringia and North Rhine 2012–2017

Region	2012		2013		2014		2015		2016		2017	
	Total	Vaccinated	Total	Vaccinated	Total	Vaccinated	Total	Vaccinated	Total	Vaccinated	Total	Vaccinated
Indication: Chronic impairment of renal function (EBM 13600)												
Schleswig-Holstein	1463	594	3247	1523	3325	1622	3490	1617	3817	1804	4236	1967
Thuringia	2389	1198	6938	3767	8910	4792	9115	4777	9675	5058	9997	5378
North Rhine	9334	3621	21 635	9223	24 141	10 051	26 612	10 804	27 852	11 340	–	–
Overall	13 186	5413	30 949	14 513	36 376	16 465	39 217	17 198	41 344	18 202	14 233	7345
Indication: Renal transplantation (EBM 13601)												
Schleswig-Holstein	1096	385	1166	445	1241	434	1249	462	1293	516	1329	525
Thuringia	1041	396	960	375	945	352	953	350	983	381	954	384
North Rhine	3825	1108	3813	1108	3748	1205	3937	1153	3937	1197	–	–
Overall	5962	1889	5939	1928	5934	1991	6139	1965	6213	2094	2283	909
Indication: Dependence on dialysis (EBM 13602)												
Schleswig-Holstein	2391	1151	2441	1285	2528	1194	2532	1215	2568	1239	2680	1320
Thuringia	3170	1411	3131	1404	3001	1372	3015	1428	2999	1385	2973	1396
North Rhine	9289	3870	9442	4029	9597	3895	9934	4057	10 116	4150	–	–
Overall	14 850	6432	15 014	6718	15 126	6461	15 481	6700	15 683	6774	5653	2716

EBM, Physicians' Fee Schedule; ASHIP, Association of Statutory Health Insurance Physicians

eTABLE 2

Vaccination rate, age-related indication for vaccination, and number of physician contacts per quarter in the ASHIP Schleswig-Holstein for the billing year 2017

	Chronic impairment of renal function (EBM 13600)	Renal transplantation (EBM 13601)	Dependence on dialysis (EBM 13602)
Vaccination rate	46.4%	39.5%	49.3%
Proportion of patients >60 years of age	79.5%	43.1%	66.4%
Number of physician contacts per quarter			
– Nephrologist	6.8	10.1	32.9
– Primary care physician	5.8	2.0	2.6
– Overall	12.6	12.1	35.5
Vaccinated by			
– Nephrologist	14%	66%	77%
– Primary care physician	84%	30%	22%

EBM, Physicians' Fee Schedule; ASHIP, Association of Statutory Health Insurance Physicians

eTABLE 3

Characteristics of the renal transplant patients in the intervention group and the control group

	First survey (n = 250)	Second survey (n = 207)	Intervention group (n = 111)	Control group (n = 96)	p value*
Sex					
Female	113	86	43	43	p = 0.68
Male	137	121	68	53	
Age (years)					
<40	14	10	4	6	p = 0.21
40–60	126	99	47	52	
>60	109	98	60	38	
No data	1	0	0	0	
Type of donation					
Living donor	57	50	26	24	p = 0.60
Deceased donor	189	149	82	67	
No data	4	8	3	5	
Years since transplantation					
>6	141	112	56	56	p = 0.76
5–6	36	27	17	10	
3–4	42	36	21	15	
<3	27	28	15	13	
No data	4	4	2	2	

* Comparison between control group and intervention group

eTABLE 4

Per protocol analysis of the patient-centered intervention study*

	First survey (2015/2016)	Control group (2016/2017)	Intervention group (2016/2017)	p value
Primary endpoint				
Vaccination rate	64.8%	69.8%	77.5%	p = 0.14
Secondary endpoint				
– Fear of adverse effects	20.5%	15.6%	16.0%	p = 0.42
– Perception of disease severity	75.1%	86.7%	77.6%	p = 0.03

* The p values relate to comparisons of the control group with the intervention group. The vaccination rates for the per protocol population are higher because in the intention to treat population all patients for whom there was no response were classified as unvaccinated.

eTABLE 5

Characteristics of the office-based nephrologists in the intervention group and the control group

	Intervention group (n = 70)	Control group (n = 71)	p value
Sex			
Female	13	16	0.84
Male	55	53	
No data	2	2	
Age (years)			
<50	18	22	0.78
50–60	36	37	
>60	14	10	
No data	2	2	