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Improving the vaccination status of liver transplant patients: Effectiveness of personally addressing patients and written recommendations to family physicians after 3 years

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Abstract

Background: After documenting insufficient vaccinations in 444 liver transplant (LT) patients, we investigated the effects of a combined strategy (addressing both patients and primary care physicians) on immunization prevalences after a 3-year follow-up.

Methods: The primary care physicians of all adult LT patients from a university center received a written recommendation addressing immunization needs. Patients were asked for their vaccination documents by phone. Changes in immunization rates for vaccine-preventable diseases after the intervention were calculated based on patients' immunization documents from 2014-2016.

Results: The study cohort consisted of 401 patients. Prevalence rates for all vaccinations improved during the intervention period compared to the baseline study: tetanus from 88.3% to 92.8%, diphtheria from 80.0% to 89.0%, hepatitis A from 50.1% to 60.8%, hepatitis B from 66.3% to 77.1%, and pneumococci from 62.8% to 76.3%. The influenza vaccination rate improved, but remained at a low level before (2010:13%, 2011:11.5%, 2012:19%) and during the intervention (2014:27.4%, 2015:24.4%, 2016:23.2%). Despite these vaccinations, the prevalence rates of the quality indicators *standard vaccinations completed* (2013:17.2%; 2016:21.2%), *indicated vaccinations completed* (2013:2.7%, 2016:4.5%), and *all vaccinations completed* (2013:1%; 2016 1.5%) improved only slightly.

Conclusions: Our results demonstrated that intensified communication by written information to the primary care physician and phone calls to the patients improved the number of vaccinations. Nonetheless, a potential for further improvement persists, especially with regard to annual influenza vaccinations.

KEYWORDS

intervention strategy, liver transplantation, vaccination

1 | INTRODUCTION

Insufficient vaccination rates are documented for high-risk patients, for example recipients of solid organ transplants (SOT),[1] even though vaccinations are necessary to reduce risks of infection, especially pneumococcal infections, which occur in 146 per 100 000 transplant patients per year. This is 12.8 times higher than in the general population (11.5 per 100 000 persons per

year).[2] Crucial for our study is that liver transplant patients exhibit the highest rate among SOT recipients (354 pneumococcal infections per 100 000 liver transplant patients per year).[2] Multiple factors are responsible for this high rate, for example the immunosuppressive therapy, insufficient vaccination status, poor antibody response to vaccines, malfunction of the spleen, and defective opsonizing antibodies present in chronic liver disease.[3] Consistent with studies of kidney and lung transplant recipients, we recently documented insufficient vaccination rates for LT patients: only 1% of the patients had immunization coverage according to current recommendations.[1]

There are different approaches to improve vaccination rates that have already been compared in various Cochrane reviews: client-based interventions focus on information and advice in the form of brochures, letters, emails, and telephone calls to educate patients on the need of vaccinations.[4] Provider-based interventions aim to increase physicians' focus on vaccinations to increase vaccination rates. Such interventions provide information material, install reminder systems and/or give feedback to healthcare services.[4,5] The studies analyzed in the Cochrane reviews included both developed countries[5-7] as well as low- and middle-income countries[7-9]; the target was to improve immunization rates both among children[6,7,9] and adults.[5,6] However, the question of how to specifically increase the vaccination coverage of liver transplant patients has not been explored thus far.

This study aimed at improving the vaccination status among adult LT patients of the outpatient clinic of the Post Liver Transplant Clinic of the University Hospital Essen, Germany. The study was a cooperation of this clinic with the Institute for General Medicine, both located at the University Hospital Essen, University of Duisburg-Essen. The study assessed the effectiveness of a combined strategy (addressing both patients and primary care physicians) on vaccination prevalences among LT patients 3 years after the start of the intervention.

2 | PATIENTS AND METHODS

Baseline data were collected in 2013.[1] Starting on January 1, 2014, an intervention was launched which addressed primary care physicians and patients. First, the primary care physicians of all participating LT patients received a written guideline-based recommendation for immunizations along with the tertiary care centers' quarterly patient report. Secondly, in an attempt to increase patients' awareness for the need to vaccinate, patients were contacted by phone by the LT outpatient clinic before a scheduled visit there and were asked to bring their immunization documents to their next visit to extract the immunization history which was then entered in a pseudonymized dataset. The follow-up data collection was performed between January 2015 and December 2018. All vaccinations administered between January 1, 2014 and December 31, 2016 were included in the follow-up analysis.

Prevalence rates for pneumococcal, influenza (for the current season), hepatitis B, hepatitis A, tetanus, and diphtheria vaccinations were calculated because these are recommended in current guidelines specifically addressing SOT patients.[10,11] The immunization rates and the changes in the prevalences for these vaccinations recommended for LT patients were calculated by comparing and analyzing baseline (updated data were used) and follow-up data for the intervention period 2014-2016. For influenza vaccinations, the vaccination rates were presented for the period 2010-2016 in order to identify a possible intervention effect of this seasonal vaccination.

Based on the recommendations issued by the German Standing Committee on Vaccination,[10,11] three quality indicators were already defined in the baseline study to characterize patients' vaccination status [1]:

1. "Standard vaccinations completed": Patient completed all vaccinations recommended for the general adult population, that is three baseline vaccinations for tetanus, diphtheria, and polio, and subsequent tetanus-diphtheria boosters every 10 years for adults, supplemented by a pertussis vaccine once in adulthood;
2. "Indicated vaccinations completed": Patient completed vaccinations for disease or age-dependent vaccinations: for seniors of the general population (≥60 years) an annual influenza and a once-per-lifetime immunization against pneumococci is recommended; for LT patients, the recommendations include recurrent vaccinations against pneumococci (every 5 years), hepatitis A, hepatitis B, and seasonal influenza.
3. "All vaccinations completed": If an individual had received all standard and indication vaccinations, this quality indicator was fulfilled.

All analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp.). All participants received written information and signed informed consent forms. Ethical approval was obtained from the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (reference number: 13-5633-BO, date of approval: 29/01/2014).

3 | RESULTS

3.1 | Study population

Of the 812 registered LT patients, 581 visited the outpatient clinic at least once during the recruitment phase and were asked for study participation. A total of 469 patients participated and provided documentation of their immunization history, which was legible in 444 cases (76.4%), and constituted the study population. Of these 444 patients, 43 (9.7%) died during the intervention period. Accordingly, the final study population consisted of 401 patients. The causes of death were not analyzed because data were not accessible in many cases.

57.1% (n = 229) of the 401 included study participants were male; the mean age of the patients was 52.3 years at the start of the intervention. The majority of the patients had received a transplant due to chronic liver failure (77.0%). For details, we refer to the baseline study.[1]

3.2 | Immunization rates among LT patients

Of the 401 study participants, the number of patients who received at least one necessary pneumococcal vaccination per year increased during the intervention period: while the annual vaccination rate was 46.4% (n = 186) at baseline, it increased to an average annual vaccination rate of 58.5% (n = 234) during the intervention period (vaccination rate per year: 2014:56.9% [n = 228], 2015:58.4% [n = 234], 2016:60.1% [n = 241]). For details see Figure 1.

In 2013, only 62.8% (n = 252) of the patients received at least one pneumococcal vaccination in their life; in 2016 the rate was 76.3% (n = 306). For details see Figure 2.

Based on the recommendation for pneumococcal booster vaccinations after 5 years in SOT recipients, a total of 21.2% (n = 65) LT patients needed a booster vaccination in 2016; in 2013 this figure was 26.2% (n = 66). The recommendations changed in 2017.

At baseline, 65.1% (n = 261) of the LT patients received at least one necessary diphtheria vaccination per year; in the course of the intervention period this already increased to 73.8% (n = 296) in 2014, 77.1% (n = 309) in 2015 and 75.3% (n = 302) in 2016 (average annual vaccination rate 2014-2016:75.4% [n = 302]). Thus, the proportion of patients who received at least one diphtheria vaccination in their life increased from 80.0% (n = 321) in 2013 to 89.0% (n = 357) in 2016, and those with a completed course of diphtheria immunization

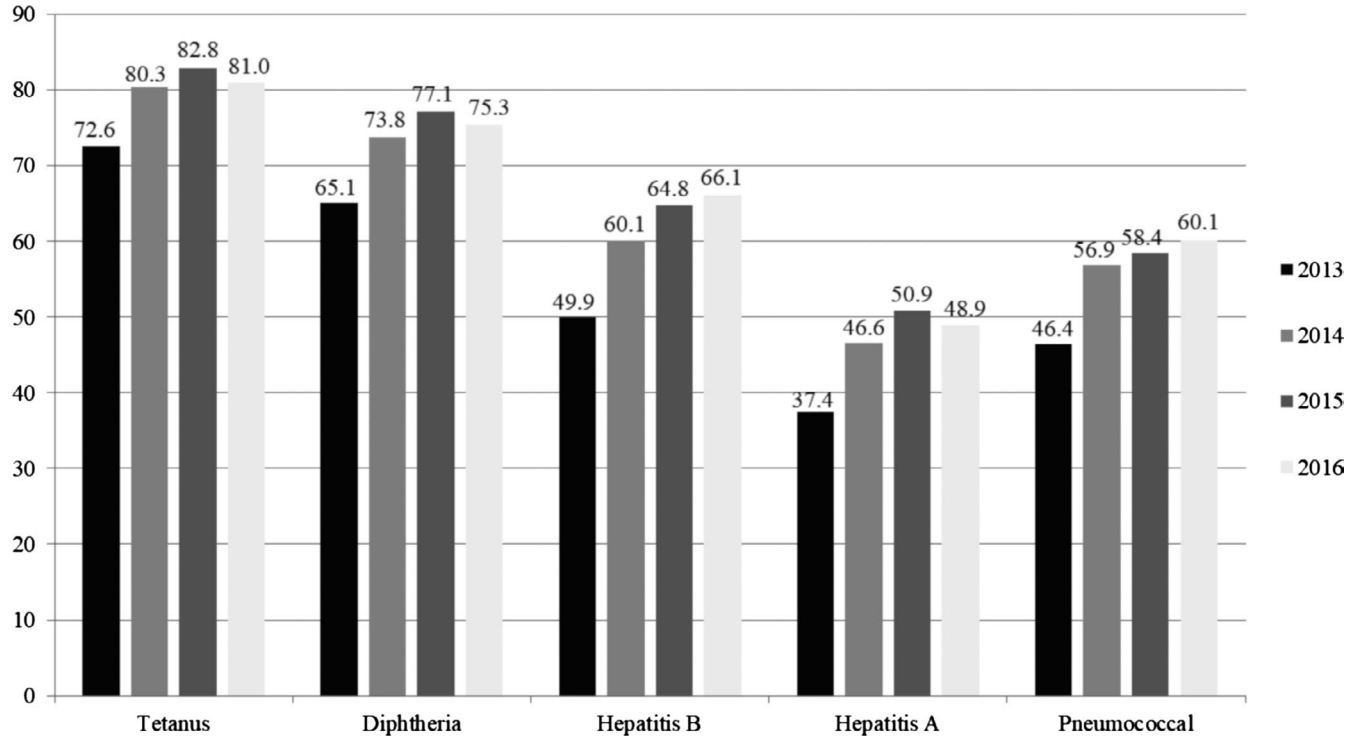

FIGURE 1 Comparison of vaccination rates per year at baseline 2013 and during the intervention period 2014-2016 in % (n = 401)

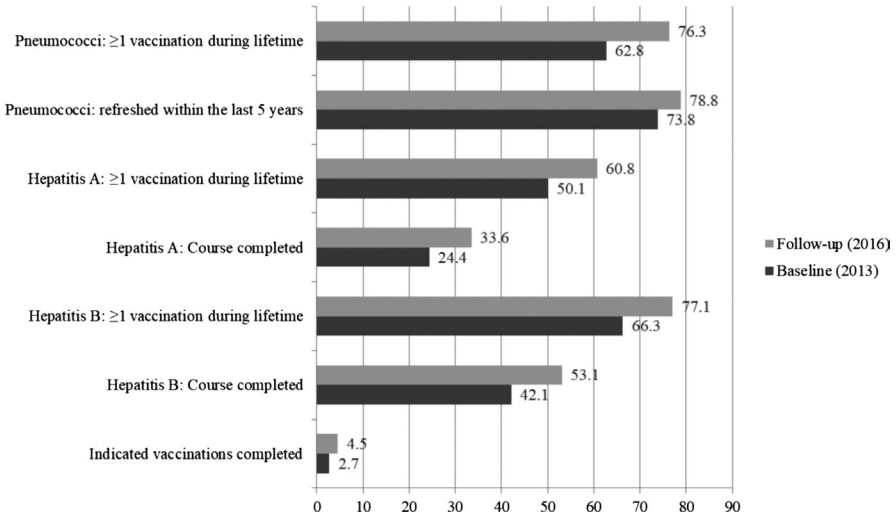

FIGURE 2 Comparison of vaccination rates and quality indicator for indicated vaccinations in % (n = 401)

rose from 31.7% (n = 127) in 2013 to 40.4% (n = 162) after the intervention in 2016.

A similar trend was observed in the annual vaccination rates for tetanus: compared to 2013 (72.6% [n = 291]), the immunization rate for tetanus improved significantly with an average annual vaccination rate of 81.4% (n = 326) during the intervention period (≥1 tetanus vaccination/y: 2014:322 patients [80.3%], 2015:332 patients [82.8%], 2016:325 patients [81.0%]). In 2013, 88.3% (n = 354) of the patients had received at least one tetanus vaccination in their life, in 2016 this had increased to 92.8% (n = 372) of LT patients. Accordingly, more patients showed a complete course of the tetanus vaccination: 42.1% (n = 169) in 2013 and 51.6% (n = 207) in 2016. For details see Figure 3.

The number of patients who received at least one necessary hepatitis B vaccination per year during the intervention period (average annual vaccination rate: 63.6% [n = 255]; 2014:60.1% [n = 241], 2015:64.8% [n = 260], 2016:66.1% [n = 265]) was significantly higher than at baseline in 2013 (49.9% [n = 200]). While 66.3% (n = 266) of LT patients had received at least one vaccination against hepatitis B in their life at baseline, this number had increased to 77.1% (n = 309) in 2016. The proportion of patients without the need for a hepatitis B booster vaccination was higher after the intervention in 2016 (53.1%; n = 213) than at baseline 2013 (42.1%; n = 169). Similar results were documented for the annual hepatitis A vaccination rates: 2013:37.4% (n = 150) received at least one necessary hepatitis A vaccination, whereas during the intervention period an average of 48.8% (n = 195) received this vaccination (2014:46.6% [n = 187], 2015:50.9% [n = 204], 2016:48.9% [n = 196]). Correspondingly, the proportion of patients who had received at least one hepatitis A vaccination in their life increased (2013:50.1% [n = 201], 2016:60.8% [n = 244]), and fewer patients needed a booster for hepatitis A (completed hepatitis A vaccination course 2013:24.4% (n = 98), 2016:33.6% [n = 135]). For details see Figure 2.

While most patients were vaccinated against influenza at baseline (28.9%, n = 116), in the subsequent years the vaccination rate decreased (2014:27.4% (n = 110), 2015:24.4% (n = 98), 2016:23.2% (n = 93); average annual vaccination rate: 25%), but remained well above the pre-intervention level (2010:13% [n = 52], 2011:11.5% [n = 46], 2012:19% [n = 76]; average annual vaccination rate: 14.5%). For details see Figure 4.

3.3 | Quality indicators

The quality indicator "standard vaccinations completed" was met by 21.2% of the patients (n = 85), whereas in the baseline study 17.2% (n = 69) of the patients fulfilled this indicator. In 2016, eighteen

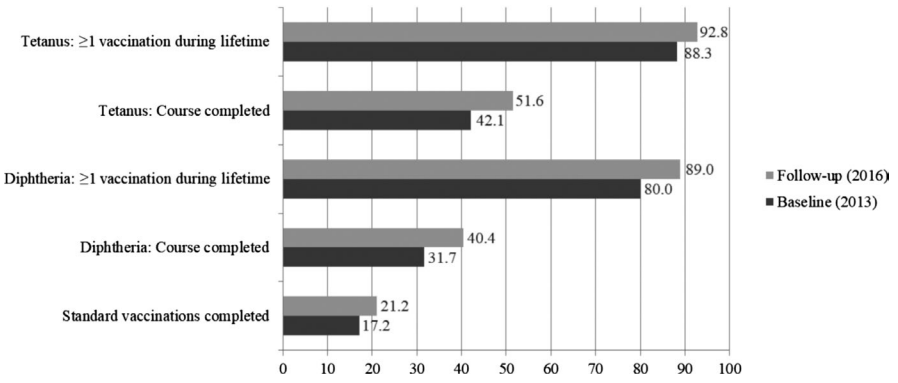

FIGURE 3 Comparison of vaccination rates and quality indicator for standard vaccinations in % (n = 401)

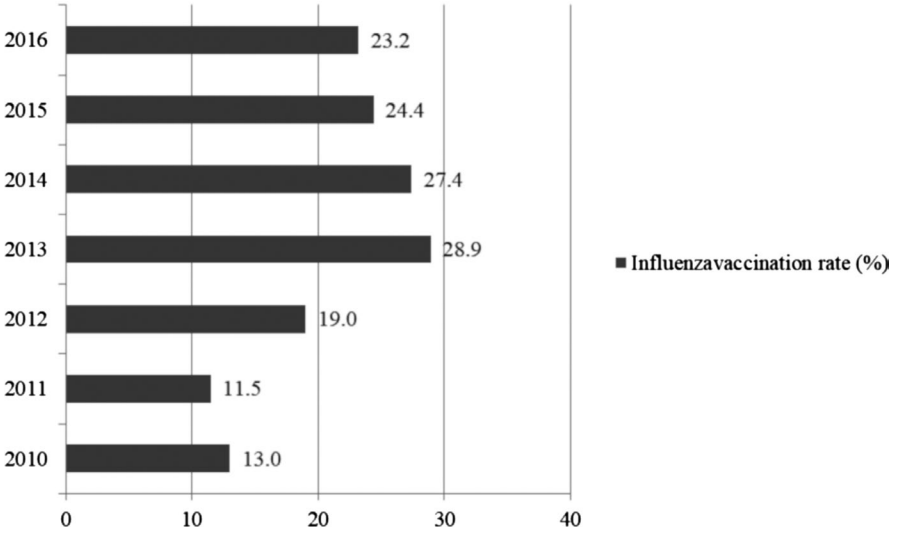

FIGURE 4 Influenza vaccination rates in % over time (n = 401)

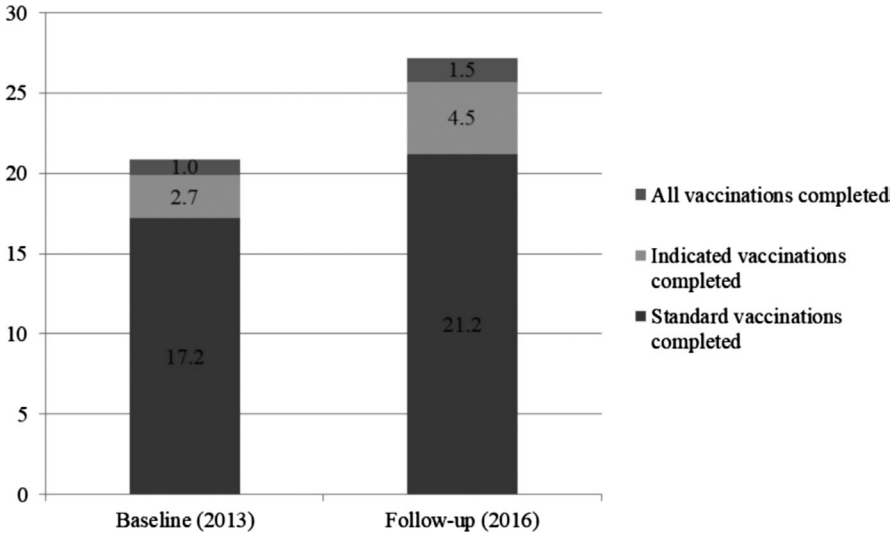

FIGURE 5 Comparison of quality indicators at baseline and at follow-up in % (n = 401)

patients (4.5%) met the quality indicator "indicated vaccinations completed," in 2013 this had been met by eleven patients (2.7%). Only four patients (1.0%) fulfilled both criteria ("all vaccinations completed") at baseline, at follow-up six patients (1.5%) fulfilled it. For details see Figure 5.

4 | DISCUSSION

Our baseline study elucidates an urgent need to optimize immunizations in LT patients: only 62.8% received at least one pneumococcal vaccine, 28.9% an influenza vaccine in the current season, 17.2% all standard vaccines (tetanus, diphtheria, polio), and only four patients (1.0%) were covered with all standard and disease-specific vaccinations.[1] These findings were consistent with those of other studies of SOT patient populations from other countries: for example in a cohort study of 157 US American lung transplant candidates, only 98 (62.4%) patients reported prior pneumococcal vaccination.[12] Therefore, there is a strong need for effective interventions to improve vaccination rates.

There are various Cochrane reviews, in particular a recent one,[4] which compared the effect of different interventions to improve immunization rates. Many studies confirmed that more intense interventions are more effective. Client-oriented interventions focused for example on the effect of a single letter compared to a combination of a letter and a leaflet/postcard (OR 1.11) as well as the effectiveness of telephone calls from a trained physician plus an educational brochure in contrast to general publicity (OR 3.33).[5] In comparison to no intervention at all, recalls in written form like letters (OR 1.79) and postcards (OR 1.44) or telephone calls (OR 1.92) were found to be effective. The combination of a patient- and provider-reminder intervention (OR 3.65) also proved to be more effective than a patient-based intervention only.[6] Another way to increase vaccination rates seems to be a provider-based intervention[5]: Reminding physicians about all their patients to be vaccinated was much more effective than reminding them about only half of their patients (OR 2.47).[5] Computer reminders were another effective provider-based intervention which resulted in a median improvement of 3.8% for vaccinations.[13] In summary, all types of reminders are more or less effective. In line with these studies addressing non-transplant patients, we showed that the combined strategy addressing patients and primary care physicians is an effective way of increasing vaccination rates in LT patients.

In 2012, Roca et al[14] reported scarcely improved vaccination rates (improvement of 4.3%) among elderly Spanish patients (n = 2402 participants) following a patient-based intervention, which included a letter with information regarding the effectiveness and safety of the influenza vaccination. A study by Hull et al[15] showed that a telephone call from a practice receptionist offering an appointment for influenza vaccinations was slightly more effective (increasing the vaccination rate by 6 percentage points) among 1820 participants aged over 65 years in east London than the intervention of Roca. In accordance with that the vaccination rates for influenza in our study differed significantly from those before starting our intervention, but the vaccination rates remained far below the WHO target of a 75% vaccination coverage for influenza. Furthermore, the baseline was significantly lower in our study compared to the above-mentioned studies (influenza immunization rate: Hull: control group 44%, intervention group 50%, Roca: control group 37.4%, intervention group 41.7%.; LT: average annual vaccination rate 2014-2016:25%, 2010-2012:14.5%).[14,15] Data from the Robert Koch Institute showed that the influenza vaccination rates among people aged over 60 years in Germany have fallen since 2010 (2010:43.6%, 2011:41.8%) and then stabilized at a low level (2012:37.2%, 2013:38.1%, 2014:36.5%, 2015:35.3%, 2016:34.8%).[16] In contrast to this trend, the influenza vaccination rates of the LT patients improved. One possible reason for the overall persistently low influenza vaccination rate could be the concern of LT patients about side effects or the assumption of inadequate effectiveness.

Our intervention yielded higher vaccination rates for the standard vaccinations tetanus and diphtheria. In comparison to the data of a representative population sample of the Robert Koch Institute (German Health Interview and Examination survey for adults, First

Wave of data collection [DEGS1], n = 7988), higher immunization rates for at least one diphtheria vaccination were achieved (DES1: 81.5%, LT: 89.0%). Although an improvement in the tetanus vaccination rate was shown, the vaccination rate remained below that of the DEGS1 study (DEGS1: 96.0%, LT: 92.8%).[17] In 1992, a Canadian study by Rosser et al[18] analyzing 8069 participants ≥20 years in Ottawa showed that all three reminder systems (patient-based intervention: receiving either a letter or a telephone call, and provider-based intervention: reminding the physician to evaluate patients' tetanus status and to offer a vaccination) were effective in increasing tetanus vaccination rates, though the vaccination rate continued to remain at a low level (differences in the recorded tetanus vaccination rate between randomized control group [3.2%] and the reminder groups: physician reminder group: 19.6%, telephone reminder group: 20.8%, letter reminder group: 27.4%).

With regard to the other vaccinations, the proportion of patients who received at least one necessary vaccination also increased during the intervention period. Particularly the disease-specific vaccination rates for pneumococci, hepatitis B, and hepatitis A were significantly higher in the intervention period compared to the baseline study in 2013. Krieger et al analyzed 1246 predominantly White or African American aged ≥65 years. The authors found lower immunization rates for pneumococcal vaccination (52% [170 of 327 subjects without prior pneumococcal immunization received this vaccination]) compared to our results (76.3%) with a more intensive intervention in which the patients received an educational brochure, a reminder postcard and a telephone call. However, the effect of the intervention (Krieger et al[19]: improvement of 21.1 percentage points) was significantly higher than that of our study (improvement of 13.5 percentage points). In 2015, Pennant et al reported improvements in influenza and pneumococcal vaccination rates by using a client- (patient letters in advance of appointment), provider-based intervention (a physician reminder) or nurse-driven model (patients' screening, administration, and documentation of vaccination by nurse) in high-risk patient populations (allergy [asthma] [n = 1142], infectious disease [HIV] [n = 659], chronic lung disease [n = 2483], and rheumatology disease [immunocompromised] [n = 2898]). In contrast to the present study, Pennant et al documented significantly higher vaccination rates for pneumococci (after intervention: chronic lung disease: 79%, rheumatology disease: 87%), but especially for influenza (after intervention: allergy: 64%, infectious disease: 86%). However, the pre-intervention vaccination rates were already well above the vaccination rates of our present study.[20] In a study conducted by Sansom et al in a sexually transmitted disease clinic for men who have sexual relations with other men, a telephone reminder was ineffective regarding the proportion of patients who completed the basic immunization with the third dose of the hepatitis B vaccination (control group: 59.2% [n = 145], intervention group: 56.3% [n = 157]) or the second dose of the hepatitis A vaccination (control group: 62.9% [n = 154], intervention group: 58.1% [n = 162]). An increase in the proportion of patients receiving the second dose of the hepatitis B vaccine compared with those of the control group was documented (control group: 80.4% [n = 197], intervention group 86.7% [n = 242]).[21] In our study, however, we noted an increase in the proportion of patients with a complete vaccination status for hepatitis A (2013:24.4%, 2016:33.6%) and hepatitis B (2013:42.1%, 2016:53.1%). The vaccination rates for hepatitis A of the present study were well below those found in the study conducted by Sansom.[21]

However, while the overall number of vaccinations increased during the intervention period, there was only a marginal improvement in the quality indicators. The indicator "standard vaccinations completed" showed an improvement in vaccination rates from 17.2% (n = 69) in 2013 to 21.2% (n = 85) in 2016. The indicator "all vaccinations completed" showed also a minimal improvement between 2013 and 2016 (2013:1.0%, n = 4; 2016:1.5%, n = 6). With regard to the indicator "indicated vaccinations completed" an increase in the vaccination rates was documented between 2013 (2.7%, n = 11) and 2016 (4.5%, n = 18). One possible reason for the discrepancy between more vaccinated patients on the one hand and only marginal improvements in quality indicators on the other hand could be that primary care physicians vaccinated their patients insufficiently (eg, only a combined tetanus and diphtheria vaccine without pertussis even though the patient had never been vaccinated against pertussis). Another reason could be that primary care physicians administered vaccinations that did not need to be refreshed and did not perform indicated vaccinations. Apart from that some vaccination series might have been started during the intervention period but not yet been completed.

In summary, our study with the aim to improve the vaccination status of LT patients demonstrated an improvement of immunization rates especially for disease-specific (indicated) vaccinations. Nonetheless, the proportion of patients who had completed vaccination schedules remained low. Therefore, there is an urgent need for more intense interventions to raise the vaccination rates in this high-risk population. More effective interventions are needed, especially with regard to the influenza vaccination and the quality indicators. Since it is known that depending on the vaccine used and the type of immunosuppression after liver transplantation, the vaccination response is more or less limited,[22] an additional study addressing the vaccination responses would be helpful to assess the overall efficiency of vaccinations in LT patients.

4.1 | Strengths, limitations, and perspectives

Many strengths, limitations and perspectives of this study are similar to those of our baseline study. The vaccination rates and the documented improvement of about 10% are based on a large cohort of patients with a rare condition who showed a rather high participation rate. Our results are also consistent with similarly insufficient vaccination rates of SOT patients reported from other centers and other healthcare systems. A selection bias is unlikely because the characteristics of the participants and the nonparticipants were similar,[1] yet cannot be fully excluded in a setting with multiple influencing factors: potential incomplete recruitment in a busy ambulatory clinic scenario, high-end referral center with many patients from distant areas who receive follow-up care after LTX near their homes, and severely sick patients with a high mortality rate and not all deaths being reported to the specialist center.

A limitation is that we analyzed vaccination rates and not antibody levels, which would provide a better measure of the protection achieved. Thus, Eckerle et al[22] showed in a systematic review that the immune response is lower after solid organ transplantation than that of the healthy control group. They documented a large heterogeneity of the vaccination response, especially regarding the indicated vaccinations. One strength is the rather long follow-up of 3 years. An information bias cannot be excluded, because before starting the intervention in January 2014 we already discussed ways to increase the vaccination rates of liver transplant patients with the Post Liver Transplant Clinic, which may have passed on this information to its patients. This could be the reason why influenza vaccination rates in 2013 were significantly higher than in other years.

5 | CONCLUSIONS

In agreement with studies addressing strategies to improve vaccination rates in various populations, we documented that written physician information and phone calls to patients could improve vaccination rates in these high-risk patients. Nonetheless, there is still high potential for improvement, especially regarding annual influenza vaccination rates and the quality indicators.

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AUTHORS' CONTRIBUTION

Dorothea Dehnen: collected the data, performed statistical analysis and data interpretation, prepared the first draft of the manuscript and revised it in communication with the coauthors. Anna Herwig: collected the data, performed statistical analysis and data interpretation, prepared and revised the manuscript. Kerstin Herzer: developed the study idea and the concept, supported the data collection, revised the manuscript. Birgitta Weltermann: developed the study idea and concept, supported statistical analysis and data interpretation, prepared and revised the manuscript.

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