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Clinical efficacy of seasonal influenza vaccination: characteristics of two outbreaks of influenza A(H1N1) in immunocompromised patients

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SUMMARY

Background: Influenza A(H1N1) causes serious complications in immunocompromised patients. The efficacy of seasonal vaccination in these patients has been questioned.
Aim: To describe two outbreaks of influenza A(H1N1) in immunocompromised patients.
Methods: Two outbreaks of influenza A(H1N1) occurred in our institution: on the kidney transplant ward in 2014 including patients early after kidney or simultaneous pancreas–kidney transplantation, and on the oncology ward in 2016 including patients receiving chemotherapy for malignant tumours. Factors leading to these outbreaks and the clinical efficacy of seasonal influenza vaccination were analysed.
Findings: Altogether 86 patients were exposed to influenza A(H1N1) during the outbreaks, among whom the seasonal influenza vaccination status was unknown in 10. Only three out of 38 vaccinated patients were infected with influenza A(H1N1), compared with 20 out of 38 unvaccinated patients ($P = 0.02$). The death of one out of 38 vaccinated patients was associated with influenza, compared with seven out of 38 unvaccinated patients ($P = 0.06$). Shared factors behind the two outbreaks included outdated facilities not designed for the treatment of immunosuppressed patients. Vaccination coverage among patients was low, between 40% and 70% despite vaccination being offered to all patients free of charge. Vaccination coverage of healthcare workers on the transplant ward was low (46%), but, despite high coverage on the oncology ward (92%), the outbreak occurred.
Conclusion: Seasonal influenza vaccination was clinically effective with both a reduced risk of influenza infection and a trend towards reduced mortality in these immunocompromised patients. Several possible causes were identified behind these two outbreaks, requiring continuous awareness in healthcare professionals to prevent further outbreaks.

Introduction

Seasonal influenza vaccination has been recommended for high-risk patients for years, but since the influenza A(H1N1) pandemic in 2009, general awareness has increased, and several studies have addressed the serious consequences of

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influenza infections in immunocompromised patients, such as recipients of solid-organ transplantation [1,2]. During the 2009 pandemic, serious complications were recorded in transplant recipients infected with influenza A(H1N1), among whom pneumonia was reported in 30%, admission to intensive care unit (ICU) in 16–20%, and mortality in 4–8% of patients [2,3]. Increased rates of complications have similarly been reported in other immunocompromised patient groups, such as haematopoietic stem cell transplant recipients and patients with solid tumours, with reported mortality rates of ~6–10% [4,5]. By comparison, in healthy individuals the mortality of influenza A(H1N1) is reported as 0–2% among hospitalized patients, and the risk of ICU admission about 10–20% among hospitalized patients [6–9].

Although seasonal influenza vaccination is recommended for high-risk groups, the efficacy of vaccination has been questioned in immunocompromised patients, with seroconversion rates barely reaching 50% in several studies including solid-organ transplant recipients, patients with end-stage renal disease, or patients receiving chemotherapy [10–16].

We recently described a serious outbreak of influenza A(H1N1) in a kidney transplant unit [17]. In addition to this outbreak, another serious outbreak of influenza A(H1N1) occurred in our institution in the oncology department in 2016. Factors leading to these serious outbreaks were analysed thoroughly, and several common factors could be identified in these outbreaks despite the two somewhat different types of patient groups. The aim of this study was to describe the factors leading to these two serious influenza A(H1N1) outbreaks in a large tertiary hospital, and to describe the protective effect of vaccination observed in immunocompromised patients.

Methods

Helsinki University Hospital supplies tertiary care for a population of ~1.5 million inhabitants, and serves the whole of Finland (population ~5.5 million) for certain special treatment services, such as solid-organ transplantation. Annually ~250 kidney transplantations are performed in the transplant unit, of which 15–20 are simultaneous pancreas–kidney (SPK) transplantations.

Approximately 1000 patients are admitted to the oncology ward per year, half of whom are treated for lymphoma. The average stay is four or five days. Yearly, 25–35 autologous transplants are performed.

Primary immunosuppression after kidney or SPK transplantation is a combination of cyclosporine or tacrolimus, mycophenolate, and steroids. Patients with higher immunological risk or recipients of SPK receive induction with basiliximab or anti-thymocyte globulin. After kidney transplantation, patients remain hospitalized for about 10–21 days, after which they return for follow-up to their own district hospital. In addition to postoperative treatment early after transplantation, the kidney transplant ward also includes patients with complications after transplantation (such as acute rejection, or surgical or infectious complications). Due to ongoing renovations in the hospital facilities, the kidney transplant service was temporarily located in a ward not designed for the treatment of immunosuppressed patients. The ward had 16 patient beds: four three-bed rooms with shared sanitation, and two two-bed rooms with bathrooms, but no single rooms. Rooms were narrow and space between beds was 60–90 cm in width. Patients shared a common dining room. In addition to inpatients on the ward, it was also used for frequent outpatient visits for patients in early stages after transplantation and for patients travelling from other parts of the country.

The oncology ward – one of the two wards in the oncology department built in the 1960s – has 18 patient beds and two beds for daycare patients. The ward specializes in treating adolescents and young adults with lymphoma, testicular cancer, osteosarcoma and Ewing sarcoma together with lymphoma patients of all ages. Patients receiving high-dose chemotherapy with autologous stem cell transplantation as a part of their treatment for lymphoma, testicular cancer and Ewing sarcoma are cared for on the ward. Patients with other cancers are mainly treated for cancer therapy-induced complications and for need of immediate palliative care. There are five single rooms with their own toilet; only one has its own bathroom. Five rooms house three beds, for which there are four toilets and three showers on the corridor. The young patients especially have been encouraged to use the dayroom to find peer support.

Influenza A was diagnosed with a qualitative real-time polymerase chain reaction from nasopharyngeal swabs, as described [18]. Seasonal influenza vaccination is recommended for all patients at risk of infection, including end-stage renal disease patients on dialysis, patients after kidney transplantation, and patients receiving treatment for cancer, and the vaccination is provided free of charge. Vaccination is also recommended for all healthcare professionals free of charge. Seasonal vaccine in the 2013–2014 campaign included three antigens: influenza A/California/7/2009 (H1N1)-like virus, influenza A/Texas/50/2012 (H3N2)-like virus, and influenza B/Massachusetts/2/2012-like virus, and was either Fluarix (GlaxoSmithKline, Brentford, UK), recommended for patients aged >65 years, or Vaxigrip (Sanofi Pasteur MSD, Brussels, Belgium) for younger patients, both inactivated trivalent vaccines without adjuvant. The seasonal vaccine in the 2015–2016 campaign was Vaxigrip (Sanofi Pasteur MSD, Brussels, Belgium), containing three antigens: A/California/7/2009 (H1N1)pdm09-like virus, A/Switzerland/9715293/2013 (H3N2)-like virus, and B/Phuket/3073/2013-like virus.

Differences in variable distributions between the two groups were analysed using the non-parametric Mann–Whitney *U*-test (continuous variables), or Fisher's exact test (categorical variables). The calculations were performed with IBM SPSS Statistics (version 20; IBM Corporation, Somers, NY, USA). Two-sided $P < 0.05$ was considered statistically significant.

Results

Description of the outbreaks

The outbreak on the kidney transplant ward has been described in detail previously [17]. Briefly, in April 2014, altogether 23 patients were treated on the ward during the outbreak (Table I). After the first positive case, all patients were tested and seven patients were diagnosed with influenza A(H1N1). Of the 17 patients who had received adequate seasonal influenza vaccination, two out of 17 tested positive for influenza (one asymptomatic, one with mild cough). Influenza

Table I
Kidney and pancreas–kidney transplant patients exposed to influenza A(H1N1) during the outbreak

Variable	Exposed transplant recipients ($N = 23$)
Mean (range) age (years)	55 (32–75)
Kidney/SPK recipients	22/1
Seasonal influenza vaccination coverage pre-transplant	17 (74%)
Transplantation <1 month before the outbreak	18 (78%)
Rate of ICU admission among infected patients	3/7 (43%)

SPK, simultaneous pancreas–kidney; ICU, intensive care unit.

A(H1N1) was diagnosed in five out of six unvaccinated patients, three of whom suffered from severe respiratory failure and died due to acute respiratory distress syndrome despite being treated with mechanical ventilation in the ICU. Two unvaccinated patients suffered from mild viral pneumonitis and recovered fully.

On the oncology ward in January 2016, five patients and two members of the personnel on the ward had respiratory symptoms simultaneously, and, after the first confirmed case of influenza A(H1N1), all patients on the ward were tested with nasopharyngeal swabs. During the outbreak, which occurred in two waves, a total of 63 patients were exposed, 17 of whom were diagnosed with influenza A(H1N1). Of the 21 patients who had received adequate seasonal influenza vaccination, only one patient was diagnosed with influenza A(H1N1). This patient had been vaccinated while receiving immune-chemotherapy (R–CHOP) for aggressive lymphoma. She relapsed at the time of contracting pneumonia caused by influenza, which prevented starting chemotherapy, and she died of progressive lymphoma. Of the 32 unvaccinated patients on the oncology ward, 15 were diagnosed with influenza A(H1N1). Of these 15 patients, three were admitted to ICU and needed mechanical ventilation, and two out of these three patients died after 10–31 days of treatment in the ICU. In addition, one patient died on the ward due to pneumonia caused by influenza, and another unvaccinated patient had to stop chemotherapy because of influenza-related infection and died due to progressive lymphoma. The vaccination history of 10 patients without influenza infection remains unknown. Patients exposed on the oncology ward are described in Table II.

Table II
Patients exposed on the oncology ward

Variable	Exposed patients with malignant disease ($N = 63$)
Mean (range) age (years)	59 (20–87)
Type of cancer	
Non-Hodgkin lymphoma	27[a]
Intestinal	6
Thyroid	6
Prostata	5
Hodgkin lymphoma	4[a]
Liver	3
Ewing sarcoma	2[a]
Testicular	2
Other	8[b]
Seasonal influenza vaccination coverage of the patients with known status	21/53 (40%)
Rate of ICU admission among infected patients	3/16 (19%)

[a] One patient with non-Hodgkin lymphoma, one patient with Hodgkin lymphoma, and one patient with Ewing sarcoma had received high-dose chemotherapy with autologous stem cell transplantation; none of them had received seasonal influenza vaccination.
[b] Other types of cancer (one of each): brain, melanoma, breast, oesophagus, multiple myeloma, ovarian, lung, head and neck.

Analysis of the possible reasons behind the outbreaks

Poor design of the treatment facilities

Both wards were located in old hospital buildings, built in the 1950s and 1960s, in which modern infection control is not possible. The oncology ward had 18 patient beds, of which only five are located in single-bed rooms, and the other five rooms were three-bed rooms with a short distance between the beds (90–120 cm). The transplant ward had 16 patient beds, of which only two rooms included two patient beds; the other rooms had three patient beds with similarly very short distance between the beds (90–120 cm). The two-bed rooms had their own toilet and shower, but the other four rooms (12 patients) shared two toilets and showers. After the first cases had been diagnosed, symptomatic patients were rapidly isolated and cohorted and all the patients on the ward were tested for influenza with nasopharyngeal swabs. Symptomatic patients were started on oseltamivir (treatment dose 75 mg twice daily or adjusted for renal function), and asymptomatic patients were started on a prophylactic dose of oseltamivir (75 mg once daily or adjusted for renal function). Both wards were closed temporarily and no new patients were admitted due to lack of adequate isolation facilities.

Vaccination coverage of the patients and protective effect of vaccination

The vaccination coverage of the patients with a known vaccination history on the oncology ward outbreak was 21 out of 53 (40%), and 17 out of 23 (74%) on the transplant ward. In total, 20 out of 38 (53%) of the unvaccinated patients were diagnosed with influenza A(H1N1), whereas of the vaccinated patients only three out of 38 (8%) were infected. The relative risk of influenza infection in the unvaccinated patients was 9.8 (95% confidence interval (CI): 1.4–69.0; $P = 0.002$). Of the unvaccinated exposed patients, seven out of 38 (18%) died due to influenza-related causes, compared to one out of 38 (3%) of the vaccinated patients. The relative risk of death in the unvaccinated patients was 7.0 (95% CI: 0.90–54.2; $P = 0.06$) compared to patients with vaccination. If only direct deaths caused by influenza (pneumonia and respiratory failure) are included, six out of 38 (16%) of the unvaccinated patients died, compared to none of the vaccinated patients, with the relative risk being 13.0 (95% CI: 0.76–223.0; $P = 0.07$). Table III compares the risk of infection and mortality in vaccinated and unvaccinated patients. Three patients on the oncology ward had received high-dose chemotherapy with autologous haematopoietic stem cell transplantation and none of them had

Table III
Outcome of the exposed patients in both influenza A(H1N1) outbreaks

Variable	Transplant service 2014	Oncology service 2016	No./total
Infected vs exposed patients	7/23	17/63	24/86
No. of vaccinated patients	17	21[a]	38
No. of infected patients among vaccinated	2/17 (12%)	1/21 (5%)	3/38 (8%)[b]
No. of infected patients among unvaccinated	5/6 (83%)	15/32 (47%)[a]	20/38 (53%)[b]
Mortality among vaccinated	0/17	1/21 (5%)	1/38 (3%)[c]
Mortality among unvaccinated	3/6 (50%)	4/32 (13%)	7/38 (18%)[c]

[a] The vaccination history of 10 patients exposed on the oncology ward was unknown.
[b] $P = 0.002$ for the increased risk of infection in patients with no vaccination vs vaccination.
[c] $P = 0.06$ for the increased risk of death in patients with no vaccination vs vaccination.

received seasonal influenza vaccination. Two of these patients were diagnosed with influenza A(H1N1), of whom one died.

Vaccination coverage of the healthcare personnel

On the transplant ward, the vaccination coverage of the healthcare personnel was alarmingly low: only 46% of the personnel had received adequate seasonal influenza vaccination. Eight healthcare workers (five unvaccinated and three vaccinated) had respiratory tract symptoms. However, they were not tested for influenza infection. On the oncology ward, 92% of the healthcare personnel had received adequate seasonal influenza vaccination. Of the two unvaccinated employees with respiratory tract symptoms, influenza A(H1N1) was diagnosed in one person.

Discussion

This report describes the circumstances and events behind two serious outbreaks of influenza A(H1N1) in immunocompromised patients. Although similarities were found between the outbreaks — most importantly poor, outdated facilities not designed for the treatment of immunosuppressed patients — differences were also noted between the outbreaks. In both outbreaks, the clinical real-world efficacy of seasonal influenza vaccination was better than described in studies analysing most often serological response to vaccination. Increased risk of both influenza A(H1N1) infection and mortality was detected in unvaccinated patients. The difference was more pronounced in the kidney transplant recipients, but a similar trend for increasing mortality was also seen in unvaccinated patients receiving intensive chemotherapy for cancer.

Although several previous studies have shown poor serological response to influenza vaccination among recipients of solid-organ transplantation, patients with end-stage renal disease, and otherwise immunosuppressed patients, our current analysis supports the clinical efficacy of seasonal influenza vaccination in preventing serious disease. Although it is well known that serological responses to vaccinations remain poor in immunosuppressed patients, some studies show that cellular immune response to influenza vaccine may be comparable to the healthy population, supporting our findings of clinical efficacy [10–16,19,20].

When analysing the reasons leading to the outbreaks, some differences were detected. The vaccination coverage of the healthcare personnel was high in the oncology ward outbreak, and exceeded, for example, the US national target of 90% [21]. Nevertheless an outbreak occurred, suggesting that other factors may play a role, most importantly the vaccination coverage of the patients and the poor facilities on the wards. In our analyses, the vaccination coverage among kidney and SPK recipients was 74%, which is similar to vaccination coverage between 52% and 88% reported in previous studies among solid-organ transplant recipients [22,23]. Vaccination coverage in patients with malignant disease in our study was lower compared to that of transplant recipients (only 40%), yet within the range of 13–70% reported in other studies in patients with malignant disease [24–26].

After the outbreaks, several measures were taken in the transplantation unit to prevent further outbreaks. In 2015 the transplantation service moved to a new building with modern facilities and the means for infectious isolation. In addition, patient and health care personnel education on the importance of the vaccination was increased, and the process of vaccinating transplant and dialysis patients has been simplified with easy access to vaccination at dialysis units, cancer hospital, and outpatient clinics. Similarly, the vaccination procedure for healthcare personnel was simplified in our hospitals, and the vaccination coverage of the personnel has increased and reached >90% in the season 2016–2017.

Another possible measure to prevent further outbreaks would be to introduce the policy to use surgical masks with all healthcare personnel and visitors, or even patients, as there is evidence suggesting that the use of surgical masks in all patient contacts regardless of symptoms or season may reduce the incidence of respiratory viral infections, especially in stem cell transplant patients [27–29]. Even before the outbreak, symptomatic visitors were not allowed to visit the patients on either of the wards, hand disinfection was recommended to all visitors, and a surgical mask was recommended for close contact for visitors on the oncology ward. The source of influenza A(H1N1) in both outbreaks remained unidentified, and, despite the protective measures, visitors may have had a role in introducing the infection to the wards.

This study had some limitations. First, although some common possible factors were identified, which could increase the risk for outbreaks on the wards, causality cannot be concluded from this retrospective analysis. In addition, patients treated on the oncology ward were a heterogeneous group of patients receiving chemotherapy for different types of malignant tumours, and the timing of the vaccination with regard to the chemotherapy was not adjusted for. It may also be debated whether patients with immunosuppression early after organ transplantation and patients receiving chemotherapy can

simply be compared or included in the same analyses. Yet, within this analysis several similar characteristics were identified behind these outbreaks, which could potentially be addressed, leading to improved conditions on the ward to prevent further outbreaks. The small number of cases in our analysis did not allow extensive multivariable analyses for the protective effect of vaccination. However, despite these limitations a clear association was seen in the increased risk of influenza infection and death due to influenza in the unvaccinated patients, supporting the clinical efficacy of seasonal influenza vaccination also in immunocompromised patients.

In conclusion, we describe two serious outbreaks of influenza A(H1N1) in immunocompromised patients, in whom seasonal influenza vaccination was associated with a reduced risk for influenza infection and mortality. Several possible causes were identified behind the outbreaks that require continuous awareness in healthcare professionals to prevent further outbreaks.

Conflict of interest statement
None declared.

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