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Concise Communication

Incidence and etiology of fever following seasonal influenza vaccination in hospitalized patients

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Abstract

We conducted a retrospective cohort to examine the incidence and etiology of fever postinfluenza vaccination among hospitalized patients during the 2015–2016 influenza season. Fever occurred in 63 (1.5%) of 4,185 vaccinated patients. Medical patients had fever predominantly associated with concurrent infections; surgical patients had fever explained by noninfectious etiologies.

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Influenza vaccination is an important strategy for preventing influenza infection and its sequelae. Traditionally, the rate of influenza vaccination in hospitalized patients has been low, ranging from 9.6% to 40.3%.[1,2] This is partly due to provider concerns regarding influenza vaccine safety and immunogenicity among hospitalized patients with acute illnesses.[3,4] There is also a concern of postvaccination fever resulting in additional, unwarranted diagnostic evaluations.[2] The rate of postvaccination fever in the adult outpatient population is low, ranging from 0.4% to 1.5%.[5,6]

Several studies have found no evidence of increased vaccine-associated adverse events in hospitalized surgical patients who received influenza immunization.[7,8] However, these studies assessed only postdischarge fever. Data regarding the incidence and causes of fever postinfluenza vaccination (PIV) among hospitalized patients while still in the hospital are limited. Understanding PIV fever is important for improving clinician acceptance of in-hospital vaccination programs and compliance with government quality measures for influenza vaccination.

Methods

We performed a retrospective cohort study at Barnes-Jewish Hospital, a 1,250-bed teaching hospital, during the 2015–2016 influenza season. All patients aged ≥ 18 years who received influenza vaccination during their hospitalization were identified by querying the medical informatics database. Postinfluenza vaccination fever was defined as a recorded body temperature of ≥38.3°C within 48 hours after vaccination. Other collected data included patient demographics, admission diagnosis, date and time of vaccination and fever onset, any perioperative fever <48 hours postprocedure, and any clinical laboratory evaluations for infections (including blood cultures, urinalysis, urine culture, and chest plain radiograph). A concomitant source of infection was defined by a documented diagnosis of infection (subcategorized into pulmonary, cardiovascular, gastrointestinal, genitourinary, skin and soft tissue, bone and joint, primary bacteremia, and febrile neutropenia) and whether the patient received a course of antimicrobial therapy for ≥ 4 days.

The causes of fever were classified into infectious and noninfectious. Fever was attributed to infection when a concomitant source of infection was present as defined above. Noninfectious etiology of fever included benign postoperative fever, central fever, vaccine-associated fever, and others. Benign postoperative fever was defined as a fever <48 hours after surgery, without clinical signs of infection, with negative infectious workup and/or no antibiotic prescription.[9] Central fever was classified as fever occurring <72 hours of hospitalization in patients with subarachnoid hemorrhage, intraventricular hemorrhage, or tumor and without documented diagnosis of infection or sepsis syndrome. Vaccine-associated fever was defined as fever <48 hours PIV without other identifiable infectious and noninfectious (eg, acute pancreatitis, myocardial infection) causes for fever.

During the study period, our institution administered Fluzone quadrivalent (Sanofi Pasteur, Swiftwater, PA) and Fluzone high-dose (Sanofi Pasteur, Swiftwater, PA) vaccine to patients aged 18–64 and ≥65 years, respectively. All inpatients were screened for influenza vaccine status by nurses and vaccinated if indicated and consent was obtained. This procedure followed the Centers for Medicare and Medicaid Services Influenza Immunization Core Measure (IMM-2).

Statistical analysis

Demographic and baseline characteristics were described in number (percentage) for categorical variables and median (interquartile range,

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Table 1. Comparison of Febrile, Vaccinated Surgical Patients by Surgical Status

Variable	Surgery Service[a]		
	Elective Surgery (n = 13)	Nonelective Surgery (n = 16)	*P* Value
No. of patients who received influenza vaccination			
• Prior to the surgical procedure, no. (%)	3 (23.1)	8 (50)	.14
• After the surgical procedure, no. (%)	10 (76.9)	8 (50)	
Fever within 48 h of vaccination, no. (%)	12 (92.3)	7 (43.6)	.01
Maximum temperature (°C), median (IQR)	38.5 (38.4–38.7)	38.4 (38.3–38.7)	.53
Time of vaccination to fever postvaccination, median (IQR)	11.1 (6.3–25.6)	19.1 (4.6–24.9)	.78
Infectious investigations, no. (%)[b]	6 (46.1)	3 (18.6)	.11
• Positive for infection, no.	0	0	
• Negative for infection, no.	6	3	
Length of stay, median (IQR)	5.0 (3.0–7.5)	14.5 (6.0–29.3)	.02

[a]6 surgical patients did not undergo any procedure.
[b]Infectious investigation was defined as obtaining one or more of the following within 48 hours of fever onset: blood cultures, urinalysis, urine cultures and/or chest X-ray.

IQR) for continuous variables. We used χ^2 and Mann-Whitney *U* tests for comparisons where appropriate. All tests were 2-tailed, and a *P* value of < .05 was considered statistically significant. The Washington University Human Research Protection Office approved this study.

Results

Of 32,998 admissions, 96% were screened for influenza vaccination status and 4,185 patients (12.7%) were vaccinated. Medical patients received vaccination earlier in their hospital admission than surgical patients: 13.0 hours (IQR, 5.2–27.8) versus 25.9 hours (IQR, 15.0–165.2) ($P = .001$). Moreover, sixty-three vaccinated inpatients (1.5%) experienced PIV fever. Among them, 28 (44.4%) and 35 (55.6%) patients were admitted to medical and surgical services, respectively. The median maximum temperature was significantly higher among medical vs. surgical patients: 38.7°C (IQR, 38.4–39.3) versus 38.4°C (IQR, 38.3–38.7) ($P = .04$). The mean time to fever after vaccination was not different between the medical and surgical patients: 10.9 hours (IQR, 5.4–27.3) versus 19.0 hours (IQR, 9.2–25.3) ($P = .38$). There was no difference between the median length of stay between febrile and nonfebrile patients postvaccination: 7 days versus 8 days ($P = .58$).

In the subgroup analysis of febrile surgical patients, 13 (37.1%) and 16 (45.7%) patients underwent elective and nonelective procedures <48 hours after vaccination, respectively (Table 1). The remaining 6 patients (17.1%) did not have surgery. Compared with the nonelective procedure subgroup, patients who had elective surgery were more likely to develop perioperative fever within 48 hours PIV ($P = .01$). Nevertheless, there was no significant difference in the proportion of patients who underwent an infectious investigation between the 2 subgroups ($P = .11$). None of the investigations were positive for an infectious etiology (Table 1). The nonelective subgroup tended to have a higher length of hospital stay than the elective surgical patients ($P = .02$).

In total, 21 (75%) medical patients had fever attributable to concomitant infections (Table 2). Most of the surgical patients (76.9%) who underwent elective procedure had fever potentially explained by benign postoperative fever, while 10 (62.5%) cases in the nonelective surgical subgroup had fever more likely caused by concomitant infection. Overall, medical patients had fever predominantly caused by infections, while surgical patients had febrile illness explained by noninfectious etiologies ($P = .03$). None of the patients with noninfectious fever PIV were started on antibiotics within 48 hours of their fever.

Table 2. Causes of Fever Following Influenza Vaccination in the Hospitalized Medicine and Surgical Patients

		Surgical Service (n = 35)		
	Medical Service[a] (n = 28)	Elective Surgery (n = 13)	Nonelective Surgery (n = 16)	No Surgical Intervention (n = 6)
Infections				
Pulmonary	4	0	1	2
Cardiovascular	0	0	1	1
Gastrointestinal	3	0	4	1
Genitourinary	5	0	2	0
Skin and soft tissue infection	2	1	2	1
Bone and joint	3	0	0	0
Bloodstream infection	6	0	0	1
Febrile neutropenia	2	0	0	0
Noninfectious causes				
Postsurgical fever	0	10	3	0
Central fever	1	2	3	0
Postvaccination fever	1	0	0	0
Others[b]	5	0	0	0

[a]Some patients could have 2 or more infectious processes.
[b]Others include acute pancreatitis or myocardial infection.

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Discussion

Fever PIV is a recognized adverse event, but the rate remains low in both outpatient and inpatient settings.[5–8] In our cohort, the incidence of fever PIV during hospitalization was 1.5%, which is consistent with a previously published range of 1.5%–2.0%.[7,8] A prospective study found similar self-reported fever PIV among hospitalized (2%) and clinic patients (2%).[7] Tartof et al[8] reported that 1.5% of hospitalized surgical patients had a postdischarge fever following vaccination, versus 1.1% of unvaccinated patients.

It is often assumed that a fever PIV is generally due to vaccination itself. However, no studies have investigated the etiologies of fever PIV. Kohl et al[10] suggested evaluating patients with fever PIV for alternative explanations. Most febrile episodes in our cohort were attributable to concomitant infections, benign postoperative fever, or central fever. Only 1 medical patient had a postvaccination fever without an alternative explanation. Fever due to infection was more common among medical patients; 75% of these patients in our cohort were admitted because of an infection.

Although elective surgical patients were more likely to develop perioperative fever within 48 hours PIV compared with nonelective surgical subgroup, there was no increase in the proportion undergoing additional evaluation for infection. Our finding is consistent with a previous study.[8] The length of hospital stay was longer in the nonelective surgical subgroup, which was more likely due to the complexity of their underlying medical conditions.

The limitations of our study include retrospective analysis in a single institution, with a single vaccine manufacturer during a single influenza season. Therefore, our findings may not be generalizable to other populations. Because our data only included fever within the first 48 hours postvaccination, we may have missed patients who developed fever after 48 hours.

This is the first study examining the incidence and etiologies of fever within 48 hours PIV among an inpatient population. Our data suggest that incidence of fever PIV in hospitalized patients was low and was primarily caused by concurrent infectious processes and other noninfectious causes rather than influenza vaccination itself.

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