Influenza Vaccination: An Unmet Need in Patients With Diabetes

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Vaccination of people at risk for complications from influenza, such as those with diabetes, is a key U.S. public health strategy for preventing associated morbidity and mortality. Despite recommendations from the Centers for Disease Control and Prevention (CDC), the American Diabetes Association (ADA), and others to administer influenza vaccines annually to all diabetic patients who are 6 months of age and older, influenza vaccination rates in this population remain low (Figure 1). The current level of vaccination falls far short of the 2010 national health objectives call for a 90% vaccination rate for all elderly people (≥65 years of age) and 60% for younger people who have risk factors (e.g., diabetes). In fact, >10 million Americans with diabetes currently lack the protection afforded by a single annual influenza vaccination.

Increasing Incidence of Diabetes
The obesity epidemic of the 21st century has broad-reaching collateral effects, including the clinically significant increasing number of patients with newly diagnosed diabetes. The overall U.S. prevalence of diabetes, defined by a fasting glucose >126 mg/dl or a 2-hour plasma glucose of 200 mg/dl after an oral glucose load (oral glucose tolerance testing, OGTT), was estimated in 2005 at 7% (nearly 21 million people), with certain minority groups and the elderly disproportionately affected (e.g., 18% [age-adjusted prevalence] in American Indians/Alaska Natives, 21% in people ≥60 years of age). The at-risk population for complications also includes the even larger (41 million) pre-diabetic group, defined as those with impaired fasting glucose (100–125 mg/dl) and/or impaired glucose tolerance (OGTT 2-hour plasma glucose 140–199 mg/dl). If the trend of increasing incidence continues, more than one-third of Americans born in 2000 will develop diabetes.

The myriad complications of diabetes are a function of both the degree and duration of poor glycemic control, although insulin resistance, the sentinel defect in most type 2 diabetic patients, leads to microvascular and macrovascular changes that pre-date frank hyperglycemia or diabetes diagnosis. Although traditionally considered strictly a disorder of glucose metabolism, diabetes imparts a significant two- to fourfold increased risk for cardiovascular disease, which affects up to 80% of these individuals and accounts for ~70% of their mortality. For individuals who are diagnosed with diabetes at 40 years of age, it is estimated that men and women will lose 11.6 and 14.3 life-years, respectively. In 2004, diabetes was the sixth leading cause of death in the United States, and cardiovascular disease, a common comorbidity, was the most common cause of death.

Impact of Influenza
Influenza is a common and potentially serious viral infection, with an incidence of 5–20% annually in the United States. During the past decade, influ-
enza contributed to an estimated 36,000 deaths and > 200,000 hospitalizations in the United States each year.

The current annual rates of hospital admissions and deaths due to influenza are likely higher because more individuals have moved into high-risk groups (e.g., the elderly and individuals with diabetes). Historically, annual direct medical costs associated with influenza illness have been estimated at $3 billion.

The indirect costs of illness, including absenteeism in businesses, schools, and daycare centers during yearly influenza outbreaks, are estimated at $12 billion each year.

Classic influenza illness is characterized by abrupt onset of high fever, nonproductive cough, chills, headache, sore throat, nasal congestion, myalgia, and malaise. Children may present with symptoms uncommon in adults, such as abdominal pain, diarrhea, and vomiting. It is noteworthy that patients and their health care providers often confuse influenza with many other, less severe respiratory viral infections. Poehling et al. found that the diagnosis of influenza was made by a provider for only a minority (17%) of culture-positive children who were either febrile or symptomatic.

The course of influenza illness can either be uncomplicated and self-limited or associated with sequelae. An uncomplicated course of influenza can last up to 15 days, with restricted activity for 5–6 days, including 3–4 days of bed rest. Profound fatigue may continue for weeks after resolution of other symptoms. While people of all ages are at risk of influenza infection, complications are most common in those at the extremes of age and with certain underlying medical conditions, such as diabetes, asthma, and cardiovascular disease. Complications include secondary bacterial pneumonia, sinusitis, bronchitis, and myocarditis, as well as croup, bronchiolitis, and acute otitis media in children.

All bacterial and viral infections, including influenza, are associated with significant morbidity and mortality in patients with diabetes, in part because of poor glycemic control and acidosis, as well as comorbid conditions (e.g., advanced age, renal disease, and cardiovascular disease). The incidences of diabetic ketoacidosis and associated hospital admissions were noted to be increased during influenza epidemic years. In a population-based study conducted by Bouter et al., the risk of hospitalization was increased sixfold in patients with diabetes, compared with age- and sex-matched control subjects. At-risk patients, including those with diabetes, are also at increased risk of death from influenza and secondary pneumonia.

In a case-control study (control subjects matched for age and sex), mortality risk due to influenza was doubled in diabetic patients compared with nondiabetic patients (odds ratio 2.0, 95% confidence interval [CI] 0.4–14.8). Although not specifically studied in patients with diabetes, evidence suggests that influenza can trigger acute myocardial infarction and increase coronary heart disease death (odds ratio 1.3). These results take on special significance for patients with diabetes, whose risk of an acute cardiovascular event, as well as short-term (inpatient) and long-term risk of death following acute myocardial infarction is two- to fourfold higher (P ≤ 0.001) than in patients without diabetes.

**Vaccination Outcomes in Patients With Diabetes**

Sero logical protection from influenza infection after vaccination has been shown to be comparable between patients with diabetes and healthy control subjects in four case-control studies. Furthermore, several research groups have documented the safety and efficacy of vaccination against the serious morbidity and mortality of influenza infection in patients with diabetes in high-risk patients, including those with diabetes and/or cardiovascular disease, and in subgroup analysis of patients with diabetes.

Across clinical studies, the vaccine was generally well tolerated, with mild soreness at the vaccination site being the most common side effect.

Looijmans-Van Den Akker et al. reported on the effectiveness of influenza vaccination among 9,238 adults with diabetes who were enrolled in a large, nested, case-control study. According to multivariate logistic regression with adjustments for potential confounders (i.e., age, sex; health insurance; presence of heart, lung, or other high-risk disease; number of medications; and number of general practitioner visits during the 12 months before the influenza epidemic), influenza vaccination was associated with a 54% (95% CI 26–71%) reduction in hospitalizations (P = 0.002) and a 58% (95% CI 13–80%) reduction in death (P = 0.019).

In a smaller case-control study, Colquhoun et al. determined the effectiveness of influenza vaccination in children and adults with diabetes during two influenza epidemic seasons. After controlling for sex, age, type of diabetes, year of epidemic, and number of general practitioner visits in the previous 12 months, influenza vaccination was associated with a 79% (95% CI 19–95%) reduction in hospital admissions among people with diabetes. These results are supported by those of Nicholson et al., who reported an 89% (95% CI 19–95%) reduction in hospital admissions with vaccination.

Schade and McCombs determined the age-, sex-, and comorbidity-adjusted odds ratio for death in people with diabetes based on vaccination status during two influenza seasons. In their study, vaccination was associated with a 36% (95% CI 28–44%) and 40% (95% CI 31–47%) decreased risk of death during the two assessment years among diabetic patients who were vaccinated compared with those who were not. These results were confirmed by Hak et al. in a subgroup analysis of a large cohort of elderly patients, 14,915 of whom had...
diabetes. Influenza vaccination was associated with a significant reduction in the combined outcome of hospitalization for pneumonia/influenza or death due to any cause of 50% (95% CI 37–60%; P < 0.001 vs. no vaccination) and 21% (95% CI 6–34%; P = 0.009) in the influenza seasons of 1996–1997 and 1997–1998, respectively. Taken together, study findings support the value of influenza vaccination for patients with diabetes, with data showing benefits based on fewer hospitalizations and deaths.

Vaccination Recommendations for People With Diabetes
Based on the results from clinical studies, the ADA and CDC recommend annual influenza vaccination for all patients with diabetes who are ≥ 6 months of age (Table 1). Vaccination each year is required because of waning immunity and changes in circulating strains (antigenic drift). For children < 9 years of age who have never been vaccinated, the Advisory Committee on Immunization Practices recommends administration of two influenza vaccine doses, separated by at least 1 month, with the second dose administered before December. In addition, close household contacts of and health care workers providing care to people with diabetes should receive annual influenza vaccinations to decrease person-to-person transmission.

Strategies to Increase the Reach of Influenza Vaccination
People with diabetes will benefit from increased influenza vaccination rates. As recommended by professional and other organizations, medical practices that serve people with diabetes and associated cardiovascular disease should include annual influenza vaccinations as a routine component of patient care. Specific intervention strategies are recommended to increase reach to those who are ≥ 65 years of age, those who are residents of nursing homes or other chronic care facilities, those who require regular medical care or hospitalization, and those who have comorbid cardiopulmonary disease. Many different types of practices and many types of health care professionals (e.g., physicians, nurses, nurse practitioners, physicians assistants, pharmacists, and diabetes educators) serve diabetes patients, and all can contribute to increasing influenza immunization rates. In a survey of people with diabetes, belief in vaccine efficacy (odds ratio 5.6), recommendation by a health professional (odds ratio 14), and previous vaccination (odds ratio 40) were factors significantly associated with vaccine uptake. In a report by Van Amburgh et al., the vaccination immunization rate increased from 28 to 54% (P < 0.05) among high-risk patients through a pharmacist-managed initiative. The initiative involved the mailing of an educational package on influenza immunization to high-risk patients and vaccine provision not only during routine clinic visits but also in vaccine-only clinics run by pharmacists.

Influenza vaccination rates may be positively affected by interventions that increase vaccine access, increase demand, and overcome practice-related barriers (Table 2). Practices that do not provide vaccination services should recommend the vaccine to their diabetic patients and refer those patients to vaccine clinics and other providers who vaccinate. As previously mentioned, recommendations made directly by medical providers are the most effective. However, recommendations can be made through other channels, such as in writing (e.g., prominently displayed posters, postcards, e-mails, and notices on websites) or by nonmedical staff members who provide a scripted message (“The doctor recommends that all of his/her patients with diabetes get an influenza vaccine.”). Finally, professional organizations that promote optimal care for people with diabetes should add annual vaccinations to their quality assurance checklists. This will help ensure that their constituencies offer people with diabetes complete care according to national recommendations.

In summary, influenza virus causes an unpleasant and potentially debilitat-ing viral illness, resulting in clinically significant sequelae and mortality in some affected individuals. Influenza vaccination is simple, effective, and safe; it should be offered to all adults and children ≥ 6 months of age who have diabetes. Influenza vaccination rates in this population remain low. Communication by a health care professional about the need for vaccination and improvements in service provision are recommended to increase vaccination rates in at-risk diabetic patients.

Table 1. Recommendations for Influenza Vaccination in Patients With Diabetes and Their Close Contacts

<table>
<thead>
<tr>
<th>Annual influenza vaccination is recommended for:</th>
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<tr>
<td>• All patients with diabetes ≥ 6 months of age. (Children &lt; 9 years of age with diabetes who have never been vaccinated should receive two influenza vaccine doses separated by at least 1 month)</td>
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<tr>
<td>• Close household contacts of people with diabetes</td>
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<tr>
<td>• Health care workers providing care to people with diabetes</td>
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Table 2. Strategies to Increase the Reach of Influenza Vaccination

| • Increase vaccine access |
| - vaccine-only clinics |
| - extended office hours |
| - vaccinate at all visit types |
| - vaccinate into December and beyond |
| • Increase demand |
| - consumer education |
| - strong provider recommendations |
| • Overcome practice-related barriers |
| - standing orders |
| - provider reminders |
| - addition of influenza vaccination to quality-care checklists |
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Note of disclosure: Dr. Rehm has received honoraria for speaking engagements from Roche Pharmaceuticals, which manufactures an antiviral medication that is active against influenza virus.