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Diabetes and Influenza-Attributable Illness: The Rationale for Targeted Influenza Vaccinations in Adults with Diabetes

by

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Dedications

To Emily, my wife. Your patience and support made the journey possible; having you near made it worthwhile.

To my parents and sisters – particularly Jessica and Alison, whose enthusiasm for my academic milestones was often greater than my own.

Abstract

While guidelines for seasonal influenza vaccinations single out working age (< 65) adults with diabetes, vaccination rates in this group remain below national targets. Historically, there has been limited evidence to support these guidelines. This dissertation comprises four studies investigating the clinical need for, and benefits of, vaccination; and identifying effective means of improving vaccination rates in adults with diabetes, emphasizing those of working age.

Our first two studies identified the effects of influenza on a large population-based cohort. In working age adults with diabetes, influenza contributed a substantial proportion of visits and hospitalizations for influenza-like illness (13%), pneumonia and influenza (PI) hospitalizations (26%), and all-cause hospitalizations (6%) during influenza season. The effect of influenza on all-cause hospitalizations was higher in adults with diabetes. However, such individuals did not experience increased deaths or hospitalizations attributable to influenza when followed after acute respiratory infections. These results suggest that adults with diabetes indeed experience a higher relative frequency, though not severity, of illness attributable to influenza.

We then examined the effectiveness of influenza vaccine in working age adults with diabetes, compared to the elderly, for whom vaccination recommendations are well accepted. We observed comparable relative reductions in PI (43-55%)

and all-cause (28-34%) hospitalizations, in all groups – both during and outside of influenza season. These results suggest that many observational studies, our own included, have over-estimated the benefits of vaccine.

In practice, public health authorities remain committed to influenza vaccination despite uncertainty in the supporting evidence. We thus performed a systematic review summarizing the effectiveness of interventions for improving influenza and pneumococcal vaccination rates in community-dwelling adults. Interventions that assign vaccination responsibilities to non-physician personnel, or that activate patients through personal contact showed particular promise, although the small extent of benefits suggests a need for further innovation.

We have contributed new evidence showing that efforts to mitigate the effects of influenza in diabetic adults may be warranted by increased risk, although the benefits of vaccination remain uncertain. Our work highlights a need for randomized trials of vaccine effectiveness, and for studies examining the local factors mitigating or potentiating efforts to improve vaccination rates.

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List of Abbreviations

ADG	Aggregated diagnosis group
ALL	All-cause hospitalizations
ARI	Acute respiratory infection
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CQI	Continuous quality improvement
f	Attributable fraction
ICD	International Classification of Disease
ILI	Influenza-like illness
IQR	Interquartile range
IRR	Incidence rate ratio (equivalent to rate ratio)
MCHP	Manitoba Centre for Health Policy
NNT	Number needed to treat
NNV	Number needed to vaccinate
OR	Odds ratio
PI	Pneumonia and influenza
POST	Post-influenza season period
PRE	Pre-influenza season period
RR	Rate ratio (equivalent to incidence rate ratio)
RSV	Respiratory syncytial virus
SES	Socio-economic status
VE	Vaccine effectiveness

Chapter 1: Introduction

1.1. Overview

Influenza is an acute respiratory illness responsible for substantial morbidity and mortality during discrete periods of viral circulation each year (1-4). Adverse sequelae of influenza are thought to be concentrated in certain high-risk groups. These groups include elderly adults (age >= 65) and adults with diabetes (5, 6).

Diabetes is a common chronic condition associated with increased morbidity and mortality due to micro- and macro-vascular complications, including kidney failure, blindness, limb disease, myocardial infarctions, and stroke (7, 8). Patients with diabetes are also thought to be at increased risk of infectious diseases, including pneumonia and influenza (9-11). Consequently, clinical practice guidelines identify diabetes as a high-risk indication for vaccination (6, 12-14). Given existing recommendations for universal vaccination of the elderly, these guidelines effectively single out working age (< 65) adults with diabetes for vaccination. However, vaccine uptake in diabetic adults, whether elderly or working age, has consistently fallen under national targets (15, 16).

The uptake of vaccination is a complex social health behavior affected by numerous patient, provider, and system-level factors (17-19). While research regarding the determinants of vaccination uptake in working age, high-risk patients is scant, two issues deserve particular attention. First, there is little rigorous comparative evidence that adults with diabetes actually suffer either increased frequency or increased severity of illness due to influenza, or that influenza vaccinations can improve clinical outcomes in this risk group.

As a result, diabetes-specific vaccination guidelines are considered low grade, based primarily on expert opinion (12). Uncertainty in the evidence underpinning clinical guidelines may have implications for vaccination practices in primary care, since patients and physicians may be unaware or confused about the need for vaccinations in working age adults with particular conditions (20, 21).

Second, vaccinations, along with many other preventive procedures, are being crowded out by urgent concerns in primary care practices ill-equipped to promote proactive care (22). Quality improvement interventions are intended to improve the likelihood of evidence-based, guideline-concordant care, by altering the processes of health care delivery (23). The presence of quality improvement interventions has been associated with higher rates of vaccination (24, 25). However, substantial confusion about the effectiveness of particular quality improvement interventions exists, given the wealth and diversity of relevant studies.

This dissertation encapsulates a program of research intended to address these issues. Using the administrative databases of Manitoba Health, we examined the extent to which patients with diabetes actually suffer increased sequelae due to influenza, compared to non-diabetic adults; and the extent to which influenza vaccine may prevent influenza-like illness and hospital admissions in diabetic adults. These studies examined the extent to which targeting diabetic adults for vaccinations is warranted. We then performed a systematic review of quality improvement interventions, to identify the best means of promoting influenza vaccinations in community-dwelling adults.

1.2. Influenza and influenza-attributable illness

Influenza is a highly contagious viral respiratory infection, which presents with an abrupt onset of fever and chills, accompanied by headache, sore

throat, myalgias, malaise, and dry cough (26). Though typically self-limiting, influenza infections can lead to primary viral and secondary bacterial pneumonia, both of which are associated with high rates of morbidity and mortality (26, 27). Influenza is thought to affect 9% of elderly and 7% of working age adults each year (28, 29). In Canada, influenza has been implicated in 2% of all deaths and 8-10% of adult primary respiratory hospital admissions (3, 4). As a result, influenza causes substantial economic losses to society (29).

Infections with numerous other viruses may manifest in a clinical presentation similar to that of influenza. This has given rise to the appellation “influenza-like illness” (ILI) for syndromes characterized by fever and cough with one or more of the above symptoms, which could be due to influenza virus (30). In Canada, influenza virus is detected in 20% to 33% of sampled ILI specimens during the peak of influenza season, but only sporadically during the influenza off-season (i.e.: in less than 1% of isolates per week) (31, 32). Distinguishing influenza from other causes of ILI is important, since the impact of influenza may be mitigated by vaccination. However, clinical ILI has low predictive value for actual influenza infection (33-37). Influenza may also manifest as many other respiratory, as well as cardiovascular and non-respiratory, conditions aside from ILI. Such manifestations include bronchitis, colds, pneumonia, and myocardial infarctions (38-42). ICD codes for influenza are usually reserved for cases with laboratory confirmation of influenza infection, which occur rarely outside of surveillance settings. Indeed, only 8% of deaths thought to be due to influenza are actually coded as influenza (4).

Because the direct measurement of influenza infection is practically infeasible, studies examining the burden of influenza have instead estimated the influenza-attributable portion of non-specific outcomes, by correlating outcomes to community-level indicators of influenza activity (1-

4, 43). The influenza-attributable portion of ILI may then be distinguished by subtracting the expected events in the absence of influenza from the observed events. Such an analysis may be as simple as subtracting influenza season from off-season outcome rates (44), although most studies now use regression methods to exclude alternative explanations for variations in outcome rates.

1.3. General predisposition to infection in patients with diabetes

Diabetes is a common chronic disease, affecting 6.2% of Canadians, and 8.0% of Canadian adults aged >= 20 years (45, 46). In addition to the micro- and macro-vascular complications of diabetes (7), patients with diabetes may suffer increased morbidity and mortality from infections (47, 48). *In vitro* studies have demonstrated a variety of immune defects in patients with diabetes, including glycosylation of antibodies, defects in proliferative T-cell antigen responses, and defects in innate immunity (10, 49, 50). Patients with diabetes suffer many infections more frequently than patients without diabetes (9, 10), including upper and lower respiratory tract infections of both viral and bacterial etiology (11).

1.4. Specific predisposition to influenza in patients with diabetes

1.4.1. Vaccination recommendations

Clinical practice guidelines, including those of the Canadian Diabetes Association and the American Diabetes Association, recommend that all patients with diabetes be targeted for routine vaccination against seasonal influenza (12, 13, 51, 52). Guidelines of the US Centers for Disease Control and Prevention have recently promulgated a policy universal vaccination for all adults, regardless of risk status (6). However, US guidelines, like those of Canada and the UK, continue to prioritize high-risk adults for vaccination, including the elderly (age >= 65 years), pregnant women, and adults with chronic diseases, such as chronic obstructive pulmonary disease, heart failure, and diabetes. The

incremental effect of including diabetes as a high-risk group is to single out patients with diabetes who are working age and who are otherwise free from pre-existing cardiovascular or pulmonary diseases. In 2005, working age adults represented 65% of those with diabetes, approximately 3% of Alberta's adult population (Unpublished analysis of Canadian Community Health Survey public microfile data, Cycle 3.1, 2005).

Guidelines targeting diabetic adults are presumably based on three premises:

1. Working age, otherwise healthy adults with diabetes are more likely to contract influenza than those without diabetes.
2. Working age, otherwise healthy adults with diabetes with influenza are more likely to experience severe disease, manifesting in a greater risk of major adverse events compared to those without diabetes.
3. Influenza vaccine is effective in working age adults with diabetes.

However, the evidence for these premises is limited (53). The Canadian Diabetes Association has assigned these vaccination recommendations an evidence grade of D, for recommendations based on expert consensus, recognizing a lack of data focused specifically on influenza and influenza-attributable outcomes in patients with diabetes (12, 53).

1.4.2. Premise 1: Adults with diabetes are at increased risk of illness due to influenza

Several studies have reported that patients with diabetes have a higher risk of death due to pneumonia and influenza (PI) compared to those without diabetes. The relative risk of PI death ranged from 1.7 to 4.0 (54, 55). However, these studies did not distinguish PI deaths due to influenza from those contributed by etiologies. Early studies of influenza-attributable deaths found increased numbers of death caused by diabetes during influenza season, relative to off-season periods (56-58). These studies

suggest that influenza may trigger metabolic decompensation in vulnerable adults. However, because these studies did not compare more common manifestations of influenza (e.g.: acute respiratory infections, acute cardiovascular events) in those with and without diabetes, their findings may not be applicable to the vast majority of adults with diabetes. To our knowledge, only three studies have compared influenza-attributable rates of general outcomes, such as all-cause mortality and cardiopulmonary hospitalizations, in adults with and without diabetes (44, 59, 60). Among other limitations, these studies did not adjust for comorbidities or vaccination status.

1.4.3. Premise 2: Adults with diabetes who contract influenza suffer more severe disease, manifesting in a greater risk of adverse outcomes

Numerous studies have examined the extent to which diabetes affects outcomes after community-acquired pneumonia, a potential complication of influenza. Although a meta-analysis of community-acquired pneumonia cohorts published before 1995 found that diabetes was associated with increased odds of death in hospitalized patients (61), several recent studies have not found an association between a prior history of diabetes and adverse outcomes (62-64). These studies suggest that any apparent effect of diabetes may actually be due to concomitant congestive heart failure, chronic renal failure, or dysglycemia, diabetes status notwithstanding (63, 65, 66). No studies have compared rates of adverse outcomes following influenza in patients with and without diabetes.

1.4.4. Premise 3: Influenza vaccine is effective in adults with diabetes

Four observational studies have examined influenza vaccine effectiveness in adults with diabetes. (67-70). Of these studies, Colquhoun et al. and Looijmans-Van Den Akker et al. reported results for working age adults, showing up to 70% relative reductions in hospitalizations in vaccinated

subjects (69, 70). However, these studies examined composite outcomes consisting primarily (> 85%) of acute complications of diabetes, which may be heavily influenced by unmeasured factors related to health behaviors and attitudes, such as adequate glucose monitoring and adherence to insulin therapy. Consequently, the outcomes of these studies may be particularly vulnerable to “healthy vaccinee” bias, which has been previously identified as a pervasive problem for observational studies of influenza vaccination effectiveness in the elderly (71). Neither Colquhoun et al. nor Looijmans-Van Den Akker et al. assessed the potential for unmeasured confounding by examining the effectiveness of influenza vaccinations during a control period outside of influenza season (72, 73).

1.5. Vaccination rates in patients with diabetes

Despite these limitations, national policy targets for vaccination rates have been promulgated in the US and Canada. In Canada, the National Consensus Conference for Vaccine-Preventable Diseases has called for 80% of working age high-risk adults to receive influenza vaccinations (51). However, only 53% of adults aged 35 to 64 years with diabetes in Canada have received recent vaccinations (15), much lower than the 71% achieved in elderly Canadians (74). Similarly, while the US Healthy People 2020 policies call for vaccination rates of 90% in high-risk working age adults (75), only 57% of diabetic adults aged 50 to 64 years have received recent vaccinations, with younger adults exhibiting even lower rates (16).

Previous surveys have identified patient safety concerns and perceptions of low personal risk as important patient-level factors responsible for missed vaccinations in the elderly (76). The latter may be particularly relevant to working age adults with diabetes, who may be unaware of vaccination guidelines, or who may not see themselves as sufficiently vulnerable to warrant vaccination (20). Because many of these perceptions are amenable to recommendations from health care providers

(77), sub-optimal vaccination rates may represent missed opportunities to recommend vaccinations in primary care (78-80). In turn, surveys of primary care providers have consistently identified system-level barriers to achieving desired vaccination rates, such as inadequate time, or difficulty identifying high-risk patients (17-19, 81). It would appear that vaccinations, along with many other preventive procedures, are being crowded out by urgent concerns in primary care practices badly designed to promote proactive care (22). Quality improvement interventions may improve influenza vaccination rates (25). However, substantial confusion about the effectiveness of particular quality improvement interventions exists, given the wealth and diversity of quality improvement studies, as well as substantial variations in their results (82).

1.6. Objectives and Program of Research

Current vaccination guidelines effectively single out working age adults with diabetes for annual vaccinations against seasonal influenza. In Canada, this sub-group represents up to 3% of the population. Despite these guidelines, vaccination rates in patients with diabetes remain below national targets. Because such individuals are seen more frequently in primary care than healthy working age adults, future efforts to increase vaccination rates in patients with diabetes will depend not only on increased public awareness efforts through public health-led vaccination campaigns, but also on primary care practice interventions intended to decrease the prevalence of missed vaccination opportunities. However, before such efforts can be undertaken, two knowledge gaps must be addressed. First, there is little rigorous comparative evidence that adults with diabetes suffer either increased frequency or increased severity of illness due to influenza, or that influenza vaccinations can improve clinical outcomes in this risk group (53). Second, the effectiveness of particular interventions for increasing vaccination rates in the community remains unclear, due to the substantial quantity and diversity of quality

improvement studies, interventions, and results. Research is needed to evaluate the extent to which those with diabetes may benefit differentially from influenza vaccinations, compared to non-diabetic adults; and to identify promising interventions for delivering these vaccinations.

This dissertation encompasses a program of research, with the following objectives:

1. To examine the extent to which diabetes is associated with greater incidence of ILI or hospitalizations attributable to influenza.
2. To compare the effects of circulating influenza on adverse outcomes following acute respiratory infections in patients with, and without, diabetes.
3. To estimate the effectiveness of influenza vaccinations for reducing ILI, PI hospitalizations, and all-cause hospitalizations in working age adults with diabetes.
4. To systematically review studies of the effectiveness of quality improvement interventions for increasing adult influenza and pneumococcal vaccination rates in the community.

The first three of these objectives were addressed in a series of cohort studies using the administrative claims databases of Manitoba Health. Like those of other Canadian provinces, Manitoba's databases capture services, diagnoses, and interventions provided to patients during physician visits and hospital admissions covered by Manitoba's publically funded, universal health insurance program (83). Manitoba data additionally capture influenza and pneumococcal vaccinations provided in the community to Manitoba residents, an essential component of our research (84). The final objective was accomplished as a systematic review and meta-analysis, intended to provide a comprehensive, quantitative, and up-to-date summary of the results achieved by previous quality improvement studies. The findings of these studies will help ensure

that policies for targeted vaccinations in those with diabetes are clinically beneficial, and effectively implemented.

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Chapter 2: Is Diabetes Associated With Increased Susceptibility to Influenza? A Population-Based Cohort Study*

Abstract

Objectives: Guidelines recommending routine seasonal influenza vaccinations suggest targeting working age (age < 65) adults with diabetes, presumably because they experience a higher risk of contracting influenza. We examined this presumption by comparing population-based rates of influenza-attributable illness in adults with and without diabetes.

Methods: We performed a cohort study using administrative claims data from Manitoba, Canada, between 2000 to 2008. All adults (18 years and older) with diabetes were identified and matched to two non-diabetic controls. Outcomes were physician visits and hospitalizations for influenza-like illness (ILI), pneumonia and influenza hospitalizations (PI), and all-cause hospitalizations (ALL). Using multivariable Poisson regression, we estimated differences in the influenza-attributable rates of each outcome for patients with and without diabetes during periods of known circulating influenza, stratified by working and elderly (>= 65) age.

Results: We included 1.21 million person-years of follow-up among 261570 subjects. Of 429,026 diabetic person-years, 58% occurred in

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working age adults. Overall, there were 412,043 physician visits or hospitalizations for ILI, 7,338 PI hospitalizations, and 134,799 all-cause hospitalizations. In those with diabetes, seasonal influenza increased event rates (% and [95% CI]) by 14% [12-15%] (ILI), 20% [11-30%] (PI), and 6% [4-8%] (ALL), relative to non-influenza periods. For those without diabetes, influenza increased event rates relatively by 13% [12-14%] (ILI), 8% [-1-19%] (PI), and 7% [4-9%] (ALL). In working age adults, influenza was associated with a 6% greater (RR = 1.06 [1.00, 1.11], p = 0.04) increase in all-cause hospitalizations in adults with diabetes, compared to those without, representing an additional 54 hospitalizations (approximately 1 per 1000 adults) among the former.

Conclusions: Adults with diabetes appear to experience a greater risk of influenza. In particular, for working age adults with diabetes, influenza was associated with a greater risk of all-cause hospitalizations, providing much needed evidence supporting the identification of diabetic adults as a high-risk indication for efforts to mitigate the effects of influenza.

2.1. Introduction

Numerous defects in immune function have been characterized in those with diabetes (1, 2). In addition to increased risks of micro- and macro-vascular complications (3), these individuals experience certain bacterial and fungal infections more frequently than their non-diabetic counterparts (2, 4), and may also be at increased risk from influenza and other acute respiratory infections (5). Consequently, clinical practice guidelines recommend annual vaccination for seasonal influenza in adults with diabetes (6-9). Since vaccinations are already recommended in the elderly (age >= 65), these guidelines effectively single out working age (age < 65) adults with diabetes as a high-risk group. Even US guidelines recommending universal vaccination in working age adults suggest prioritizing those with diabetes. However, the evidence supporting these guidelines is limited (1, 6, 7).

Influenza is a common viral illness (10) responsible for substantial morbidity and mortality (11-14). Influenza-like illness (ILI), defined as fever and cough with systemic symptoms, is the classic presentation of influenza (15). However, influenza is isolated in less than 30% of ILI during influenza season (16). Additionally, influenza contributes to the morbidity and mortality of many other respiratory (17-20), as well as cardiovascular and other non-respiratory, conditions (14, 21, 22). Consequently, influenza infections may not be suspected, and if suspected, are rarely laboratory-confirmed, making direct measurement of infection difficult. Studies examining the burden of influenza have instead estimated the influenza-*attributable* portion of non-specific outcomes, correlating outcomes to community-level indicators of influenza activity (11-14, 21-23).

To our knowledge, 3 studies have used this method to compare the incidence of influenza in adults with and without diabetes. These studies

have several limitations, including potential bias from the use of hospital-based comparison groups (24); reliance on death certificates or admission diagnoses to ascertain diabetes status (24), lack of adjustment for comorbidities and vaccination status (24-26); and inadequate adjustment for seasonality (26). Therefore, we examined the extent to which diabetes was associated with greater rates of ILI or hospitalizations attributable to influenza.

2.2. Methods

We performed a large population-based cohort study using administrative data from Manitoba, Canada. Nearly all Manitoba residents have provincially funded health care benefits under Manitoba's system of universal health insurance. The databases of Manitoba Health capture services, diagnoses, and interventions provided to patients during hospital admissions and physician visits; demographics; pharmaceuticals dispensed in the community at the point of sale; and vaccinations provided to Manitoba residents (27, 28).

We identified a cohort of adults (age >= 18 years) with diabetes, from July 1, 2000 to June 30, 2008, using a well validated claims-based definition of diabetes, defined as 2 ambulatory physician claims or one hospital discharge for diabetes (ICD-9 code 250 or ICD-10 codes E10-E11) (29). Diabetic subject were individually matched to two non-diabetic controls by age (i.e.: +/- 1 year), sex, and health region.

We divided calendar time into "influenza years" from July 1 to June 30 (26). Influenza season was defined as a continuous period between the first and last occurrences of at least 2 consecutive weeks with 2 or more isolates positive for influenza, according to provincial surveillance data (30). Subjects were followed until June 30, 2008, for any occurrences of three outcomes, based on ICD diagnostic codes: physician visits or

hospitalizations for ILI, hospitalizations for pneumonia and influenza (PI), and all-cause hospitalizations. ILI consisted of a broad bundle of diagnoses, including bronchitis, pneumonia, cold, cough, and exacerbations of chronic obstructive pulmonary disease (see Supplement Table S2-1). This case definition, determined in a pilot study of 6 emergency departments in a neighboring Canadian province is similar to those of other studies showing correlations with influenza activity (31, 32). ILI was chosen to represent the common manifestations of influenza, PI hospitalizations to depict more serious and specific respiratory sequelae, and all-cause hospitalizations to indicate the overall burden of influenza on serious morbidity.

We fitted unconditional Poisson regression models describing rates of each outcome as a function of diabetes and influenza activity. A time-varying analysis was performed, with each subject's follow-up time split into weeks. Models included follow-up time in person-years as an offset term. Influenza activity was represented by a binary indicator for influenza season. Seasonal and secular trends were modeled using indicator variables for months and years, respectively.

Our models also included age, sex, urban or rural residence, socioeconomic status (SES), comorbidities, number of physician visits in the previous year, and current vaccinations for influenza and pneumococcus. SES was based on the census-derived income quintile of each subject's postal code area of residence (33, 34). Comorbidity was represented by the number of major Aggregate Diagnostic Groups (ADG) accrued during the previous 2 years (35). All variables were updated every July 1, except vaccination status, which was updated upon receipt of vaccination.

We estimated incidence rate ratios (RR) from our models to express the average effect of influenza during influenza season. The influenza-attributable fraction of each outcome was then calculated as $f = (RR - 1.00) / RR$ (36). The inclusion of a *diabetes x influenza* interaction term allowed us to estimate the effect of influenza for adults with and without diabetes.

To better illustrate the public health impact of influenza, we calculated the average annual number of events attributable to influenza. Finally, the potential benefits of vaccination were depicted using numbers needed to vaccinate (NNV) to prevent one influenza-attributable event. For illustrative purposes, NNVs are shown for otherwise healthy, urban men residing in below-median income communities, assuming vaccine effectiveness of 80%. NNVs under alternate assumptions are reported in a supplement.

Because current vaccination guidelines single out working age patients with diabetes (6, 7), we performed our analysis for subjects of all ages, and then within strata of working age (< 65 years) and elderly (>= 65 years) adults. To check for over-dispersion, we repeated our analyses with negative binomial regression. Results were virtually identical (data not shown). Analyses were performed using SAS 9.2. This study was approved by the Institutional Review Board of the University of Alberta, and by the Health Information and Privacy Committee of Manitoba.

2.3. Results

2.3.1. Cohort composition

We identified 99781 adults with diabetes in Manitoba from 2000 to 2008. Of these, 95624 adults were matched to one or more non-diabetic control subjects. Our study included 91,605 adults with diabetes and 169,965 non-diabetic controls with complete data. These subjects contributed 1.21

million person-years of follow-up. The median age of included person-years was 59 years, with person-time evenly split between females and males. Patients with diabetes were more likely to have a below-median income, more physician visits, and had greater comorbidity based on major ADGs, and were more likely to have been vaccinated for influenza or pneumococcus, compared to non-diabetic controls ($p < 0.001$) (Table 2-1). A substantial proportion (56513 adults, 62%) of included adults with diabetes were working age. On average, 31139 working age adults with diabetes were followed each year, representing 58% of all diabetic adults, and approximately 3% of the entire Manitoba population.

During the follow-up period, we observed 412,042 ILI, 7,338 PI hospitalizations, and 134,799 all-cause hospitalizations (Figure 2-1). Outcomes demonstrated a seasonal rise and fall. In addition to seasonal variations, we distinguished an excess of outcomes during influenza season. These trends are illustrated for working age adults (Figure 2-2 – See Supplement Figure S2-1 for outcomes in elderly adults).

2.3.2. All ages

In adults with diabetes compared to those without diabetes, influenza was associated with similar relative increases in the rates of ILI and all-cause hospitalizations, but a larger and statistically significant increase in PI hospitalizations (Table 2-2). The influenza-attributable rate ratio for PI hospitalizations was 1.11 (95% CI: 1.00, 1.22; $p = 0.044$ for the interaction term) times greater in those with compared to those without diabetes.

About 11-12% and 5-6% of all ILI and all-cause hospitalizations occurring during influenza season were attributable to influenza (Table 2-2). For PI hospitalizations, the influenza-attributable fraction was 7% in those without diabetes compared to 17% in those with diabetes. Patients with diabetes experienced 930 ILI, 30 PI hospitalizations, and 155 all-cause

hospitalizations due to influenza. Of these influenza-attributable events, 22 PI hospitalizations occurred because their diabetes.

2.3.3. Working age adults

Among working age adults with diabetes, influenza was associated with statistically significant increases in the rates of all outcomes studied (Table 2-2). The difference in influenza-attributable all-cause hospitalizations between those with and without diabetes was statistically significant (RR = 1.06, 95% CI: 1.00, 1.11; p = 0.044 for the interaction term).

Based on these relative risks, 13-15% of ILI and 12-26% of PI hospitalizations in working age subjects were attributable to influenza during influenza season (Table 2-2). For all-cause hospitalizations, influenza-attributable fractions were 6% in those with, compared to 0.3% in those without, diabetes (actual and expected hospitalizations shown in Figure 2-2c). In working age diabetic adults, influenza was associated with 627 ILI, 16 PI hospitalizations, and 55 all-cause hospitalizations per year (Table 2-3). Having diabetes accounted for nearly all (54/55) of these influenza-attributable all-cause hospitalizations.

2.3.4. Elderly adults

In elderly patients with diabetes, the relative effects of influenza were similar for all-cause hospitalizations, but greater for PI hospitalizations and ILI, compared to those without diabetes (Table 2-2). While the difference in influenza-attributable RRs for PI hospitalization was not statistically significant (p=0.27), the effect of influenza on ILI was 1.03 (interaction RR 95% CI: 1.01, 1.05; p = 0.013) times greater for diabetic compared to non-diabetic subjects.

On average, 7-10% of ILI, 7-12% of PI hospitalizations, and 5-7% of all-cause hospitalizations during influenza season were attributable to

influenza in the elderly (Table 2-2). In patients with diabetes, circulating influenza accounted for 291 ILI, 15 PI hospitalizations, and 97 all-cause hospitalizations per year (Table 2-3). Of these, 82 ILI were contributed by patients' diabetes status.

2.3.5. Numbers Needed to Vaccinate

NNVs for ILI ranged from 35 to over 100000 (Table 2-4). Elderly adults generally required fewer vaccinations to prevent an influenza-related ILI. While NNVs were similar for preventing ILI in working age adults regardless of diabetes status, NNVs in patients with diabetes were substantially lower than NNVs in those without diabetes for PI and all-cause hospitalizations. For example, NNVs for all-cause hospitalizations in working age adults ranged from 624 (ages 45 to 64) to 2703 (ages 18 to 24) in those with diabetes, compared to 32778 (ages 45-64) to 142059 (ages 18-24) in control subjects without diabetes (Table 2-4), reflecting the lack of influenza-attributable events amenable to vaccination among the latter (Table 2-2).

2.4. Discussion

We have distinguished the effects of seasonal influenza on health care utilization in Manitoba adults with and without diabetes. In adults with diabetes, influenza was associated with increased rates of each outcome studied, accounting for 10-13% of physician visits and hospitalizations for ILI, 12-26% of PI hospitalizations, and 5-6% of all-cause hospitalizations during influenza season. Of particular note, compared to those without diabetes, working age adults with diabetes experienced a 6% greater influenza-attributable increase in all-cause hospitalizations, representing an additional 54 hospitalizations in this group. Our findings suggest that adults with diabetes experience greater susceptibility to influenza, and support the identification of diabetes as a high-risk indication for vaccination.

Three previous studies have compared influenza-attributable outcomes in patients with and without diabetes. Schanzer et al. found that influenza-attributable primary respiratory admissions were higher in patients with diabetes compared to those without (25). Bouter et al. found that the association between diabetes and pneumonia hospitalizations was stronger during years with a discernable influenza season compared to years without significant influenza activity (24). Extrapolating from these results, diabetes was associated with 26 to 62% increases in rates of influenza-related pneumonia, which are much higher than our estimates (i.e.: 7 to 19% increases). Finally, Neuzil et al., in a population-based cohort study (26), reported a substantial, 5-fold (unadjusted) higher rate of influenza-attributable cardiopulmonary hospitalizations or deaths in working age women with diabetes compared with low-risk controls. Each of these studies had important limitations mitigated by key features of our study. To our knowledge, our study is one of only two studies to have followed individuals for influenza-attributable outcomes (26). Previous studies have attributed outcomes to risk groups by death certificate or outcome admission diagnoses (25), which provide incomplete ascertainment of previously diagnosed diabetes (37-39). Our study provides used a validated case definition for diabetes (29), and is also the first and only study to have adjusted concomitantly for comorbidities, vaccination status, and seasonal trends apart from influenza. We have thus provided the highest quality evidence to date concerning the rationale for vaccinating diabetic adults.

Nonetheless, our study has several limitations. First, because we relied on a community-level indicator for influenza, ecologic bias may arise if outcomes attributed to influenza did not actually occur in patients infected with influenza. For example, respiratory syncytial virus (RSV) co-circulates with influenza and causes a similar illness (12). Since patterns of RSV and

influenza circulation differ during influenza season, the use of a continuous indicator of influenza activity would help to exclude non-influenza cases. As a sensitivity analysis, we refitted our models using the proportion of surveillance isolates positive for influenza and found no substantive changes in results (data not shown). Second, our data is limited to outcomes presenting to medical attention, which may underrepresent the burden of influenza (40). Surveillance bias may also occur if patients with diabetes were more likely to seek medical attention, or to be hospitalized. However, while health care utilization does not capture the total burden of influenza, it does capture the clinically important events of most concern for vaccination policy.

Current vaccination policies single out working age adults with diabetes. Our results suggest that such adults are indeed at greater risk of influenza-related all-cause hospitalizations, which comprise an important fraction of outcomes for these patients. The public health impact of diabetes on the burden of influenza in working age adults may be summarized as 6.1 hospitalizations per 1000 diabetic person-years, or 54 additional hospitalizations per year. Our NNV analysis provides additional perspective. From 624 (age 45-64) to 2703 (age 18-24) working age adults with diabetes would have to be vaccinated to prevent one hospitalization, compared to 32,778 (age 45-64) to 142,059 (age 18-24) non-diabetic adults. Since the direct cost of vaccinating 624 adults may be similar to that of a single PI hospitalization (41), our data suggest a possible rationale for targeting diabetic adults aged 45 to 64. Formal economic studies are required, to ascertain the extent to which identifying diabetes as a high risk indication for vaccination may mitigate the healthcare utilization and costs associated with influenza.

In conclusion, compared to their non-diabetic counterparts, adults with diabetes appear to experience increased incidence of influenza-

attributable illness. In working age adults, seasonal influenza was associated with all-cause hospitalizations in those with, but not those without, diabetes, contributing 6% of all such outcomes in the former. These results support current vaccination guidelines that distinguish diabetes as a high-risk indication for vaccination. Given the small numbers of influenza-attributable hospitalizations in working age adults generally, economic studies are required to ascertain the extent to which improving vaccinations in diabetic adults is cost-effective. Nevertheless, special efforts to mitigate the effects of influenza in diabetic adults may be warranted by an increased risk of influenza.

Tables and Figures

Table 2-1: Characteristics of included person-time

Variable	Value	Diabetes N [1]	Diabetes P [1]	No diabetes N	No diabetes P
Age (median, IQR)	Years	61	21.00	59	22.00
Sex	Male	214533	0.50	381834	0.49
	Female	214493	0.50	403119	0.51
Income quintile	Upper	188973	0.44	418206	0.53
	Lower	240053	0.56	366747	0.47
Residence	Urban	253859	0.59	467892	0.60
	Rural	175167	0.41	317061	0.40
Medical visits [2]	0	237829	0.55	539174	0.69
	1-2	104700	0.24	159452	0.20
	3 or more	86497	0.20	86327	0.11
Major ADGs [3]	0	155737	0.36	410214	0.52
	1	130823	0.30	224236	0.29
	2 or more	142466	0.33	150503	0.19
Influenza vaccination [4]	Yes	171202	0.40	197422	0.25
	No	257824	0.60	587531	0.75
Pneumococcal vaccination [5]	Yes	122104	0.28	131794	0.17
	No	306922	0.72	653159	0.83

Table enumerates subjects at follow-up every July. All between group differences $p < 0.001$ on Wilcoxon rank-sum or chi-squared tests.

[1] N = Number of subjects. P = Proportion of subjects.

[2] Number of medical visits over the previous year.

[3] Number of major ADGs over the previous 2 years: ADG3 (time limited: major), ADG4 (time limited: major – primary infections), ADG9 (likely to recur: progressive), ADG11 (chronic medical: unstable), ADG16 (chronic specialty: unstable – orthopedic), ADG22 (injuries / adverse effects: major), ADG25 (psychosocial: recurrent or persistent, unstable), and ADG32 (malignancy).

[4] Influenza vaccination during the previous year.

[5] Any previous record of pneumococcal vaccination.

Table 2-2: Relative effects of influenza in adults with and without diabetes according to age group

		No diabetes				Diabetes				Interaction		
Age group	Outcome[1]	RR[2]	95% CI	*f*[3]	P-value	RR[4]	95% CI	*f*[3]	P-value	RR[5]	95% CI	P-value
All ages	ILI	1.13	[1.12, 1.14]	11.5%	0.000	1.14	[1.12, 1.15]	12.3%	0.000	1.00	[0.99, 1.02]	0.476
	PI	1.08	[0.99, 1.19]	7.4%	0.082	1.20	[1.11, 1.30]	16.7%	0.000	**1.11**	**[1.00, 1.22]**	**0.044**
	ALL	1.07	[1.04, 1.09]	6.5%	0.000	1.06	[1.04, 1.08]	5.7%	0.000	0.99	[0.97, 1.02]	0.555
Working age	ILI	1.17	[1.15, 1.18]	14.5%	0.000	1.15	[1.13, 1.17]	13.0%	0.000	0.98	[0.97, 1.00]	0.057
	PI	1.13	[0.91, 1.39]	11.5%	0.265	1.35	[1.16, 1.56]	25.9%	0.000	1.19	[0.96, 1.48]	0.107
	ALL	1.00	[0.95, 1.06]	0.3%	0.889	1.06	[1.02, 1.10]	5.7%	0.001	**1.06**	**[1.00, 1.11]**	**0.044**
Elderly	ILI	1.08	[1.06, 1.10]	7.4%	0.000	1.11	[1.09, 1.13]	9.9%	0.000	**1.03**	**[1.01, 1.05]**	**0.013**
	PI	1.07	[0.97, 1.19]	6.5%	0.163	1.14	[1.04, 1.26]	12.3%	0.006	1.07	[0.95, 1.19]	0.271
	ALL	1.08	[1.05, 1.11]	7.4%	0.000	1.05	[1.03, 1.08]	4.8%	0.000	0.98	[0.95, 1.00]	0.098

Notes:

[1] Outcome abbreviations: ILI – influenza-like illness, PI – pneumonia and influenza hospitalization, ALL – all-cause hospitalization.

[2] Risk ratio representing the relative effect of circulating influenza on outcomes in adults without diabetes.

[3] *f* – Influenza-attributable fraction of outcomes during influenza season.

[4] Risk ratio representing the relative effect of circulating influenza on outcomes in adults with diabetes.

[5] The interaction RR provides a formal test of differences in the effects of influenza between those with and without diabetes. The interaction RR is the ratio of the two previous RRs (i.e.: in columns 3 and 7). E.g.: An interaction RR = 1.11 shows an 11% greater effect of circulating influenza in those with diabetes compared to those without.

Table 2-3: Numbers of influenza-attributable events in adults with and without diabetes according to age

		Diabetes				No diabetes (matched controls)	
		Total [2]		Amount due to diabetes [3]		Total [2]	
Outcome[1]	Age group	N	Rates	N	Rates	N	Rates
ILI	All ages	930	0.062*	148	0.010	8462	0.041*
	Working age	627	0.071*	38	0.004	6353	0.049*
	Elderly	291	0.046*	82	0.013**	2193	0.029*
PI	All ages	30	0.002*	22	0.001**	75	0.000
	Working age	16	0.002*	13	0.001	19	0.000
	Elderly	15	0.002*	9	0.002	56	0.001
HOSP	All ages	155	0.010*	62	0.004	934	0.005*
	Working age	55	0.006*	54	0.006**	9	0.000
	Elderly	97	0.015*	6	0.001	939	0.012*

Notes:

Counts and rates for adults without diabetes were estimated for a 2:1 matched group of controls, and therefore do not represent the actual numbers of influenza-attributable outcomes in Manitoba adults without diabetes. Event counts for elderly and working age subjects do not sum to all ages event counts because separate models were fitted for each age category.

[1] Outcome abbreviations: ILI – influenza-like illness, PI – pneumonia and influenza hospitalization, ALL – all-cause hospitalization.

[2] Total projected numbers of influenza-attributable events per year, during influenza season.

[3] Influenza-attributable events contributed by the greater effect of influenza in adults with diabetes. These events were calculated by subtracting the number of influenza-attributable events that would have occurred in diabetic adults if they had not had diabetes, from the total number of influenza-attributable events for this group (column 3).

* Statistically significant relative effect of influenza confirmed – See rate ratios in Table 2.

** Difference in the relative effects of influenza confirmed by interaction terms – See Table 2.

Table 2-4: Numbers needed to vaccinate to prevent a single influenza-attributable event

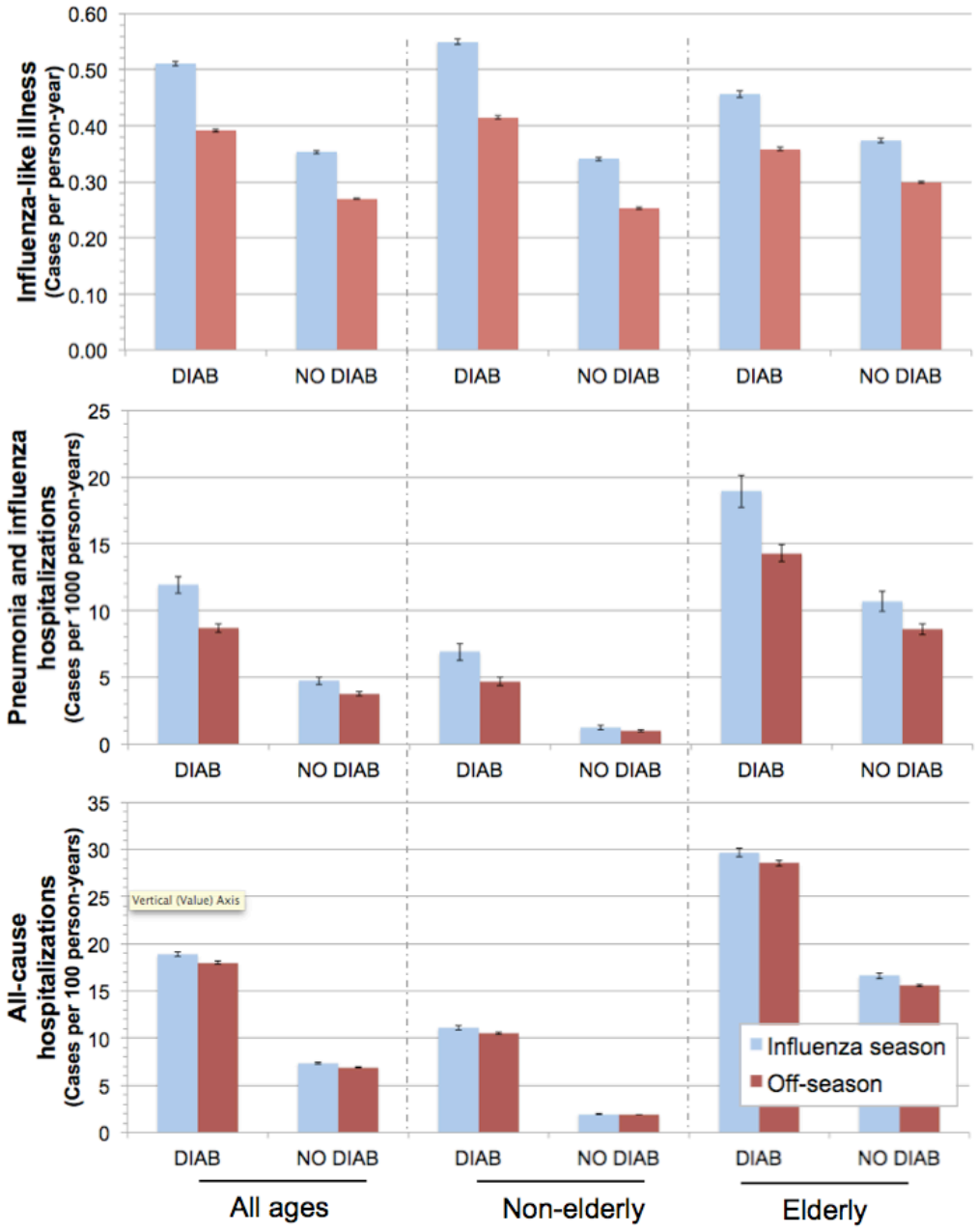
Outcome	Age	Diabetes Event rate[1]	Diabetes NNV[2]	No diabetes Event rate	No diabetes NNV
ILI	18 to 24	**37.0**	**34**	**34.7**	**36**
	25 to 44	**38.0**	**33**	**35.7**	**35**
	45 to 64	**30.2**	**41**	**28.3**	**44**
	65 to 84	**24.2**	**52**	**17.4**	**72**
	85 and older	**25.5**	**49**	**18.3**	**68**
PI	18 to 24	**0.3**	**4570**	0.0	29344
	25 to 44	**0.4**	**3344**	0.1	21476
	45 to 64	**0.4**	**2909**	0.1	18679
	65 to 84	**0.8**	**1584**	0.3	4242
	85 and older	**1.5**	**855**	0.5	2290
ALL	18 to 24	**0.5**	**2703**	0.0	142059
	25 to 44	**1.0**	**1272**	0.0	66858
	45 to 64	**2.0**	**624**	0.0	32778
	65 to 84	**6.7**	**187**	**6.3**	**200**
	85 and older	**8.8**	**142**	**8.3**	**151**

Absolute influenza-attributable event rates and NNVs estimated for a hypothetical group of otherwise healthy (i.e.: no major ADGs in the previous 2 years, and no medical visits in the previous year) urban men residing in below-median income communities, assuming a vaccine with 80% relative effectiveness (see Supplement Table S2-2 for NNVs under alternate assumptions). Bolded results are for groups in which statistically significant influenza-attributable relative effects on outcomes were observed (Table 2).

[1] Event rate – Projected absolute influenza-attributable event rates *per thousand person-years*.

[2] NNV – Number needed to vaccinate to prevent one influenza-attributable event.

Figure 2-1: Crude outcome rates in subjects with and without diabetes stratified by the presence of circulating influenza



Error bars represent 95% confidence intervals of the crude rates.

Figure 2-2: Actual and projected outcomes in working age adults

Outcome numbers in adults without diabetes were estimated for a 2:1 matched group of controls, and therefore do not represent actual numbers for Manitoba adults without diabetes.

Legend: “+” – Weekly numbers of each outcome. Green line – Projected number of events. Blue line – Projected number of events in the absence of circulating influenza. Red line – Number of influenza-attributable events per week (i.e.: green line minus blue line).

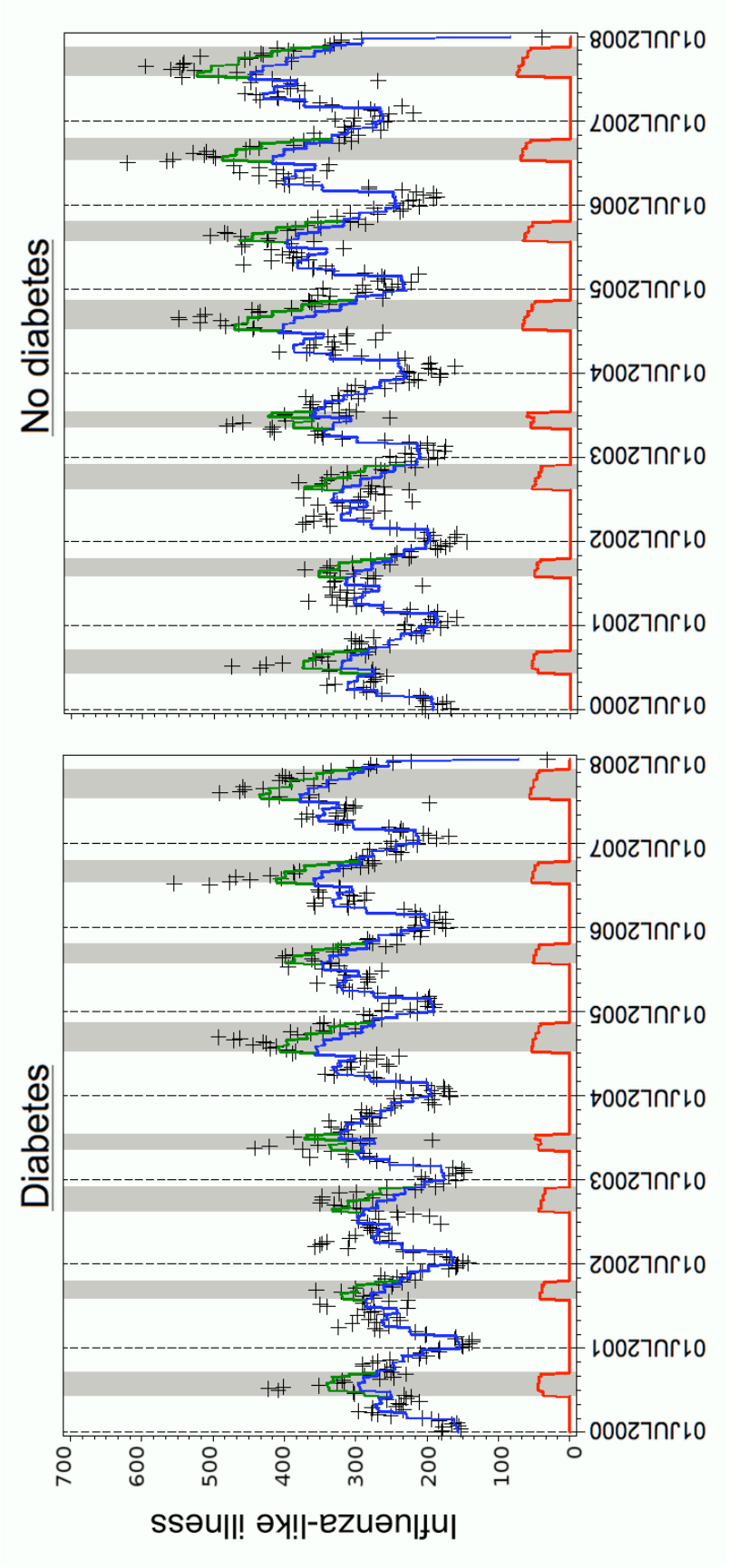


Figure 2-2a: Actual and projected influenza-like illness (ILI) visits and hospitalizations in working age adults

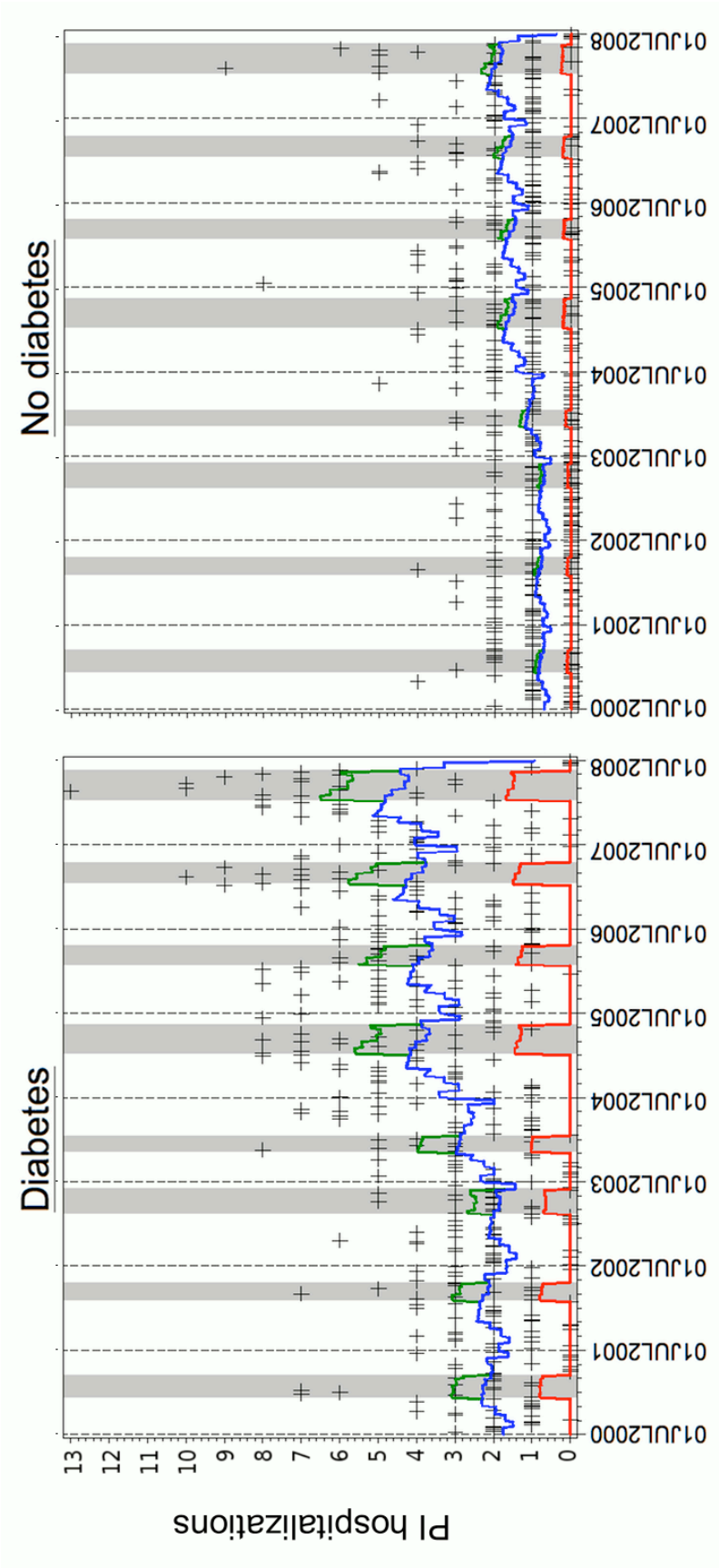


Figure 2-2b: Actual and projected pneumonia and influenza (PI) hospitalizations in working age adults

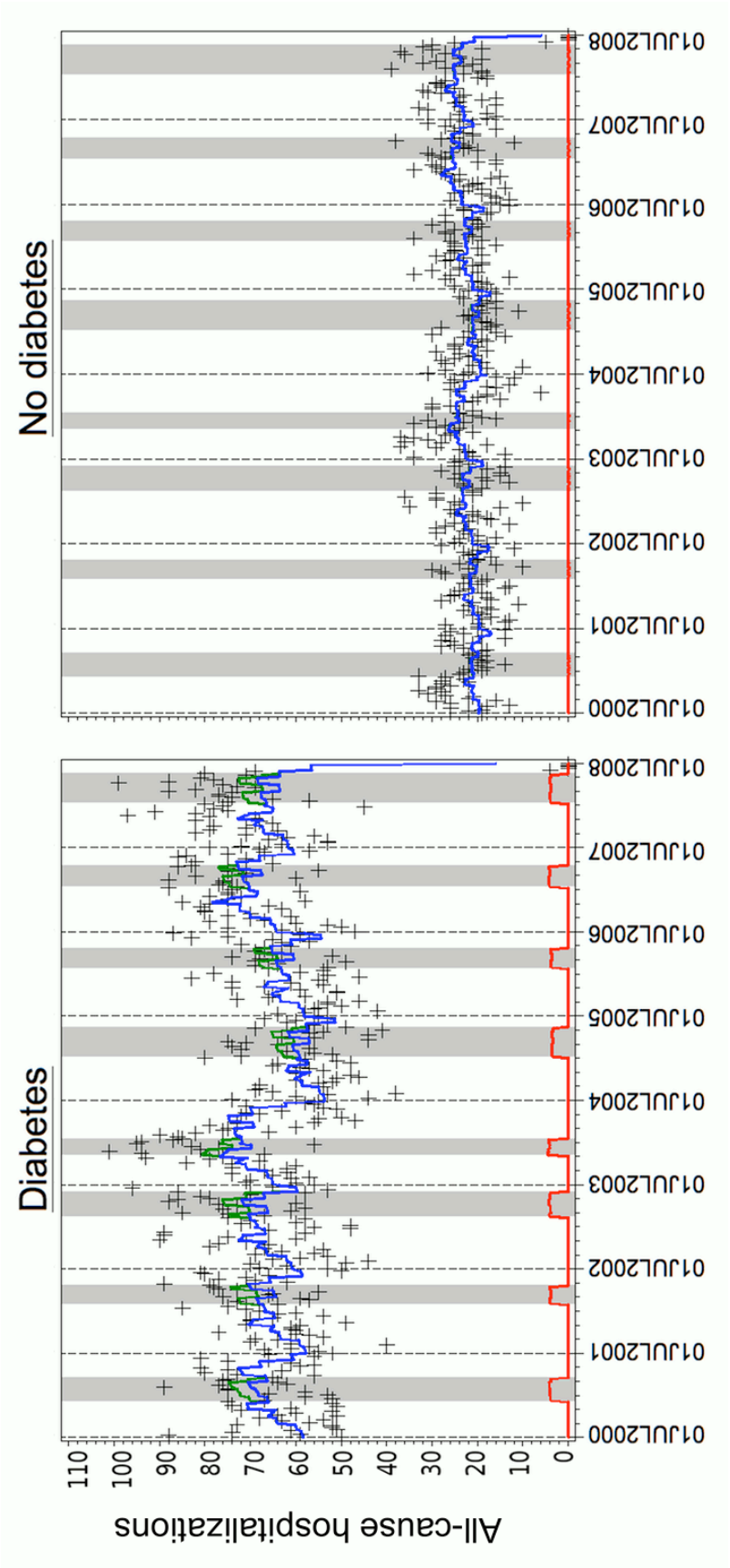


Figure 2-2c: Actual and projected all-cause hospitalizations in working age adults

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Chapter 2 Supplementary Tables and Figures

Table S2-1: Outcome case definitions

Table S2-1a: List of ICD-10-CA and ICD-9-CM codes comprising an administrative case definition of influenza-like illness (ILI)

Diagnosis	ICD-10-CA code	ICD-9-CM code
Cold	J00	460
Sinusitis	J01 or J32	461
Pharyngitis	J02	462
Laryngitis, tracheitis, or laryngotracheitis	J04	464
Upper respiratory tract infection	J06.8 or J06.9	465.8, 465.9
Influenza	J10 or J11	487 or 488
Viral pneumonia	J12	480
Pneumonia	J18	481-486
Acute bronchitis or bronchitis NOS or obstructive bronchitis	J20 or J40 or J44.8	466, 490, 496
Bronchiolitis	J21	466
Acute lower respiratory tract infection, not otherwise specified	J22	None
COPD with acute lower respiratory tract infection (includes pneumonia)	J44.0	491.22
COPD with acute exacerbation	J441	491.21
Cough	R05	786.2
Pleurisy	R09.1	511

Developed using pilot data from emergency departments in Edmonton, Alberta. ICD codes were extracted from randomly selected cases comprising 15% of all emergency department visits with a main ambulatory care diagnosis of influenza.

Table S2-1b: List of ICD-10-CA and ICD-9-CM codes comprising an administrative case definition of pneumonia and influenza (PI)

Diagnosis	ICD-10-CA code	ICD-9-CM code
Influenza	J10 or J11	487 or 488
Viral pneumonia	J12	480
Pneumonia	J13 or J14 or J15 or J16	481 or 482 or 483
Pneumonia, organism unspecified	J18	485 or 486

Table S2-2: Numbers needed to vaccinate to prevent a single influenza-attributable event

NNVs estimated for a hypothetical group of otherwise healthy (i.e.: no ADGs or medical visits in the previous year) subjects. ILI = influenza-like illness, PI = pneumonia and influenza hospitalization, ALL = all-cause hospitalization, Diab = subjects with diabetes, Nodiab = subjects without diabetes.

Table S2-2a: Assumptions – Vaccine effectiveness = 80%, sex = male

			Urban males				Rural males			
			Lower income		Upper income		Lower income		Upper income	
		Age	DM	nDM	DM	nDM	DM	nDM	DM	nDM
Outcome	ILI	18 to 24	34	36	41	44	38	41	47	50
		25 to 44	33	35	40	43	37	39	45	48
		45 to 64	41	44	51	54	47	50	57	61
		65 to 84	52	72	60	83	50	69	57	80
		85+	49	68	57	79	47	66	55	76
	PI	18 to 24	4570	29344	8713	55953	1927	12375	3674	23596
		25 to 44	3344	21476	6377	40949	1410	9056	2689	17268
		45 to 64	2909	18679	5546	35616	1227	7877	2339	15019
		65 to 84	1584	4242	2125	5693	736	1971	988	2646
		85+	855	2290	1147	3073	397	1064	533	1428
	ALL	18 to 24	2703	142059	3517	184828	2003	105281	2606	136988
		25 to 44	1272	66858	1655	86988	943	49541	1227	64460
		45 to 64	624	32778	811	42647	462	24290	601	31604
		65 to 84	187	200	218	232	147	157	171	182
		85+	142	151	165	176	112	119	129	138

Grey region – Results shown in main report.

Table S2-2b: Assumptions – Vaccine effectiveness = 80%, sex = female

Outcomes		Urban females				Rural females			
		Lower income		Upper income		Lower income		Upper income	
	Age	DM	nDM	DM	nDM	DM	nDM	DM	nDM
ILI	18 to 24	22	24	27	29	25	27	31	33
	25 to 44	22	23	27	28	25	26	30	32
	45 to 64	28	29	34	36	31	33	38	40
	65 to 84	47	66	54	76	45	63	52	73
	85+	45	62	52	72	43	60	50	69
PI	18 to 24	4499	28894	8579	55093	1897	12185	3618	23233
	25 to 44	3293	21146	6279	40320	1389	8917	2648	17003
	45 to 64	2864	18392	5461	35069	1208	7756	2303	14789
	65 to 84	2027	5430	2721	7288	942	2523	1264	3387
	85+	1094	2931	1468	3934	508	1362	682	1828
ALL	18 to 24	3379	177581	4397	231096	2504	131605	3258	171234
	25 to 44	1590	83573	2069	108742	1178	61930	1533	80577
	45 to 64	780	40975	1014	53312	578	30363	752	39506
	65 to 84	202	215	234	249	158	169	184	196
	85+	153	163	177	189	120	128	139	148

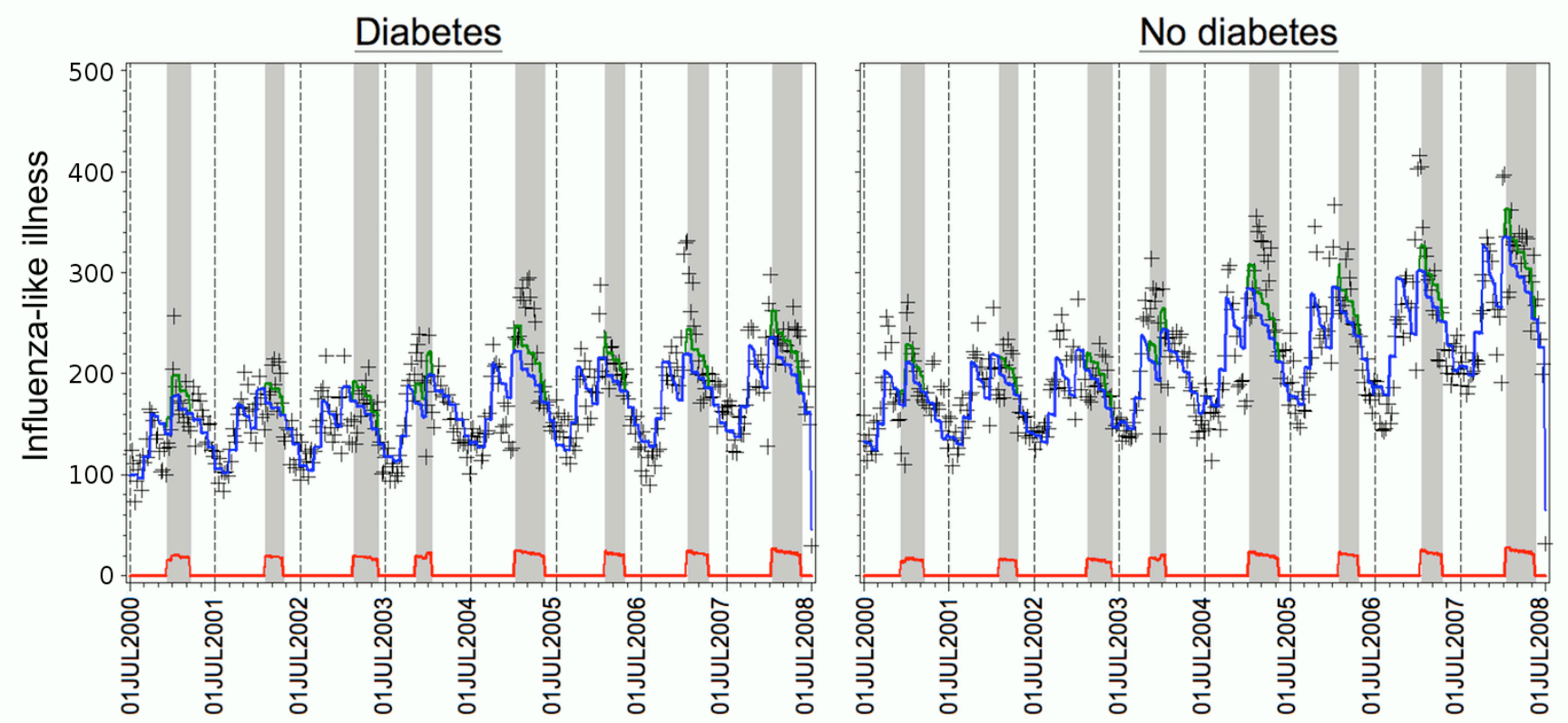
Table S2-2c: Assumptions – Vaccine effectiveness = 50%, sex = male

			Urban males				Rural males			
			Lower income		Upper income		Lower income		Upper income	
		Age	DM	nDM	DM	nDM	DM	nDM	DM	nDM
Outcome	ILI	18 to 24	54	58	66	70	61	65	75	79
		25 to 44	53	56	64	69	59	63	73	77
		45 to 64	66	71	81	86	75	80	91	97
		65 to 84	82	115	96	133	79	111	92	128
		85+	78	109	91	126	75	105	87	122
	PI	18 to 24	7311	46951	13941	89526	3083	19799	5879	37753
		25 to 44	5351	34361	10203	65518	2257	14490	4303	27629
		45 to 64	4654	29886	8874	56985	1963	12603	3742	24031
		65 to 84	2534	6787	3401	9109	1177	3154	1580	4233
		85+	1368	3663	1835	4917	636	1702	853	2285
	ALL	18 to 24	4325	227295	5627	295725	3205	168450	4170	219181
		25 to 44	2035	106973	2648	139180	1508	79266	1962	103135
		45 to 64	998	52445	1298	68235	739	38864	962	50567
		65 to 84	300	320	348	371	236	251	273	291
		85+	227	242	264	281	178	190	207	221

Table S2-2d: Assumptions – Vaccine effectiveness = 50%, sex = female

Outcome		Urban females				Rural females			
		Lower income		Upper income		Lower income		Upper income	
	Age	DM	nDM	DM	nDM	DM	nDM	DM	nDM
ILI	18 to 24	36	38	44	47	40	43	49	53
	25 to 44	35	37	43	46	39	42	48	51
	45 to 64	44	47	54	57	50	53	61	65
	65 to 84	75	105	87	121	72	101	84	117
	85+	71	100	83	115	69	96	80	111
PI	18 to 24	7199	46230	13727	88148	3036	19495	5789	37173
	25 to 44	5269	33833	10046	64512	2222	14268	4237	27205
	45 to 64	4583	29427	8738	56110	1932	12409	3685	23662
	65 to 84	3243	8688	4353	11661	1507	4037	2023	5419
	85+	1751	4689	2350	6294	814	2179	1092	2925
ALL	18 to 24	5407	284129	7035	369754	4006	210569	5213	273975
	25 to 44	2544	133716	3310	173988	1885	99088	2453	128924
	45 to 64	1247	65560	1623	85299	924	48581	1203	63210
	65 to 84	322	344	374	399	253	270	294	313
	85+	244	260	284	302	192	204	223	237

Figure S2-1a: Actual and projected influenza-like illness (ILI) visits and hospitalizations in elderly adults



Notes: Outcome numbers in adults without diabetes were estimated for a 2:1 matched group of controls, and therefore do not represent actual numbers for Manitoba adults without diabetes.

Legend: "+" – Weekly numbers of each outcome. Green line – Projected number of events. Blue line – Projected number of events in the absence of circulating influenza. Red line – Number of influenza-attributable events per week (i.e.: green line minus blue line).

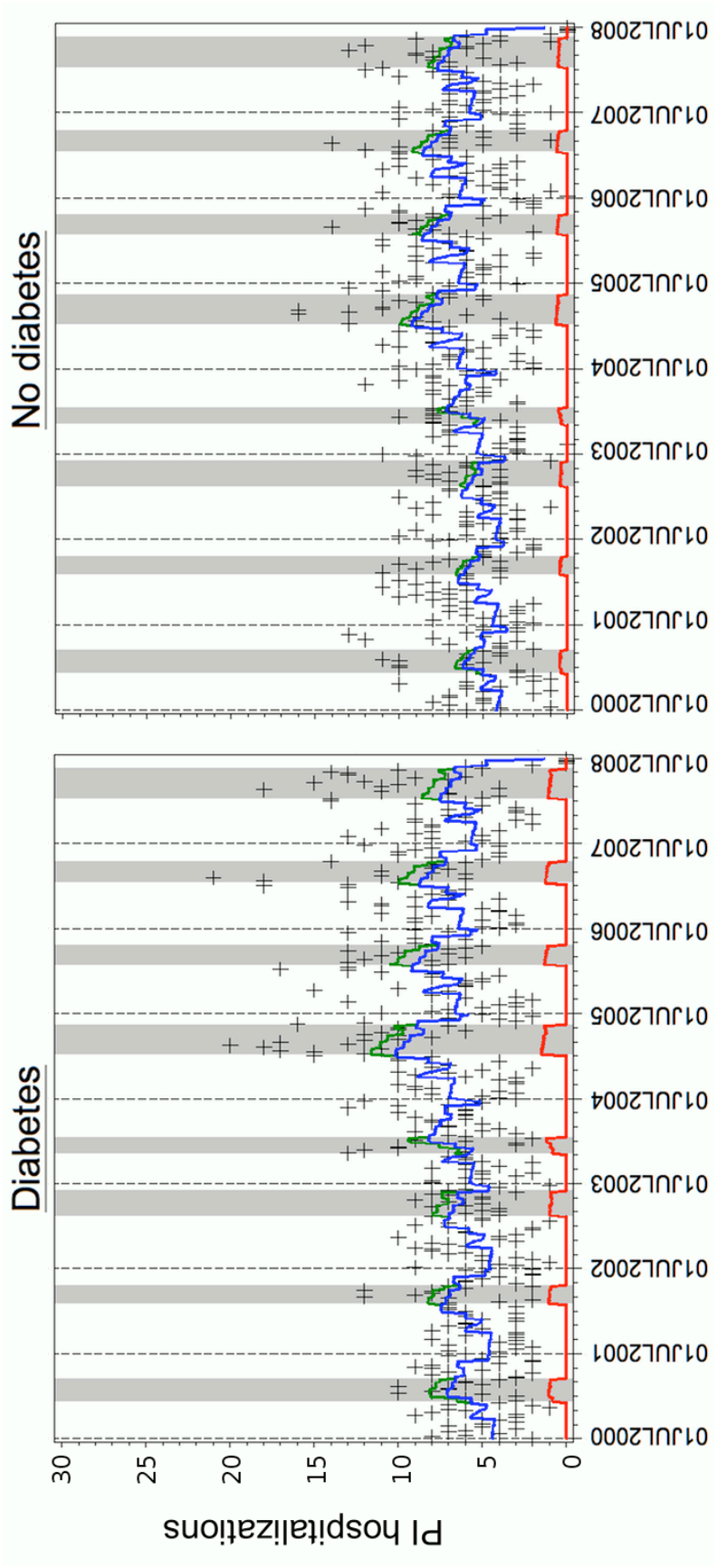


Figure S2-1b: Actual and projected pneumonia and influenza (PI) hospitalizations in elderly adults

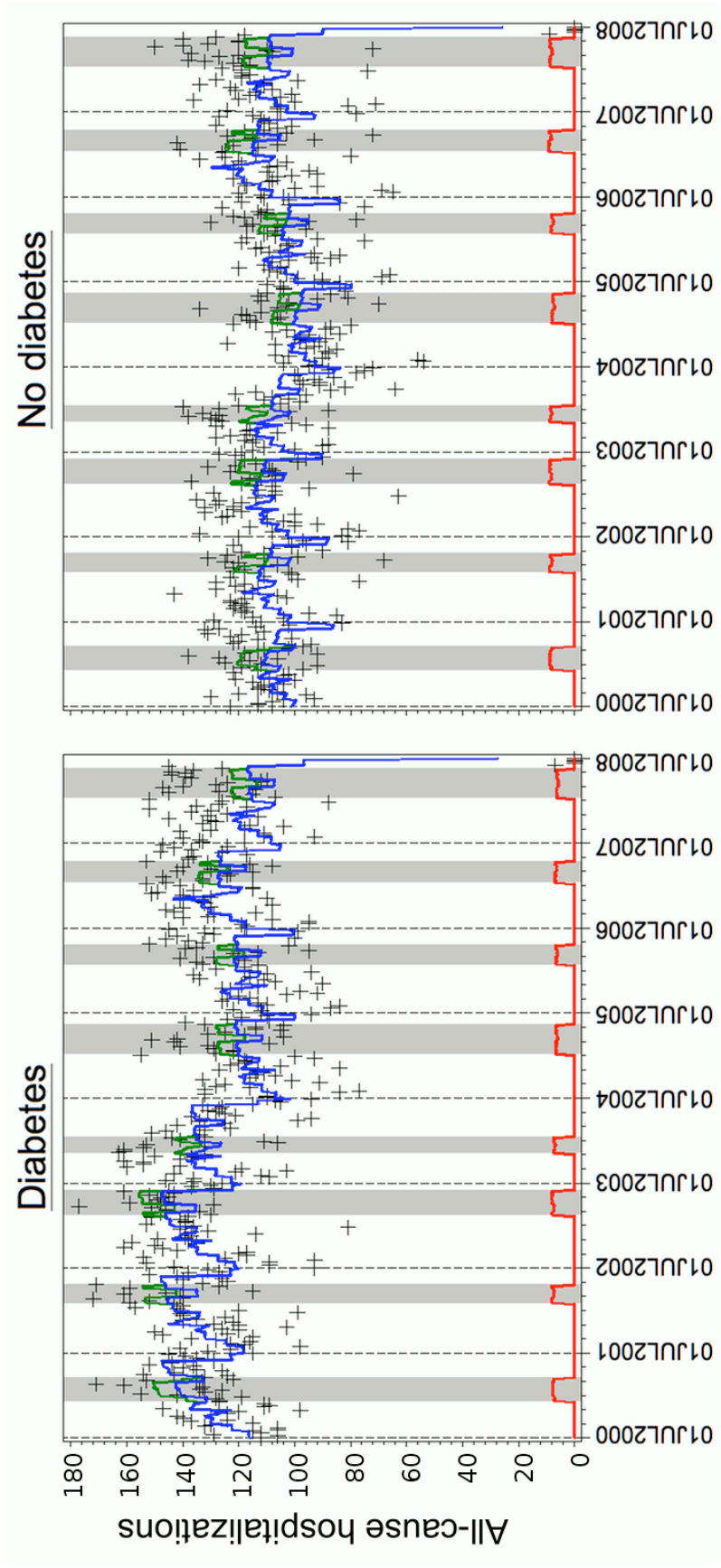


Figure S2-1b: Actual and projected all-cause hospitalizations in elderly adults

Chapter 3: Does Diabetes Potentiate the Population-Level Effects of Seasonal Influenza on Adverse Events Following Acute Respiratory Infections? Results of a Population-Based Cohort Study[†]

Abstract

Objectives: Guidelines for seasonal influenza vaccinations single out working age (< 65) adults with diabetes, in part because of a presumed increase in disease severity in this group. We compared the population-level effects of seasonal influenza on adverse events following acute respiratory illness (ARI) in patients with and without diabetes.

Methods: We performed a cohort study using administrative claims data from Manitoba, Canada, between 2000 to 2008. All adults (18 years and older) with diabetes were identified and matched with up to two non-diabetic controls. All occurrences of ARI, defined as outpatient influenza-like illness (ILI), hospital ILI, and hospital pneumonia and influenza (PI) admissions were included. Multivariable logistic regression was used to estimate the effect of circulating influenza on death or (re-) hospitalization within 30-days of ARI by comparing event rates during influenza season with off-season rates in subjects with and without diabetes, stratified by working and elderly (>= 65) age.

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Results: Our cohort included 303,920 outpatient ILI, 15,111 hospital ILI, and 7,003 hospital PI occurrences. Circulating influenza was not associated with deaths or (re-) hospitalizations ($p >= 0.15$) following ARI in working age adults. However, elderly adults experienced influenza-attributable increases in such events following outpatient ILI (OR = 1.14, 95% CI: 1.07, 1.21; $p < 0.001$), hospital ILI (OR = 1.14, 95% CI: 1.03, 1.26; $p = 0.009$), and hospital PI (OR = 1.20, 95% CI: 1.04, 1.39; $p = 0.011$). In neither working age adults nor the elderly was diabetes associated with increased influenza-related morbidity and mortality following ARI ($p >= 0.13$).

Conclusions: We found no evidence that circulating influenza contributes to increased deaths or hospitalizations following ARI in working age adults, regardless of diabetes status. While further strategies for mitigating the effects of influenza appear warranted by increased disease severity in elderly adults, vaccination guidelines targeting those with diabetes cannot be similarly justified.

3.1. Introduction

Clinical practice guidelines recommend routine vaccinations against seasonal influenza in all adults with diabetes (1-4). Since recommendations already exist for universal vaccination of elderly adults, these guidelines effectively single out working age adults with diabetes as a high-risk group (1-4). The rationale for targeting diabetes is presumably based either on increased frequency or increased severity of influenza in diabetic adults. Since the evidence for either premise is limited, vaccination guidelines rely on expert opinion (1, 2, 5).

The severity of influenza in the community is difficult to measure. While the frequency of adverse events, such as death or hospitalization, following influenza is often used to indicate the severity of influenza infection (6, 7), the identification of such cases is challenging. Most influenza-like illness (ILI) is caused by other etiologies (8, 9), and only 8% of respiratory infections caused by influenza are diagnosed as influenza (10). Thus, studies examining the burden of influenza have estimated the *influenza-attributable* portion of less specific events, correlating these adverse events to community-level indicators of influenza activity (11, 12).

One such study found that patients with diabetes experienced a greater risk of death after hospitalization when compared to non-diabetic controls (13). The association between diabetes and death after hospitalization was accentuated during years of higher influenza activity, suggesting a greater (crude rate ratios from 1.37 to 2.96) adverse impact of influenza on deaths in hospital patients with diabetes. This study's findings were un-adjusted for potential confounders, and did not distinguish working age from elderly adults. To our knowledge, no previous study has attempted to examine the severity of illness due to influenza in diabetic adults. We therefore estimated the population-level effects of circulating influenza on death or (re-) hospitalization within 30 days of ARI by comparing rates of

adverse events rates during influenza season with those outside of influenza season, when influenza circulation is minimal, in subjects with, and without, diabetes.

3.2. Methods

We performed a population-based cohort study using administrative health care claims data from Manitoba, Canada. Nearly all Manitoba residents receive provincially funded health care benefits under Manitoba's system of universal health insurance. The databases of Manitoba Health capture services, diagnoses, and interventions provided to patients during hospital admissions and physician visits; demographics; pharmaceuticals dispensed in the community at the point of sale; and vaccinations provided to Manitoba residents (14, 15).

We identified all adults (age >= 18 years) with prevalent or incident diabetes from July 1, 2000 to June 30, 2008. Diabetes was identified using a well-validated case definition, consisting of two ambulatory physician claims or one hospital discharge for diabetes (ICD-9 code 250 or ICD-10 codes E10-E11) (16). Each diabetic subject was matched with up to two non-diabetic controls by age, sex, and health region of residence, from the general population at cohort entry.

For each subject, we identified all occurrences of outpatient ILI, hospital ILI, and hospital pneumonia and influenza (PI). Collectively, we refer to these events as acute respiratory infections (ARI). Because there is no diagnostic code for ILI, we relied on an administrative case definition, consisting of a broad bundle of diagnoses (e.g.: bronchitis, pneumonia, cold, cough and exacerbations of chronic obstructive pulmonary disease – see Supplement Table S3-1). These diagnoses were determined in a pilot study of 6 emergency departments in a neighboring Canadian province. Similar definitions have been shown to correlate well with influenza activity

(6, 17). Outpatient and hospital ILI were identified from community physician claims and from hospital discharge records, respectively. We considered only the primary diagnosis in each record. Additionally, we considered hospitalizations for PI (ICD-10 codes J10-J16, and J18; ICD-9 codes 480-483, 485-488), to represent more serious and specific manifestations of influenza. ARI occurrences were excluded if they occurred within the 30-day follow-up period of a previously included ARI of the same kind; and if the subject was receiving anti-influenza drugs begun at an earlier date, according to Manitoba Drug Database claims.

We divided calendar time into years from July 1 to June 30. Influenza season was defined as a continuous period between the first and last occurrences of at least 2 consecutive weeks with 2 or more ILI isolates positive for influenza (18), according to provincial surveillance data. Each subject was followed for 30 days after an included ARI for adverse events, defined as a composite of death or (re-) hospitalizations for any reason.

We fitted separate multivariable logistic regression models describing the odds of an adverse event following outpatient ILI, hospital ILI, and hospital PI. Influenza activity was represented by a binary variable for ARI occurring during influenza season. Yearly cyclic and secular trends were modeled using a dummy indicator for the winter months of December, January, and February; and by indicators for each year, respectively. Our models also included age, sex, urban or rural residence, socioeconomic status (SES), comorbidities, number of physician visits in the previous year, and current vaccinations for influenza and pneumococcus. SES was based on the census-derived income quintile of each subject's postal code area of residence (19, 20). Comorbid health status was represented by the number of major Aggregate Diagnostic Groups (ADG) accrued during the previous 2 years (21).

We estimated adjusted odds ratios (OR) from our models describing the relative rate of adverse events following ARI during influenza season, compared to the off-season, when influenza circulation is minimal. These ORs express the average effect of circulating influenza on adverse events following ARI. To better illustrate the public health impact of influenza, we calculated the annual, absolute number of adverse events attributable to influenza.

Models were fitted separately for those with and without diabetes. Models including all patients were also fitted, with diabetes status and a diabetes*influenza interaction term as covariates, to provide a formal test of differences in the effects of circulating influenza between those with and without diabetes. Because current vaccination guidelines single out working age patients with diabetes, we performed our analysis separately within strata of working age (age < 65 years) and elderly (age >= 65 years) adults. Some individuals contributed more than one ARI. We performed a sensitivity analysis including only the first occurrence of ARI for each individual, and found our results unchanged (data not shown). This study was approved by the Institutional Review Board of the University of Alberta, and by the Health Information and Privacy Committee of Manitoba. Analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

3.3. Results

3.3.1. Cohort composition

We identified 99781 adults with diabetes in Manitoba from 2000 to 2008. Of these, 95624 adults (96%) were matched to one or more non-diabetic control subjects. Our source cohort was composed of 91605 adults with diabetes (92% of all diabetic adults identified) and 169965 matched controls, for whom data were complete. Included person-years were evenly split between males and females, with a median age of 59 years

(IQR = 22 years). On average, 31139 working age adults with diabetes were followed each year, representing 58% of all diabetic adults, and approximately 3% of the entire Manitoba population.

Included subjects contributed 303,920 outpatient ILI, 15,111 hospital ILI, and 7,003 hospital PI to our analysis. Diabetic subjects with outpatient ILI were significantly ($p<0.001$) more likely to have had a lower income, incurred more previous medical visits, and had greater comorbidity than non-diabetic controls. They were also more likely to have received vaccinations for influenza and pneumococcus (Table 3-1). Similar trends were observed among hospital ILI and PI patients (Table 3-1). Of those with diabetes, working age adults accounted for 65% of outpatient ILI, 30% of hospital ILI, and 32% of hospital PI. Numbers of ARI and 30-day adverse events are shown in Table 3-2, with crude rates illustrated in Figure 3-1.

3.3.2. Working age adults

In working age adults, influenza was not associated with any difference in the rates of 30-day adverse outcomes following ARI, either for those with, or those without, diabetes ($p >= 0.15$) (Table 3-3). Interaction terms were non-significant for differences in the effects of influenza by diabetes status ($p >= 0.13$) (results not shown).

3.3.3. Elderly adults

In elderly non-diabetic adults, circulating influenza was associated with increased deaths or hospitalizations following any of the ARI (Table 3-3). Odds ratios associated with influenza ranged from 1.12 (outpatient ILI, 95% CI: 1.03, 1.22; $p = 0.011$) to 1.28 (hospital PI, 95% CI: 1.04, 1.56; $p = 0.018$). For those with diabetes, an influenza-attributable effect on 30-day adverse events was observed only for outpatient ILI (OR = 1.15, 95% CI: 1.05, 1.26; $p = 0.002$). However, point estimates for influenza-attributable

effects following hospital ILI and hospital PI were consistent with 1.10 and 1.14-fold increases in adverse events, respectively ($p >= 0.19$). Interaction terms were again non-significant for differences between those with and without diabetes ($p >= 0.20$) (results not shown).

3.3.4. Numbers of influenza-attributable events

Elderly adults with diabetes experienced 14 additional deaths or hospitalizations following outpatient ILI during influenza season (7 per 1000 outpatient ILI) (Table 3-4). This represents 13% of all deaths or hospitalizations following outpatient ILI for these subjects. Influenza-attributable adverse event rates for other subgroups are presented in Table 3-4.

3.4. Discussion

We found that while elderly adults experienced 14 to 20% increases in influenza-attributable adverse events following outpatient ILI, hospital ILI, or hospital PI, circulating influenza did not appear to affect the outcomes of ARI in working age adults. Our analyses suggest a similar pattern of risk in both diabetic and non-diabetic adults. Altogether, we found no evidence that the effects of circulating influenza differed by diabetes status, in elderly or working age adults.

To our knowledge, only one previous report has examined the effects of influenza on the risk of death in hospitalized patients with and without diabetes. (13). Bouter et al. found that diabetes increased the risk of death to a greater extent during years of high influenza activity, compared to years without significant influenza epidemics. From these results, the authors inferred a diabetes-specific susceptibility to death due to influenza, in hospitalized patients. This study had several limitations, however, as it compared diabetic patients to hospitalized controls with duodenal ulcers; did not account for potential confounders; did not distinguish elderly from

working age adults; and examined hospitalizations with diabetes listed as a primary or secondary diagnosis, which may have selected for particularly sick individuals (e.g.: in acute metabolic decompensation). In contrast, we examined outcomes following outpatient ILI, hospital ILI, and hospital PI, which comprise the common respiratory manifestations of influenza. After adjustment for potential confounders, we did not observe any differences in influenza-attributable deaths or hospitalizations following ARI by diabetes status, in any age group.

Our work is subject to several limitations of its own. First, lower severity of ARI at presentation or hospital admission in diabetic patients may provide an alternate explanation for the lack of significant differences in influenza-attributable effects by diabetes status (22, 23). We accounted for differential ARI severity by adjusting for diabetes status using a stratified approach. Second, our population-level estimates may have been underpowered to detect an influenza-attributable effect since influenza accounts for only 10 to 30% of ARI during influenza season. That said, our models were able to detect, as statistically significant, risks amounting to as few as 4 additional outcomes per 1000 ARI in elderly subjects. Third, we have attempted to distinguish the effects of influenza on severity of ARI. However, because included ARI may be the result of non-influenza etiologies, deaths or hospitalizations following ARI may alternatively be due to new-onset influenza-related illness, with no causal link to the preceding ARI whatsoever. Finally, our analyses may have misattributed to influenza the effects of respiratory syncytial, or other, viruses with seasonal variation (12). Because such biases would have been directed away from the null, they are unlikely to have affected our results in working age subjects.

Current guidelines effectively single out working age adults with diabetes for influenza vaccination. Our findings suggest that, in terms of serious

morbidity or mortality, these individuals do not experience worse outcomes following ARI during influenza season. Indeed, in an average year, among over 31,000 working age adults with diabetes, influenza contributed only 4 deaths or hospitalizations within 30 days of an ARI. This figure does not represent the total burden of influenza, which must also include ARIs due to influenza that resolve without leading to further deaths or hospitalizations. It does, however, show that the potential vaccination-related benefit from mitigating the severity of influenza-related ARI in working age diabetic adults is small, and might not justify designating this group a high-risk target for vaccination. In fact, we found no evidence that the population influenza-attributable effect on adverse events following ARI differs in any respect by diabetes status.

Although there is much evidence interpreted as supporting the vaccination of elderly adults (24), evidence related to the vaccination of working age adults with high-risk indications, like diabetes, remains sparse. We conclude that, while efforts to mitigate the effects of influenza in the elderly appear warranted, guidelines promoting the vaccination of working age adults with diabetes cannot be justified on the basis of preventing adverse events following ARI. More robust evidence is needed for prioritizing putative high-risk populations in vaccination guidelines.

Tables and figures

Table 3-1: Characteristics of patients at ARI diagnosis

Table 3-1a: Characteristics of patients with outpatient ILI

Variable	Value	Diabetes N[1]	Diabetes P[2]	No diabetes N	No diabetes P	P-value
Outpatient ILI						
Influenza activity	Off-season	90539	0.67	114218	0.68	0.061
	Influenza season	44205	0.33	54958	0.32	
Age	Years (median, IQR)	58	22.00	58	24.00	0.000
Sex	Male	55099	0.41	69634	0.41	0.134
	Female	79645	0.59	99542	0.59	
Income quintile[3]	Upper	51073	0.38	83881	0.50	0.000
	Lower	83671	0.62	85295	0.50	
Residence	Urban	80087	0.59	103997	0.61	0.000
	Rural	54657	0.41	65179	0.39	
Number of medical visits[4]	Number (mean, sd)	3.31	5.46	2.14	4.09	0.000
Number of major ADGs[5]	0	37640	0.28	69259	0.41	0.000
	1	41199	0.31	54091	0.32	
	2 or more	55905	0.41	45826	0.27	
Influenza vaccination	Yes	40894	0.30	36897	0.22	0.000
	No	93850	0.70	132279	0.78	
Pneumococcal vaccination	Yes	40879	0.30	35362	0.21	0.000
	No	93865	0.70	133814	0.79	
Death or hospitalization	Yes	3940	0.03	3594	0.02	0.000
	No	130804	0.97	165582	0.98	

[1] N = Number of subjects. P = Proportion of subjects.

[2] P-values from Wilcoxon rank-sum or chi-squared tests.

[3] Income quintiles were stratified by rural / urban status, then divided into the top 5 and bottom 5 categories.

[4] Number of medical visits over the previous year.

[5] Number of major ADGs over the previous 2 years. Major ADGs included the following: ADG3 (time limited: major), ADG4 (time limited: major – primary infections), ADG9 (likely to recur: progressive), ADG11 (chronic medical: unstable), ADG16 (chronic specialty: unstable – orthopedic), ADG22 (injuries / adverse effects: major), ADG25 (psychosocial: recurrent or persistent, unstable), and ADG32 (malignancy) (21).

Table 3-1b: Characteristics of patients with hospital ILI

Variable	Value	Diabetes N	Diabetes P	No diabetes N	No diabetes P	P-value
Hospital ILI						
Influenza activity	Off-season	5315	0.67	4906	0.69	0.005
	Influenza season	2661	0.33	2229	0.31	
Age	Years (median, IQR)	73	19.00	77	14.00	0.000
Sex	Male	4056	0.51	3871	0.54	0.000
	Female	3920	0.49	3264	0.46	
Income quintile	Upper	2339	0.29	2529	0.35	0.000
	Lower	5637	0.71	4606	0.65	
Residence	Urban	3583	0.45	3368	0.47	0.005
	Rural	4393	0.55	3767	0.53	
Number of medical visits	Number (mean, sd)	8.05	10.19	8.13	10.83	0.652
Number of major ADGs	0	553	0.07	732	0.10	0.000
	1	1559	0.20	1805	0.25	
	2 or more	5864	0.74	4598	0.64	
Influenza vaccination	Yes	1965	0.25	1547	0.22	0.000
	No	6011	0.75	5588	0.78	
Pneumococcal vaccination	Yes	2480	0.31	2054	0.29	0.002
	No	5496	0.69	5081	0.71	
Death or re-hospitalization	Yes	1693	0.21	1624	0.23	0.023
	No	6283	0.79	5511	0.77	

Table 3-1c: Characteristics of patients with hospital PI

Variable	Value	Diabetes N	Diabetes P	No diabetes N	No diabetes P	P-value
Hospital PI						
Influenza activity	Off-season	2650	0.66	2050	0.69	0.031
	Influenza season	1361	0.34	942	0.31	
Age	Years (median, IQR)	73	21.00	79	15.00	0.000
Sex	Male	2106	0.53	1635	0.55	0.076
	Female	1905	0.47	1357	0.45	
Income quintile	Upper	1158	0.29	1009	0.34	0.000
	Lower	2853	0.71	1983	0.66	
Residence	Urban	1560	0.39	1107	0.37	0.106
	Rural	2451	0.61	1885	0.63	
Number of medical visits	Number (mean, sd)	6.04	8.29	4.97	7.32	0.000
Number of major ADGs	0	359	0.09	391	0.13	0.000
	1	723	0.18	696	0.23	
	2 or more	2929	0.73	1905	0.64	
Influenza vaccination	Yes	871	0.22	550	0.18	0.001
	No	3140	0.78	2442	0.82	
Pneumococcal vaccination	Yes	1098	0.27	712	0.24	0.001
	No	2913	0.73	2280	0.76	
Death or re-hospitalization	Yes	916	0.23	805	0.27	0.000
	No	3095	0.77	2187	0.73	

Table 3-2: Numbers of ARI occurrences and deaths or hospitalizations, according to the presence or absence of circulating influenza

	Age group	Diabetes	Outpatient ILI		Hospital ILI		Hospital PI	
			N	A	N	A	N	A
Influenza season	**All**	**Diabetes**	**44205**	**1307**	**2661**	**551**	**1361**	**301**
		Control	**54958**	**1107**	**2229**	**505**	**942**	**268**
	Working age	Diabetes	29075	451	823	135	451	80
		Control	35591	168	366	48	155	29
	Elderly	Diabetes	15130	856	1838	416	910	221
		Control	19367	939	1863	457	787	239
Off-season	**All**	**Diabetes**	**90539**	**2633**	**5315**	**1142**	**2650**	**615**
		Control	**114218**	**2487**	**4906**	**1119**	**2050**	**537**
	Working age	Diabetes	59024	904	1551	270	819	152
		Control	72287	393	799	115	341	54
	Elderly	Diabetes	31515	1729	3764	872	1831	463
		Control	41931	2094	4107	1004	1709	483

N = Number of ARI, A = Number of deaths or hospitalizations.

Table 3-3: Relative effects of circulating influenza in adults with and without diabetes

Age group	Diabetes status	Association between circulating influenza (influenza-season vs off-season) and adverse events following …								
		Outpatient ILI			Hospital ILI			Hospital PI		
		OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Non-elderly	Any	1.04	[0.94, 1.15]	0.479	0.96	[0.78, 1.18]	0.679	1.02	[0.77, 1.34]	0.911
	DM	1.09	[0.97, 1.23]	0.148	0.98	[0.77, 1.25]	0.902	0.98	[0.71, 1.35]	0.881
	No DM	0.91	[0.76, 1.11]	0.361	0.89	[0.60, 1.32]	0.565	1.16	[0.66, 2.04]	0.595
Elderly	Any	1.14	[1.07, 1.21]	0.000	1.14	[1.03, 1.26]	0.009	1.20	[1.04, 1.39]	0.011
	DM	1.15	[1.05, 1.26]	0.002	1.10	[0.95, 1.27]	0.195	1.14	[0.93, 1.40]	0.193
	No DM	1.12	[1.03, 1.22]	0.011	1.18	[1.03, 1.36]	0.020	1.28	[1.04, 1.56]	0.018

Models adjusted for age, sex, community of residence income below / above median income, urban / rural residence, number of medical visits in the previous year, number of major ADGs in the previous 2 years, and vaccinations.

[1] Association between diabetes and death or hospitalization following ARI.

[2] Association between influenza season and death or hospitalization following ARI.

[3] Interaction between diabetes status and influenza season on adverse events following ARI. The interaction odds ratio is a ratio of odds ratios, comparing the effect of influenza season in those with diabetes and without diabetes.

Table 3-4: Average annual numbers of influenza-attributable adverse events following ARI

		Diabetes					No diabetes *(matched controls)*				
		Total[1]	Adverse events		Influenza-attributable outcomes		Total	Adverse events		Influenza-attributable outcomes	
Age group	ARI		All[2]	Infl[3]	Rate[4]	Fraction[5]		All	Infl	Rate	Fraction
Working age	Outpatient ILI	3648	56	4	0.001	7.7%	4463	21	-2	0.000	-8.7%
	Hospital ILI	104	17	0	-0.004	-2.2%	46	6	-1	-0.016	-12.3%
	Hospital PI	57	10	0	-0.005	-2.6%	20	4	0	0.015	8.3%
Elderly	Outpatient ILI	1898	107	14	0.007	12.8%	2424	117	10	0.004	8.5%
	Hospital ILI	231	52	3	0.013	5.8%	233	57	7	0.028	11.6%
	Hospital PI	115	28	1	0.013	5.3%	99	30	5	0.051	16.7%

Yearly numbers of adverse events (i.e.: death or hospitalizations within 30 days of ARI). Influenza-attributable events in those without diabetes are reported for comparative purposes only, since the matched control cohort is non-representative of, and substantially smaller than, the source population of all ARI experienced by non-diabetic Manitoba adults. Interaction terms showed no significant differences in the relative effects of circulating influenza between those with and without diabetes.

[1] Average number of ARI per year.

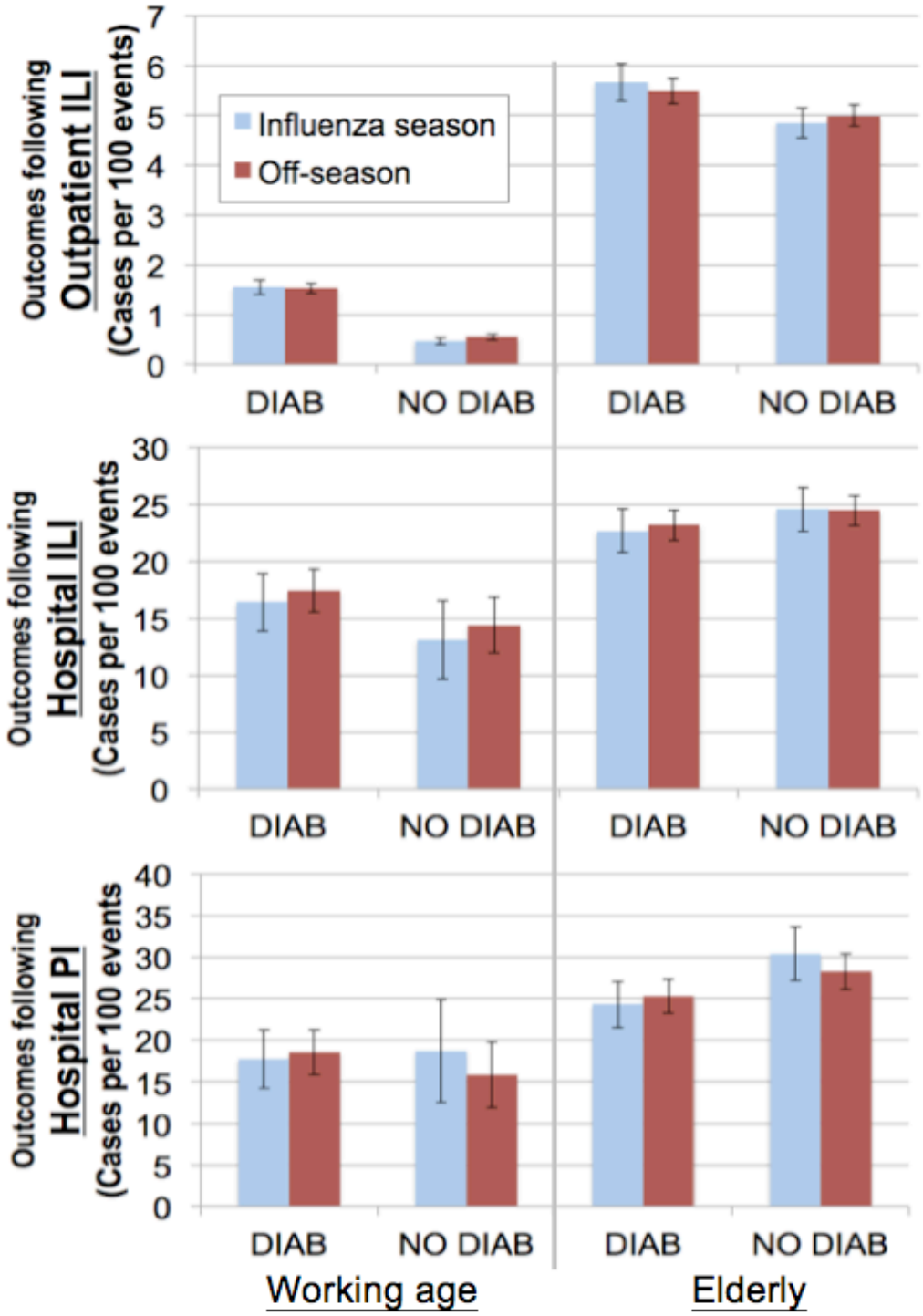
[2] Number of ARI followed by death or hospitalization within 30 days.

[3] Number of ARI followed by death or hospitalizations, attributable to circulating influenza.

[4] Rate of influenza-attributable adverse events (cases per ARI).

[5] Influenza-attributable fraction of all 30-day adverse events.

Figure 3-1: Crude rates of death or hospitalization within 30 days following ARI



Error bars indicate 95% confidence intervals.

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Chapter 3 Supplementary Tables

Table S3-1: Acute respiratory infection (ARI) case definitions

Table S3-1a: List of ICD-10-CA and ICD-9-CM codes comprising an administrative case definition of influenza-like illness (ILI) (Reproduced from Table S2-1a)

Diagnosis	ICD-10-CA code	ICD-9-CM code
Cold	J00	460
Sinusitis	J01 or J32	461
Pharyngitis	J02	462
Laryngitis, tracheitis, or laryngotracheitis	J04	464
Upper respiratory tract infection	J06.8 or J06.9	465.8, 465.9
Influenza	J10 or J11	487 or 488
Viral pneumonia	J12	480
Pneumonia	J18	481-486
Acute bronchitis or bronchitis NOS or obstructive bronchitis	J20 or J40 or J44.8	466, 490, 496
Bronchiolitis	J21	466
Acute lower respiratory tract infection, not otherwise specified	J22	None
COPD with acute lower respiratory tract infection (includes pneumonia)	J44.0	491.22
COPD with acute exacerbation	J441	491.21
Cough	R05	786.2
Pleurisy	R09.1	511

Developed using pilot data from emergency departments in Edmonton, Alberta. ICD codes were extracted from randomly selected cases comprising 15% of all emergency department visits with a main ambulatory care diagnosis of influenza.

Table S3-1b: List of ICD-10-CA and ICD-9-CM codes comprising an administrative case definition of pneumonia and influenza (PI) (Reproduced from Table S2-1b)

Diagnosis	ICD-10-CA code	ICD-9-CM code
Influenza	J10 or J11	487 or 488
Viral pneumonia	J12	480
Pneumonia	J13 or J14 or J15 or J16	481 or 482 or 483
Pneumonia, organism unspecified	J18	485 or 486

Chapter 4: Effectiveness of Influenza Vaccination in Working Age Adults With Diabetes: A Population-Based Cohort Study[‡]

Abstract

Objectives: Guidelines recommend routine influenza vaccinations in all diabetics and all elderly adults, but there is limited evidence to support vaccinating working age (< 65 years) diabetic adults. We examined the effectiveness of influenza vaccine in this subgroup, compared with elderly (>= 65 years) adults, with and without diabetes, for whom vaccination guidelines are well accepted.

Methods: From 2000 to 2008, we identified all adults with diabetes using administrative claims data from Manitoba, Canada. For comparison with elderly adults without diabetes, we also obtained up to 2 controls matched on age and sex. Using multivariable Poisson regression, we estimated vaccine effectiveness on all-cause hospitalizations (ALL), pneumonia and influenza hospitalizations (PI), and influenza-like illnesses (ILI) during periods of known circulating influenza. Analyses were replicated outside of influenza season to rule out residual confounding.

Results: We included 543367 person-years of follow-up, during which 94988 ALL, 5422 PI, and 223920 ILI occurred. The majority (58%) of all Manitoba adults with diabetes were working age. In this group, influenza

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vaccination was associated with reductions in ALL (28%, 95% CI: 24-32%) and PI (43%, 95% CI: 28-54%), but not ILI (-1%, 95% CI: -3-1%). Vaccine effectiveness in working age diabetic adults was broadly similar to effectiveness in elderly adults with or without diabetes, for ALL (33-34%) and PI (45-55%), but not ILI (12-13%). However, similar estimates of vaccine effectiveness were also observed for all 3 groups during non-influenza control periods.

Conclusions: During influenza season, working age adults with diabetes appear to derive similar benefits from influenza vaccination as elderly adults, supporting current diabetes-specific recommendations. However, these benefits were also manifest outside influenza season, suggesting that randomized trials are needed to provide valid estimates of vaccine effectiveness.

4.1. Introduction

Influenza is a common acute respiratory infection, which typically circulates during the winter-spring months of the year (1). Morbidity and mortality due to influenza is substantial, and thought to be concentrated in certain high-risk groups (2-4), including adults with diabetes (5). Though studies concerning the sequelae of influenza infection in those with diabetes are sparse, clinical practice guidelines recommend targeted vaccination against influenza in all adults with diabetes (3, 6, 7). Even US guidelines, which advocate the universal vaccination of all adults, prioritize those with diabetes (4). Since recommendations for universal vaccination of the elderly (age >= 65) (3, 4) are already well accepted (8, 9), these guidelines effectively single out working age adults (age < 65) with diabetes for vaccination.

Four observational studies have examined the effectiveness of influenza vaccinations in adults with diabetes (10-13). Two of these studies, both case-control designs, involved working age adults, observing 70 to 79% reductions in hospitalizations associated with vaccination (12, 13). These studies have several limitations. Their composite outcomes, comprised mostly of acute complications of diabetes, did not capture more common influenza complications or outpatient visits. Moreover, neither study assessed unmeasured confounding by examining vaccine effectiveness during control periods outside of influenza season (14).

Thus, we examined the effectiveness of influenza vaccine for reducing influenza-like illness (ILI), pneumonia and influenza (PI) hospitalizations, and all-cause (ALL) hospitalizations. Working age adults (age < 65 years) with diabetes comprised our population of primary interest. Elderly adults (age => 65 years) with and without diabetes were chosen as reference groups for comparison, since vaccinations in elderly adults are generally universally accepted (8, 9). Additionally, outcomes in adults with diabetes

may be comparable to those of non-diabetic adults approximately 10 years older (15). In particular, the rate of influenza-attributable hospitalizations in non-elderly adults with diabetes (16) is similar to that of elderly adults (17, 18). We included off-season control periods to assess the extent of residual confounding related to the “healthy vaccinee effect” in studies of vaccine effectiveness (19).

4.2. Methods

We performed a population-based cohort study using administrative data from Manitoba, Canada. Nearly all residents receive health care benefits under Manitoba’s system of universal health care insurance. The administrative databases of Manitoba Health capture basic demographic data, diagnoses and procedures provided during community physician visits and hospital admissions, and pharmaceuticals dispensed at the point of sale (20, 21). Additionally, the Manitoba Immunization Monitoring System records influenza and pneumococcal vaccinations provided by physicians and public health clinics in the community (22). These databases are reposited for research use at the Manitoba Centre for Health Policy (MCHP).

We identified all adults (age >= 18 years) with prevalent or incident diabetes from July 1, 2000 to June 30, 2008. Diabetes was defined as 2 ambulatory physician claims or one hospital discharge for diabetes (ICD-9 code 250 or ICD-10 codes E10-E11) (23). We also identified a sample of elderly non-diabetic adults. The latter were selected by matching to elderly diabetic adults in a ratio of 2:1 from the general population of Manitoba on the basis of age, sex, and residence. We thus compared influenza vaccine effectiveness in 3 distinct subgroups: working age diabetic adults, our primary group of interest, versus elderly adults with and without diabetes. After matching, we excluded person-years of follow-up during which a

subject received any dispensations for anti-influenza drugs, which are sometimes used as influenza prophylaxis in vulnerable adults.

We divided calendar time into years from July 1 to June 30 (16). Influenza season was defined as a continuous period between the first and last occurrences of at least 2 consecutive weeks with 2 or more ILI isolates positive for influenza, according to provincial surveillance data (24). We split off-season time into two discrete periods: a pre-season period from October 1 to the beginning of influenza season, and a post-season period from the end of influenza season until June 30 each year (14).

Subjects were followed until June 30, 2008, for any occurrences of three outcomes, based on ICD diagnostic codes: Physician visits or hospitalizations for ILI, PI hospitalizations, and all-cause hospitalizations. ILI consisted of a broad bundle of diagnoses, including bronchitis, pneumonia, cold, cough, and exacerbations of chronic obstructive pulmonary disease (see Supplement). Our definition of ILI was determined by a pilot study in Edmonton, Alberta, and is similar to other definitions showing strong correlations with seasonal influenza activity (25, 26). ILI was chosen to represent the common manifestations of influenza, PI hospitalizations to depict more serious and specific respiratory sequelae, and ALL hospitalizations to indicate the potential overall burden of influenza on serious morbidity and mortality.

We fitted logistic regression models to examine the predictors of influenza vaccination each year. Potential predictors were diabetes status, age, sex, urban or rural residence, socioeconomic status (SES), comorbid health status, and number of physician visits in the previous year. SES was based on the census-derived income quintile of each subject's postal code area of residence (27-29). Comorbid health status was represented using two ADG-based variables: One indicating the number of major ADGs, and

another indicating the number of minor ADGs, accrued in the previous 2 years (22). Covariates were updated every July 1.

We then fitted Poisson regression models describing the incidence rates of each outcome as a function of influenza vaccination status. The resulting incidence rate ratios (IRR) were used to estimate vaccine effectiveness (VE = 1 – IRR). Time-varying analyses were performed, with each subject's follow-up time split into vaccinated and unvaccinated weeks. Models included follow-up time in person-years as an offset term. In addition to the above predictors, models included pneumococcal vaccination status, and dummy variables for each month and year as covariates. VE was estimated for influenza season, and for the two off-season periods. Because influenza circulation is minimal during the off-season, any apparent effect of influenza vaccine on outcomes during these periods suggests bias (14).

Vaccine effectiveness was estimated separately for each subgroup of interest. Analyses were performed using SAS 9.2. This study was approved by the Health Research Ethics Board of the University of Alberta, and by the Health Information and Privacy Committee of Manitoba.

4.3. Results

4.3.1. Cohort composition

We identified 99781 adults with diabetes in Manitoba from 2000 to 2008. After matching, our analytic cohort was composed of 91605 diabetic adults with complete data (92% of all diabetic adults identified). Of these, 56513 were working age adults with diabetes. Working age adults with diabetes were generally healthier, though less likely to have received influenza or pneumococcal vaccinations, than elderly adults (Table 4-1). On average, 31139 working age adults with diabetes were followed each year, representing 58% of all diabetic adults, and approximately 3% of the entire

Manitoba population. Including both off-season and influenza season time, working age adults with diabetes contributed 195299 person-years of follow-up. Elderly adults with and without diabetes contributed 138606 and 209461 person-years, respectively. All together, included subjects experienced 223920 ILI, 5422 PI hospitalizations, and 94988 ALL hospitalizations (Table 4-2).

4.3.2. Predictors of vaccination status

Vaccination rates ranged from 35% in working age adults with diabetes, to 51-56% in elderly adults without and with diabetes, respectively. Increasing age, female sex, diabetes, and better socioeconomic status were each significantly associated with a greater odds of vaccination (Table 4-3). In contrast, poorer health status, indicated by increasing numbers of major ADGs and medical visits, was associated with increased vaccinations in working age adults, but decreased vaccination odds in the elderly (Table 4-3). These trends were similar regardless of diabetes status.

4.3.3. Vaccine effectiveness during influenza season

In working age adults with diabetes, influenza vaccine had no apparent effect on ILI (VE = 1%, 95% CI: -1-3%; $p = 0.402$), but was associated with 43% (95% CI: 28-54%; $p < 0.001$) and 28% (95% CI: 24-32%; $p < 0.001$) decreases in PI and all-cause hospitalizations, respectively (Table 4-4). In elderly adults, influenza vaccine was similarly effective against all outcomes (VE – ILI = 12-13%, PI = 45-55%, ALL = 33-34%), regardless of diabetes status. Compared to elderly adults, influenza vaccine in working age adults with diabetes was associated with broadly similar reductions in PI and ALL hospitalizations, but no reduction in ILI.

4.3.4. Vaccine effectiveness during off-season periods

In working age adults with diabetes, influenza vaccine reduced all-cause hospitalizations by 22-31% outside of influenza season (Table 4-5). Additionally, VE point estimates were suggestive of reduced PI hospitalizations during the post-season period (post-season VE = 24%, 95% CI: -4-45%; p = 0.085). In a similar manner, influenza vaccine was associated with reductions each of ILI (7-29%), PI hospitalizations (39-61%), and all-cause hospitalizations (30-40%) during both pre- and post-influenza season periods, among elderly adults (Table 5).

4.4. Discussion

We performed a large cohort study examining influenza vaccine effectiveness. In working age adults with diabetes, influenza vaccine was associated with 43% and 28% reductions in PI and all-cause hospitalizations, respectively. Similar estimates of vaccine effectiveness were observed in elderly adults, a group for whom vaccination guidelines are generally well accepted. Thus, using conventional analytic approaches, our study provides evidence supporting vaccination in working age adults with diabetes, of a degree similar to that in the elderly (30). However, a vaccine-attributable reduction in outcomes was also observed during off-season time, suggesting residual confounding, possibly due to the healthy vaccinee effect (19).

Guidelines recommending vaccinations in elderly adults are well accepted by both primary care clinicians and public health professionals, as physician surveys (8, 9, 31) and the impressive commitment of resources to vaccination campaigns each year (32) attest. The general enthusiasm for vaccination in the health care community is based on evidence of substantial benefits, derived primarily from observational studies of elderly adults (30). Using similar methods, we observed similar benefits of vaccination in working age adults with diabetes. Thus, our study provides relative support for the inclusion of diabetes as an indication for influenza

vaccination in the guidelines promulgated by the American and Canadian Diabetes Associations (6, 7), as well as national public health authorities (3, 4).

However, there is also increasing skepticism of the large reductions, particularly in all-cause mortality, associated with influenza vaccination observed in elderly adults (14, 33-35). Indeed, our data may be alternatively interpreted as indicating healthy user bias in diabetic and elderly adults, alike (14). We observed positive estimates of vaccine effectiveness before and after influenza season, when influenza circulation was minimal. It is likely that vaccinated individuals were healthier (19), or at the least, more health-seeking (36), than their unvaccinated counterparts, quite apart from their vaccination status. Previous studies have documented the pervasive effects contributed by this “healthy vaccinee bias” (19) in observational studies of elderly adults (14, 34, 37, 38). Our results suggest that these effects may apply similarly to non-elderly adults with high-risk indications.

Only two previous case-control studies have reported influenza vaccine effectiveness in working age adults with diabetes. These studies examined composite outcomes comprised heavily (> 85%) of hospital admissions for acute diabetic complications, yielding vaccine effectiveness estimates of 70-79% (12, 13). These results appear over-optimistic. Our own estimates of effectiveness against PI hospitalizations and all-cause hospitalizations were substantially lower, though, as we have shown, not immune to residual confounding. Randomized trials may ultimately be required to produce definitive estimates of vaccine effectiveness (34, 39).

We have performed a large study with adjustment for a wide range of administrative database-derived variables. However, the following limitations should be considered. First, lack of detailed clinical data, such

as smoking status or diabetes control, probably contributed to the residual confounding indicated by our off-season analyses (34, 38). Second, we were unable to measure influenza infection directly. The use of non-specific surrogates for influenza may have attenuated estimates of vaccine effectiveness while concomitantly increasing their vulnerability to healthy vaccinee bias (19). Third, we were unable to distinguish type 1 from type 2 diabetes, although it should be noted that current vaccination recommendations also do not distinguish between the types of diabetes (6, 7).

In our study, influenza vaccine was associated with reductions in PI hospitalizations (VE = 43-55%) and all-cause hospitalizations (28-34%) in all groups during influenza season, providing relative support for guidelines singling out diabetes as a high-risk indication for vaccination. However, our data also indicated vaccine effectiveness during the off-season, suggesting that many observational studies (10, 12, 13, 40), our present study included, have almost certainly over-estimated the benefits of vaccination. Thus, the extent to which current vaccination guidelines are justified remains uncertain. While additional clinical data (34, 38) and analytic innovation (35, 41, 42) may help improve observational estimates of inactivated influenza vaccine effectiveness, resolving this uncertainty may require long overdue, randomized trials (34, 39).

Tables and Figures

Table 4-1: Characteristics of included person-time

Variable	Value	Working age		Elderly			
		Diabetes		Diabetes		No diabetes (matched controls)	
		N[1]	P[1]	N	P	N	P
Age (median, IQR)	Years	53	13.00	74	11.00	74	11.00
Sex	Male	129638	0.52	84895	0.47	127211	0.44
	Female	119473	0.48	95020	0.53	161076	0.56
Income quintile	Upper	111167	0.45	77806	0.43	137303	0.48
	Lower	137944	0.55	102109	0.57	150984	0.52
Residence	Urban	145712	0.58	108147	0.60	173204	0.60
	Rural	103399	0.42	71768	0.40	115083	0.40
Medical visits[2]	0	145564	0.58	92265	0.51	174940	0.61
	1-2	62666	0.25	42034	0.23	60511	0.21
	3 or more	40881	0.16	45616	0.25	52836	0.18
Major ADGs[3]	0	109107	0.44	46630	0.26	102347	0.36
	1	74930	0.30	55893	0.31	92029	0.32
	2 or more	65074	0.26	77392	0.43	93911	0.33
Influenza vaccination[4]	Yes	86222	0.35	96463	0.54	139114	0.48
	No	162889	0.65	83452	0.46	149173	0.52
Pneumococcal vaccination[5]	Yes	40020	0.16	82084	0.46	116178	0.40
	No	209091	0.84	97831	0.54	172109	0.60

Table caption – see following page.

Table enumerates subjects at follow-up every July. All differences between elderly adults and working age diabetic adults $p < 0.001$ on Wilcoxon rank-sum or chi-squared tests.

[1] N = Number of subjects. P = Proportion of subjects. [2] Number of medical visits over the previous year. [3] Number of major ADGs over the previous 2 years: ADG3 (time limited: major), ADG4 (time limited: major – primary infections), ADG9 (likely to recur: progressive), ADG11 (chronic medical: unstable), ADG16 (chronic specialty: unstable – orthopedic), ADG22 (injuries / adverse effects: major), ADG25 (psychosocial: recurrent or persistent, unstable), and ADG32 (malignancy). [4] Influenza vaccination during the previous year. [5] Any previous record of pneumococcal vaccination.

Table 4-2: Included person-years and events

Diabetes	Period[1]	N (PY)	Number of outcomes[2] ILI	PI	ALL
Working age					
Diabetes	PRE	70415	33518	387	7584
	INS	70380	38804	487	7829
	POST	54504	21842	236	5683
Elderly					
Diabetes	PRE	49877	20569	775	14326
	INS	50308	23008	953	14945
	POST	38421	13598	550	10928
No diabetes	PRE	77347	27376	725	12374
(matched controls)	INS	76233	28499	815	12679
	POST	55881	16706	494	8640

[1] PRE = Pre-season period from October to the beginning of influenza season; INS = Influenza season; POST = Post-season period from the end of influenza season until June 30 each year.

[2] Outcomes: ILI = Influenza-like illness; PI = Pneumonia and influenza hospitalizations; ALL = All-cause hospitalizations.

Table 4-3: Predictors of vaccination status in elderly and working age adults with and without diabetes

		Working age		Elderly			
		Diabetes		Diabetes		No diabetes (matched controls)	
Variable	Value	OR	95% CI	OR	95% CI	OR	95% CI
Sex	Female	1.36	[1.34, 1.38]	1.03	[1.01, 1.05]	1.14	[1.12, 1.16]
Age	18-25 years	Ref.	Ref.	-	-	-	-
	26-45 years	1.63	[1.51, 1.77]	-	-	-	-
	46-65 years	3.24	[3.00, 3.51]	-	-	-	-
	66-85 years	-	-	Ref.	Ref.	Ref.	Ref.
	86+ years	-	-	0.69	[0.67, 0.71]	0.72	[0.70, 0.74]
Income	Upper	1.25	[1.23, 1.27]	1.23	[1.21, 1.26]	1.17	[1.15, 1.19]
Residence	Urban	1.34	[1.31, 1.36]	1.31	[1.29, 1.34]	1.15	[1.13, 1.17]
Minor ADGs	2 to 3	1.58	[1.50, 1.67]	1.78	[1.66, 1.90]	3.57	[3.44, 3.71]
	4 or more	2.17	[2.06, 2.28]	2.50	[2.35, 2.67]	5.77	[5.57, 5.98]
Major ADGs	1	1.14	[1.11, 1.16]	1.02	[0.99, 1.04]	1.15	[1.13, 1.17]
	2 or more	1.15	[1.13, 1.18]	0.78	[0.76, 0.80]	0.94	[0.92, 0.96]
Medical visits	2 to 3	1.17	[1.14, 1.20]	1.05	[1.02, 1.08]	1.08	[1.05, 1.11]
	4 or more	1.23	[1.19, 1.26]	0.85	[0.83, 0.87]	0.97	[0.95, 1.00]

All p-values less than 0.001. Reference groups: Sex (male), age (18-25 years or 66-85 years), income (below-median), residence (rural), minor ADGs (0 to 1 ADGs), major ADGs (0 ADGs), medical visits (0 to 1 visits). ADGs cumulated over the previous 2 years. Medical visits cumulated over the previous year.

Table 4-4: Adjusted associations between influenza vaccination status and outcomes during influenza season

		Influenza-like illness			PI hospitalizations			All-cause hospitalizations		
Age group	Diabetes	IRR[1]	CI	P-value	IRR	CI	P-value	IRR	CI	P-value
Working age	DM	0.99	[0.97, 1.01]	0.402	0.57	[0.46, 0.72]	0.000	0.72	[0.68, 0.76]	0.000
Elderly	DM	0.87	[0.84, 0.90]	0.000	0.55	[0.47, 0.66]	0.000	0.67	[0.64, 0.70]	0.000
	No DM	0.88	[0.85, 0.90]	0.000	0.45	[0.37, 0.55]	0.000	0.66	[0.63, 0.69]	0.000

[1] IRR = Incidence rate ratio (vaccinated vs not vaccinated), adjusted for sex, age (20-year age bands), income (upper vs lower), pneumococcal vaccination receipt, number of medical visits in the previous year, number of minor ADGs in the previous 2 years, number of major ADGs in the previous 2 years, month, and year.

Table 4-5: Adjusted associations between influenza vaccination status and outcomes before and after influenza season

			Influenza-like illness			PI hospitalizations			All-cause hospitalizations		
Period[1]	Age group	Diabetes	IRR[2]	CI	P-value	IRR	CI	P-value	IRR	CI	P-value
PRE	Working age	DM	0.95	[0.92, 0.98]	0.000	0.99	[0.76, 1.28]	0.939	0.78	[0.73, 0.83]	0.000
	Elderly	DM	0.76	[0.73, 0.79]	0.000	0.58	[0.47, 0.72]	0.000	0.70	[0.67, 0.74]	0.000
		No DM	0.71	[0.69, 0.74]	0.000	0.61	[0.49, 0.77]	0.000	0.65	[0.62, 0.68]	0.000
POST	Working age	DM	1.06	[1.03, 1.09]	0.000	0.76	[0.55, 1.04]	0.085	0.69	[0.65, 0.74]	0.000
	Elderly	DM	0.89	[0.85, 0.93]	0.000	0.39	[0.31, 0.50]	0.000	0.62	[0.59, 0.65]	0.000
		No DM	0.93	[0.89, 0.97]	0.000	0.48	[0.36, 0.62]	0.000	0.60	[0.57, 0.64]	0.000

[1] PRE = Pre-season period from October to the beginning of influenza season; POST = Post-season period from the end of influenza season until June 30 each year.

[2] IRR = Incidence rate ratio (vaccinated vs not vaccinated), adjusted for sex, age (20-year age bands), income (upper vs lower), pneumococcal vaccination receipt, number of medical visits in the previous year, number of minor ADGs in the previous 2 years, number of major ADGs in the previous 2 years, month, and year.

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Chapter 4 Supplementary Tables

Table S4-1: Outcome case definitions

Table S4-1a: List of ICD-10-CA and ICD-9-CM codes comprising an administrative case definition of influenza-like illness (ILI) (Reproduced from Table S2-1a)

Diagnosis	ICD-10-CA code	ICD-9-CM code
Cold	J00	460
Sinusitis	J01 or J32	461
Pharyngitis	J02	462
Laryngitis, tracheitis, or laryngotracheitis	J04	464
Upper respiratory tract infection	J06.8 or J06.9	465.8, 465.9
Influenza	J10 or J11	487 or 488
Viral pneumonia	J12	480
Pneumonia	J18	481-486
Acute bronchitis or bronchitis NOS or obstructive bronchitis	J20 or J40 or J44.8	466, 490, 496
Bronchiolitis	J21	466
Acute lower respiratory tract infection, not otherwise specified	J22	None
COPD with acute lower respiratory tract infection (includes pneumonia)	J44.0	491.22
COPD with acute exacerbation	J441	491.21
Cough	R05	786.2
Pleurisy	R09.1	511

Developed using pilot data from emergency departments in Edmonton, Alberta. ICD codes were extracted from randomly selected cases comprising 15% of all emergency department visits with a main ambulatory care diagnosis of influenza.

Table S4-1b: List of ICD-10-CA and ICD-9-CM codes comprising an administrative case definition of pneumonia and influenza (PI) (Reproduced from Table S2-1b)

Diagnosis	ICD-10-CA code	ICD-9-CM code
Influenza	J10 or J11	487 or 488
Viral pneumonia	J12	480
Pneumonia	J13 or J14 or J15 or J16	481 or 482 or 483
Pneumonia, organism unspecified	J18	485 or 486

Chapter 5: Interventions to Improve Influenza and Pneumococcal Vaccination Rates Among Community-Dwelling Adults: A Systematic Review and Meta-Analysis[II]

Abstract

Objectives: Influenza and pneumococcal vaccination rates remain below national targets. We systematically reviewed the effectiveness of quality improvement interventions for increasing the rates of influenza and pneumococcal vaccinations among community dwelling adults.

Methods: Randomized and non-randomized studies with a concurrent control group were included. Pooled odds ratios were estimated using random effects models. The Downs and Black tool was used to assess the quality of included studies.

Results: Most studies involved elderly primary care patients. Interventions were associated with improvements in the rates of any vaccination (111 comparisons in 77 studies, pooled OR = 1.61 [1.49, 1.75]), and influenza (93 comparisons, 65 studies, OR = 1.46 [1.35, 1.57]) and pneumococcal (58 comparisons, 35 studies, OR = 2.01 [1.72, 2.36]) vaccinations. Interventions that appeared effective were: patient financial incentives

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[II] A version of this chapter has been accepted for publication by Annals of Family Medicine (AFM-423-11 revised and accepted March 2, 2012). Co-authors: Jia Hu, BA[1], Sumit R. Majumdar, MD, MPH[2], Dale A. Storie, MLIS[3], Sandra E. Rees, BScPharm[4], Jeffrey A. Johnson (Supervisor), PhD[1,4] ([1]Department of Public Health Sciences, University of Alberta, Edmonton, AB, Canada; [2]Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada; [3]John W. Scott Health Sciences Library, University of Alberta, Edmonton, AB, Canada; [4]Institute of Health Economics, Edmonton, AB, Canada).

(influenza only), audit and feedback (influenza only), clinician reminders, clinician financial incentives (influenza only), team change, patient outreach, delivery site changes (influenza only), clinician education (pneumococcus only), and case management (pneumococcus only). Patient outreach was more effective if personal contact was involved. Team changes were more effective where nurses administered influenza vaccinations independently. However, heterogeneity in some pooled odds ratios was high, and funnel plots showed signs of potential publication bias. Study quality varied, but was not associated with outcomes.

Conclusions: Quality improvement interventions, especially those that assign vaccination responsibilities to non-physician personnel, or that activate patients through personal contact, can modestly improve vaccination rates in community dwelling adults. To meet national policy targets, more potent interventions should be developed and evaluated.

5.1. Introduction

Influenza and pneumococcal disease are vaccine-preventable causes of morbidity and mortality (1-3). Clinical practice guidelines have recommended routine influenza and pneumococcal vaccinations for elderly and non-elderly high risk patients (4-8). More recently, US authorities have recommended influenza vaccinations for all individuals above 6 months in age (9). However, vaccination rates remain under national targets (10-14) (Box 5-1).

Studies of interventions for improving adult influenza and pneumococcal vaccination rates are numerous, and have been synthesized in several systematic reviews. Jacobson and Szilagyi found that patient reminder and recall systems improved vaccination rates (15). The US Preventive Services Task Force's (USPSTF) Community Guide to Preventive Services found supporting evidence for numerous interventions aimed at universally recommended vaccines (16), and for combinations of multiple intervention for vaccines targeted to high-risk groups (17, 18). Stone et al. found that interventions involving organizational changes and teamwork were most effective for improving influenza or pneumococcal vaccination rates (19). Most recently, Thomas et al. found evidence of moderate quality that increasing community demand, vaccinating seniors during home visits, and deploying prevention facilitators working with health professionals improved influenza vaccination rates (20)

Though important, these reviews have a variety of limitations. For example, Thomas et al. included randomized controlled trials, most of which were graded low in quality. Consequently, the authors were able to recommend only that practitioners implement home visits (2 studies) and practice prevention facilitators (4 studies), to improve vaccination rates (20). The work of the USPSTF combined many vaccinations for different patient

groups under “targeted” and “universally recommended” vaccinations (16, 17). Stone et al., in their review of controlled clinical trials, examined the evidence over a decade ago. We know of over 50 additional studies that could be included, today (19).

Because previous reviews may be of limited currency and breadth, we undertook a systematic review and meta-analysis of randomized and non-randomized studies of the effectiveness of quality improvement interventions for improving adult influenza and pneumococcal vaccination rates in the community. Our review is intended to provide a comprehensive quantitative summary of the results achieved by previous quality improvement studies.

5.2. Methods

5.2.1. Study selection and data extraction

We searched medical literature databases, including Medline, EMBASE, Cochrane Library, Web of Science, and 5 other databases, as well as the reference lists of previous reviews up to August 2010 for relevant studies (Supplement A). English language studies published in peer-reviewed journals were included if they involved elderly adults or adults with chronic diseases; involved a quality improvement intervention (see below); featured a parallel control group; and reported influenza or pneumococcal vaccination rates. We focused exclusively on the community setting to maximize relevance to primary care. Studies reporting sufficient data to estimate log odds ratios (OR) and standard errors were eligible for meta-analysis.

Two reviewers (DL and JH) selected studies and extracted data from each study in duplicate. Study quality was measured using the Downs and

Black instrument, which assesses both randomized and non-randomized studies on the same items (21) (reproduced in Supplement A, Table S5-A1). Disagreements were resolved by consensus; remaining disagreements were resolved by the senior authors (JAJ and SRM).

5.2.2. Data synthesis

We synthesized results by performing random effects meta-analyses of log odds ratios. We stratified analyses by vaccination type and intervention category. To categorize the interventions, we modified the taxonomy developed by Shojania et al. (Box 5-2) (22, 23). Comparisons were included in meta-analyses if the control group was usual care; a control intervention aimed at non-vaccination behaviors; or a different intervention for improving vaccination rates, if the intervention was provided to both study arms. When study arms contributed to more than one comparison in a meta-analysis, the vaccination rate numerator and denominator were divided among the comparisons to avoid "double-counting" patients. We accounted for unit of analysis errors by adjusting standard errors for literature-based values of intra-cluster correlations (24, 25). Although we reported all pooled odds ratios, we interpreted only those odds ratios comprised of 3 or more comparisons.

Heterogeneity was characterized with I^2 statistics. We explored heterogeneity by sub-stratifying interventions with clear grounds for delineating strata, and sufficient studies to divide into strata of 3 or more comparisons. Clinician reminders were stratified according to whether the reminder system was immunization-specific, or targeted a range of preventive care behaviors; and whether reminders were generated from patients' medical histories. Patient outreach interventions were stratified by communication medium. Finally, team change interventions were stratified by type of personnel involved, and whether they administered vaccine independently.

The effects of Downs and Black scores and randomization on pooled odds ratios were examined by meta-regression. Finally, we tested for publication bias by visual inspection of funnel plots and by using Harbord's test (26). Harbord's test is an alternative to Egger's test that mitigates false positives in meta-analyses of odds ratios. Analyses were performed using Stata 11 (27).

5.3. Results

5.3.1. Overview of studies

We included 106 and excluded 208 citations (Figure 5-1). Citations were most commonly excluded because they lacked a concurrent control group (n = 112, 54%) or took place in hospital or in a nursing home (n = 27, 13%) (Supplement A, Tables S5-A2 and S5-A3). Inter-reviewer reliability for inclusion of electronic search citations was substantial (91% agreement, kappa = 0.8).

The included studies featured 470175 patients (Table 5-1) (see Supplement A, Table S5-A4 for included studies). Studies took place primarily in the US (82 studies), Canada (9 studies), and the United Kingdom (6 studies). A range of settings was represented, including academic primary care practices (41 studies), community practices (21 studies), managed care organizations (13 studies), Medicare-affiliated organizations (11 studies), and Veterans' Affairs medical centers (8 studies). A few studies intervened at non-clinical sites, such as senior centers or workplaces. Most studies targeted the elderly for vaccination, either alone (54 studies), or in combination with high-risk non-elderly patients (27 studies).

5.3.2. Quality of included studies

Seventy-seven studies provided sufficient data for meta-analyses of odds

ratios (Table 5-1 and Supplement A, Table S5-A6). Fifty-eight studies (75%) were randomized or quasi-randomized controlled trials. The remaining studies were controlled before-and-after (7 studies) and observational (12 studies) designs. The median Downs and Black scores ranged from 14 to 26, with a median score of 21 points.

We examined individual items of the Downs and Black instrument (Supplements B and C). The most important weaknesses were unit of analyses errors, and insufficient reporting and adjustment for potential confounders. Unit of analysis errors were corrected for in 38 (51%) of studies. Potential confounders include previous vaccination status, health status, and demographic characteristics. The proportion of studies reporting and accounting for these confounders, whether by demonstrating that randomization achieved a balanced distribution of covariates, or by statistical adjustment, was 60%. Additional methodological weaknesses were lack of blinding of study subjects or assessors to intervention allocation, and contamination, in which the intervention may have affected the treatment of non-intervention patients at the same site. Contamination is prevented by allocation at the physician, practice, or region-level, which occurred in only 31 studies (40%).

5.3.3. Main meta-analyses

One-hundred and eleven comparisons from 77 studies contributed to the overall meta-analysis (Table 5-1). The pooled odds ratio expressing the effectiveness of all quality improvement interventions for either vaccination was 1.61 (95% CI [1.49, 1.75], $p < 0.001$, $I^2 = 85\%$).

5.3.3.a. Influenza vaccination

Ninety-three comparisons from 65 studies were included in meta-analyses for influenza vaccinations. The median treatment and control group vaccination rates were 0.45 (IQR [0.27, 0.66]), and 0.31 (IQR [0.20, 0.52]),

respectively. The odds ratio for influenza vaccination, pooled across all interventions, was 1.46 (95% CI [1.35, 1.57], I^2 = 81%). Fewer than 3 comparisons were available for each of community engagement, visit structure change, and CQI-like interventions. Excluding these interventions, most components were associated with statistically significant improvements in vaccination rates (Figure 5-2 – see Supplement B for forest plots featuring individual studies). Interventions featuring patient financial incentives (OR = 1.98, 95% CI [1.54, 2.56], I^2 = 37%) and audit and feedback (OR = 1.83, 95% CI [1.28, 2.61], I^2 = 0%) were effective. Patient incentives that eliminated out-of-pocket costs in a patient-pay environment (28, 29) appeared to be more effective than those providing a small reward in addition to pre-existing third-party vaccination coverage (30, 31). However, insufficient studies were available to test this hypothesis statistically. Audit and feedback findings were driven largely by results from the one study by Buffington et al., who were able to improve vaccination rates with regularly updated posters in physician offices tracking vaccination progress (32)

Clinician reminders (OR = 1.53, 95% CI [1.26, 1.85], I^2 = 71%), clinician financial incentives (OR = 1.52, 95% CI [1.20, 1.93], I^2 = 49%), team change (OR = 1.44, 95% CI [1.16, 1.79], I^2 = 67%), patient outreach (OR = 1.42, 95% CI [1.30, 1.55], I^2 = 84%), and delivery site changes (OR = 1.32, 95% CI [1.14, 1.52], I^2 = 17%) were also associated with improvements in vaccination rates. Delivery site changes included workplace vaccination clinics (33) and clinics in public housing buildings (34). These interventions were effective overall, but *what* elements of these were effective, and *where*, are difficult to discern, since a wide variety of intervention sites were implemented in a small number of studies. Case-management and clinician education were ineffective.

5.3.3.b. Pneumococcal vaccinations

Forty-eight comparisons from 35 studies were included in meta-analyses. The median treatment and control group vaccination rates were 0.19 (IQR [0.11, 0.33]), and 0.08 (IQR [0.04, 0.22]), respectively. The odds ratio for pneumococcal vaccinations, pooled across all interventions, was 2.01 (95% CI [1.72, 2.36], I^2 = 72%). Three or more comparisons were available for clinician reminders, team change, patient outreach, clinician education, case management and audit and feedback. Except for audit and feedback (OR = 1.18, 95% CI [0.57, 2.45], I^2 = 7%), these interventions were associated with improvements in vaccination rates (Figure 5-3 – see Supplement C for forest plots featuring individual studies).

Interventions featuring clinician reminders (OR = 2.13, 95% CI [1.50, 3.03], I^2 = 75%), team change (OR = 2.09, 95% CI [1.48, 2.95], I^2 = 51%), and patient outreach (OR = 1.80, 95% CI [1.54, 2.11], I^2 = 67%) had the highest odds ratios. Clinician education (OR = 1.54, 95% CI [1.19, 1.99], I^2 = 72%) and case management (OR = 1.49, 95% CI [1.05, 2.13], I^2 = 0%) were also associated with improvements in pneumococcal vaccination rates.

5.3.4. Meta-analyses within intervention sub-strata

Interventions featuring clinician reminders, team change and patient outreach, had moderate to high heterogeneity and sufficient comparisons for sub-stratification. For clinician reminders, most heterogeneity was explained by declining odds ratios over time. For patient outreach and team change, the results of meta-analyses within intervention sub-strata are presented in Table 5-2 (forest plots in Supplement D).

Several findings require qualification. Among patient outreach strategies for influenza, community media campaigns appeared most effective. However, this finding should be interpreted cautiously, since studies took place in settings with relatively captive audiences and a high prevalence of

high-risk patients (e.g.: seniors' centers) (34, 35). For pneumococcal vaccination, the pooled odds ratio for waiting/exam room posters may also be misleadingly high, since there were few comparisons (n = 5), and the highest performing comparisons combined posters with other effective interventions (36, 37). In two studies that considered them alone, waiting and exam room posters were not significantly associated with vaccination rates (36, 37)

Generally, outreach methods involving personal contact with patients achieved higher pooled odds ratios. For influenza vaccinations, the most effective intervention, excepting community media campaigns, was telephone reminders delivered by clinic staff. For pneumococcal vaccinations, office brochures handed out to eligible patients by clinic staff prior to their appointments was most effective. Meta-regression detected significant differences between pneumococcal vaccination outreach strategies. Office brochures at the point of care were 3.87 times more effective than mailed reminders, while community media campaigns, patient-held preventive care checklists and waiting or exam room posters were, respectively, 0.85, 0.77, and 0.75 times less effective than mailed reminders.

Among team change interventions for influenza vaccinations, we found that having nurses assume responsibility for administering vaccinations was effective, while interventions in which nurses or pharmacists assessed patients and reminded physicians, but did not themselves administer vaccinations, were ineffective. We were unable to examine this relationship in studies of pneumococcal vaccinations, due to insufficient comparisons.

5.3.5. Numbers needed to treat

Results for effective quality improvement strategies are summarized as

numbers needed to treat (NNT), assuming baseline levels of vaccination similar to those reported in community studies of elderly adults (12) (Table 5-3 and Supplement D, Tables S5-D9 and S5-D10).

5.3.6. Sensitivity Analyses and Publication Bias

Randomized study design was not significantly associated with study odds ratios within intervention strata. After excluding two clear outlier studies (38, 39), quality score was also not significantly associated with study OR for any intervention.

Funnel plots showed higher odds ratios in smaller studies. Harbord's test was positive for small study effects among studies of patient outreach for influenza and pneumococcal vaccinations, and team change for influenza vaccinations. These findings suggest potential publication bias.

5.4. Discussion

We reviewed the evidence for effectiveness of quality improvement interventions for increasing influenza and pneumococcal vaccination rates. Most interventions were associated with modest improvements in vaccination rates.

Team change, patient outreach, and clinician reminders were effective for both influenza and pneumococcal vaccinations. We found that interventions involving team change were effective, especially where nurses had been assigned responsibilities for administering vaccine. Configuring additional personnel so that they are able relieve physicians of vaccinations seems important to successful team change (19). Additionally, patient outreach may better increase vaccinations, to the extent that direct personal contact is achieved. A previous review has similarly reported that reminders involving person-to-person telephone contact were most effective (15).

Clinician reminders and education were associated with greater improvements for pneumococcal than for influenza vaccinations. Awareness and support may be less common for pneumococcal (40) than for influenza vaccinations (41-43), making pneumococcal vaccinations relatively “low hang fruit”. Audit and feedback appeared effective for influenza, but not pneumococcal, vaccinations. Audit and feedback may have been effective for influenza vaccinations due to the prominent tracking posters used in Buffington et al (32). The use of materials with high visual appeal and clarity has been previously associated with increased vaccination rates (19)

Clinician and patient financial incentives were both effective for influenza vaccinations, but could not be evaluated for pneumococcal vaccinations. The two successful studies of patient financial incentives took place in out-of-pocket payment environments (28, 29). Where demand for vaccinations is not pent up by inability to pay, the benefit of patient incentives may be smaller (30, 31). Case management, surprisingly, was not very effective – possibly because case managers may have prioritized other disease-related process of care.

Several limitations of our review should be borne in mind. Our funnel plots and associated tests suggested publication bias, which may have led our pooled odds ratios to be overly optimistic. Our review also did not address the economic value of the interventions. Additionally, the included studies may not generalize well to non-elderly adults, or adults not in physician care, for whom vaccinations recommendations have recently been expanded (9).

More importantly, we have taken a highly inclusive approach towards meta-analysis. There are two major limitations of this approach. First, our analysis of Downs and Black items identified a high prevalence of design or reporting flaws in the included studies. Lack of blinding may be relatively unimportant for quality improvement interventions designed to act, in part, by increasing awareness of vaccinations; and for outcomes that can be measured relatively objectively by reviewing charts or billing data. However, only 60% of studies reported and accounted adequately for potential confounders. This proportion was higher in randomized than in observational studies.

We have nonetheless reported odds ratios pooled from all studies. Neither randomization nor Downs and Black scores were associated with significant differences in odds ratios. The inclusion of a wide range of studies allowed us to produce quantitative summaries for many intervention categories. In particular, interventions requiring policy support or action on a community scale, such as audit and feedback and community media campaigns, are difficult to randomize – observational studies comprise an important source of insight (44). Our study quality tables (Supplements B and C) provide further detail on methodological issues for potential users.

Second, many of our pooled estimates contained residual heterogeneity. Our ability to explore heterogeneity was limited by lack of evidence (45). For example, reasons for decreases in the effectiveness of clinician reminders in recent years are unknown. We have incorporated heterogeneity into our meta-analysis by using a random-effects approach. Users should interpret pooled odds ratios as estimates of the average intervention effect, as opposed to a single, “true” effect. Our 95%

confidence limits may provide bounds on the expected performance of the intervention under most circumstances. In any event, a single “true” effect would not likely be useful, since most users can identify mitigating or potentiating factors unique to their circumstances. Our estimates provide a preliminary basis for selecting interventions; potential users should examine our summaries of individual studies (Supplement A, Table S5-A4) and intervention-specific forest plots (Supplements B and C) in light of their own circumstances, and a theoretical understanding of behavior change (46, 47).

Building on previous reviews, we have produced a comprehensive, quantitative summary of the effectiveness of interventions to improve influenza and pneumococcal vaccination rates. Our results suggest that shifting vaccine administration from physicians to members of the primary care team with clear responsibilities for chronic and preventive care, and activating patients through personal outreach, may stand the best chance of improving vaccination rates in community dwelling adults. Nonetheless, practitioners and policy-makers should temper their expectations of quality improvement interventions. In few treatment arms had vaccination rates improved sufficiently to meet national policy targets (10, 11). Further research is required to develop and evaluate more potent approaches, and to better understand how and why they work.

Tables and Figures

Box 5-1: Influenza and pneumococcal vaccination recommendations

2010 Influenza vaccination recommendations (adults)

- All persons aged >= 6 months

ACIP, 2010

2009 Influenza vaccination recommendations (adults)

These recommendations have been succeeded by a policy of universal vaccination. However, ACIP considers the following groups "high risk", and therefore deserving of particular emphasis during periods of limited vaccine supply, or in the transition from targeted to universal vaccination.

- All persons aged >/= 50 years
- Women who will be pregnant during the influenza season
- Persons who have chronic pulmonary, cardiovascular, renal, hepatic, neurological/neuromuscular, hematologic, or metabolic disorders (including diabetes mellitus)
- Adults who have immunosuppression
- Residents of nursing homes and other long-term care facilities.

ACIP, 2009

Pneumococcal vaccination recommendations (adults)

- All persons aged >/= 65 years
- Persons with chronic cardiovascular disease, chronic pulmonary disease (including asthma), or diabetes mellitus
- Persons with alcoholism, chronic liver disease, or cerebrospinal fluid leaks
- Persons with cochlear implants
- Persons with functional or anatomic asplenia
- Persons living in special environments or social settings
- Immunocompromised persons
- Smokers

Revaccination

- A second dose is recommended 5 years after the first dose for persons with functional or anatomic asplenia and for immunocompromised persons.
- Those who received vaccination before age 65 years should receive another dose of vaccine at age 65 years or later if >= 5 years have passed since their previous dose.

ACIP updated recommendations
(Reported by Nuorti and Whitney, 2010)

Box 5-2: Categories of quality improvement interventions

Audit and feedback – Feedback of performance over a specified period of time to individual providers.

Case management – A system for coordinating diagnosis, treatment, or ongoing patient management by a person or multidisciplinary team in collaboration or supplementary to the primary care clinician.

Clinician education – Interventions designed to promote increased understanding of vaccination recommendations.

Clinician reminders – Paper-based or electronic system intended to prompt a health professional to provide vaccinations.

Community engagement – Involvement of intended vaccines and other stakeholders in the design and implementation of the intervention.

Continuous quality improvement (CQI) (or similar) – Interventions that explicitly use techniques of continuous quality improvement, total quality management, or plan-do-study-act; or those that apply an iterative small-group process for implementing and evaluating practice change.

Delivery site change – Interventions involving the provision of vaccinations in settings other than public health clinics and physician offices.

Financial incentives (clinicians) – The interventions included financial incentives based on achievement of performance goals, as well as alternative reimbursement systems.

Financial incentives (patients) – Interventions that encourage patients to receive vaccination by providing payments or non-monetary incentives.

Patient outreach – Interventions designed to promote increased understanding of vaccination recommendations, or specific vaccination reminders or recommendations.

Team change – The assumption of additional or expanded roles related to providing vaccinations by non-physician clinical personnel.

Visit structure change – Group visits, patient pre-activation, or planned preventive care visits with a usual physician.

Modified from Shojania et al., 2006 (23).

Table 5-1: Patients, studies, and comparisons by quality improvement strategy

Quality improvement intervention	Number of patients	Number of studies	Number of comparisons	Comparisons eligible for meta-analysis
Audit and feedback	103577	13	15	5
Case management	2924	6	6	4
Clinician education	20806	18	20	10
Clinician reminders	48614	40	48	36
Community engagement	23879	3	3	3
CQI (or similar)	20097	9	9	3
Delivery site change	35163	9	12	7
Financial incentive (clinicians)	87260	4	5	3
Financial incentive (patients)	16395	4	5	5
Patient outreach	371218	72	102	71
Team change	155726	26	28	23
Visit structure change	321	1	1	1
Overall	**470175**	**106**	**151**	**111**

Table 5-2: Results of meta-analyses within sub-strata of patient outreach and team change

Table 5-2a: Patient outreach

Patient outreach					
Influenza vaccination			Pneumococcal vaccination		
Outreach medium	Pooled OR	I^2	Outreach medium	Pooled OR	I^2
Community media campaign†	3.16 (1.35, 7.37)	0	EMT outreach*	8.65 (0.02, 4899.87)	100
Telephone reminders†	2.74 (1.23, 6.12)	67	Brochures at office visit†	5.86 (3.29, 10.44)	0
Waiting/exam room posters*	1.78 (0.53, 6.01)	95	Telephone reminders*	2.86 (2.31, 3.56)	0
Mailed print material†	1.45 (1.30, 1.61)	89	Waiting/exam room posters†	1.92 (1.09, 3.40)	57
Brochures at office visit*	1.38 (0.82, 2.33)	0	Mailed print material†	1.66 (1.59, 1.74)	0
Pt.-held preventive care schedule	1.28 (0.82, 1.99)	53	Home visit education*	1.52 (0.74, 3.11)	100
Home visit education*	0.94 (0.64, 1.40)	0	Community media campaign†	1.31 (1.28, 1.55)	0
EMT outreach*	0.67 (0.01, 36.06)	100	Pt.-held preventive care schedule†	1.29 (1.06, 1.57)	0

See forest plots in Supplement S5-D for more detail. * – *N* less than 3. While we avoided interpreting pooled odds ratios from fewer than 3 studies, they are presented here for completeness. † – Pooled odds ratios significant at $p < 0.05$.

Table 5-2b: Team change

Team change					
Influenza vaccination			Pneumococcal vaccination		
Type of additional personnel	Pooled OR	I^2	Type of additional personnel	Pooled OR	I^2
Multi-disciplinary team*	2.44 (1.42, 4.20)	100	EMT	8.65 (0.02, 4899.87)	100
Nurse - autonomous vaccinations†	1.63 (1.30, 2.04)	7	Nurse - autonomous vaccinations*	7.03 (2.98, 16.57)	0
Nurse - no autonomous vaccinations	1.14 (0.88, 1.48)	60	Multi-disciplinary team*	2.25 (1.30, 3.92)	100
Pharmacist	1.11 (0.62, 1.98)	0	Nurse - no autonomous vaccinations†	1.96 (1.28, 3.03)	60
EMT*	0.67 (0.01, 36.06)	100	Pharmacist	1.03 (0.62, 1.74)	0

See forest plots in Supplement S5-D for more detail.

* – *N* less than 3. While we avoided interpreting pooled odds ratios from fewer than 3 studies, they are presented here for completeness.

† – Pooled odds ratios significant at $p < 0.05$.

Table 5-3: Numbers needed to treat to obtain an additional vaccination

A. Influenza vaccinations Baseline vaccination rate of 70% assumed	NNT
Patient outreach (community media)	6
Patient outreach (telephone reminders)	6
Financial incentives, patient	8
Audit and feedback	9
Team change (nurse vaccine administration)	11
Clinician reminders	12
Financial incentives, clinician	13
Patient outreach (mailed print materials)	14
Team change (overall)	14
Patient outreach (overall)	15
Delivery site change	18

B. Pneumococcal vaccinations Baseline vaccination rate of 60% assumed	NNT
Patient outreach (brochures handed out before appointments)	3
Clinician reminders	6
Team change (overall)	6
Team change (nurses w/o vaccine administration responsibilities)	7
Patient outreach (waiting / exam room posters)	7
Patient outreach (overall)	8
Clinician education	9
Patient outreach (mailed print materials)	9
Case management	11
Patient outreach (community media)	13
Patient outreach (preventive care checklists)	17

Interventions included in this table had summary odds ratios statistically greater than 1.0 ($p < 0.05$) based on 3 or more studies. Numbers needed to treat are provided assuming other baseline vaccination rates in Supplement D, Tables S5-D9 and S5-D10.

Figure 5-1: Citation flow

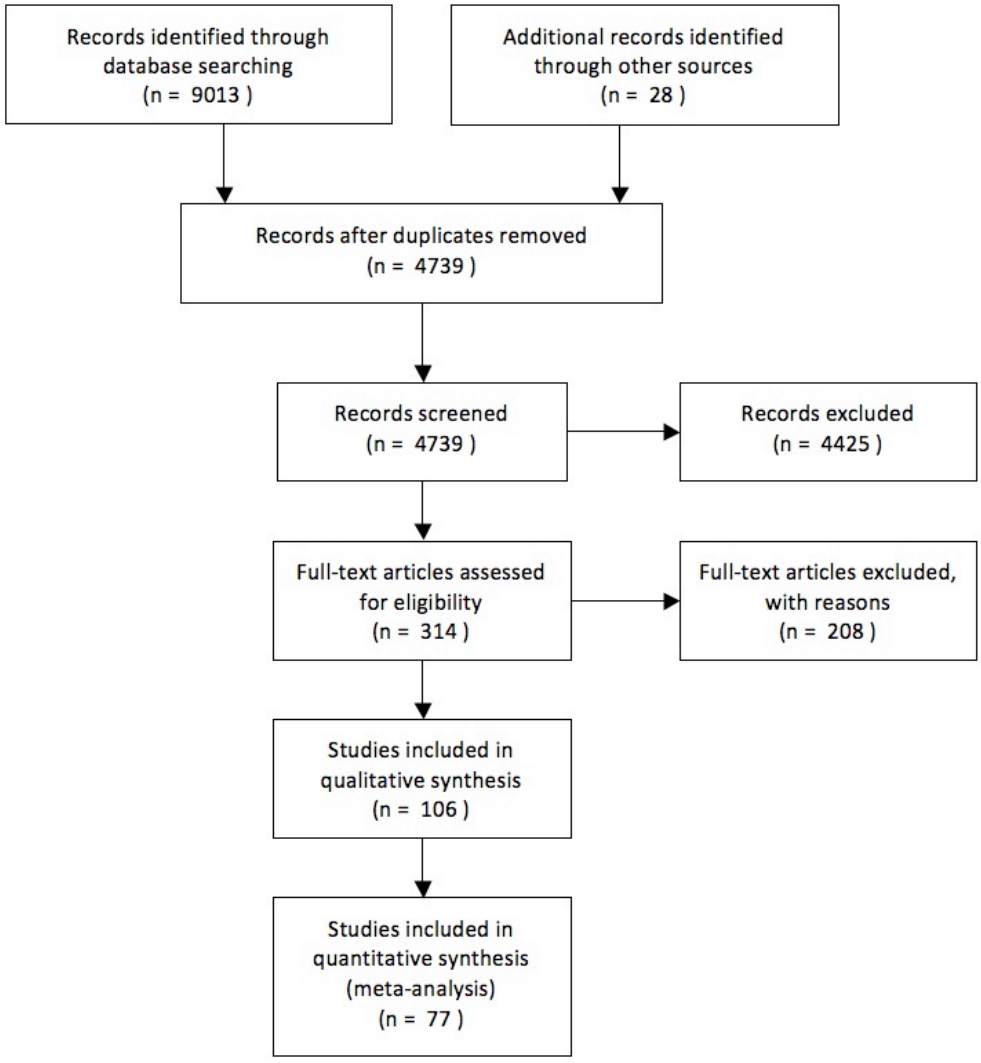
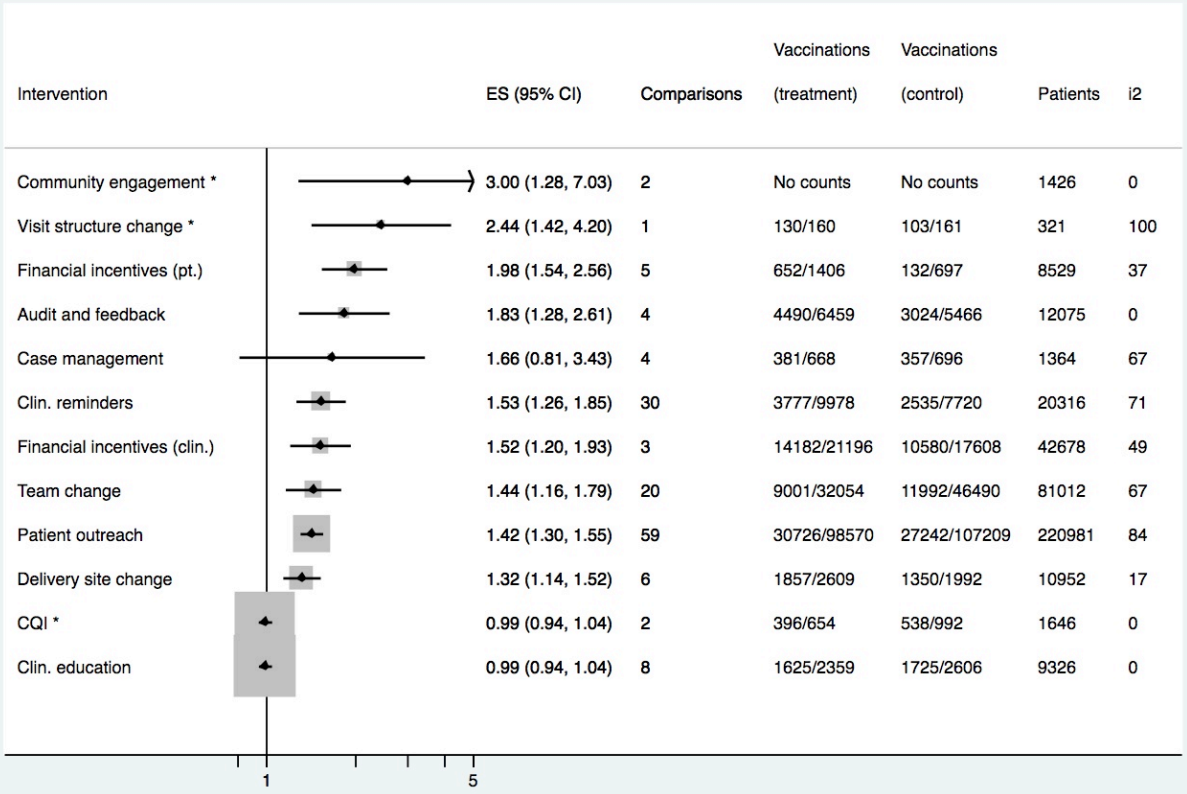


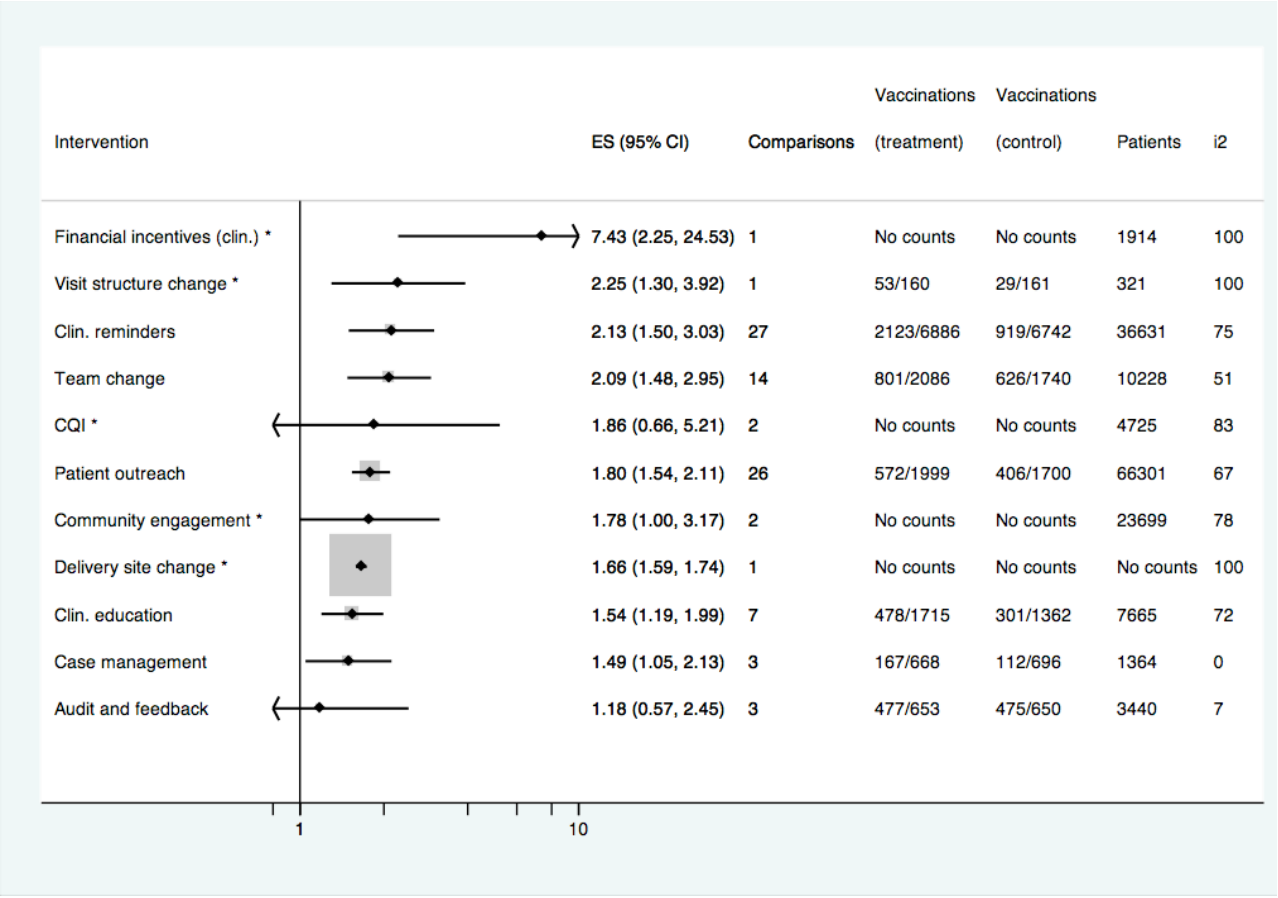
Figure 5-2: Effect of quality improvement interventions on influenza vaccination rates



Forest plot showing pooled odds ratios from random effects meta-analyses. Vaccination rates provided are crude estimates generated by summing patients among studies. Many studies contributing odds ratios for meta-analysis did not provide crude counts.

* Pooled odds ratios from fewer than 3 comparisons are reported, but considered insufficient for interpretation.

Figure 5-3: Effect of quality improvement interventions on pneumococcal vaccination rates



Forest plot showing pooled odds ratios from random effects meta-analyses. Vaccination rates provided are crude estimates generated by summing patients among studies. Many studies contributing odds ratios for meta-analysis did not provide crude counts.

* Pooled odds ratios from fewer than 3 comparisons are reported, but considered insufficient for interpretation. No comparisons involving patient financial incentives were available for meta-analysis.

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Chapter 5 Supplements

All supplements to Chapter 5 are located online. A bibliography of included studies follows.

Supplement A: Included and Excluded Studies

Contents: Methodological details and data from excluded and included studies

Location: http://hdl.handle.net/10402/era.28474

Supplement B: Meta-Analyses of Quality Improvement Interventions – Influenza Vaccinations

Contents: Forest plots and study quality tables

Location: http://hdl.handle.net/10402/era.28475

Supplement C: Meta-Analyses of Quality Improvement Interventions – Pneumococcal Vaccinations

Contents: Forest plots and study quality tables

Location: http://hdl.handle.net/10402/era.28476

Supplement D: Sub-Stratified Quality Improvement Interventions and Numbers Needed to Treat

Contents: Forest plots and tables of numbers needed to treat

Location: http://hdl.handle.net/10402/era.28477

Bibliography of included studies (alphabetical order)

(See Supplement A, online, for a complete bibliography with both included and excluded studies.)

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Chapter 6: Conclusion

6.1. Overview of research

Diabetes has emerged as an important health care priority. The prevalence of diagnosed diabetes among adults aged >= 20 years in Canada has increased from 6.4% in 2002-03 to 8.0% in 2006-07 (1). Since up to a third of diabetes may remain undiagnosed, diabetes may be prevalent in well over 10% of Canadian adults (2). The long-term sequelae of diabetes include micro- and macro-vascular complications associated with substantial health care costs, and reductions in the length and quality of life (3-5). Additionally, numerous immunological defects have been characterized in patients with diabetes, including altered antibody, leukocyte, and cell-mediated immune responses (6). Patients with diabetes experience certain bacterial and fungal infections more frequently than their non-diabetic counterparts (6, 7), and may also be at increased risk from influenza and other acute respiratory infections (8). Diabetes has been identified as a “chief cause” of influenza as early as 1932 (9), and has been included as high-risk indication for routine vaccination in recent clinical practice guidelines (10-13), effectively singling out working age diabetic adults for vaccination.

Vaccination is the primary means of mitigating influenza. Vaccination campaigns are high profile public health programs commanding substantial resources each year. US national policy targets call for yearly influenza vaccinations in 80% of

low risk working age adults (18 <= age < 65), 90% of working adults with high-risk indications, and 90% of elderly (age >= 65) adults (14). Similarly, Canadian policy calls for vaccination rates of 80% (15). Despite the inclusion of diabetes as a high-risk indication for vaccination, only 53-57% of working age adults with diabetes receive routine vaccinations (16, 17). Public health campaigns and primary care practice interventions may help improve vaccination rates among such individuals (18, 19). However, two knowledge gaps must be addressed before such efforts are undertaken. First, there is little rigorous comparative evidence that adults with diabetes actually suffer either increased frequency or increased severity of illness due to influenza, or that influenza vaccinations can improve clinical outcomes in this risk group (20). Second, the effectiveness of particular interventions for increasing vaccination rates in the community remains unclear, due to the substantial quantity and diversity of quality improvement studies, interventions, and results. We undertook a program of research intended to address these knowledge gaps.

In a 1932 paper, Selwyn Collins used a time series approach to estimate the number of deaths from a variety of causes to which influenza may have contributed (9). Influenza was suspected to play a causative role in approximately 16% of diabetes-coded deaths, accounting for 6.3% of total influenza-attributable mortality. Similar findings have been reported by more recent studies (21, 22). Since diabetes is frequently under-represented in death certifications for the most common causes of death (i.e.: cardiovascular disease), diabetes-coded deaths

likely represented acute metabolic decompensation in a small subset of patients with uncontrolled diabetes (23-25). Previous studies therefore signify that influenza likely increases the risk of metabolic decompensation in diabetic adults. Does influenza also increase the risk of more common outcomes, such as acute respiratory infection and cardiovascular disease, which contribute the vast majority of morbidity and mortality in diabetic adults? Initial studies examining a broader range of outcomes reported influenza-attributable increases in pneumonia and influenza hospitalizations (26), and cardio-pulmonary deaths or hospitalizations (27) specific to those with diabetes. However, the effects of influenza remained unclear, due in part to study design limitations and unaccounted confounders.

Our first study examined the incidence of influenza-attributable illness, addressing these limitations using a historical cohort design with individual-level data linkage to a wide range of potential confounders. In adults with diabetes, the presence of circulating influenza contributed 10-13% of physician visits and hospitalizations for influenza-like illness (ILI), 12-26% of pneumonia and influenza (PI) hospitalizations, and 5-6% of all-cause hospitalizations during influenza season. Notably, compared to working age adults without diabetes, the effects of circulating influenza on all-cause hospitalization were 6% higher (RR = 1.06, 95% CI: 1.00, 1.11; p = 0.044) in adults with diabetes, representing an additional 54 hospitalizations (6 per 1000 adults) in this group. To our knowledge,

these results offer the highest quality evidence to date that adults with diabetes do, in fact, experience a higher relative incidence of influenza-attributable illness.

Diabetic adults may also be considered at “high risk” from influenza if, in addition to greater incidence of illness, they suffer greater severity of illness than their non-diabetic counterparts. Our second study examined the effects of seasonal influenza on the population-level risk of adverse outcomes following acute respiratory infections (ARI). We observed that the presence of circulating influenza increased the odds of death or (re-) hospitalization during the 30 days following each of outpatient ILI, hospital ILI, and hospital PI in elderly, but not working age, adults. More importantly, we found no evidence that the effects of circulating influenza differed by diabetes status. These results are consistent with recent studies of community-acquired pneumonia, suggesting that any apparent effect of diabetes on adverse outcomes may actually be due to particular comorbidities or dysglycemia, regardless of diabetes status (28-30).

Diabetic adults are thought to experience increased risk from influenza due to defects in immune function. It is possible that these immune deficiencies may also affect the immunogenicity and effectiveness of influenza vaccine. Previous studies have compared antibody- and cell-mediate responses to influenza, from natural exposure and immunization, in diabetic and non-diabetic adults, with mixed results (20). Despite these deficiencies, immune responses considered adequate for protection have been observed in the majority of diabetic patients in

many studies (20, 31, 32). Indeed, previous observational studies have shown influenza vaccine to be highly effective in working age adults with diabetes (33, 34). However, the true effectiveness of influenza vaccine in diabetic adults remained unclear, since previous studies may have been limited by unrecognized residual confounding (35-37).

We examined influenza vaccine effectiveness in working age adults with diabetes relative to two reference groups: elderly adults with, and without, diabetes. These comparisons were intended to aid interpretation, since elderly adults experience a comparable magnitude of incident influenza-related illness (27, 38, 39), and recommendations for annual vaccinations are well accepted based on previous observational studies (40, 41). Using similar methods, we observed comparable 43-55% and 28-34% reductions in PI and all-cause hospitalizations, respectively, in all study groups. These findings provide a degree of relative support for diabetes-specific vaccination guidelines. However, our data also indicated similar levels of vaccine effectiveness during time periods outside of influenza season, suggesting that many observational studies, our own included, have over-estimated the benefits of vaccination as a result of the “healthy vaccinee" effect (36, 42). Our findings thus highlight the need for long overdue randomized trials of vaccine effectiveness (43, 44).

In practice, public health authorities have received studies questioning the benefits of influenza vaccine with ambivalence. Though somewhat counter to the

notion of evidence-based policy, vaccinations remain an important public health priority (45-47). For most providers, then, as well as public health agencies and other bodies charged with implementing health care policy, the question is not *whether* we should provide vaccinations, but *how* we might do so more effectively. To address this question, we performed a systematic review and meta-analysis of quality improvement interventions to increase vaccination rates in community-dwelling adults. We included 106 peer-reviewed studies involving elderly adults or working age adults with chronic diseases. Most interventions were associated with modest improvements in vaccination rates. Particularly effective were team change interventions where nurses had been assigned responsibilities for administering vaccine, highlighting the importance of vesting non-physician team members with independent responsibilities. Direct personal contact with a trusted provider also emerged, as a key component of successful patient outreach. These findings provide potential directions for innovation, for clinicians and public health professionals interested in improving vaccination rates.

6.2. Implications for practice

6.2.1. Should adults with diabetes be targeted for influenza vaccinations?

Given the existence of well-accepted recommendations for universal vaccination of the elderly, clinical practice guidelines identifying diabetes as a high-risk condition effectively single out diabetic individuals from the population of otherwise healthy working age adults (10-13). An evidence-based rationale for

targeting these individuals requires that the following conditions be demonstrated in working age adults with diabetes, relative to healthy adults:

1. That those with diabetes experience greater clinical need due to increased susceptibility to or severity of influenza.
2. That influenza vaccine is effective in diabetic adults.
3. That influenza vaccinations and the associated effort required to achieve adequate vaccine uptake are cost-effective, providing either cost savings, or health benefits at an acceptable additional cost.

These conditions assume that the safety of influenza vaccine is similarly acceptable for those with and without diabetes, given the low frequency with which the most feared vaccine side effects (e.g.: Guillain-Barre syndrome, oculo-respiratory syndrome, and Bell's palsy) occur (48).

Our research has demonstrated that diabetic adults experience greater clinical need, in the form of increased incidence, but not severity, of influenza-attributable illness. During influenza season, influenza contributed 5.7% of all hospitalizations in working age adults with diabetes, compared to 0.3% in similar non-diabetic adults. Only 624 adults with diabetes aged 45 to 64 would have to be vaccinated to prevent one hospitalization, compared to 32778 similarly aged healthy adults, assuming a vaccine with a uniform effectiveness of 80%.

However, the effectiveness of influenza vaccine cannot be taken for granted. Our results suggest that observational studies of vaccine effectiveness studies are

beset by residual bias, in diabetic and elderly adults alike. The actual effectiveness of influenza vaccine in this population is therefore not known. Although randomized trial data are available for healthy adults without diabetes, such trials may not generalize to working age adults with diabetes, and have not demonstrated reductions in either all-cause or PI hospitalizations (49).

Finally, given the small numbers of influenza-attributable hospitalizations in working age adults generally, formal economic studies are required to ascertain the extent to which improving vaccinations in diabetic adults is cost-effective. The decision to vaccinate working age adults with diabetes thus remains a matter of discretion, for which the evidence base is incomplete. In the US, where authorities consider universal vaccination justified by the benefits of reduced symptomatic ILI (12), promoting vaccinations to adults both with and without diabetes appears appropriate. In Canada, where universal vaccination in working age adults is not the norm for most provinces (15), clinicians may vaccinate working age adults with diabetes to mitigate their increased risk of influenza-attributable hospitalizations, at least until the evidence base improves.

6.2.2. Improving vaccination rates in the community

Influenza vaccination has become a high profile public health priority Canada and the US (14, 15). Elderly adults and working adults identified as high-risk, including those with diabetes, are seen frequently in primary care. These individuals are highly amenable to vaccination, if recommended by a trusted

clinician (50-52). However, many patients for whom vaccinations are indicated conclude their primary care visits without receiving influenza vaccine or vaccination counseling (53-55). National surveys suggest that many primary care providers would like to improve their vaccination rates, but encounter substantial practice barriers to success (40, 41, 56). For such clinicians, whether they choose to target diabetic adults, adults with other high-risk conditions, elderly adults, or all adults generally, our systematic review offers relevant insights into the potential benefits of quality improvement interventions. The most promising innovations appear to involve shifting vaccine administration from physicians to other members of the primary care team with clear responsibilities for chronic and preventive care, and engaging or enlisting patients through personal outreach. Nonetheless, clinicians and policy-makers should temper their expectations of these interventions, since in few treatment arms had vaccination rates improved sufficiently to meet national policy targets.

6.3. Implications for future research

During the course of our work, we have encountered numerous limitations, which may be distilled into three directions for future research. First, prospective studies of a defined population with active surveillance and confirmation of infection would provide better estimates of influenza incidence and complication rates. Studies of health care utilization capture influenza-related outcomes incompletely, since less than 8% of all influenza cases are actually diagnosed as influenza (57). The on-season vs off-season methodology we have applied in our work can

distinguish influenza-attributable outcomes despite lack of a corresponding diagnosis (58), but is unable to detect the vast majority of influenza infections (approximately 75%), which cause ILI but generate no medical visits or health care services utilization whatsoever (59, 60). Prospective studies have previously been instrumental in defining the social costs of influenza (60), and in characterizing both seasonal and pandemic influenza strains with adequate consistency for comparisons (61).

Second, randomized studies of vaccine effectiveness are sorely needed, particularly in populations considered high risk. Observational studies of vaccine effectiveness are subject to residual “healthy vacinee” bias that is often worsened, instead of improved, by database methods of adjusting for comorbidity (35, 43). Prospective studies with confirmed influenza as their outcomes would provide a specific outcome less prone to bias (42), but would remain subject to uncontrolled confounders that continue to resist even advanced statistical methods of control (62, 63). Though long overdue, randomized trials have not been forthcoming due to the widespread acceptance of influenza vaccine, leading to a perceived loss of clinical equipoise (44). Yet without accurate estimates of vaccine effectiveness, vaccination campaigns consume resources that could be invested in proper evaluations or other health interventions of proven effectiveness. Thus, “far from being unethical […] such trials are desperately needed and we should invest in them without delay” (44).

Third, quality improvement interventions exhibited a high degree of heterogeneity in our meta-analysis. Such heterogeneity is common for complex interventions, which are mutli-faceted, embedded in social systems, and context-dependent (64, 65). Explanations for why and how interventions work are often not well articulated (66, 67), and particular contextual and process-related factors affecting intervention performance rarely considered or measured (68). Complex interventions are often treated as “black boxes” (69), leading to considerable difficulty applying aggregate meta-analytic findings to particular circumstances (70, 71). The large number and modest impact, at best, of vaccination quality improvement studies suggest a need for research that matches context to innovation, exploring not only the extent to which these interventions work, but how and why they work – or fail to work, as well.

6.4. Conclusions

We have evaluated key premises related to the rationale for targeting adults with diabetes for vaccination. While we have provided the highest quality evidence to date demonstrating an increased incidence of hospitalizations due to influenza in working age adults with diabetes, the evidence supporting targeted vaccination efforts in this group remains incomplete. The decision to prioritize adults with diabetes for vaccination thus remains a matter of discretion, to be considered in light of local policies and conditions. For those clinicians and public health officials who make improving vaccination rates a practice priority, we have summarized the effectiveness of numerous quality improvement interventions.

Influenza is an important public health priority, particularly given the emergence of novel influenza strains such as Avian H5N1 (72, 73) and swine-origin influenza A H1N1 (74). During the 2009 H1N1 outbreak, only 40% of Canadians received H1N1 vaccine (75, 76), in an atmosphere characterized by increasing public wariness and mistrust of public health messaging (77). Our work highlights a substantial need for further research improving the evidence for high-risk vaccination policies in working age adults, and examining the local factors mitigating or potentiating efforts to improve vaccination rates. Research along these lines is needed, if we are to understand and control the threat posed by seasonal, let alone emerging, influenza.

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