Use of Influenza and Pneumococcal Vaccines in People With Diabetes

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Leonard Thompson, the first individual to receive insulin for diabetes, died in 1935 from complications related to a staphylococcal pneumonia that occurred after an episode of presumed influenza (1,2). Before the clinical use of insulin and antibiotics, infection often precipitated ketoacidosis and other acute metabolic complications and was responsible for significant morbidity and mortality in people with diabetes (3). With the introduction of insulin, oral hypoglycemics, and antibiotics, the end-stage complications of eye, neurologic, kidney, and vascular disease have become the major cause of death and suffering for people with diabetes. In addition to the introduction of effective therapies for metabolic control and infectious disease, the Advisory Committee on Immunization Practices (ACIP) has recommended that individuals with diabetes receive influenza and pneumococcal immunization because they are regarded as a moderate- to high-risk population group.

Internationally, there are differences regarding vaccine recommendations for people with diabetes, and few countries have vaccine policies endorsed by medical or patient organizations (4). Where such policy statements endorsing influenza and pneumococcal immunization for moderate- and high-risk individuals exist, many countries (including the U.S.) have deficiencies in vaccine distribution and/or immunization rates (4–6). This fact suggests that patients and/or their primary providers are not convinced of the threat of certain infectious illnesses or the likelihood of benefit from vaccination. Alternatively, immunization of individuals with diabetes may be one of the many clinical processes of care that has been shown to be deficient for this group of patients (7–10).

Initially for practical reasons and later for ethical reasons, there have been few placebo-controlled studies designed to demonstrate the efficacy of influenza and pneumococcal immunization specifically in individuals with diabetes. In addition, there are few clinical studies that have examined the benefit of glycemic control, antibiotics, antiviral agents, and other nonvaccine measures in preventing and controlling infection. Current vaccine recommendations for people with diabetes are based on historical observations in studies from population groups that have included only a minority of patients with diabetes. What is the evidence that people with diabetes benefit from these immunizations?

For the purpose of this review, we will examine the impact of two vaccine-preventable illnesses: influenza and pneumococcal infection. We will first examine the evidence regarding the immune response to viral and bacterial illness in people with diabetes. We will also review the evidence for the risks of infection in diabetes as it relates to antibody response, cell-mediated immunity, leukocyte function, colonization rates, epidemiologic evidence for infection, immune response to immunization, and efficacy of vaccination. We will then systematically review the clinical reports of infection, vaccine immunogenicity, and vaccine effectiveness for influenza and pneumococcus in people with diabetes. Finally, we will review general vaccine implementation strategies.

Because most studies reporting patient cohorts and outcomes give limited and variable information about patients with diabetes, we felt that combining research results (a meta-analysis) would not be valid. In addition to our concerns about this heterogeneity, confounders such as age and underlying cardiopulmonary disease make risk assessment of diabetes by itself difficult. Therefore, we have elected to provide a narrative review. Primary articles were identified from a Medline literature search without time restriction, using the key words immunization, vaccination, influenza, pneumococcus, and diabetes. Additional sources were then identified from the references listed from these primary sources. Searches were performed using the last 2 years of Current Contents. Further information was also obtained from contacts with the primary authors of published articles.

DIABETES AND RISKS OF INFECTION

— The primary public health goal of immunization is to prevent morbidity and mortality as well as transmission of infectious disease within a population. It has been reported for many years that people with diabetes suffer significant morbidity and mortality from bacterial and viral infections (11,12). This risk has been attributed to genetic and metabolic abnormalities—in particular, poor glycemic control and acidemia (13–16). Other factors associated with diabetes (age, renal disease, and cardiovascular disease) have been shown to be significant comorbid factors that can increase the risk of sequelae of certain illnesses. Because of these factors, it is difficult to exclude the potential impact of these factors when assessing diabetes and the risks for viral and bacterial disease.

It has been assumed that specific aberrations in host defense mechanisms (antibody response, cell-mediated immunity, leukocyte function, and colonization rates) account for the increased case fatality rate

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Abbreviations: ACIP, Advisory Committee on Immunization Practices; CQI, continuous quality improvement; DKA, diabetic ketoacidosis.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

that results from bacterial and viral infections such as influenza and pneumococcus.

Poor antibody response has been shown to be a marker of immunologic susceptibility to infection and its sequelae (17). Immunity (as measured by in vitro opsonic activity of serum from vaccinated patients), however, has not always been correlated with level of antibody measured by radioimmunoassay (18,19). Antibody responses to the pneumococcal vaccine in people with diabetes have been examined and have been shown to be no different than in people without diabetes (20–22). Observations of impaired antibody response to the influenza vaccine, in particular when there is poor metabolic control, has led some to question the value of the influenza vaccination in people with diabetes (23–26).

Cell-mediated abnormalities (and related humoral responses), such as decreased CD4/CD8 lymphocyte ratios, changes in natural killer cell function, reduced lymphocyte blastogenesis, acquired defects in interleukin-2 production, and a reduced phagocytic function of monocytes, have all been reported in people with diabetes (27–30) and could account for an increased risk of infection (both bacterial and viral) and poor antibody response to vaccination. It has also been proposed that cell-mediated immunity may be a more reliable predictor of adequate immune response as it relates to viral infections such as influenza infection (25).

Leukocyte function is important in the primary immune response to bacterial infections (both primary and secondary infections complicating viral infections). Poorly controlled diabetes has been associated with altered granulocyte function (31–33). It appears from these studies that the complex cellular processes of bacteria engulfment and killing could be influenced by glycemic control independent of active infection. Bacterial colonization, if significant, could contribute to patients' risks for complicating nosocomial infection from primary infections. Patients with diabetes have been shown to have a higher incidence of positive surveillance cultures (and carrier rates) for coagulase-positive *Staphylococcus* and Group B streptococci (34), whereas others have reported a colonization rate for people with diabetes that is no higher than that expected for other individuals (35). Carrier status appears to be associated with glycemic control (34,36). While it is tempting to speculate how colonization may have contributed to Leonard Thompson's complicating staphylococcal pneumonia (1), it is difficult to assess colonization's specific impact on the morbidity and mortality of disease for people with diabetes.

Epidemiological evidence

There are limited studies reporting the incidence, morbidity, and mortality of viral and bacterial infections specifically in patients with diabetes. Tables 1 and 2 summarize the observational studies that have reported morbidity and mortality statistics of population groups for influenza and pneumococcal infections. Because most of these studies report incidence rates for groups of patients with comorbid conditions not limited to diabetes (classified as high-risk, moderate-risk, low-risk, immunocompetent, or immunocompromised) and infrequently by specific diseases, there are limited morbidity and mortality data specifically concerning patients with diabetes. A number of cautionary comments regarding the quality of data and evidence included in each study are provided in Tables 1–4. Incidence rates and responses to immunization for influenza and pneumococcal disease (when available) in patients with diabetes are reported in parentheses. These significant limitations make interpretation of available evidence problematic. There are no reports regarding the risks from these infections and their specific relation to glycemic control.

Epidemiologically, it has been observed that influenza epidemics are associated with an increased number of hospitalizations and deaths from a variety of conditions, including diabetes. There are case series describing an increased incidence of diabetic ketoacidosis (DKA) during epidemic years (37,38). Most of the studies reporting on influenza (Table 1) and all of those cited for pneumococcal disease (Table 2) are hospital-based cohorts. Because diabetes is a frequent cause for hospitalization, this potential bias could overestimate the incidence of diabetes in these types of infections and lead one to suspect that diabetes is a risk factor for susceptibility. Although this type of bias in observational studies may not allow one to adequately answer questions about diabetes, immune function, and risk of disease, such observations are helpful in planning population-based immunization strategies and in targeting people at risk for hospitalization because of these infections (see VACCINE IMPLEMENTATION STRATEGIES).

Another inherent problem with many clinical studies is the nature of the estimates based on case identification by billing codes and other administrative identifiers (which are not validated in most studies) (39). This is particularly problematic with regard to influenza, where viral cultures are rarely done or reported. Very few studies have included serological or viral culture confirmation of infection, and in those studies that have, sufficient clinical detail to identify and assess outcomes in patients with diabetes is often not included (40,41). With regard to pneumococcal infection, identification of these infections is most often based on the identification of the organism (and serological typing) from sterile body fluids (blood, cerebrospinal, or pleural) and, thus, a larger proportion of patients who did not have cultures performed or who had infection limited to the lung or bronchial tree could have been missed. This systematic bias again could overestimate diabetes as a risk factor.

Additional concerns for all studies reported include the number of patients investigated in some population groups, the techniques for sampling, the details regarding estimates of excess mortality, and the identification of a control population (if one was included). In many other series, although there are references to diabetes in case fatality rates, there are insufficient details to make more than general conclusions (41).

DIABETES AND IMMUNE RESPONSE TO VACCINATION

— There have been differences in the reported immune responses to vaccines in people with diabetes. Patients with diabetes have been reported to have a "slow" response to immunization (11), defined as the delayed but similar vaccination-induced immune titers in patients with diabetes as compared with healthy control subjects. Because of a variety of T-cell abnormalities (with and without good metabolic control), it has been reported that some patients may have impaired capacity to produce circulating B-cells and specific IgM and IgG antibody in response to a vaccine (27–30,42,43). Limited data suggest that a subgroup of patients who do not respond to initial immunization may respond with repeated vaccination (43). It has also been stated that because the immune response to pneumococcal polysaccharide vaccines is T-cell independent, it may be normal in people with diabetes (20).

It is assumed that an adequate immune response is necessary to benefit from vaccination. This point has not always been appreciated by some who have argued that

Table 1—*Influenza and diabetes: epidemiological observations of morbidity and mortality*

Author (reference)	Years observed	Study type*	Population studied	Country	Sample size (% diabetes)	Primary outcome measures	Results (diabetes)	Comments†
Stocks and Camb (52)	1921–1931	PopB	Annual Register	England Wales	—	Death Excess mortality	(6–14%)	A, B, O
Finland et al. (137)	1940–1941	CaseS	Boston City Hospital	U.S.	66 (3)	Staph pneumonia		A, C, O
Stuart-Harris et al. (89)	1949–1950	CaseS	Hospital and other	England	85	Death Prevalence	— (4.5%)	C, E, F, O
Eickhoff et al. (53)	1955–1960	PopB	Registrar National Office of Vital Statistics	U.S.	—	Death Excess mortality	(4–14%)	A
Housworth and Langmuir (55)	1957–1966	PopB	Registrar National Office of Vital Statistics	U.S.	—	Death Relative intensity	(0.5–7.7)	A
Martin et al. (138,139)	1957–1958	CaseS	Hospitals in Boston	U.S.	32 (6.25)	Death	—	C, J, O
Petersdorf et al. (54)	1957	CaseS	New Haven Hospital	U.S.	91 (4.4)	Pneumonia death Case fatality	12% (0%)	A, C, O
Oseasohn et al. (140)	1957	CaseS	Autopsy series, Cleveland hospitals	U.S.	33 (3)	Death	—	A, E, O
Giles and Shuttleworth (64)	1957	CaseS	Autopsy series North Staffordshire	England	46 (4.3)	Death	—	A, C, H, O
Barker and Mullooly (59)	1968–1973	CC	HMO, Portland, Oregon	U.S.	38 (13)	Pneumonia Death	—	A, K, I, O
Schwarzmann et al. (40)	1968–1969	CC	Grady Memorial Hospital, Atlanta	U.S.	108 (14)	Pneumonia	—	A, C, O
Bisno et al. (41)	1968–1969	CaseS	City of Memphis hospitals	U.S.	79 (10)	Pneumonia Case fatality	13%	C, D, G, J, O
Cameron et al. (56)	1969–1981	CC	Australia Bureau of Statistics	Australia	4,095	Death Odds ratio 95% CI	(2.0) (0.4–14.8)	A, G
Watkins et al. (37)	1969–1970	CaseS	Hospitals, Birmingham	England	29 (100)	DKA Death Case fatality	(24%)	C, E, O
Bouter et al. (38)	1976–1979	CC	Dutch National Medical Registrar	Netherlands	—	DKA Relative risk Pneumonia Relative risk Hospitalization 95% CI Death 95% CI	(15.9) (25.6) (5.7–6.2) (42.4–91.8)	A, F
Carrat and Valleron (58)	1986–1990	PopB	National Center of Mortality Statistics	France	7,700	Death Rates	481.5–378.8 $(6.2–5.6)/10^5$	A, E
McBean et al. (57)	1989–1991	CC	Medicare hospital billing records	U.S.	30×10^5	Influenza A Hospitalization Relative risk 95% CI Death Relative risk 95% CI	(1.04) (1.0–1.08) (1.64) (1.21–2.21)	A, L

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Table 1 *(continued)*

Author (reference)	Years observed	Study type*	Population studied	Country	Sample size (% diabetes)	Primary outcome measures	Results (diabetes)	Comments†
McBean et al. (57)	1989–1991	CC	Medicare Hospital billing records	U.S.	30×10^5	Influenza B Hospitalization Relative risk 95% CI Death Relative risk 95% CI	 (0.98) (0.95–1.20) (1.51) (1.13–2.02)	A, L
Diepersloot et al. (2)	—	R	—	—	—	Pneumonia Death	—	O
Neuzil et al. (141)	1973–1993	PopB	Nonpregnant women 15–64 years of age Tennessee Medicaid	U.S.	21×10^6 (6.5%)	Cardiopulmonary Events Relative risk 95% CI	 (16.4) (11.9–20.9)	A, B, F, L

*CC, case control; CaseS, case series; PopB, population-based descriptive; R, review. †A, no or incomplete serological confirmation of infection, based on clinical diagnosis; B, methodology of calculating expected mortality (use of "annual decrements or increments thus calculated from the decade . . . assumed to continue constant"); C, referral: hospital-based cohort; D, historical control subjects or from a different population group; E, insufficient reporting of details to confirm details concerning patients with diabetes; F, selection method: selection method–reporting of a convenience representative sample from cohort; G, selection method: nonrandom or without mention of selection technique for sample cohort; H, selection method: one of two patients with diabetes had acromegaly and suspect secondary diabetes; I, selection method: HMO population; J, selection method: results section indicated that case finding was incomplete; K, incomplete medical record review: results section indicated missing medical records; L, incomplete medical record review: administrative data set only without medical record validation; O, depended exclusively or heavily on narrative review. HMO, health maintenance organization.

because most people with diabetes have appropriate immune responses, they do not have an indication for immunization (17). On the contrary, if people with diabetes have appropriate responses to vaccination and evidence for increased risk from vaccine-preventable illness such as influenza and pneumococcal disease, it is reasonable to assume that immunization may be of value.

DIABETES AND EFFICACY OF VACCINATION — It is unlikely that a randomized placebo-controlled study of influenza and pneumococcal immunization in people with diabetes will be performed in the U.S. because of the large number of patients required and ethical questions of randomization to placebo. Because of this fact, studies to answer the question of immunization efficacy have fallen under three categories (Tables 3 and 4): clinical trials involving at-risk patient groups (which include patients with diabetes), case-control studies, and indirect cohort analysis (44,45). Although case-control studies provide a practical means for achieving adequate statistical power, they often include a heterogeneous group of at-risk patients and thus provide limited information about vaccine efficacy specific for people with diabetes. The indirect cohort method has been frequently used in studying pneumococcal immunization (44,45–48). With this method, immunization efficacy is determined by comparing the distribution of pneumococcal serotypes that cause infection in vaccinated and unvaccinated individuals (assuming that the risk of infection with vaccine-type organisms is similar in both populations).

Because of the lack of randomized clinical trials, there is inherent bias in these types of studies of vaccine efficacy. Individuals chosen as control subjects (in case-control series) are likely to have had circumstances that lead to their immunization (or lack of immunization). Individuals receiving vaccine are more likely to have comorbid conditions such as diabetes, whereas others may have not received vaccination and have had worse outcomes because of other characteristics that are obstacles to timely health care and immunization (such as dementia or stroke) (49). Additional limitations for many studies include the bias that not all people with diabetes are represented in studies of institutionalized patients (e.g., nursing home or hospital). Differences in opportunities for exposure to contagious illnesses such as influenza may bias some reports. Selection bias exists for cohort studies from referral hospitals because these patients are more often severely ill (and thus more likely to be hospitalized) and in turn may be more likely to be immunized. In contrast, other individuals who have more health concerns (and healthy lifestyles) may also actively seek and elect to receive immunization. Finally, many studies use recall as a method of documentation of vaccination, despite the fact that the accuracy of patient historical recall has been estimated to be 80% at best (50).

INFLUENZA

Clinical reports of infection

The first descriptions of large outbreaks of influenza were reported in 1847–1848 (51). The death rate due to influenza epidemics remained high during the following decade and then steadily declined in the subsequent 30 years until influenza as a recorded cause of death almost disappeared. With the epidemic of 1890–1891, an increase in death rate and significant morbidity associated with influenza epidemics was again observed (51).

Until the 20th century, there was limited information regarding the risks of influenza in people with diabetes. Stocks and Camb (52) were two of the first investigators in the 1900s (1921–1931) to report an increase in death rate (6–14%) from influenza in people with diabetes. Eickhoff et al. (53) reported 20 years later that people with diabetes had a moderate increase in death during a 6-month influenza outbreak

Table 2—*Pneumococcal infection and diabetes: epidemiological observations of morbidity and mortality*

Author (reference)	Years observed	Study type*	Population studied	Country	Sample size (% diabetes)	Primary outcome measures	Results (diabetes)	Comments†
Austrian and Gold (15)	1952–1962	CaseS	Kings County Hospital, Brooklyn	U.S.	457 (4.6)	Pneumonia Septicemia Death	—	A, C, F, O
Mufson et al. (101)	1967–1970	CaseS	Cook County Hospital, Chicago	U.S.	325 (3.7)	Pneumonia Extra pulmonary infection Septicemia Death Case fatality rate	— 28% (42%)	A, C, O
Fedson and Chiarello (91)	1970–1981	CaseS	University of Chicago hospitals, Chicago	U.S.	205 (12.3)	Pneumonia Septicemia Death Case fatality rate	— 21% (32%)	A, C, K, O
Gransden et al. (103)	1970–1984	CaseS	St. Thomas Hospital	England	325 (3.3)	Septicemia Case fatality rate	 29% (9.1%)	C, O
Finkelstein et al. (92)	1972–1981	CaseS	Bellevue Hospital	U.S.	187 (9.1)	Septicemia	—	C, G, K, O
Hook et al. (102)	1974–1980	CaseS	Harbor View Medical Center, Seattle	U.S.	134 (4)	Septicemia Death Case fatality rate	 31% (40%)	C, K, O
Gruer et al. (104)	1974–1981	CaseS	E. Birmingham Hospital	England	103 (2)	Septicemia	—	C, K, O
Mylotte and Beam (93)	1977–1980	CaseS	Veterans Hospital, Buffalo	U.S.	62 (19)	Pneumonia Septicemia Death	—	C, H, O
Kramer et al. (14)	1977–1985	CaseS and R	Shaare Zedek Medical Center	—	55 (1)	Pneumonia Septicemia Death Case fatality rate	— 36% (67%)	C, H, O
Watanakunakorn et al. (94)	1980–1989	CaseS and R	Community hospital(s), Ohio	U.S.	385 (12)	Pneumonia Septicemia Death Case fatality rate Odds ratio SE	— 25% (37%) 1.0‡ 0.4	C, G, O
Alvarez et al. (95)	1980–1985	CaseS	Veterans Hospital, Johnson City	U.S.	55 (12.7)	Septicemia	—	C, H, O
Perlino and Rimland (16)	1980–1981	CaseS	Grady Memorial and Veterans Hospital, Atlanta	U.S.	93 (10.8)	Pneumonia Septicemia Death	— 	C, H, O

*CaseS, case series; R, review. †A, no or incomplete strain typing for confirmation of infection, based on clinical diagnosis; C, referral: hospital-based cohort; F, selection method: cohort with positive blood cultures ordered only per physician/clinical suspicion; G, selection method: nonrandom or without mention of selection technique for sample cohort; H, selection method: small cohort; K, incomplete medical record review: results section indicated missing medical records; O, depended exclusively or heavily on narrative review. ‡$P = 0.05$.

(1957–1958), while Petersdorf et al. (54) reported a series of 91 patients (4.4% with diabetes) who had a 12% incidence of death from pneumonia (but none of whom had diabetes). In addition, Housworth and Langmuir (55) found that excess deaths in individuals with diabetes were significant (increased by 5–12%) in six of seven epidemics from 1957 to 1966 (excluding 1966). Cameron et al. (56) reported the odds ratio for death in patients with diabetes as 2.0 (95% CI 0.4–14.8), and Bouter et al. (38) reported two times the number of patients with diabetes dying after hospitalization for pneumonia or DKA in the influenza epidemic years of 1976 and 1978 as compared with the nonepidemic years of 1977 and 1979. In other series of hospitalized patients, the incidence of diabetes in influenza epidemic and nonepidemic years has been remarkably constant (54,57). These reports suggest that people with diabetes (in comparison to individuals without similar chronic disease) are at increased risk during both epidemic and nonepidemic control periods (40,54,58). The average hospitalization rate from 1989 to 1991 was 4 per 1,000 Medicare beneficiaries who had the diagnosis of diabetes (57).

Although it is reported that patients with diabetes are at increased risk of death from influenza and complicating pneumonia (38,52,53,55,56), in several series, age and cardiac and pulmonary disease have been the greatest risks for death (7,41). Chronic obstructive pulmonary disease and

Table 3—*Influenza and diabetes: efficacy of immunization*

Author (reference)	Years observed	Study type*	Population studied	Country	Sample size (% diabetes)	Primary outcome measures	Results (diabetes)		Comments†
Barker and Mullooly (81)	1968–1973	RC	HMO, California	U.S.	1,100 (12–15)	Hospitalization	Vaccine		A, E, I
							Yes	No	
	1968–1969					Rates	4/1,120	15/2,820	
	1972–1973					Rates	2/1,100	24/3,700§	
						Death			
	1968–1969					Rates	3/1,120	1/2,820	
	1972–1973					Rates	0/1,100	3/3,700§	
Saah et al. (82)	1979–1982	RC	Nursing home, Manhattan	U.S.	1,362 (14.5)	Pneumonia			A, C, E, G, O
						Death	No vaccine		
	1979					60-Day risk ratio	3.3§		
	1980					60-Day risk ratio	2.9§		
	1981					60-Day risk ratio	0.9		
Mullooly et al. (83)	1980–1989	RC	HMO, California	U.S.	251,034 person-periods	Pneumonia	No vaccine		A, H, E, I, L
						Odds ratio	1.4		
						95% CI	1.2–1.73		
						Death			
						Odds ratio	1.49		
						95% CI	0.9–2.36		
Fedson et al. (73)	1982	CC	Noninstitutional, Manitoba	Canada	976 (5.8)	Pneumonia	No vaccine		A, D, E, J, L
						Relative risk	1.47		
						95% CI	1.09–2.08		
						Influenza death			
						Relative risk	2.86		
						95% CI	1.28–6.25		
	1985				878 (5.9)	Pneumonia			
						Relative risk	1.61		
						95% CI	1.23–2.08		
						Influenza death			
						Relative risk	2.17		
						95% CI	1.08–4.55		
Nguyen-Van-Tam et al. (84)	1989–1990	CC	Leicestershire Hospital	England	156	Hospitalization	No vaccine		A, C, D, K
						Odds ratio	(1.48)		
						95% CI	(0.7–3.34)		
Foster et al. (74)	1989–1990	CC	Medicare vaccine demo, Michigan	U.S.	721 (13)	Hospitalization	No vaccine		A, B, K, L
						Odds ratio	(1.2)		
						95% CI	(0.8–1.88)‖		
Monto et al. (85)‡	1989–1990	CC	Medicare vaccine demo, Michigan	U.S.	721 (13)	Hospitalization	No vaccine		A, B, K, L
						"height of epidemic"			
						Odds ratio	(0.97)‖		
Nicholson et al. (87)	1989–1994	CC	Leicestershire hospital register	England	80 (100)	Hospitalization	Vaccine		A, D, G, J, L
						Odds ratio	(0.21)		
						95% CI	(0.05–0.81)		
Strikas et al. (50)	1990–1991	CC	Noninstitutional Medicare billing records, Ohio and Pennsylvania	U.S.	481	Pneumonia community control subjects	No vaccine		A, B, C, G
						Odds ratio	(1.07)		
						Hospital control subjects			
						Odds ratios	(0.8)		
Nichol et al. (49)	1990–1991	CC	Group health HMO, St. Paul	U.S.	~25,000 per cohort	Hospitalization			A, E, I, H
	1991–1992				Total: 78,527	Pneumonia			
	1992–1993				(6.4–11.6)	Heart failure "costs"			
						Death	Vaccine		
						Rate reduction	27–57%		

*CC, case control; RC, retrospective cohort. †A, no or incomplete serological confirmation of infection, based on clinical diagnosis; B, methodology: use of survey and self-reporting for diagnoses/vaccination; C, referral: hospital nursing home–based cohort; D, bias: control group; E, insufficient reporting of details to confirm details concerning patients with diabetes: odds ratio and relative risk expressed for "high risk" conditions and risk ratio for entire group; F, selection method: selection method–reporting of a convenience representative sample from cohort; G, selection method: nonrandom or without mention of selection technique for sample cohort; H, selection method: high incidence of other comorbid conditions (pulmonary and cardiac disease); I, selection method: HMO population; J, selection method: results section indicated case finding was incomplete; K, incomplete medical record review: results section indicated missing medical records; L, incomplete medical record review: administrative data set only without medical record validation; O, depended exclusively or heavily on narrative review. ‡Apparent same cohort as Reference 84. §$P < 0.05$; ‖NS. HMO, health maintenance organization.

cardiovascular disease as causes for hospitalization have been the most frequently reported disease categories during epidemic influenza periods (39,59,60). Several reports and case series either have not identified diabetes as an individual comorbid condition (61) or have not found diabetes among their patients (62,63). In addition, Giles and Shuttleworth (64) reported only two patients with diabetes (4.3%) in their autopsy series, one of whom had acromegaly as an unusual secondary cause of diabetes.

Morbidity and mortality from influenza are often influenced by factors other than the patient's comorbid diagnoses. Alling et al. (60) have pointed out that some epidemics of influenza are accompanied by a greater excess mortality than others, partly because of viral antigenic variation such as the introduction of a new antigenic subtype or of variants derived by the process of antigenic drift and shift. Sabin (65) observed a decrease in the mortality from influenza and pneumonia during influenza epidemics occurring between 1971 and 1975, and no excess mortality was reported from the influenza epidemics of 1953, 1965, 1978, and 1979 (56). During these latter years, influenza more often caused illness in children and young adults (56), reinforcing the fact that age, a significant risk factor for influenza, is likely to bias observations concerning diabetes, which has a greater incidence and risk for complications in the elderly. Because it is not possible to control for these factors in studies that have been reported to date, there is a potential for both an over- and underestimate of diabetes as a risk factor.

Although one series noted an increase (threefold) in hospital admissions for the acute metabolic complications of DKA during influenza epidemics (37), there are limited population-based studies that have supported this observation. Other metabolic abnormalities (hypokalemia) in people with diabetes have also been reported during epidemics and are noted to occur out of proportion to that usually associated with DKA alone (37). The largest population-based study with detailed data concluded that during epidemic years, patients with diabetes were six times more likely to be hospitalized with a diagnosis of influenza than age- and sex-matched control subjects (38).

Independent of diabetes, influenza has been shown to be associated with excess mortality in individuals >65 years of age and in those with cardiovascular disease (7,53,60). The estimated relative risk of dying from influenza during hospitalization for people with diabetes has been reported as high as 92 or an incidence of 481 per 10^5 patients during the epidemic year 1978 (38,59) and as low as 5.26–6.2 per 10^5 patients in the subsequent epidemics of 1985–1986 and 1989–1990 (58). Again, the differences may be explained in part because of the older age of the cohort in 1978 (≥75 years) and their higher incidence of reported deaths from respiratory, cardiovascular, and end-stage renal diseases. Details from these studies do not allow assessment of these factors.

Conclusion. Published case series and population-based cohorts are not able to answer the question about the true incidence of influenza and its complications in patients with diabetes. In addition, they are unable to answer the question regarding the role of metabolic control and its influence on the attack rate and severity of illness in this same group of patients. Independent of these limitations, many have interpreted these data to suggest that patients with diabetes and its complications (who are also likely to be patients with frequent hospitalizations) are at increased risk for the morbidity, mortality, and health care costs resulting from influenza infection.

Vaccine immunogenicity

Influenza immunization and subsequent immunity results from stimulation of humoral and cell-mediated immune responses (66). The antibody- and cell-mediated responses (from natural exposure and immunization) in patients with diabetes have been comparable to those in control subjects in some reports (24,26,66–68) but not in others (21,22,27,69,70). In the presence of end-organ disease such as uremia and dialysis, response to immunization in patients with diabetes has been reported to be very poor (71).

Poor immunological response to influenza vaccination has been attributed to impairment of antigen-specific antibodies because of nonenzymatic glycosylation of serum IgG resulting from poor glycemic control (21). Others have not observed that antibody production is related to metabolic control and suggest that failure to respond may be unique to the type of diabetes and susceptibility genes for type 1 diabetes and dysregulation of the immune response (22,69,70,72). Despite these speculations, a sufficient immune response has been reported in >70% of patients in many studies (2,22,24,67), and vaccination has been shown to be effective in preventing hospitalization with pneumonia and influenza in high-risk noninstitutionalized elderly individuals (including patients with diabetes) (73,74).

Vaccine effectiveness

Discussion of flu vaccine efficacy is more complex than it might seem at first. In part, it depends on what is measured, i.e., the efficacy of flu vaccine against symptoms or against mortality. So, for example, the efficacy of flu vaccine against symptomatic influenza is 70–90% in healthy adults versus 30–40% in frail elderly individuals. However, the efficacy of influenza vaccine against lower respiratory tract involvement, hospitalization, and death is far higher. In addition, efficacy varies each year because the influenza vaccine is essentially a new vaccine each year. Thus, efficacy also depends on how well the vaccine strains and the circulating strains match. Finally, efficacy can appear falsely low depending on the presence of cocirculating viruses against which the influenza vaccine is not protective (coxsackie virus, adenovirus, parainfluenza, etc.).

In many intervention studies (75–78), it has been demonstrated that vaccination against influenza (during epidemic and nonepidemic years) is associated with less frequent hospitalizations for complications of influenza, fewer deaths during the influenza season, and direct savings in health care costs. Two reviews and a metanalysis support this conclusion (79,80), but none of these reports mentions people with diabetes as a specific population group or as part of an at-risk group.

Several of the studies listed in Table 3 (with reported prevalence rates of diabetes of 6–14.5%) describe outcomes for heterogeneous at-risk patient groups and thus provide insufficient detail to discern the potential benefit of immunization specifically for people with diabetes (49,73, 81–83). These studies demonstrate the efficacy of immunization in at-risk patients for most but not all epidemic influenza periods. In another study, subgroup analysis of patients with diabetes demonstrated the efficacy of influenza vaccination that could not be demonstrated in other population groups (84). In contrast, odds ratios have been reported in favor of protection in large heterogeneous population groups (in particular, groups with concomitant heart and lung disease) but without specific benefit for patients with diabetes (74,85). Incomplete medical record review, dependence on

Table 4—*Pneumococcus and diabetes: efficacy of immunization*

Author (reference)	Years observed	Study type*	Population studied	Country	Sample size (% diabetes)	Primary outcome measures	Results (diabetes)	Comments†
Broome et al. (44)	1978–1980	IC	Samples for requested serotyping by CDC	U.S.	35 (3)	+Culture (sterile body fluid)	—	C, G, J, M
						% Vaccine efficacy	60%	
Shapiro and Clemens (112)	1978–1982	CC	Yale-New Haven Hospital	U.S.	90	+Culture (sterile body fluid)	—	C, E, P
						% Vaccine efficacy	67%	
						95% CI	13–87%	
Bolan et al. (46)	1978–1984	IC	CDC surveillance of U.S. hospitals	U.S.	1,887 (2)	+Culture (sterile body fluid)	—	B
						% Vaccine efficacy	55% (90%)	
Butler et al. (45)	1978–1992	IC and CC	CDC National Surveillance Study	U.S.	2,837 (5)	+Culture (sterile body fluid)	—	B, C, M
						% Vaccine efficacy	57% (84%)	
						95% CI	45–66% (50–95%)	
Forrester et al. (47)	1979–1985	IC and CC	Denver Veterans Medical Center	U.S.	89	Bacteremia	—	A, B, C, D, E, J, H, K, P
Sims et al. (113)	1980–1986	CC	Five hospitals in Philadelphia	U.S.	122 (14.8)	+Culture (sterile body fluid)	—	B, C, E, K
						% Vaccine efficacy	70%	
						95% CI	36–86%§	
Simberkoff et al. (108)	1981–1985	RCT	Veterans Administration	U.S.	2,354 (30)	Bacteremia Pneumonia Bronchitis		A, D, N, M
						Relative risk	1.15 (0.90)	
						95% CI	0.89–1.48 (0.7–1.24)‖	
Koivula et al. (114)	1982–1985	PC	Varkaus	Finland	4,167 (13.1)	Pneumonia		A, N, E, H
						Odds ratio	1.66	
						95% CI	0.77–3.57	
Shapiro et al. (48)	1983–1990		Major hospitals, Connecticut	U.S.	1,054 (4.6)	+Culture (sterile body fluid)	—	A, C, D, N, P
		PC and IC				% Vaccine efficacy	56%	
						% Vaccine efficacy	48%	

*CC, case control; PC, prospective cohort; IC, indirect cohort; RCT, randomized control trial. †A, no or incomplete serological confirmation of infection, based on clinical diagnosis; B, methodology: use of survey, self-reporting, or not stated for diagnoses/vaccination status; C, referral: hospital nursing home–based cohort; D, bias: control group (lower incidence of bacteremia, risk stratification, and age than match cases); E, insufficient reporting of details to confirm details concerning patients with diabetes: odds ratio, relative risk, vaccine efficacy expressed for "high-risk" conditions; F, selection method: selection method–reporting of a convenience representative sample from cohort; G, selection method: nonrandom or without mention of selection technique for sample cohort of samples of serotyping; H, selection method: high incidence of other comorbid conditions (i.e., pulmonary, cardiac, liver, renal disease); I, selection method: health maintenance organization population; J, selection method: case finding was incomplete or had very small numbers of patients; K, incomplete medical record review: missing medical records; L, incomplete medical record review: administrative data set only without medical record validation; M, large number of cohort <18 years of age; N, testing 14-valent vaccine; P, no specific data concerning patients with diabetes. Not included is "% vaccine efficacy" (with 95% CI) given for a subgroup of patients with chronic disease, some with diabetes. §$P < 0.005$; ‖NS. CDC, Centers for Disease Control.

patient surveys for documentation of both diabetes diagnosis and vaccination, and assigning individuals who did not return surveys as "not vaccinated" are examples of bias that make interpretation of the last two studies (74,85) difficult. Because of the high incidence of the comorbid illnesses such as chronic respiratory conditions and congestive heart failure contributing to adverse outcomes, Nichol et al. (49) did not consider diabetes in their multivariate model of the cost-effectiveness of influenza vaccination. Strikas et al. (50) could not document a protective effect of influenza vaccination for high-risk patients (including diabetes) against influenza B during the years 1990–1991; however, this may have been due to poorly matched vaccines and lack of

significant disease (morbidity and mortality) from influenza during this study period. Finally, in many studies where vaccine effectiveness is described for subgroups of population cohorts, there is often a category of "metabolic diseases." While this category includes patients with diabetes, the additional comorbid conditions in this category (renal failure and hepatic insufficiency) make interpretation specifically for diabetes impossible (86).

Conclusion. Definitive proof of the efficacy of influenza vaccination specifically in people with diabetes is lacking. Studies that include diabetes as one of the at-risk patient groups, however, support immunization in this patient group. In particular, these same studies consistently support influenza vaccination when there are comorbid conditions with diabetes such as age and cardiovascular complications. In the limited studies that included a sufficient number of people with diabetes for statistical power (87), influenza immunization was effective in reducing hospital admissions during influenza epidemics.

PNEUMOCOCCUS

Clinical reports of infection

Pneumococcal pneumonia is the most common form of acute bacterial community-acquired pneumonia (88). Notwithstanding the prior discussions of influenza and diabetes in this article, the pneumococcus has been the organism most frequently associated with pneumonia in epidemic and nonepidemic influenza years (40,41,56,89). Pneumococcal infection has accounted for 48% of pneumonia in cases associated with the Hong Kong influenza epidemic period (1968–1969) and up to 62% in a nonepidemic control period (1967–1968) (40). Bacteremia is seen in 8–50% of individuals with pneumococcal infections, and of these, 15–20% are fatal despite antibiotics (19). This high case fatality rate from bacteremic pneumococcal disease supports the concept that a reduction in the number of deaths related to this infection can only be accomplished by widespread immunoprophylactic measures.

Not all agree that diabetes is a risk factor for pneumococcal disease. A retrospective survey of select referral clinics for people with diabetes did not support an increased risk (90). The number of patients with diabetes in other case series of pneumococcal infection has been as little as 1–3% in patient groups <50 years of age and 12–19% in older groups (16,91–95). Several reviews and series of pneumococcal bacteremia fail to mention individual patients with diabetes (96–100). These reports either failed to classify their patients according to chronic disease (96–98) or made no mention of diabetes among the chronic diseases listed for their patients (99,100).

Diabetes as well as increased age, an extrapulmonary site of pneumococcal infection, the presence of cirrhosis, alcoholism, azotemia, and infection with certain capsular types (such as type 3) appear to contribute the most to the risk of death from bacteremic pneumococcal disease (14,91,92, 94,101,102). Because age has such a strong impact on the frequency of diabetes reported in cohorts of bacteremic patients (102) and mortality in others (13–15,92–94,98,101–104), it is difficult to assess the impact of diabetes as an independent risk factor. Case fatality rates for children are typically low (94,97,100). Adults (<50 years of age) have reported fatality rates of 2.4% compared with 15% in patients >50 years of age (103). Some series have reported high fatality rates (up to 50%) with nosocomial pneumococcal bacteremia (93,95), whereas others have reported rates of 7–9% (16,94). In series reporting both high and low fatality rates, patients with diabetes have had a high incidence (20–29%) of nosocomial acquired infections (16,95).

Conclusion. Published studies support the fact that people with diabetes are at least as likely to be susceptible to pneumococcal infection as other patients with chronic disease. Many studies suggest that diabetes may be a unique risk factor for an increased incidence of bacteremia associated with this organism.

Vaccine immunogenicity

In 1983, a 23-valent vaccine replaced the original 14-valent vaccine first released in 1977 (45). Although antibody response to pneumococcal polysaccharides may proceed independent of T-cell–mediated help (22), vaccine efficacy has been questioned because of the potential for poor metabolic control to influence cellular immune response (delayed hypersensitivity and cytotoxic T-cell response) (22,23,67). Giebink et al. (20) reported that individuals with diabetes and complications such as nephrotic syndrome may have appropriate serological responses (e.g., type specific antibody responses of twofold over baseline, similar to normal control subjects, and a postvaccination geometric mean antibody concentration >300 ng/ml).

Vaccine effectiveness

There are few studies to assess the effectiveness of pneumococcal vaccine in people with diabetes. Although not specific to diabetes, efficacy for prevention of pneumococcal pneumonia was shown in randomized double-blind placebo-controlled clinical trials conducted among young, otherwise healthy individuals where the disease was endemic (e.g., South African gold miners and Air Force recruits) (105–107). Efficacy was not demonstrated in a clinical trial among U.S. veterans (50 years or older) with a variety of chronic disease, including 664 patients with diabetes (with relative risk of 0.8–1.92; 95% CI for vaccine suptypes) (108). This is the only randomized control trial published that allows examination of sufficient detail concerning patients with diabetes. However, significant limitations of this study included the use of the older 14-valent vaccine, problems with the clinical definition of nonbacteremic illness, infrequent bacteremic illness, and an extremely low statistical power to demonstrate efficacy (45,109). Because the U.S. population (even those with chronic illness) has a lower incidence of pneumococcal infection than the previously studied population groups, many have questioned the efficacy of this vaccine for many chronic diseases (107,108,110,111).

To overcome the problems of making a clinical diagnosis of nonbacteremic illness and the limited statistical power associated with studying only infection with associated bacteremia, Broome et al. (44) first advocated the use of indirect cohort analysis to compare the serotypes of isolates from pneumococcal infections in vaccinated and unvaccinated patients. Broome et al. also raised concerns about pneumococcal vaccine's efficacy in individuals with chronic disease; however, in their series of 35 patients (most of whom had splenectomy as an indication for vaccination), there was only one person with diabetes (44). In addition, vaccine efficacy would not have been expected in this individual with diabetes who had sepsis from an underlying nonvaccine serotype pneumococcal pneumonia.

Additional indirect cohort and case-control studies (Table 4) have shown vaccine efficacy to be 77–90% for prevention of invasive pneumococcal infection in patients with diabetes (44–48,108, 112–114). Despite the fact that the administration of the vaccine in these studies was according to the preferences of individual providers and patients during the course of clinical care, matching control subjects for comorbid conditions (in case-control

series) and logistical analysis for potentially confounding variables such as race, economic status, prior hospitalization, and prior receipt of immunization suggests that a systematic bias would have been an unlikely explanation to explain the authors' observations (48,112). Shapiro et al. (48) reported a prospective study over 6 years in an attempt to control for these biases and demonstrated vaccine efficacy in their case-control study and indirect cohort analysis. Additional reports demonstrate clinical efficacy in at-risk population groups, including groups where 4–15% of subjects had diabetes (113,114).

Forrester et al. (47) failed to demonstrate efficacy of the pneumococcal vaccine using both an indirect cohort and case-control design. Bias in this study included limiting the documentation of vaccination status to what was recorded only in the hospital record, missing medical records in 7% of the original cohort, 30% of cases having apparent nosocomial infections, and a higher incidence of bacteremia in cases compared with control subjects (18 vs. 7%). In addition, the analysis was limited to 89 patients of which 23% would be considered immune incompetent patients (e.g., having asplenia, dysglobulinemia, renal transplantation, nephrotic syndrome, hematological malignancies, and drug-induced immunosuppression). The "medium-risk patient group" (which included patients with diabetes) accounted for only 64% of the total cohort of patients. Independent of concerns regarding the power to detect vaccine efficacy in these patients, there were no specific details concerning the patients with diabetes. Because of these issues, it is not possible to draw conclusions about patients with diabetes.

It has been suggested that pneumococcal vaccine might be effective in preventing bacteremic pneumococcal disease but not other forms of pneumococcal infection (26). Although this could be unique to the vaccine, it might also be because of the difficulty in making a definitive clinical diagnosis of pneumococcal infection without documentation of bacteremia. Either explanation might account for lower efficacy rates in studies reporting nonbacteremic presentation of pneumococcal infection.

Conclusion. Many studies have shown that the vaccine is effective in reducing pneumococcal bacteremia, a common complication of pneumococcal infection with a high mortality rate (46,47,105,106,112). This efficacy alone supports its use in people with diabetes, despite the uncertainty of pneumococcal vaccine's efficacy in nonbacteremic illness.

VACCINE IMPLEMENTATION STRATEGIES — The ACIP recommends that individuals with diabetes receive at least one lifetime immunization with pneumococcal vaccine and annual influenza vaccinations (88,115). An immunization rate of at least 60% is a national health objective (116). The Health Care Financing Administration has encouraged collaboration on immunization quality improvement projects among health care plans and providers. Financial issues have been raised as a significant barrier in effective immunization (117). However, when countries have provided free immunization to targeted groups, this has not always translated into success (58). Despite coverage for the Medicare population, 65–80% of a hospitalized cohort (1994–1995) missed opportunities for influenza and pneumococcal vaccination (118). In this group of patients, 67% (95% CI 64.7–68.4) were identified as having at least one chronic condition (to include diabetes).

In the last 10 years, the concepts and tools of continuous quality improvement (CQI) have been used to improve compliance rates for preventive services, including immunization (119,120). Despite this effort, immunization rates remain unacceptably low, whereas systematic approaches to preventive services have become more and more complex. Improving immunization rates for people with diabetes is only part of the larger health system's difficulties in implementing preventive services and guidelines for management of chronic diseases. The number of overlapping CQI efforts can be overwhelming, even for the most motivated providers and patients. A user-friendly tracking system is essential to achieve successful prioritization, scheduling, and record keeping.

A number of paper and paper/computer databases have assisted in implementation strategies (10,121,122). Timely reporting to provider and patient is essential for success in using these implementation strategies (121). Previous hospitalization has been identified as a risk factor for subsequent serious influenza and pneumococcal infection (123–125). Based on the observation that hospitalization may be a marker for this increased risk, the ACIP and the American Hospital Association have encouraged obtaining vaccination histories from all inpatients and have suggested that vaccinations be implemented as part of prolonged admissions or discharge plans (88,115). Additional health system processes that have helped facilitate improved vaccination rates have included empowered nursing staff with standing orders to vaccinate, standardized information and documentation forms (paper and electronic), targeted educational efforts to patients and providers, special immunization programs throughout the year, notification, and mailings (126–133). Although case management has been used to improve immunization rates, the cost is significant (134). Targeting patients attending specialty clinics for diabetes care can provide a simple and effective method to provide routine immunization and monitoring without major systems reengineering. Although there are no reports regarding the value of influenza vaccination for the health care team, specifically in caring for people with diabetes, this should also be considered as part of a health systems approach to preventive services and is recommended by the ACIP.

Knowledge and attitudes of patients and providers as well as health system processes and barriers influence vaccination rates (126,135,136). Individuals who believe that influenza and pneumococcal disease are serious illnesses and vaccination is effective and safe are more likely to be immunized if they are advised to do so by their provider (6,126). Provider recommendation is a highly significant and independent predictor of successful immunization (126).

Conclusion

Provider recommendation is a cost-effective immunization implementation strategy. Health system processes and CQI can support the provider and patient in this and other effective implementation strategies. Although data collection and tracking appears essential in effective implementation strategies, targeting at-risk groups in subspecialty clinics and during hospitalizations can greatly simplify this process and translate into significant cost savings and the prevention of disease.

CONCLUSIONS — Individuals with diabetes have at least the same, if not increased, risk of influenza and pneumococcal infection as other patients with chronic diseases. In addition, patients with diabetes often have associated comorbid conditions that increase this risk. Certain aspects of their care and the acute and chronic complications of their disease appear to uniquely increase their risk for

these infections. While specific acquired and genetic defects in immune surveillance may increase the risks for infection and the lack of robust immune response to immunization, it appears that immunization in this at-risk patient population is effective. Effective implementation strategies for immunization in this patient population appear justified.

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