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Glycaemic control, antidiabetic medications and influenza vaccination coverage among patients with diabetes in Udine, Italy

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ABSTRACT

Objective The objectives of this study were to estimate influenza vaccination coverage among patients with diabetes mellitus in an Italian 250 000-inhabitant area in the 2017–2018 season and to assess whether glycaemic control and pharmacological treatment were associated with the likelihood of being vaccinated.

Design In this cross-sectional study, we analysed anonymous health administrative databases, linked with each other at the individual patient level through a stochastic key: diabetes mellitus registry, vaccinations, drug prescriptions and laboratory database.

Setting The study was conducted in the catchment area of the University Hospital of Udine ('the Udine area'), a 250 000-inhabitant area in the northeast of Italy.

Participants The study included all subjects included in the regional registry of patients with diabetes mellitus, living in the Udine area as of 1 October 2017.

Main outcome measures Vaccination coverage in the 2017–2018 influenza season was calculated. The association between patients' characteristics and the likelihood of being vaccinated was assessed through multivariate log binomial regression.

Result 53.0% of 15 900 patients with diabetes living in the area were vaccinated. Coverage increased with age, approaching 75% at ≥85 years. Patients lacking recent glycated haemoglobin testing were less likely to be vaccinated (43.4% vaccination coverage), as were those not treated pharmacologically (44.4% vaccination coverage). Patients treated with both insulin, metformin and other antidiabetic medications were more likely to be vaccinated than those treated with metformin alone (58.1% vaccination coverage; adjusted relative risk=1.07, 95% CI 1.01 to 1.14).

Conclusion Influenza vaccination coverage was suboptimal in this Italian population of patients with diabetes. Strategies to improve diabetes management could in turn positively affect influenza coverage.

INTRODUCTION

Seasonal influenza epidemic is caused by influenza viruses and affects every year 5%–15% of the world population,[1 2] accounting for 3–5 million annual cases of severe illness and 290 000–650 000 000 deaths, with an increasing trend.[3 4] In the 2017–2018 early influenza season, European Member States experienced increasing influenza activity with excess mortality in the elderly.[5] In the same season, Italy was among the European Countries with high or very high influenza intensity for 5 weeks or more.[6]

People older than 65 years, those with respiratory or chronic disease or those with an impaired immune system have a higher risk of developing severe influenza and related complications,[1] and the influenza annual epidemic represents a significant healthcare challenge for the 21st century, where multipathology is common.[7 8] The interaction between chronic diseases and influenza became evident after the 2009 H1N1 influenza pandemic.[9] Specifically, this pandemic highlighted that people with diabetes developed more severe influenza symptoms than people with no underlying medical condition.[7 10 11]

Diabetes mellitus affects 425 million people worldwide and 58 million in Europe with an increasing prevalence trend.[12] Deaths attributable to diabetes mellitus doubled in the 1990–2010 period and disability-adjusted life years increased by 30%.[1 13–15] Since diabetes mellitus is one of the chronic conditions associated with a worsened outcome of influenza, international public health organisations (WHO and Centers for Disease Control and Prevention) and national and international diabetes associations recommend annual influenza vaccination for persons with diabetes mellitus.[16]

Influenza may increase the risk of deep venous thrombosis and pulmonary embolism,[17] of both microvascular and macrovascular disease,[18] and even of cardiovascular diseases and myocardial infarction.[1 19] In addition, risk of developing vascular diseases, which is already increased in case of diabetes mellitus, may be worsened by procoagulant changes induced by influenza. It is also important to note that often subjects with diabetes have many other conditions that can affect the influenza severity. For example, approximately 90% of type 2 diabetes patients are overweight, and obesity is a known independent risk factor for severe influenza.[20] Furthermore hyperglycaemia can increase the incidence and severity of bacterial infections with an increasing risk of superinfections on viral episodes.[7] However, influenza virus infection can lead to hyperglycaemic episodes or to ketoacidosis in patients with diabetes.[21]

The Italian National Institute of Statistics reports that 5.3% of the Italian population has diabetes, corresponding to 3 million people.[22] The influenza vaccination is actively offered and free of charge to all of them as well as to other population groups who are at high risk of influenza-related complications or hospitalisations (all persons ≥65 years of age, women in the second or third pregnancy trimester at the beginning of the epidemic season or subjects 6 months–64 years of age suffering from other chronic diseases).[23]

During the 2017–2018 season, influenza vaccination coverage in Italy was 15.3% in the general population, with great variability depending on age group, from a minimum of approximately 2% in the paediatric population to 52.7% in the population ≥65 years of age,[24] for whom the vaccination is recommended.[25] The minimum goal set by the Italian Ministry of Health for the elderly population, that is, 75% coverage, was not met. The same goal was set for younger persons with diseases that increase the risk of influenza complications, like diabetes mellitus.[26]

Worldwide, influenza vaccine coverage in patients with diabetes is generally below the target of 75%, with variation by country. Greater severity of the disease was described as one of the factors associated with higher coverage, whereas the perception of not being at high risk is among the reasons for refusing the vaccine.[1] In the USA, the likelihood of vaccination among subjects with diabetes was higher in non-poor population groups and increased with age.[27]

In Italy, data on influenza vaccination coverage among patients with diabetes are limited to children with type 1 diabetes,[28] and there is no information on which subgroups of the overall diabetic population are less likely to be vaccinated.

This study was conducted to estimate the influenza vaccination coverage in the diabetic population living in 37 municipalities corresponding to the local health unit of the University Hospital of Udine, a 250 000-inhabitant area in the northeast of Italy and to assess whether age, latency from diagnosis, glycaemic control and type of pharmacological therapy are associated with the likelihood of receiving the vaccine.

METHODS

This cross-sectional study used the administrative databases of the University Hospital of Udine as the source of information. Those databases contain information on all the subjects living in the 37 municipalities of the local health unit of the University Hospital of Udine ('the Udine area'), are integrated in a repository storing completely anonymous data and can be deterministically linked with each other at the individual patient level through a univocal stochastic key. For the present study, the following databases were analysed: registry of patients with diabetes mellitus, vaccination database, drug prescription database and laboratory database.

The registry of patients with diabetes mellitus relies on the linkage of administrative data (hospital admissions, antidiabetic drug prescriptions and exemption from medical copayment) to identify cases of diabetes. The detailed algorithm and structure of the registry are described elsewhere.[29]

In short, a person is included in the registry if he or she fulfils at least one of the following criteria: (A) at least one hospitalisation with any discharge diagnosis ICD-9-CM 250, or (B) the prescription of at least three packages of antidiabetic medication (anatomical therapeutic chemical (ATC) codes A10A or A10B) in a 365-day period, or (C) an exemption from medical charges with exemption code of diabetes mellitus 013. In Italy, healthcare beneficiaries who are either in selected age groups or who have low income or chronic diseases receive free medications and outpatient specialist care. Specific codes are assigned by the Italian Ministry of Health to all the diseases that entitle patients to exemptions, including diabetes mellitus.[30]

All the prevalent diabetic subjects living in the Udine area as of 1 October 2017 were included in the analysis described in this article. The result of the most recent glycated haemoglobin (HbA1c) measurement in the 365 days before 1 October, if any, was abstracted from the laboratory database. Results expressed as % were converted into mmol/mol using the formula HbA1c (mmol/mol)=(HbA1c (%) − 2.15) × 10.929. HbA1c values were then categorised as <42 mmol/mol, <48 mmol/mol, <53 mmol/mol, <64 mmol/mol and ≥64 mmol/mol.[31] Antidiabetic medications prescribed in 2017, before 1 October, were abstracted from the prescription database, and patients were categorised into the following groups: no medications prescribed (NONE); insulin only (I); metformin only (M); other oral antidiabetic drugs only (O); insulin and metformin (IM); insulin and other oral antidiabetic medications (IO); metformin and other oral antidiabetic medications (MO); insulin, metoformin and other oral antidiabetic medications (IMO). Metformin was considered separately from the other oral drugs since it is the preferred initial pharmacologic agent for the treatment of type 2 diabetes.[32]

The latency from diagnosis has been calculated as the difference between vaccination date and diabetes incidence date for vaccinated patients and between 1 October 2017 and diabetes incidence date for the others. The latency has been categorised as ≤1 year, ≤5 years, ≤10 years and >10 years.

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The vaccination coverage was calculated overall and stratified by patient's sex, age category (<18, 18–64, 65–74, 75–84 and ≥85 years of age), glycaemic control category, prescribed medication category and latency from diagnosis category. Statistical significance of differences in coverage across groups of patients was tested through χ^2 tests. P values <0.05 were considered statistically significant. Multivariate log binomial regression analyses were conducted to evaluate the effect of each of the previously described variables on the likelihood of being vaccinated, adjusting for the potential mutual confounding of each variable on the others. The associations were shown as relative risks with 95% CI. The analyses were repeated after excluding subjects who died before 31 December 2017.

All the analyses were conducted using SAS V.9.4.

RESULTS

As of 1 October 2017, 15 900 patients with diabetes mellitus were living in the study area. Mean age was 69±14 years (median 71) and 54.1% were men. A percentage of 35.3 of patients had no HbA1c measurements in the previous 365 days; among the others, the mean HbA1c concentration in the most recent measurement was 56.1±13.6 mmol/mol (median 54). Overall, 53% of patients were vaccinated against influenza. Vaccination coverage in different groups of patients is shown in table 1.

Coverage increased with increasing age and with increasing latency from diagnosis and was lower among patients with no HbA1c measurement or medication prescriptions in the previous 365 days, whereas no significant difference was observed between males and females.

Table 2 shows the association between vaccination coverage and patient's characteristics, adjusting for the potential mutual confounding of each variable on the others. The associations observed in bivariate analyses were confirmed except for prescribed medications; in addition, a significant association with patient's sex emerged.

The results did not change after excluding 167 patients who died before 31 December 2017 (data not shown).

DISCUSSION

Influenza vaccination is recommended in patients with diabetes who are at high risk of developing severe disease and complications[7 10 11 21] and are often affected by multiple chronic conditions which, in turn, further increase the risk of severe influenza.[20]

In the pool of patients with diabetes living in the Udine area, northeast of Italy, influenza vaccine coverage during the 2017–2018 influenza season was overall lower than the 75% recommended proportion. Nonetheless, in all age subgroups, it was higher than age-specific coverage in the national general population.[24] In this area, vaccination likelihood in the diabetic population increased with increasing age, being around 70% in patients ≥75 years of age.

In the diabetic population <65 years of age, influenza vaccination coverage in the Udine area (34.6%) was lower than coverage described among patients with chronic medical conditions in other European Union (EU) countries, such as England (48.6: 2016–2017 season), Northern Ireland (56: 2017–2018 season) or France (39.1: 2015–2016 season) according to the European Centre for Disease Prevention and Control (ECDC) technical report.[33] Coverage in Udine was also lower than the one reported in the Netherlands for chronic patients <59 years of age (20.12 vs 32.7).[31] Conversely, coverage among the elderly was higher in Udine than in Norway (the only data reported), 62.1 versus 55.4 (2016–2017 season).[33]

Age is then an important factor that affects coverage. Possible reasons for lower coverage in younger patients may include lower disease awareness or a busier life, leading to a neglect sanitary self-care. In addition, the higher vaccination adherence in older patients may be an effect of the campaign addressed to the general population ≥65 years, so elderly patients with diabetes have a double reason to take in. It would be certainly interesting to understand the reasons for lower adherence in working-age patients with diabetes and to disentangle possible patient-related factors from those related to their doctors or to the local healthcare organisation. An ad hoc survey might be conducted to shed light on this issue.

Glycaemic control is another factor that was associated with influenza vaccination coverage in the literature. According to a Spanish study by Jiménez-Garcia *et al*, mean HbA1c was lower in patients who were vaccinated in 2013 than in the others.[16] In Udine, glycaemic control was associated with the likelihood of being vaccinated; however, the fact of having HbA1c monitored was more important than the actual HbA1c value. In fact, patients with HbA1c tested in the previous year were less likely to be vaccinated than patients who had at least one test, regardless of the test result. This suggests that factors such as patient's motivation to avoid unhealthiness or general practitioner's quality of patient care may be stronger determinants of vaccination than the actual success of glycaemic control. The belief of not belonging to a high-risk group may also characterise some patients with diabetes, who neglect both glycaemic monitoring and influenza vaccine.[1] The perception of being healthy, and thus at no risk of complications in case of influenza, may also influence patients who do not require their diabetes to be treated pharmacologically. In fact, patients who were prescribed no antidiabetic medications in 2017 were less likely to be vaccinated than those treated with metformin, the suggested initial medication for type 2 diabetes.[32]

However, compared with patients treated exclusively with metformin, those receiving insulin, metformin and other oral antidiabetic medications had higher vaccine coverage, indicating that patients with more severe disease may be more likely to be vaccinated, as shown by others.[34]

Table 1 Influenza vaccination coverage among patients with diabetes mellitus in the Italian area of Udine, from 1 October to 31 December 2017

	Influenza vaccination			
	No	Yes	Tot	
	N (%)	N (%)	N	P value
Sex				0.33
Female	3458 (47.4)	3837 (52.6)	7295	
Male	4012 (46.6)	4593 (53.4)	8605	
Age category (years)				<0.001
<18	73 (93.6)	5 (6.4)	78	
18–64	3583 (75.1)	1188 (24.9)	4771	
65–74	1696 (41.5)	2778 (58.5)	4747	
75–84	1380 (30.4)	3153 (69.6)	4533	
≥85	465 (26.3)	1306 (73.7)	1771	
HbA1c				<0.001
None in 365 days	3175 (56.6)	2434 (43.4)	5609	
<42 mmol/mol	412 (46.7)	471 (53.3)	883	
42–48 mmol/mol	759 (39.5)	1161 (60.5)	1920	
48–53 mmol/mol	749 (40.2)	1114 (59.8)	1863	
53–64 mmol/mol	1396 (40.9)	2019 (59.1)	3415	
≥64 mmol/mol	979 (44.3)	1231 (55.7)	2210	
Prescribed medications*				<0.001
None in 2017	2383 (55.6)	1904 (44.4)	4286	
I	786 (45.9)	925 (54.1)	1711	
M	2004 (45.6)	2388 (54.4)	4392	
O	359 (39.9)	541 (60.1)	900	
IM	320 (42.0)	442 (58.0)	762	
IO	90 (36.7)	155 (63.3)	245	
MO	1233 (42.5)	1666 (57.5)	2899	
IMO	295 (41.9)	409 (58.1)	704	
Latency from diagnosis				<0.001
≤1 year	948 (59.4)	648 (40.6)	1596	
>1 and ≤5 years	1718 (50.8)	1666 (49.2)	3384	
>5 and ≤10 years	2005 (48.9)	2093 (51.1)	4098	
>10 years	2799 (41.0)	4023 (59.0)	6822	
Total	7470 (47.0)	8430 (53.0)	15 900	

HbA1c, glycated haemoglobin; I, insulin only; IM, insulin and metformin; IMO, insulin, metformin and other oral antidiabetic medications; IO, insulin and other oral antidiabetic medications; M, metformin only; MO, metformin and other oral antidiabetic medications; O, other oral antidiabetic drugs only.

In addition, longer latency from diagnosis was associated with higher percentage of vaccinated patients. This might be explained by greater risk awareness in patients with long-lasting disease.

A study from Saudi Arabia showed that poor knowledge and illiteracy were associated with non-vaccination in patients with diabetes and that fear of vaccine side effects was the barrier most commonly reported by patients; however, advice by healthcare professionals was a frequently reported motivator.[35]

One limit of the present study is that only administrative databases were used as the source of information. Therefore, data on a number of factors that might have influenced the likelihood of being vaccinated are lacking (eg, patient's literacy, socioeconomic status and motivations). However, the use of administrative data is also one of the main strengths of this study: in fact, these databases allowed to study a very large patient population, with virtually complete identification of all cases of diabetes mellitus and of all vaccinations in the population living in

Table 2 Association between influenza vaccination coverage and patient's characteristics among patients with diabetes mellitus in the Italian area of Udine, from 1 October to 31 December 2017 (multivariate log binomial regression analysis)

	RR	95% CI	P value
Sex			
Female	1.00	–	–
Male	1.05	1.02 to 1.08	<0.001
Age category (years)			
<18	0.25	0.11 to 0.59	0.001
18–64	1.00	–	–
65–74	2.25	2.13 to 2.37	<0.001
75–84	2.64	2.50 to 2.78	<0.001
≥85	2.86	2.70 to 3.03	<0.001
HbA1c			
None in 365 days	1.00	–	–
<42 mmol/mol	1.15	1.08 to 1.22	<0.001
42–48 mmol/mol	1.21	1.16 to 1.26	<0.001
48–53 mmol/mol	1.19	1.14 to 1.24	<0.001
53–64 mmol/mol	1.15	1.11 to 1.20	<0.001
≥64 mmol/mol	1.11	1.06 to 1.17	<0.001
Prescribed medications			
None in 2017	0.94	0.91 to 0.98	0.004
I	1.02	0.98 to 1.07	0.35
M	1.00	–	–
O	0.96	0.91 to 1.01	0.14
IM	1.05	0.99 to 1.12	0.07
IO	0.98	0.90 to 1.08	0.75
MO	0.98	0.95 to 1.02	0.36
IMO	1.07	1.01 to 1.14	0.022
Latency from diagnosis			
≤1 year	1.00	–	–
>1 and ≤5 years	1.15	1.08 to 1.23	<0.001
>5 and≤10 years	1.13	1.06 to 1.20	<0.001
>10 years	1.21	1.15 to 1.29	<0.001

HbA1c, glycated haemoglobin; I, insulin only; IM, insulin and metformin; IMO, insulin, metformin and other oral antidiabetic medications; IO, insulin and other oral antidiabetic medications; M, metformin only; MO, metformin and other oral antidiabetic medications; O, other oral antidiabetic drugs only; RR, relative risk.

the 37 municipality of the local health unit of the University Hospital of Udine, avoided recall bias and made the use of laboratory and prescription data feasible. Administrative data are also the first data source for the ECDC overview report on vaccination coverage rates in EU/European Economic Area Member States.[33] Our study shows interesting data and features lacking in this reference report.

The finding that patients with diabetes with no recent HbA1c measurements are less likely to be vaccinated against influenza might even suggest the existence of subjects who actually have the disease (they either used antidiabetic medications, or received a hospital discharge diagnosis of diabetes, or were officially certified as diabetic to be exempted from medical copayments) without their doctor knowing it (and thus, neither prescribing HbA1c testing nor administering the influenza vaccine).

In Italy, both routine diabetes management and influenza vaccination for high-risk subjects are provided by family doctors at no cost for the patient. The beginning of the influenza season may be seen as an occasion for family doctors for offering the vaccine to patients with known high-risk conditions and for checking whether patients with diabetes are meeting their glycaemic targets or for actively contacting patients and updating their medical records, in particular patients in working age.

Despite there is some variability in influenza vaccination coverage across the Italian regions,[24] there are common patterns and time trends all over Italy.[24] Thus the vaccination coverage found among patients with diabetes in the Udine area may not be generalisable to the entire country. Nonetheless, it is reasonable to believe that also in the rest of Italy patients with diabetes are more vaccinated than the general population and that the factors associated with higher likelihood of vaccination are similar.

CONCLUSION

This Italian study showed that influenza vaccination coverage in the diabetic population is still suboptimal, although in the elderly, it approaches the minimum 75% target. Strengthening doctor–patient communication before the beginning of the influenza season might be one way to further improve both diabetes management and vaccination coverage in patients with diabetes, mostly in young ones. In addition, reasons for avoiding vaccination in this group of patients deserve investigation, so that strategies for active vaccination offer can be more effective. In particular, a well-managed and methodical communication strategy is highly encouraged in Italy to contrast antivaccination activities and misinformation coming from social and mass media.[36]

Key points

- The aims of this study were to estimate the influenza vaccination coverage among patients with diabetes mellitus in an Italian 250 000-inhabitant area in the 2017–2018 season and to assess whether there is an association between diabetes mellitus management and vaccination.
- Overall vaccination coverage was 53% and increased with age. Patients with recent glycated haemoglobin measurements, those with longer disease duration and those treated with both metformin, insulin and other antidiabetic medications were more likely to be vaccinated.
- Some groups of patients with diabetes, possibly unaware or unconcerned of their chronic condition, are less likely to be vaccinated against influenza. Proactive and intense follow-up of patients with diabetes by family doctors might both improve the management of diabetes and prevent complications such as influenza in these patients.

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Patient consent for publication Not required.

Ethics approval The authors assert that all of the procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and the Helsinki Declaration of 1975 as revised in 2008. This article does not contain any studies of human or animal subjects performed by any of the authors. Since this analysis was based on anonymous administrative data, patient informed consent and ethical committee approval were not required in Italy.

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