Multi-disciplinary Consensus Statement Document

Vaccinal prevention in adult patients with diabetes mellitus

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Keywords

Diabetic patients • Vaccinations

Introduction

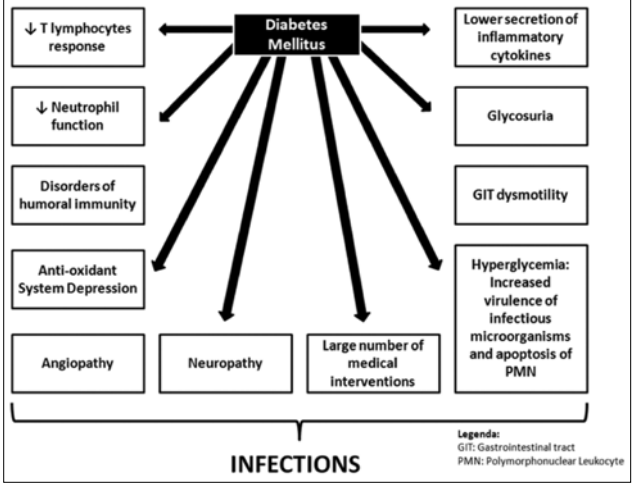
It is widely recognized diabetes represents a relevant public health issue worldwide, due to the remarkable social, economic and healthcare burden this disorder is responsible for, mainly through the development of chronic complications leading to increased morbidity and mortality in the affected individuals [1].
Diabetes-associated burden has been progressively becoming even more relevant, due to the overwhelming increase in the number of patients diagnosed with this disorder which has already attained the status of an epidemic condition, as demonstrated by the doubling of people living with diabetes observed over the last two years, reaching, overall, 415 million of individuals worldwide, in 2015 [2].
Notably, as reported by the International Diabetes Federation (IDF), such a trend is expected to continue over the next years, even to a greater extent, with estimates indicating a further increase in the number of subjects suffering from diabetes reaching 642 million by 2040 worldwide [2].

Increased likelihood of infections in diabetic patients

There's increasing body of evidence supporting diabetes leads to an increased risk of developing and dying from infectious diseases [3-5].
It has been shown that certain infectious diseases, such as influenza, not only are more likely to occur in diabetes patients, but may generally have a more severe course (e.g., higher incidence of complications) in this patient group [4].

In fact, as compared to subjects with normal glucose metabolism, diabetics have been shown a higher relative risk (RR) for infection-related adverse outcomes such as hospitalization [RR: 2.17 ($p < 0,0001$)] or death [RR: 1.92 ($p < 0,0001$)] [6].
Multiple mechanisms may account for the increased risk of infections in patients with diabetes (Fig. 1), most of them related to chronic hyperglycemia which may affect several physiological pathways involved in the immune response against pathogens which virulence also appear to be higher in diabetics [3-5].
It has been described that also comorbidities, such as obesity (which often affects diabetic subjects), may contribute to pose individuals with diabetes at increased risk of developing infectious diseases [3, 4, 6].

Fig. 1. Pathophysiology of infections associated with diabetes mellitus [3].



The major points of interest are:

- Diabetes is associated with an increased likelihood of infections [3-5].
- Multiple factors appear to be involved in diabetic patients' increased risk to infections [3-5].
- Infectious diseases' course is likely to be more severe in diabetics, with higher risk for hospitalization and death compared to euglycemic subjects [6].

Influenza infection in patients with diabetes

Susceptibility to & burden of influenza, and vaccination-related benefits

Influenza infection has been shown to affect patients with diabetes to a greater extent than it does with individuals with normal glucose homeostasis, as highlighted by available literature [3, 4].

Subjects with diabetes not only have an increased risk to develop influenza during winter season, but they're more likely to experience a more severe course of this infection, as compared to general population, with higher incidence of flu-related major adverse outcomes such as all-cause hospitalizations, intensive care unit admissions, and all-cause mortality, as well [7-9].

Notably, these findings have been reported not only in diabetic elderly patients, but also in younger diabetics, as well as in both subjects with type 1 and those with type 2 diabetes [7-9].

The higher risk for severe/complicated flu in diabetic patients has been reported not only by published studies, but arises also from real-life surveillance data from, for example, 2017-2018 flu season in Italy, where the majority of individuals either hospitalized at intensive care unit or died due to laboratory-confirmed influenza suffered from at least a chronic disorder such as diabetes, COPD, cardiovascular disease [10].

Importantly, these subjects were younger than 65 years, having a mean age of 60 years, therefore, for whom recommendations by health authorities and scientific societies to get vaccinated against flu derives from the presence of a chronic disease (e.g., diabetes), rather than their age [10-13].

The increased severity of seasonal flu seen in patients with diabetes may, at least partially, result from influenza-associated deleterious impact on cardiovascular system. In fact, as reported by a recently published study by Kwong et al., a relevant association between laboratory-confirmed influenza and the likelihood of acute myocardial infarction (AMI) occurrence after laboratory confirmation was found. Indeed, study subjects (half of whom suffered from diabetes) showed a six-fold increased risk to develop AMI within 7 days after confirmed influenza which, interestingly, was mainly driven by influenza B which accounted for a ten-fold increased risk of AMI, overall, whereas influenza A was associated with a five-fold increased risk, accordingly [14].

Several mechanisms have been hypothesized to account for such an increased risk to develop AMI following influenza infection, especially in at-high cardiovascular risk individuals such as diabetics [15]. These mechanisms – leading to a worsening of atherosclerotic process – include cytokine release during acute inflammation, atherosclerotic plaque damage, hypoxia, tachycardia, vasoconstriction (following sympathetic system activation), as well as a direct harmful effect by influenza virus on myocardial tissue (Fig. 2) [15].

Influenza vaccination has been shown to be beneficial to diabetic patients, as reported by available studies conducted in this at-risk group for flu-related complications [1]. Initial evidences supporting flu vaccination-induced benefits in subjects with diabetes came from a UK study performed by Colquhoun et al. that clearly demonstrated a relevant relative risk reduction (i.e., by 79%) in hospitalization due to influenza, pneumonia, bronchitis, as well as diabetic ketoacidosis and diabetes without complications, over two flu seasons [16]. Findings from Colquhoun's et al. study were consistent with results from more recently published studies which reported improved outcomes in diabetic subjects, across different age, after receiving flu vaccination [17, 18].

Accordingly, Vamos & Coll. found how influenza vaccination, administered to over 120,000 type 2 diabetes patients, resulted in a significant relative risk (RR) reduction in major outcomes such as hospitalization due to stroke (-30%) (RR: 0.70; 95% confidence interval [CI]: 0.53-0.91), heart failure (-22%) (RR: 0.78; 95% CI: 0.65-0.92), pneumonia or influenza (-15%) (RR: 0.85; 95%CI: 0.74-0.99), and all-cause mortality (-24%) (RR: 0.76; 95%CI: 0.65-0.83) [17].

It has been shown as also diabetic elderly patient, a widely represented sub-group in daily clinical practice, may really benefit from getting vaccinated against seasonal flu, as reported by Kuan Wang et al. who found significantly lower incidence of pneumonia, influenza, respiratory failure, as well as reduced risk for hospitalization, intensive care unit admission and death in vaccinated vs. not-vaccinated elderly subjects with diabetes [18].

Protection provided by flu vaccination against influenza virus-induced harmful impact (either direct or indirect) on myocardial tissue may account for the reported im-

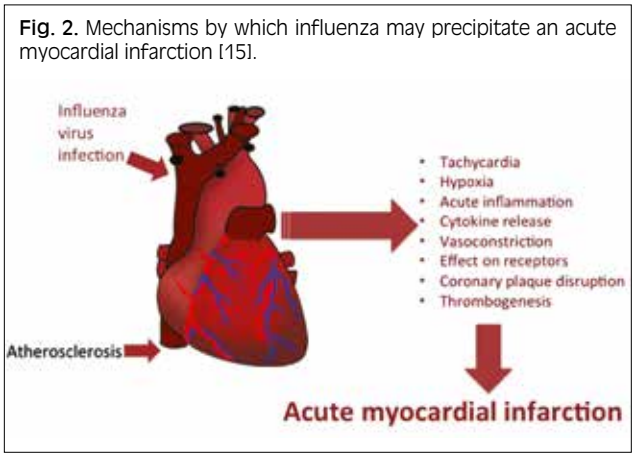


Fig. 2. Mechanisms by which influenza may precipitate an acute myocardial infarction [15].

Tab. I. Efficacy of accepted coronary interventions and influenza vaccine in the prevention of myocardial infarction [15].

Coronary intervention	Prevention	Intervention efficacy/ effectiveness against acute myocardial infarction (%)
Smoking cessation [4, 23-25]	Secondary	32-43
Statins [38]	Secondary	19-30
Antihypertensive drugs [26-29, 32]	Secondary	17-25
Influenza vaccine [5, 9, 18]	Secondary	15-45

provement of cardiovascular (CV) outcomes in patients with diabetes. This hypothesis may be supported by the flu vaccination's marked effectiveness in the secondary prevention of AMI occurrence in high CV-risk patients, which was similar to that reported by well-established CV preventive interventions such as smoking cessation, antihypertensive drugs, statins (Tab. I) [15].
It is important to point out as, although the above-mentioned impairment in the immune response seen in diabetic patients (accounting for their increased risk to experience severe flu), the latter have been shown to really benefit from receiving flu vaccination, being able to achieve an effective and sustained humoral immune response to flu vaccine, similar to that observed in subjects without diabetes [1, 19].

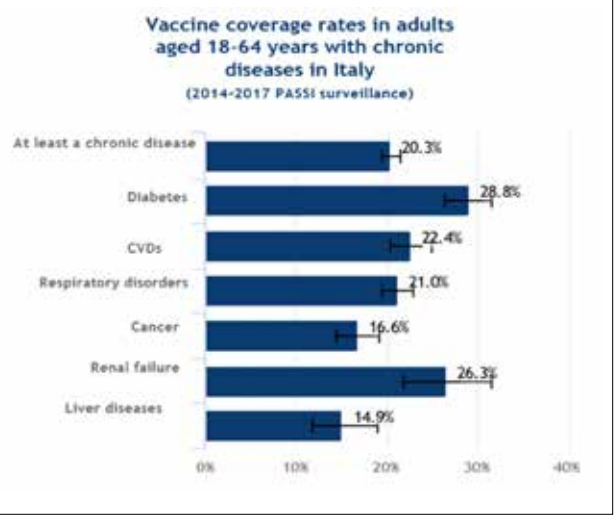
Recommendations by health authorities/ scientific societies and current coverage rates

Because of the flu-related relevant burden as well as well-established vaccination-associated benefits in diabetic subjects, both international and national bodies - such as the Italian Ministry of Health (MoH), and Diabetes Scientific Societies (i.e., AMD & SID) recommended that all individuals with diabetes (either type 1 or type 2) above 6 months of age would receive seasonal influenza vaccination to protect themselves against flu-associated adverse outcomes [11-13].
As reported in both the 2017-2019 National Immunization Plan (NIP) and Italian MoH's recommendations for 2018-2019 flu season, subjects with diabetes (as well as other chronic patients) will receive seasonal influenza vaccination via an active and free offer, being individuals at higher risk to develop flu-related morbidity and mortality [11, 12]. Both Italian MoH's 2018-2019 recommendations and 2017-2019 NIP recommend for patients with diabetes (and, in general, for those with chronic disorders) to achieve flu vaccination coverage rates of at least 75% (i.e., minimum recommended target), or, ideally, the value of 95% representing the optimal coverage goal for all at-risk individuals, regardless of their underlying disease [11, 12].
Nevertheless, despite influenza-associated burden and proven vaccination efficacy in improving major outcomes in diabetic patients aged 18-64 years, the current coverage rates in this patient group are still low (~29%), far away from the aforementioned MoH's recommended targets (Fig. 3) [12, 20].
Whereas, current influenza vaccination coverage rates in individuals with diabetes aged ≥ 65 years are unknown, so far (as other chronic conditions), since, to date, in Italy, for elderly people there's information only about the overall flu vaccination coverage rates (which were around 52% in 2016-2017 season), with no data available for each chronic disorder in this age group [12].

Patients' attitudes and/or barriers to flu vaccination

Patients' attitudes towards medical interventions - either therapeutic (i.e., pharmacological treatments) or preventive (i.e., vaccinations) - have been shown to play a key role to guarantee good patients' compliance, and therefore increase the likelihood that these interventions are successful.
Available literature has shown that multiple patient-related factors – including not being considered as at-risk individuals for flu-associated complications, fear of vaccine-associated side effects, low awareness/knowledge of vaccination-induced benefits – may account for influenza vaccination lower uptake among patients with diabetes [21].
On the other hand, advanced age, regular contacts with diabetes-treating physicians, more frequent visits at GP's office, higher number of previous influenza vaccinations, existing comorbidities (e.g., chronic respiratory disorders), longstanding diabetes, represented major factors associated with a higher likelihood to diabetic subjects to adhere to seasonal influenza vaccination [21, 22].
The above-mentioned findings highlight the critical role GPs and diabetes-treating physicians play to effectively promote influenza vaccination uptake among their diabetic patients [21, 22].
The key role played, in Italy, by both diabetes-treating physicians and GPs to promote diabetics' adherence to

Fig 3. Influenza vaccination coverage rates in patients with chronic disorders in Italy between 2014 and 2017 [20].



this vaccination has also resulted from an Italian-based research (published in 2017) carried out by Censis Institute, aiming at addressing knowledge/awareness, attitudes and behaviors of Italian people aged above 50 years with regard to influenza and the related vaccination [23]. The Censis research reported both influenza infection and flu vaccination were widely known by population involved, whereas less than 50% of the sample (i.e., 43%, overall) was aware of influenza-associated complications [23]. Moreover, this research clearly highlighted, according to 2016-2017 flu season data, that GPs play a key role, not only to administer flu vaccine, but also to actively promote patients/citizens' adherence to seasonal influenza vaccination (as reported by 63% of the interviewers) [23].

In summary the major points of interest are:

- Diabetic patients are more likely to experience severe influenza [3, 4].
- Diabetes confers an increased risk of acute myocardial infarction, admission to intensive care unit, as well as all-cause hospitalization and mortality following influenza infection [8, 9, 14].
- Vaccination against influenza results in improved outcomes in diabetics (including the elderly), leading to a reduced risk of hospitalization due to stroke, heart failure and flu/pneumonia, respiratory failure onset all-cause mortality [16, 18].
- Flu vaccination has been shown to be as effective as well-known CV preventive interventions to reduce the risk of acute myocardial infarction in high-CV risk patients [15].
- Although marked flu burden and established vaccination benefits, current coverage rates in diabetics < 65 years are less than 30% [8, 17, 20].
- 2017 Censis report and available literature have shown that advice from both diabetes-treating physicians and GPs are major factor to promote diabetic subjects' adherence to flu vaccination [21-23].

Pneumococcal infections in subjects with diabetes

Susceptibility to & impact of pneumococcal infections, and vaccination-associated benefits

Patients with diabetes have been shown to have a higher likelihood to experience pneumococcal-related infections such as pneumococcal pneumonia (1.4 fold increase) and pneumococcal invasive disease (1.4 to 1.6 fold increase), both responsible for increased rates of morbidity and mortality, as well as relevant costs for healthcare system [24, 25].

Hyperglycemia-induced deleterious effects on immune and/or pulmonary function has been hypothesized to account for diabetes patients' greater susceptibility to develop both pneumococcal pneumonia and pneumococcal invasive disease [24].

Notably, longstanding diabetes and poor glycemic control have been shown by available literature to account for an increased risk of hospitalization due to pneumococcal pneumonia in diabetic individuals [24].

A recently published retrospective Spanish study – including over 900,000 hospitalizations due to community acquired pneumonia (CAP), evaluated over 10 years – reported an increased incidence of hospitalizations, over this period, among diabetic patients compared with individuals with normal glucose metabolism [26].

Pneumococcal-associated diseases have been shown to be responsible for a high economic burden, with total direct costs of 3,7 billion of dollars yearly in U.S. adults aged > 50 years [11].

In this regard, the European Respiratory Society reported pneumonia-related costs to be higher than 10 billion of Euros within 51 European countries of WHO, with hospitalization-associated costs accounting for 6 billion of Euros yearly [11]. Because of the high clinical and economic burden of pneumococcal-related infections in diabetic patients, it is widely recognized the key role by pneumococcal vaccination to prevent pneumococcal infections-associated burden in these at-risk individuals.

Benefits associated with pneumococcal vaccination in diabetic patients have been reported by a randomized, placebo-controlled Dutch study, called *CAPiTA* (*Community-Acquired Pneumonia Immunization Trial in Adults*), which involved around 85,000 elderly subjects with chronic disorders (half of whom with diabetes) [25]. In fact, Suaya et al. showed 13-valent pneumococcal conjugate vaccine (PCV13) was associated with higher and sustained (over a 4-year period) efficacy than placebo in preventing both the first and all pneumococcal pneumonia episodes in subjects aged ≥ 65 years with chronic conditions, including diabetes [25].

Pneumococcal vaccination efficacy in diabetes patients has also been shown by a retrospective cohort study conducted in approximately 67,000 elderly subjects that, via assessing, across a 9-year period, the *Taiwanese National Health Insurance Research Database*, reported a reduced risk by 14% of pneumococcal invasive disease onset in the group who received 23-valent pneumococcal vaccine (PPV23) compared with the group not exposed to PPV23 [27].

Such a trial reported further benefits associated with Pneumococcal vaccination, since study subjects who received PPV23 experienced an improvement in – clinical and economic – outcomes such as hospitalization, respiratory failure, hospital stay and healthcare costs [27].

Importantly, it has been shown diabetes patients (including those aged ≥ 65 years) are able to mount a humoral immune response following pneumococcal vaccination which is similar (no significant differences detected) to that observed in subjects without diabetes, accounting for the ability to diabetic individuals to adequately respond to such a vaccination, thereby protecting themselves from Pneumococcal-associated diseases [28-30].

Notably, diabetic subjects who got vaccinated with pneumococcal vaccine showed similar safety profile to euglycemic individuals who received this vaccine [28].

Recommendations by health authorities/ scientific societies and current coverage rates

In Italy, both 2017-2019 NIP and 2018 AMD-SID Diabetes Mellitus Guidelines recommend patients with diabetes (either type 1 or type 2) to get vaccinated against pneumococcal-related infections [11-13]. In this regard, available recommendations state patients with diabetes should receive pneumococcal vaccination at least one time in their life, with a single revaccination for individuals aged > 64 years who got vaccinated > 5 years earlier [11-13].

Current NIP states pneumococcal vaccination should be administered all at once lifetime, in a single dose, either together with flu vaccination or not, and, in contrast to the latter, in any season of the year [11].

At this time, a relevant issue, in Italy, comes from the evidence of low pneumococcal vaccination coverage rates in patients with chronic disorders including diabetes which are far away from MoH's recommended target of 75%, although diabetics' increased likelihood to suffer from pneumococcal-related infections, as well as the well-established benefits associated with such a vaccination in these at-risk individuals [11, 31].

In fact, although In Italy pneumococcal vaccination coverage rates are not routinely collected, it has been reported these are quite low in the elderly, ranging from 0.7 to 50% across different regions [31].

Importantly, current NIP's objectives over 2017-2019 period include a progressive increase in pneumococcal vaccination coverage rates, with the goal to achieve MoH's recommended target of 75% in 2019 [11].

Patients' attitudes and/or barriers to pneumococcal vaccination

GPs' advice to diabetic subjects to get vaccinated against pneumococcal-related infections has been shown to represent a major predictive factor for this patient group to adhere to pneumococcal vaccination [32, 33]. In contrast, diabetic patients' reduced awareness/knowledge about vaccination recommendations, as well as concerns (from both patients' and physicians' side) about pneumococcal vaccination-associated potential side effects have been shown to represent relevant factors accounting for the reduced uptake of this vaccination in such individuals [32, 33].

In summary the major points of interest are:

- Diabetic patients are more likely to develop pneumococcal pneumonia and invasive disease, as well as their complications [24, 25].
- Hyperglycemia-associated harmful effects on immune and/or pulmonary function has been hypothesized to account for diabetics' greater likelihood to develop pneumococcal-related infections [24].
- Both MoH and scientific societies recommend pneumococcal vaccination in diabetics [11, 13].
- Influenza vaccination has been shown effective in diabetic patients, resulting in reduced risk of pneumonia, hospitalizations, respiratory failure, as well as shortening hospital stay [25, 27].
- In Italy, although vaccination-associated benefits and available recommendations, pneumococcal vaccination coverage rates in diabetic subjects are below MoH's established target of 75% [11, 31].
- Recommendations by GPs to diabetics to receive pneumococcal vaccination and vaccine-associated safety concerns by patients/HCPs represent major promoting and limiting factors, respectively, to diabetic patients' adherence to this vaccination [32, 33].

Herpes Zoster (HZ) in patients with diabetes

Susceptibility to HZ infection

Recently published studies reported diabetes represents a major risk factor for the development of HZ infection and its severe complication, namely the post-herpetic neuralgia (PHN) [5].

The current NIP recommends diabetes patients to get vaccinated also against herpes zoster (HZ) infection [11].

In Italy, vaccination against HZ is recommended and provided freely not only to people ≥ 65 years, but also to individuals suffering from chronic disorders such as diabetes mellitus [11].

Accordingly, a meta-analysis, conducted in the U.S., and based on 62 trials, reported patients with diabetes (especially those with type 2 diabetes [T2DM]) had an increased risk (by 30%) to develop HZ infection [34].

Another study (which was observational in the design) conducted in the U.S. showed diabetic patients were more likely to suffer from both HZ and PHN, which incidences were increased, as compared to individuals without diabetes, by 78% and 50%, respectively [35].

Consistent with findings from aforementioned trials, Weitzman's et al. retrospective cohort study, found HZ infection and PHN were associated with some risk factors including diabetes [36]. Moreover, it has been estimated each year in the U.S. that 13% of all cases of HZ occurred in subjects with diabetes the latter has also been shown to be associated with an increased severity of HZ infection course [5, 35].

Notably, it has been shown type 1 diabetes (T1MD), and not only T2DM, would represent a risk factor for HZ occurrence, as well as this infection would be more common in women and elderly diabetic individuals and also in patients with diabetic vascular complications [5].

HZ infection-related impact and vaccination-induced benefits

Diabetes subjects, in addition to being at higher risk of developing PHN, have also been shown, as compared to subjects without diabetes, to experience increased severity and persistence of PHN, the latter known to negatively affect diabetic patients' quality of life [5].

Importantly, HZ infection has also been shown to negatively affect diabetics' glycemic control, as well as increase healthcare resource utilization in this patient group, due to the higher number of outpatient visits, hos-

pitalizations, antiviral medications usage, loss of working days [5].
Based on above-mentioned data, prevention of HZ infection and PHN episodes in subjects with diabetes represent a key goal in these at-risk individuals and lies on the chance of providing such subjects with vaccination against HZ infection [5, 11].
To date, in Italy, anti-HZ vaccination is based on a marketed live attenuated vaccine, while in the future, a new, recombinant adjuvated vaccine, recently approved in Europe, and already employed in the U.S. for eligible individuals (including those with diabetes), would be made available also in Italy and in other EU countries [5].

Recommendations by health authorities/ scientific societies and current coverage rates

Although the relevant – clinical, social and economic – burden of HZ infection in patients with diabetes, as well as the proven benefits resulting from the related vaccination, the current coverage rates are still low in these high-risk subjects [5].
In Italy, vaccination against HZ infection is currently recommended in individuals with diabetes by, both 2017-2019 NIP and 2018 AMD-SID Diabetes Mellitus Guidelines [11, 13].
According to the current NIP, vaccination against HZ infection is recommended, and – actively and freely –offered (in addition to elderly individuals) to subjects aged ≥ 50 years suffering from chronic disorders such diabetes [11].
The current NIP has issued, over 2017-2019 period, the objective of a progressive increase in HZ-related vaccination coverage rates, in order to reach, in 2019, the MoH's recommended target of 50% [11].
In summary the major points of interest are:

- Diabetes represents a major risk factor for the onset of both HZ infection and PHN [5].
- Diabetes is responsible for a more severe clinical course of HZ infection [5].
- Diabetic patients show higher persistence and severity of PHN compared to subjects without diabetes [5].
- HZ infection has been shown to worsen diabetics' glycemic control and quality of life, as well as to increase related healthcare costs [5].
- Vaccination against HZ infection is recommended by both MoH and diabetes scientific societies, and is offered freely also to diabetic subjects aged > 50 years, with the goal of a progressive increase in vaccination coverage rates across 2017-2019 [11, 13].

Other vaccinations recommended in diabetic individuals

Anti-meningococcal disease

Current NIP's recommended vaccinations in diabetics also include meningococcal vaccination, to T1DM patients [11].
In this regard, NIP states subjects with certain diseases are more likely to develop meningococcal invasive infection; therefore, immunization through meningococcal conjugated vaccine is recommended in patients suffering from disorders such as T1DM [11].
Notably, the recommendation to diabetics to receive meningococcal vaccination has been included, for the first time, in 2018 AMD-SID Diabetes Mellitus Guidelines recommending meningococcal vaccinations to all subjects with T1DM [13].

Anti-Diphteria-tetanus-pertussis (dTp)

Vaccination against diphtheria, tetanus and pertussis (dTp) is also included in 2017-2019 NIP and provided (via an active offer) as a ten-year booster, and through an adult-based dosage [11].
Although current NIP doesn't specifically refer to diabetic patients while addressing anti-dTp vaccination, in contrast to the CDC (*Centers for Disease Control and Prevention*) which specifically refers to diabetics among individuals for whom such a vaccination is recommended, it is clear that current NIP-reported recipients (those aged 19-64 years) to anti-dTp vaccination also include patients with diabetes for whom this vaccination is recommended due to their increased likelihood to develop severe infections [3-5, 11, 37].

Scientific societies' recommendations about adult diabetic subject-related vaccinations

To actively promote vaccinations included in the national vaccine calendar approved by the Italian Ministry of Health, represents a deontology obligation for each Physician (Italian Ministry of Health circular. March 9, 2017. Operational aspects for the complete and consistent implementation of the 2017-2019 National Immunization Plan and the related Vaccine Calendar).
These recommendations include:

- Flu vaccination to be systematically offered by GPs to their diabetic subjects, together with also during the influenza campaign, pneumococcal vaccination (if possible and available) to diabetic individuals.
- Systematic counseling carried out by GPs to diabetic patients regarding influenza and pneumococcal vaccinations, together with, at any time, the evaluation of anti-tetanus vaccination coverage, as well as advice provided towards anti-HZ vaccination. Moreover, assessment of meningococcal vaccination coverage to be implemented in adults with type 1 diabetes.
- Diabetes-treating physicians and GPs, during the collection of patients' history, should systematically assess and report within medical records, diabetic patients' vaccinal status regarding the following vaccinations:
  - anti-flu;
  - anti-pneumococcal;
  - anti-diphtheria- tetanus-pertussis (dTp);
  - anti-herpes zoster (HZ);
  - anti-meningococcal (T1DM patients).
- Systematic vaccination counseling performed by diabetes-treating physicians, together with reporting, within either outpatient visit-associated documentation or hospital discharge-related letter (to be provid-

ed to diabetic patients) recommendations to receive the following vaccinations:
- anti-flu;
- anti-pneumococcal;
- anti-dTp;
- anti-HZ;
- anti-meningococcal (T1DM patients).

- Diabetes-treating physicians should attend educational events, organized by the related Scientific Societies, addressing the topic of vaccinations in adult patients with diabetes, in order to increase their knowledge & awareness about this matter.

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Conflict of interest statement

The topic addressed in this article by the authors (on behalf of their scientific societies) has already been addressed by the same authors (on behalf of their scientific societies) in another article comprising similar contents which has already been submitted to another journal.

Authors' contributions

All Authors have made a substantial contribution to the drafting of the article. All Authors approve the final version submitted to the Journal of Preventive Medicine and Hygiene.

References

[1] Dos Santos G, Halima T, Bekkat-Berkani. Immunogenicity, safety, and effectiveness of seasonal influenza vaccination in patients with diabetes mellitus: a systematic review. Hum Vaccin Immunother 2018;14(8):1853-66.

[2] Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabet Med 1997;14 Suppl. 5:S1-85.

[3] Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: a review of pathogenesis. Indian Journal of Endocrinol Metab 2012;16 Suppl. 1:S27-36.

[4] Goeijenbier M, van Sloten TT, Slobbe L, Mathieu C, van Genderen P, Beyer Walter EP, Osterhaus ADME. Benefits of flu vaccination for persons with diabetes mellitus: a review. Vaccine 2017;35(38):5095-101.

[5] Papagianni M, Metallidis S, Konstantinos Tziomalos T. Herpes Zoster and diabetes mellitus: a review. Diabetes Ther 2018;9(2):545-50.

[6] Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 2003;26(2):510-3.

[7] Lau D, Eurich DT, Majumdar SR, Katz A, Johnson JA. Working-age adults with diabetes experience greater susceptibility to seasonal influenza: a population-based cohort study. Diabetologia 2014;57:690-8.

[8] Allard R, Leclerc P, Tremblay C, Tannenbaum TN. Diabetes and the severity of pandemic influenza A (H1N1) infection. Diabetes Care 2010;33(7):1491-3.

[9] Mertz D, Hyong Kim T, Johnstone J, Lam PP, Science M, Kuster SP, Fadei SA,Tran D, Fernandez D, Bhatnagar N, Loeb M. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ 2013;347:f5061.

[10] Istituto Superiore di Sanità. Monitoraggio dell'andamento delle forme gravi e complicate di influenza confermata (2017-18). Available at http://www.epicentro.iss.it/problemi/influenza/FluNews/FluNews_2018-17.pdf [Accessed on 10 October, 2018].

[11] Piano Nazionale Prevenzione Vaccinale (PNPV) 2017-19. 18-2-2017. Available at http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf [Accessed on 10 October, 2018].

[12] Ministero della Salute. Direzione Generale della Prevenzione Sanitaria. Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2018-2019. Available at http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2018&codLeg=64381&parte=1%20&serie=null [Accessed on 10 October, 2018].

[13] AMD e SID: Standard Italiani per la Cura del Diabete Mellito 2018. Available at http://aemmedi.it/wp-content/uploads/2009/06/AMD-Standard-unico1.pdf [Accessed on 10 October, 2018].

[14] Kwong JC, Schwartz, KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, Katz K, Ko DT, McGeer AJ, McNally D, Richardson DC, Rosella LC, Simor A, Smieja M, Zahariadis G, Gubbay JB. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med 2018;378(4):345-53.

[15] MacIntyre CR, Mahimbo A, Moa AM, Barnes M. Influenza vaccine as a coronary intervention for prevention of myocardial infarction. Heart 2016;102(24):1953-6.

[16] Colquhoun AJ, Nicholson KJ, Botha JL, Raymond NT. Effectiveness of influenza vaccine in reducing hospital admissions in people with diabetes. Epidemiol Infect 1997;119(3):335-41.

[17] Vamos EP, Pape UJ, Curcin V, Harris MJ, Valabhji J, Majeed A, Millett C. Effectiveness of the influenza vaccine in preventing admission to hospital and death in people with type 2 diabetes. CMAJ 2016;188(14):E342-E351.

[18] Wang IK, Lin CL, Chang YC, Lin PC, Liang CC, Liu YL, Chang CT, Yen TH, Huang CC, Sung FC. Effectiveness of influenza vaccination in elderly diabetic patients: a retrospective cohort study. Vaccine 2013;31(4):718-24.

[19] Sheridan PA, Paich HA, Handy J, Karlsson EA, Schultz-Cherry S, Hudgens M, Weir S, Noah T, and Beck MA. The antibody response to influenza vaccination is not impaired in type 2 diabetics. Vaccine 2015;33(29):3306-13.

[20] Sistema Sorveglianza PASSI. Coperture vaccinali antinfluenzale malati cronici adulti (18-64 anni). Available at www.epicentro.iss.it/passi/dati/VaccinazioneAntinfluenzale.asp [Accessed on 10 October, 2010].

[21] Jiménez-Garcia R, Lopez-de-Andres A, Hernandez-Barrera V, Gómez-Campelo P, San Andrés-Rebollo FJ, de Burgos-Lunar C, Cárdenas-Valladolid J, Abánades-Herranz JC, Salinero-Fort MA. Influenza vaccination in people with type 2 diabetes, coverage, predictors of uptake, and perceptions. Result of the MADIABETES cohort a 7 years follow up study. Vaccine 2017;35(1):101-108.

[22] Verger P, Cortaredona S, Pulcini C, Casanova L, Peretti-Watel P, and Launay O. Characteristics of patients and physicians correlated with regular influenza vaccination in patients treated for type 2 diabetes: a follow-up study from 2008 to 2011 in southeastern France. Clin Microbiol Infect 2015;21(10):930.e1-9.

[23] 2017 Censis report: la vaccinazione antinfluenzale nel nuovo assetto demografico. http://www.censis.it/7?shadow_comunicato_stampa=121133

[24] Torres A, Blasi F, Dartois N, Akova M. Which individuals are

at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. Thorax 2015;70(10):984-9.

[25] Suaya JA, Jiang Q, Scott DA, Gruber WC, Webber C, Schmoele-Thoma B, Hall-Murray CK, Jodar L, Isturiz RE. Post hoc analysis of the efficacy of the 13-valent pneumococcal conjugate vaccine against vaccine-type community-acquired pneumonia in at-risk older adults. Vaccine 2018;36(11):1477-1483.

[26] Lopez-de-Andres A, de Miguel-Díez J, Jiménez-Trujillo I, Hernández-Barrera V, de Miguel-Yanes JM, Méndez-Bailón M, Pérez-Farinós N, Salinero-Fort MA, Jiménez-García R. Hospitalisation with community acquired pneumonia among patients with type 2 diabetes: an observational population-based study in Spain from 2004 to 2013. BMJ Open 2017;7(1):e013097.

[27] Kuo CS, Lu CW, Chang YK, Yang KC, Hung SH, Yang MC, Chang HH, Huang CT, Hsu CC, Huang KC. Effectiveness of 23-valent pneumococcal polysaccharide vaccine on diabetic elderly. Medicine (Baltimore) 2016;95(26):e4064.

[28] Beam TR Jr, Crigler ED, Goldman JK, Schiffman G. Antibody response to polyvalent polysaccharide vaccine in diabetics. JAMA 1980;244(23):2621-4.

[29] Friedman EA, Beyer MM, Hirsch SR, Schiffman G. Intact antibody response to pneumococcal capsular polysaccharide in uremia and diabetes. JAMA 1980;244(20):2310-1.

[30] Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbio 1999;26(3-4):259-65.

[31] Blasi F, Aliberti S, Bonanni P, Mantero M, Odone A, Signorelli C. Pneumococcal vaccination in adults: recommendations from the Italian Society of Respiratory Medicine (SIMeR) and the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI). Epidemiol Prev 2014;38(6 Suppl 2):147-51.

[32] Clancy U, Moran I, Tuthill A. Prevalence and predictors of influenza and pneumococcal vaccine uptake in patients with diabetes. Ir Med J 2012;105(9):298-300.

[33] Alvarez CE, Clichici L, Patricia Guzmán-Libreros A, Navarro-Francés M, Ena J. Survey of vaccination practices in patients with diabetes: a report examining patient and provider perceptions and barriers. J Clin Transl Endocrinol 2017;9:15-7.

[34] Kawai K, Yawn BP. Risk factors for herpes zoster: a systematic review and meta-analysis. Mayo Clin Proc 2017;92(12):1806-21.

[35] Suaya JA, Chen SY, Li Q, Burstin SJ, Levin MJ. Incidence of herpes zoster and persistent post-zoster pain in adults with or without diabetes in the United States. Open Forum Infect Dis 2014;1(2):ofu049.

[36] Weitzman D, Shavit O, Stein M, Cohen R, Chodick G, Shalev V. A population based study of the epidemiology of Herpes Zoster and its complications. J Infect 2013;67(5):463-9.

[37] Centers for Disease Control and prevention (CDC). Seasonal Influenza (Flu). Available at https://www.cdc.gov/flu/diabetes/index.htm [Accessed on 10 October, 2018].

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