Benefits of flu vaccination for persons with diabetes mellitus

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Review

Benefits of flu vaccination for persons with diabetes mellitus: A review

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ABSTRACT

Diabetes mellitus imposes a significant and increasing burden on society, with major consequences for human health, welfare and the economy worldwide. Persons with diabetes mellitus are at increased risk of developing severe complications after influenza virus infection and guidelines advise vaccination. The present evidence for influenza vaccine effectiveness in persons with diabetes mellitus is mainly based on observational studies with clinical endpoints like hospitalization and death, indicating a beneficial reduction of morbidity and mortality. Further supportive evidence comes from serological studies, in which persons with diabetes mellitus usually develop similar antibody levels after vaccination as healthy people. Observational studies may be prone to selection bias, and serological studies may not completely mirror vaccine effectiveness in the field. Although more controlled trials in persons with diabetes mellitus with laboratory-confirmed, influenza-specific outcomes would be desirable to better estimate the effect of vaccination, the currently available data justify routine influenza vaccination in persons with diabetes mellitus. As in this risk group, the use of influenza vaccine is far below target worldwide, efforts should be made to increase vaccination coverage.

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1. Introduction

Worldwide, about 382 million individuals suffer from diabetes mellitus [1]. According to the 2010 Global Burden of Disease studies, the number of deaths attributed to diabetes mellitus doubled in the period from 1990 to 2010, with a 30% increase in disability-adjusted life years (DALYs) [2–4]. Since the 1990s, most projections

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had fallen short of these figures and new predictions anticipate that the number of persons with diabetes mellitus will reach almost 600 million by 2035 [1,5]. These predictions appear conservative in view of the estimated 300 million people already demonstrating impaired glucose tolerance, and thus at risk for developing diabetes [6]. The global burden of diabetes mellitus is heavier in developing than in developed countries, with about 80% of diabetic persons currently living in low- and middle-income countries and communities, with hardest-hit regions in Asia and the Middle East [1].

A range of diabetes mellitus disorders have been described, and although most cases fall into two broad etio-pathogenetic categories (Box 1), diabetes mellitus is increasingly recognized as a highly heterogeneous disease entity influenced by genetic, epigenetic, behavioral and environmental factors. Type 1 diabetes, accounting for 5% of diabetes mellitus cases, is characterized by autoimmune β -cell destruction, eventually leading to insulin deficiency [7]. The autoimmune destruction of β cells has multiple genetic predispositions but is also associated with environmental factors that are still poorly understood. The disease is particularly prevalent in the non-Hispanic white population, starting in childhood and adolescence. Type 2 diabetes mellitus accounts for 90–95% of diabetes mellitus cases [8]. The pathophysiology of diabetes mellitus type 2 ranges from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance [7]. It is strongly associated with obesity, with the distribution of ectopic fat representing a likely link between obesity and diabetes mellitus type 2 [9]. The intrauterine environment, early life events and epigenetic factors also are increasingly recognized as determining factors in the onset of diabetes mellitus type 2 in adult life [1,10]. Thus, diabetes mellitus type 2 is a polygenetic disease, and many aspects of its pathophysiology are still unknown. In the USA, it is more frequently seen in individuals of African-American, Hispanic, Asian-Pacific-Islander and American-Indian origins [8].

Box 1 The main types of diabetes mellitus.

Diabetes mellitus type 1 is an autoimmune disorder with a selective destruction of the insulin-producing beta-cell in the pancreas, leading to insulin dependence of survival. Autoantibodies against pancreatic insulin-producing islet β cell antigens like insulin, glutamic acid decarboxylase (GAD), insulinoma-associated protein 2, tyrosine phosphatase, or zinc transporter [8] are mostly present. More frequently developing in children, type 1 diabetes may nonetheless become manifest at any age. Diabetes mellitus type 2 usually develops in adults, yet is increasingly observed in children, and results from a combination of insulin resistance and insufficient insulin secretion by β -cells in the pancreas (β -cell dysfunction). Different types of maturity-onset diabetes of the young (MODY) have been described as specific, usually inherited, genetic (autosomal) defects impairing insulin secretion by the pancreatic β cells. Diabetes is increasingly recognized as a highly heterogeneous disease, with diabetes mellitus type 1 and type 2 probably representing extremes of a range of diabetic disorders and hybrid forms of diabetes, all influenced by genetic, epigenetic, behavioral and environmental factors. In type 2 diabetes, obesity and dyslipidemia are linked with chronic activation of the innate immune system being at the basis for eventual insulin resistance. This central part in diabetes mellitus type 2 pathogenesis seems to further play a role in dysregulation of metabolic, vascular, and inflammatory pathways [13]. Hybrid forms of diabetes include the combination of insulin resistance (type 2) and pancreatic autoantibodies (type 1), and latent autoimmune diabetes in adults (LADA) [9].

Seasonal influenza is caused by influenza A or B viruses and affects every year 5–15% of the human population worldwide [11]. Severity of infection and disease is largely depending on immune and health status of the infected individual. Most seasonal influenza virus infections are associated with mild and self-limiting respiratory complaints, and most patients do not seek medical care. However, influenza can be aggravated by complications (as discussed later), predominantly in older persons or those with co-morbidities [11]. For instance, large epidemiological studies have demonstrated that people above the age of 65, those with pulmonary disease or those with an impaired immune system have a higher risk of developing severe influenza and its complications. Diabetes mellitus has been associated with a worsened outcome of influenza. Therefore, annual influenza vaccination is recommended for individuals with diabetes mellitus by the World Health Organization, the Centers for Disease Control and Prevention, the European Union, and many national and international diabetes associations [12].

Influenza virus infection increases the risk of deep venous thrombosis and pulmonary embolism [14]. Furthermore, influenza virus infection may lead to both microvascular and macrovascular disease [15]. For instance, epidemiological studies suggest that influenza infection is associated with an increased risk of cardiovascular diseases, including myocardial infarction [15,16]. Experimental animal models of influenza virus infection demonstrate hemostatic alterations both at the circulatory and at the tissue level upon influenza virus infection [17]. Pro-coagulant changes potentially resulting from influenza virus infection may well add up to the already increased risk of developing vascular disease in persons with diabetes mellitus.

With the fast-growing number of persons with diabetes mellitus worldwide and inconsistencies in national guidelines and advices concerning influenza vaccination, we aimed to review the available literature on diabetes mellitus and its impact on influenza virus infection, influenza virus vaccination and potential policy implications. We conducted a PUBMED/MEDLINE search for a combination of the Mesh Terms “Influenza virus” and “diabetes mellitus”. In addition, we gathered information from national guidelines and recommendations from CDC, ECDC, PAHO and WHO regarding influenza prevention and management in risk groups. The comparison and evaluation of the results of these searches in the light of published knowledge in the fields of influenza prevention and management, allowed us to present this comprehensive review.

2. Diabetes, infections and complications

Establishing whether diabetes mellitus (type 1 or type 2) is a risk factor for higher susceptibility to, or for a more severe outcome of viral, bacterial and fungal infections, has been attempted through prospective and retrospective studies. However, these have not resulted in definitive evidence—and sometimes generated even conflicting data—for the association between diabetes and the incidence and/or severity of infectious diseases as co-morbidities. Both selection and confounding bias may have distorted the observed associations. Many studies did not distinguish between type 1 and/or type 2 diabetes mellitus. The presence of chronic vascular and/or renal complications, and the chronic inflammatory condition characterizing persons with diabetes mellitus, further complicate the interpretation of observed higher infection-related mortality or morbidity rates in diabetes mellitus than in non-diabetes mellitus patients when co-morbidity is not taken into account [18]. Furthermore, it has been suggested that concomitant conditions such as obesity, but not necessarily diabetes mellitus itself, increase the risk of dying from the infection [19]. Nonetheless, it is generally accepted that diabetes mellitus is associated

with greater incidence of certain infections or with increased disease severity and/or more frequent complications.

Diabetes mellitus was shown to be a risk factor for premature death due to several infections [20]. Hazard ratios for death reached 1.9–2.9 for infections (excluding pneumonia) and 1.4–1.9 for pneumonia. Diabetes mellitus is a frequent underlying condition in patients with community-acquired pneumonia, typically associated with an increased severity and recurrence of the disease [21]. Altered lung functions resulting from both structural and functional changes associated with diabetes, may affect microbial clearance mechanisms leading to a higher risk of infection [21]. An interesting example comes from the tuberculosis field. The association of diabetes mellitus and re-emerging tuberculosis has lately been documented with adjusted odds ratios reaching 3 to 6 [21,22]. Tuberculosis tends to be more severe, with higher incidence of multidrug resistance in persons with diabetes mellitus and especially in those with poorly controlled diabetes mellitus. It is feared that diabetes mellitus will threaten the control of tuberculosis globally [22]. Likewise, in a Taiwanese cohort study of 17,715 individuals, diabetes in general and treated diabetes in particular were significantly associated with tuberculosis with adjusted hazard ratios of 2.09 and 2.60, respectively. The risk of developing tuberculosis increased among persons with diabetes mellitus with increasing number of diabetic complications or a higher Diabetes Complications Severity Index [23].

Although less strongly documented, persons with diabetes mellitus are considered at increased risk of developing severe bacteremia, especially upon *Streptococcus pneumoniae* infection, staphylococcal pneumonia, and pneumonia caused by gram-negative bacteria or fungi [21,22]. However, others have failed to demonstrate an association between diabetes mellitus and mortality in respiratory tract infections [18]. For example, while the clinical features of community-acquired pneumonia differed between diabetic and non-diabetic patients, the etiology and case-fatality rate were similar in the two patient groups [24]. Interestingly, an increased incidence of bacterial pneumonia and keto-acidosis among diabetes mellitus patients was reported during influenza epidemics [21,25], and diabetes mellitus was significantly associated with influenza pneumonia during the pandemic of 2009 with odds ratios reaching 4.72 [22]. In the Second Dutch National Survey of General Practice, a 12-month prospective cohort study, 705 adult patients with diabetes mellitus type 1 and 6712 adult patients with diabetes mellitus type 2 were compared with 18,911 control patients with hypertension but without diabetes, for risk of infection. Patients with diabetes mellitus type 1 and diabetes mellitus type 2 were at a 1.5 to 2-fold increased risk for lower respiratory tract infection, urinary tract infection and skin and mucous membrane infection, than control patients [26].

A recent systematic review and meta-analysis of populations at risk of developing severe or complicated influenza [27] included cohort studies with laboratory confirmation of infection. The level or quality of evidence was typically low, due to lack of power, inconsistency and heterogeneity across studies, imprecision, and lack of adjustment for confounders. Nonetheless, the meta-analysis revealed that diabetes mellitus was associated with a higher risk of hospital admission upon seasonal influenza A-H3N2 infection, and with a higher risk of death upon pandemic influenza A-H1N1 (2009) infection. Obesity resulted in an increased risk of death upon seasonal influenza in one study, and appeared to be a frequent risk factor during the 2009 influenza pandemic. It not only increased the risk of death, but also was significantly associated with hospital and intensive care unit admissions and subsequent need for ventilatory support. Furthermore, in-hospital mortality during the 2009 influenza pandemic in Spain was 2.1% among persons with diabetes mellitus type 1, 3.8% among persons with diabetes mellitus type 2, and 2.3% among

non-diabetic patients [19]. Based on surveillance data in Canada, diabetes tripled the risk of hospitalization and quadrupled the risk of intensive care unit admission once hospitalized for influenza [28]. Although influenza-attributable rates of influenza-like illness did not differ between working-age persons with and without diabetes mellitus in a recent case-control cohort study, working-age adults with diabetes mellitus experienced a significant 6% increase in influenza-attributable or all-cause hospitalization than matched non-diabetes mellitus adults [29]. Diabetes mellitus was also identified as a risk factor for severe disease due to influenza virus infection in a large cohort of medical encounters in US military personnel (RR = 2.3, 95%CI 1.5–3.6) [30]. Finally, in a recent prospective study, a non-linear association of glycated haemoglobin levels, a marker for glucose regulation, with mortality from influenza, was assessed. Self-reported diabetes mellitus was not related to an increased risk for influenza in this cohort. However, sub-optimal control of glucose levels roughly doubled the mortality risk [31].

Given the collective data presented here, and per WHO guideline, diabetes mellitus patients are therefore considered a high-risk group with a greater susceptibility for developing more severe and/or complicated influenza virus infections requiring hospitalization [32] (see Box 2). Of specific interest are activities that increase infection risk like international travel. Whereas an initial retrospective case series suggested that up to 68% of diabetic travelers had metabolic dysregulation and up to 16% of diabetic travelers acquired a febrile illness during their journey [33], a more recent prospective study among 70 travelers with diabetes mellitus type 1 and 82 travelers with diabetes mellitus type 2 concluded that travelers with diabetes do not have symptomatic infectious diseases more often or longer than travelers without diabetes [34]. In another recent retrospective study among 47 young adults with diabetes mellitus type 1, no increase in travel-related diseases was reported as compared to healthy controls. Glycemic control was suboptimal for 11% of diabetic patients traveling to developing

Box 2 Diabetes mellitus and influenza virus infections.

Observational studies first suggested that diabetes mellitus may be a risk factor for complicated influenza. For instance, deceased persons with diabetes mellitus in the U.S.A were more likely to have influenza on their death certificate compared to those without diabetes mellitus [37], and higher infection-related mortality or morbidity rates were reported in diabetic than in non-diabetic patients [18,19]. Diabetes mellitus has been associated with an increased number of hospital admissions during seasonal influenza, however not all observational studies confirmed this association during seasonal influenza of H3N2 subtype. The correlation between diabetes mellitus and disease severity seemed stronger during the H1N1 influenza pandemic, where persons with diabetes mellitus had a higher chance of intensive care admission and increased mortality than persons without diabetes mellitus [27,28]. Influenza virus infection in diabetes animal models has also been investigated. Streptozotocin-induced diabetic mice showed increased influenza virus titers for pandemic H1N1 [38], H5N1 [39] and H3N2 strains [40]. The mechanisms behind the more severe clinical course of influenza in persons with diabetes mellitus are not fully understood. Aggravating factors likely occur in persons with diabetes mellitus, such as obesity, which is associated with diabetes mellitus type 2. Recent studies suggest an increased risk of (severe) influenza in obese adults [41,42]. Potential mechanisms behind increased severity of influenza in diabetes mellitus include hyperglycemia, underlying comorbidities and glycemic oscillations [43].

countries [35]. Since influenza can be regarded as the most prevalent vaccine-preventable disease in travelers [36], upcoming travel plans should be included in the decision whether to vaccinate a person with diabetes mellitus.

3. Diabetes mellitus and immune responses to influenza virus

Pathophysiological mechanisms leading to increased susceptibility to infection and complicated disease in persons with diabetes mellitus are poorly understood, but probably related to the range of existing diabetic conditions. Obesity is associated with a state of chronic, low-grade inflammation, particularly in white adipose tissue [44], with complex cross-talk emerging between adipocytes, adipose tissue and a potential negative effect on the immune system [22]. Hyperlipidemia results in increased uptake of fatty acids by muscle cells and production of fatty acid metabolites that stimulate inflammatory cascades. Inflammatory signaling inhibits signaling downstream of the insulin receptor, leading to insulin resistance. This strongly suggests that diabetes mellitus type 2 – often associated with obesity – is an inflammatory disease [44].

Mortality upon seasonal influenza virus infection was increased in a rodent model of diet-induced obesity, and associated with reduced or delayed levels of antiviral and pro-inflammatory cytokines and impaired dendritic cell functions [45]. Cellular innate immune responses are decreased *in vitro*, and humoral innate immunity is altered in persons with diabetes mellitus. Defects in immune surveillance and innate responses similar to those observed in obese individuals may thus in part contribute to increased morbidity and mortality due to infections in persons with diabetes mellitus [25]. Lower production of interferon (IFN)- α by dendritic cells was demonstrated in persons with diabetes mellitus type 1 and diabetes mellitus type 2 [46]. Basal levels of IFN- α were likewise lower in non-obese diabetic mice than in pre-diabetic mice. However, in the former model, the levels of IFN- α were increased to levels similar to those seen in pre-diabetic mice, following immunization with influenza virus peptides, with similar clonal expansion of IFN- γ -producing CD8(+) T cells [47].

Taken together, these data indicate that the overall immune responsiveness in persons with diabetes mellitus and in laboratory *in vivo* and *ex vivo* models is altered or reduced. To what extent this would also impact the protective response to vaccination is addressed below.

4. Influenza vaccine effectiveness and safety in persons with diabetes mellitus

Hemagglutination inhibition (HI) antibody titers did not differ between vaccinated clinically well-controlled diabetes mellitus type 2 (N = 102) and non-diabetes mellitus elderly persons (N = 119) [48]. Likewise, HI titers and antibody persistence were similar in a randomized controlled vaccination study in diabetes mellitus type 2 (N = 105) and non-diabetes mellitus individuals (N = 108) [49]. Overall, B cell-specific biomarkers of optimal vaccine response such as measures of switched memory B cells and plasmablasts *ex vivo*, activation-induced cytidine deaminase in stimulated cells *in vitro*, and markers of systemic and B cell-intrinsic inflammation were similar in persons with diabetes mellitus type 2 and persons without diabetes mellitus, irrespective of age [50]. Seroconversion and mounting of protective antibody titers were observed in young persons with diabetes mellitus type 1 (N = 80) immunized with an MF59-adjuvanted pandemic influenza vaccine combined with a trivalent seasonal vaccine [51]. Comparison of the antibody and cell-mediated immune responses to three influenza virus vaccine strains did not show significant differences between persons with diabetes mellitus type 1 (N = 10),

diabetes mellitus type 2 (N = 21) and non-diabetic persons (N = 19) [52]. However, in persons with a high glycosylated haemoglobin level delayed type hypersensitivity reaction to influenza antigen was significantly decreased [53].

Six cohort and five case-control studies, compiling data of 170,924 persons with diabetes mellitus, have reported estimates of influenza vaccine effectiveness (VE), and were included in a recently-published systematic review and meta-analysis [54]. None of these studies reported data on laboratory-confirmed influenza virus infections, and no randomized controlled trials, experimental or quasi-experimental studies were identified, nor studies which reported data on influenza VE in diabetic children and adolescents.

The studies included in the meta-analysis are briefly summarized below – note that most of the studies did not specify the type of diabetes defining the diabetic patients or combined both diabetes mellitus type 1 and diabetes mellitus type 2. These will be further referred as persons with diabetes mellitus. Influenza vaccination reduced hospitalization of working-age persons with diabetes mellitus by 79% (after adjustments for confounders), during two influenza epidemics in 1989–1990 and 1993, in a case-control study [55]. A prospective cohort-study in working-age diabetes mellitus adults generated a crude odds-ratio for developing influenza-like illness of 0.76 in the vaccinated group during 1995–1996 [54,56]. In another cohort-study, the risk of death during an influenza season was approximately 1.7-fold greater in non-vaccinated than in vaccinated persons with diabetes mellitus, with adjusted odds-ratio for all-cause mortality of 0.6 in the vaccinated group during the influenza seasons of 1996–1997 and 1997–1998 [57]. This risk was reported for all age and gender subgroups, and remained largely unchanged after adjustment for comorbidity. In a serial cohort study, vaccination was shown to reduce hospitalization or death of healthy and high-risk elderly individuals, including persons with diabetes mellitus, during the influenza seasons of 1996–1997 and 1997–1998 [58], with an adjusted odds-ratio of 0.63 in vaccinated persons with diabetes mellitus [51]. The absolute risk reduction was found 1.9- to 4.7-fold higher among persons with diabetes mellitus than among healthy elderly individuals [58]. Of 450 persons with diabetes mellitus examined in an outpatient clinic between December 1999 and February 2000, none of those who had received an influenza vaccine acquired an influenza-like illness (with a corresponding crude odds-ratio of 0.34 [54]), while 20% of those who had not received the vaccine required hospitalization, with serological diagnosis of influenza [59]. A large cohort study demonstrated a 12% reduction in the rate of hospitalization of vaccinated elderly with diabetes mellitus compared to the non-vaccinated group [60]. A nested case-control study conducted during the 1999–2000 influenza season showed an association of influenza vaccination with 56% reduction in any complication, 54% reduction in hospitalizations and 58% reduction in deaths among adults and elderly with diabetes mellitus [61]. A population-based cohort study demonstrated a reduction in all-cause mortality of 33% in vaccinated elderly diabetes mellitus patients during the period of 2002–2005 [62]. In a case-control study during influenza seasons of 2000–2008, influenza vaccination was associated with a 43% reduction in hospitalization and 28% reduction in all-cause mortality in vaccinated working age persons with diabetes mellitus, with similar figures in elderly patients, while it was also associated with a 12–13% reduction in influenza-like illness in vaccinated elderly with diabetes mellitus [63]. Another case-control study in Taiwan likewise reported a reduced risk for hospitalization, intensive care unit admission and death in vaccinated elderly with diabetes mellitus during 2001–2009, with adjusted odds-ratio of 0.88, 0.30 and 0.44, respectively [54,64]. Lastly, two adjuvanted seasonal influenza vaccines were associated with a risk of hospitalization reduced by more than 90% among elderly individuals, during the

2010–2011 influenza season [65]. A subset of patients from this case-control study had diabetes mellitus, with a crude odds-ratio for hospitalization due to influenza or pneumonia of 0.20 in the vaccinated group [54].

The meta-analysis produced a pooled VE of 58% against all-cause hospitalization, whereas no significant effects on all-cause mortality and influenza-like illness were observed, in working-age diabetes mellitus patients [54]. It resulted in adjusted VE of 38% against all-cause mortality, based on cohort studies, and of 56% against all-cause mortality and 23% against all-cause hospitalization, based on case-control studies, in elderly diabetes mellitus patients [54]. The use of all-cause mortality as an end-point in observational influenza VE studies is debatable. In 2007, Simonsen and colleagues have shown that non-specific endpoints, in particular all-cause mortality, may lead to greatly exaggerated VE estimates [66]. Since the contribution of influenza within all-cause mortality during an influenza season is estimated to be around 5–10%, an estimated VE of 50% is probably the result of healthy user selection bias rather than a real risk reduction [67].

A number of recently published studies have further addressed VE in persons with diabetes mellitus. After adjusting for covariates and residual confounding, a retrospective study involving 124,503 persons with diabetes mellitus type 2 demonstrated that influenza vaccination was associated with a significant decrease in risk for hospital admission due to stroke, heart failure, and influenza or pneumonia [68]. Nonetheless, a systematic review of the range of potential bias affecting VE estimates upon seasonal influenza vaccination in diabetic patients, including indirect health outcomes, selection and health seeking bias, and the frequent absence of adjustment for pneumococcal vaccination status, indicated that the overall evidence for influenza vaccine effectiveness was low in diabetes patients [69]. However, one should keep in mind that establishing diabetes mellitus as a risk factor for complicated influenza virus infection is not an easy task. The population of diabetes mellitus patients is not homogenous and the adequate control of other concurrent risk factors can be daunting. Furthermore, despite comparable levels of antibody response to vaccination in persons with and without diabetes mellitus, defined components of the host defense against (viral) infections may be hampered in persons with diabetes mellitus. For instance, persons with diabetes mellitus type 2 tend to show an impaired function in antibody response to pneumococcal surface protein A compared to healthy controls [70].

There are few studies on influenza vaccine safety in diabetes mellitus patients. In essence, reactogenicity and severe adverse reactions in patients with diabetes mellitus are infrequent and appear to be similar to those reported in healthy adults and the elderly [54].

5. Influenza vaccination recommendations and vaccination coverage

Influenza vaccination is generally recommended for all persons with diabetes mellitus. The WHO approved a resolution during the fifty-sixth World Health Assembly, urging countries to establish and implement strategies to increase influenza vaccination coverage (VC) of all people at high risk, including the elderly and persons with underlying diseases, such as diabetes mellitus and other metabolic disorders [71]. Globally, influenza vaccination rates in diabetes mellitus patients are below the target of 75%, with variation by country, age and high-risk conditions. However, in most countries, vaccination rates are higher in high-risk adults compared to non-risk adults. Estimations from recent years indicate vaccination rates between 50% and 62% in the USA [30,72,73], but only 10% in persons with diabetes mellitus in Poland, 40% in

Germany and 70% in the Netherlands in 2004–2006 [74–77]. In Spain, 66% of persons with diabetes mellitus enrolled in the MADIABETES study had received an influenza vaccine in 2013 [12]. Of the seven EU Member States that reported influenza vaccination rates in patients with chronic medical conditions during the 2012–2013 influenza season, only one surpassed the target of 75% (Northern Ireland) [78]. Diabetes mellitus patients with greater severity and longer duration of diabetes, higher incidence of comorbidities and higher number of general practitioner and nurse visits tend to demonstrate stronger adherence to regular influenza vaccination [79–81]. Fear of adverse reaction to the vaccine or not believing to belong to a risk group are amongst the reasons for refusal of vaccination in individuals with diabetes mellitus [12].

6. Conclusion and future actions

The nature of influenza virus epidemics, with variable levels of virus circulation, circulation of different types and subtypes, and antigenic drift with risk of vaccine mismatch, has likely affected the results and conclusions of meta-analyses [82]. Nonetheless, the present evidence—even on basis of biased studies—suggests that influenza vaccination among adults and elderly with diabetes mellitus is efficacious and safe. The increasing burden caused by diabetes mellitus worldwide calls for randomized placebo-controlled trials in diabetes mellitus children, adults and elderly individuals based on laboratory-confirmed influenza-specific outcomes, to substantially inform public health authorities about the real effect size of vaccination in this high-risk group. However, with WHO and many national and international organizations advising diabetes mellitus patients to be vaccinated, one could doubt if such randomized controlled trials are to be considered ethical. Test-negative case-control trials could be an alternative to placebo-controlled trials. Implementation of strategies to reach at-risk patients, such as diabetes mellitus patients, who would likely benefit from yearly vaccination should be designed. A Canadian prospective cohort study showed that vaccinated diabetes mellitus type 2 patients often have access to well-organized preventive medicine programs, e.g. that promotes the use of lipid-lowering drugs and acetylsalicylic acid, and regular professional healthcare inspection for feet lesions. This could have important implications first for the interpretation of vaccine effectiveness in this group of patients due to the likelihood of a healthy user bias and second for optimization of vaccine effectiveness in future vaccination campaigns [83] (see Box 3).

Box 3 Policy implications.

Increasingly, influenza prevention is being touted as an integral part of a 'healthy ageing' strategy, since the bulk of the burden of non-communicable diseases occurs in the latter part of life and represents risk factors for the development of severe and complicated influenza. However, overall influenza vaccination rates in high-risk groups continue to remain below target worldwide. Vaccination coverage in household contacts of persons with diabetes mellitus of type 2 is 30% lower than in diabetes mellitus patients [84]. This suggests that conventional vaccination programs are not successful among high-risk groups and their contacts, and other strategies, such as integrated health care provision, may be more desirable. Because of a decrease in vaccine effectiveness in the elderly [82] and immunocompromised patients, health officers could consider to choose herd immunity as a prevention tool. For instance, a country like Great Britain advocates vaccination of household contacts to protect those more at risk.

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