

Influenza Diabetes Community

WHY INFLUENZA IS A DANGEROUS DISEASE FOR PEOPLE WITH DIABETES?

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European
Scientific
Working group on
Influenza



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Barcelona, Spain
16 - 20 September 2019

WEDNESDAY, 18 SEPTEMBER 2019

07:30 – 08:15
PINÓS HALL

WHY INFLUENZA IS A DANGEROUS DISEASE FOR PEOPLE WITH DIABETES

Morning Session

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

The risk of flu in patients with diabetes
Luc Martinez

Q&A

Description

Influenza is a highly contagious respiratory illness. Anyone can get influenza, but some people have a much higher risk of getting very ill from the infection. People with diabetes are 3-6 times more likely to be hospitalized during influenza epidemics. They also have a much higher rate of death associated with an influenza infection. Moreover, studies have shown that influenza can make diabetes difficult to manage. This is why yearly influenza vaccination is recommended by the World Health Organization for high-risk patients, including those with diabetes.

Organised by: **ESWI**

318

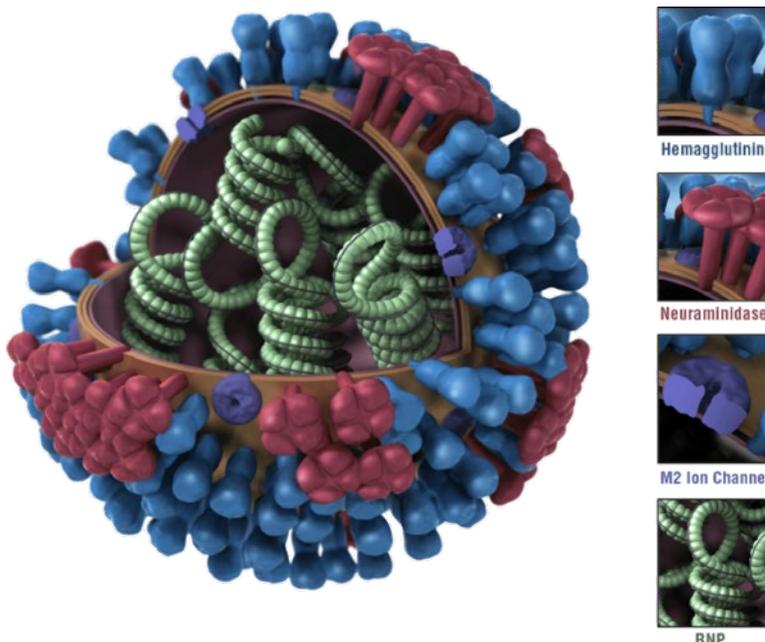
1 | The benefits of flu vaccination for persons with diabetes mellitus

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An overview of the paper “Benefits of flu vaccination for persons with diabetes mellitus” which was published in September 2017¹.

On the surface of the influenza virus are two important proteins – hemagglutinin and neuraminidase – that play a key role in attaching the virus to the cell. Slight changes in these proteins allow the virus to infect many people, year after year. Vaccination based on a combination of these proteins will only provide protection for the strain of that season. When a completely new combination of these proteins arises, there is the risk of a pandemic, which was the case in 2009 with a strain of swine flu called H1N1. This is the main reason why influenza warrants seasonal/yearly vaccination.



Artistic representation of the influenza virus

Influenza can be divided into:

- Seasonal influenza, which occurs every year and for which vaccination is available.
- Pandemic influenza. It is very important to take in mind that, when talking about data on influenza severity in people living with diabetes, most studies were performed during the pandemic in 2009. Meaning most of our recommendations are based on pandemic influenza in persons living with diabetes.
- Strains of bird flu, such as highly pathogenic avian influenza H5N1, are not transmitted from human to human. However, in specific cases they lead to high mortality rates of 60-70%, but there is little to no data regarding persons living with diabetes and bird flu.

After the influenza virus is inhaled by a person, in most cases it replicates in the upper respiratory tract where it will cause typical flu-like symptoms such as fever, myalgia, headache etc. In some cases, the virus travels down to the lower respiratory tract where it can cause complications such as influenza pneumonia or even myocarditis or encephalitis.

Every year, making a rough estimation, 10% of the world's population has symptomatic infection, which translates into 750 million influenza infections each year. Of these, 0.75% – or 5 million people – will experience the more complicated forms of influenza which can lead to prolonged treatment or hospitalization. The mortality rate of these people is 0.1%. This may seem a low rate of mortality, but because so many people are infected, this means that around half a million people die each year due to influenza virus infection.

Influenza and diabetes

In the late 1980s, a group of scientists in the USA discovered that people suffering from diabetes are three times more likely to have respiratory disease given as cause of death on their death certificate than non-diabetics. This was the first time that it was suggested that having diabetes increases the chance dying due to complicated influenza.

Data from the 2009 pandemic showed that having diabetes triples the risk of being hospitalized through influenza. It quadruples the risk that once a person is admitted to hospital, they will end up in intensive care for mechanical ventilation or at least advance respiratory support. And it doubles the risk of mortality. In 2018 the Influenza Diabetes Community was established.

Why do people with diabetes have a higher risk of getting influenza?

The reasons for increased susceptibility to infectious diseases are poorly understood. Diabetes puts a person at a greater risk of any kind of infection, whether viral or bacterial. The data certainly points to higher infection-related mortality or morbidity rates in diabetic than in non-diabetic patients².

Glucose levels can impact the severity of an influenza virus infection. Hyperglycemia is related to the worst outcome in both bacterial and viral infections³. A study showed a non-linear association between glucose regulation and HBA1C influenza mortality⁴.

Another factor is obesity, which is a major risk factor for influenza complications, especially during a pandemic, and increases the risk of death due to seasonal influenza. This correlation is clearer when the influenza season is more severe. Obesity also

significantly increases the chances of being admitted to hospital and intensive care, and the subsequent need for ventilatory support. Unfortunately, obesity can lead to problems during mechanical ventilation due to the mass of the abdomen. Clearance of the virus from an obese person also takes a longer time than from a non-obese person.

Another factor is cardiovascular disease. There is an increased incidence of acute myocardial infarction (AMI) after respiratory infection, particularly in the influenza season⁵, and a consistent association between AMI and influenza activity⁶. Yet another factor to consider is thrombosis. During the 2009 pandemic, 6% of all H1N1 patients admitted to hospitals presented with thrombosis⁷, suggesting a clear interaction between the virus and the coagulation system.

Interventional data from the FLUVACS study in 2004 and the FLUCAD study in 2008 demonstrated that influenza vaccination can prevent or protect a person from AMI. A meta-analysis of five trials confirmed this finding⁸.

Good vaccines exist

Given the clear link between diabetes and an increased risk of getting the influenza virus, vaccination would seem to make sense, particularly as some good flu vaccines exist, whether inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), or live attenuated influenza vaccine (LAIV). No preference is expressed for one influenza vaccine over another. However, the flu vaccine needs to be administered every year. Another problem is that it depends on making an educated prediction what the following year's influenza strain is likely to be. Sometimes there will be a mismatch between the vaccine strain being vaccinated and the one actually circulating.

Is vaccination effective?

Generally, influenza vaccination significantly reduces confirmed influenza virus infection in any person, although there are specific challenges, such as for people over 65 years old. One solution to this challenge is a high-dose vaccine (two doses in one shot) which works more effectively against influenza for people above 65 years old.

Also to be taken into account is that diabetes itself has been found to reduce the humoral and cellular response to influenza virus vaccination. In 1987 a large study showed that persons living with diabetes had a decreased response towards influenza vaccination⁹.

More antiviral production?

This suggests that the way ahead is to produce more antivirals such as Oseltamivir, Zanamivir and Peramivir for pre- and post-exposure prophylaxis. The problem with Oseltamivir and pre-exposure prophylaxis is that before a person develops symptoms, they are already infectious, so that the antiviral has to be taken all the time; in that way it is hard to prevent infection. Post-exposure prophylaxis is also not really proven in any risk group. What is proven is that Oseltamivir accelerates the alleviation of clinical symptoms, reduces risk of lower respiratory tract complications, and reduces the risk of admission to hospital. It's especially indicated for severe cases or those with co-morbidities, and it's only in the very early phase of the disease that it shows some risk reduction (the first 24 hours).

Geographical coverage

Influenza virus vaccination is recommended by many organizations, most notably the WHO, and is recommended for patients with all types of diabetes. In large countries such as the USA it's recommended for anyone, but in Europe the focus is more on risk groups. The WHO recommends a vaccination coverage of at least 75% among persons with diabetes. Studies have reported the following coverage:

- 50% and 62% in the USA
- 10% in persons with diabetes mellitus in Poland in 2013
- 40% in Germany, 2004–2006
- 70% in the Netherlands, 2004–2006
- In Spain, 66% of persons with diabetes mellitus enrolled in the MADIABETES study received an influenza vaccine in 2013
- Of the seven EU Member States that reported influenza vaccination in patients with chronic medical conditions during the 2012–2013 influenza season, only one surpassed the target of 75% (Northern Ireland).

These numbers are however dropping; not just for influenza vaccinations but also against other diseases such as measles. Reasons for not vaccinating include the fear of an adverse reaction to the vaccine, and no longer believing that you are in a risk group due to the chronic character of your disease.

Conclusions

Currently the available data justifies routine influenza vaccination in persons with diabetes mellitus. The evidence however is conflicting, largely due to other complications. The increased risk for severe influenza is multi-factorial. For adequate prevention, vaccination coverage should be increased, especially in those countries where the coverage is far below 75%.

1. Vaccine. 2017 Sep 12;35(38):5095-510
2. Knapp et al 2013
3. Gupta et al 2007
4. Breitling et al 2016
5. Warren-Gash et al. 2012 JID
6. (Foster et al.2013 Epid. Infect)
7. Bunce et al. 2011 CID
8. Loomba et al. 2012 JCPT
9. Diabetologia. 1986 Dec;29(12):850-4.

2 Risk of influenza in people with diabetes

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An overview of some of the data that supports the commonly held belief that people with diabetes are at higher risk for infection, including influenza virus infection, than non-diabetics.

It has been reported for many years that people with diabetes suffer significant morbidity and mortality from infections. For example, in 1935, Leonard Thompson, the first person to receive insulin, died from complications related to a Staphylococcal pneumonia infection occurring after an episode of presumed influenza. This increased risk has been attributed to genetic and metabolic abnormalities (poor glycaemic control and acidemia). Furthermore, specific aberrations in host defense mechanisms are assumed to account for the increased case fatality rate from infection ¹

The growing burden of diabetes

The incidence of diabetes mellitus is still increasing. Between 2015 and 2017 there were 18 million new cases of people with diabetes, 8 million of whom are 65 years old and over². These people are at a high risk of infection due to the combination of a decline in immunity defense and a high level of co-morbidity.

Using the data from the National Health Interview Survey linked with those of the National Death Index from 1988-94 to 2010-15 in the USA, Gregg et al showed that people with diabetes had significantly higher death rates from all causes and from vascular causes, compared to people without diabetes. During this period of 30 years of follow-up, the death rates from all causes declined by 20% every 10 years in people with diabetes, and the deaths from vascular causes decreased by 32% every 10 years. What is worthy of note during the same period, is that death rates from vascular causes also declined significantly every 10 years among people without diabetes, but at a less extent (25,5% versus 31,9%).³ It can be assumed that this benefit in terms of prevention of vascular complications of diabetes is related to the launch of more effective drugs and to better management of people with diabetes as well. On the other hand, the proportion of deaths from non-vascular, non-cancer causes increased by 13% and therefore offset the benefits of good glycaemic control. This resulted in a change in the landscape of cause-specific mortality among people with diabetes during the last 3 decades, putting to centre stage causes that

are consistently associated with diabetes (sepsis, influenza and liver diseases).

Susceptibility of people with diabetes to influenza infection

Shah and al. conducted in 1999 one of the first comparative study (retrospective cohort study) with aim of quantifying the risk of infectious diseases for people with diabetes.⁴ Using population-based administrative data of Ontario residents (Canada) (n=513,746 diabetic and non-diabetic people), it was shown that the risk ratio for having at least one hospitalisation or physician claim for an infectious disease was increased by 20% (RR=1.21; 99% CI 1.20-1.22) and the risk of death was almost doubled (RR=1.92 ; 99% CI 1.7-2.05).

More specifically, a cohort study using administrative data from Manitoba (Canada) between 2000 and 2008 compared the incidence of illness attributable to influenza and its complications in working-age adults aged <65 years with and without diabetes. (5) In adults with diabetes, the relative effect of circulating influenza was associated with significant increases in the rates of physician visits or hospitalisations for influenza-like illness (ILI), hospitalisations for pneumonia and influenza (PI) and all-cause hospitalisations (ALL). The change in the effect of influenza by diabetes status was significantly greater (6% increase) in influenza attributable ALLs in people with diabetic compared to non-diabetic people. Since a similar difference was not observed for ILI, the authors inferred that people with diabetes experience a greater susceptibility to more serious manifestations of influenza requiring hospitalisation compared to non-diabetic people.

Risk of morbidity and mortality in people with diabetes suffering from influenza

Most of the information initially came from AH1N1 influenza pandemic in 2009.

A survey among the 239 residents from Montreal (Canada) with a PCR positive specimen for influenza A H1N1 and hospitalized in connection with the infection in 2009 showed that diabetes increases the risk of intensive care admission by almost 5 times and that the increase is largely independent of difference in age and chronic cardiac disease between people with and without diabetes.⁶

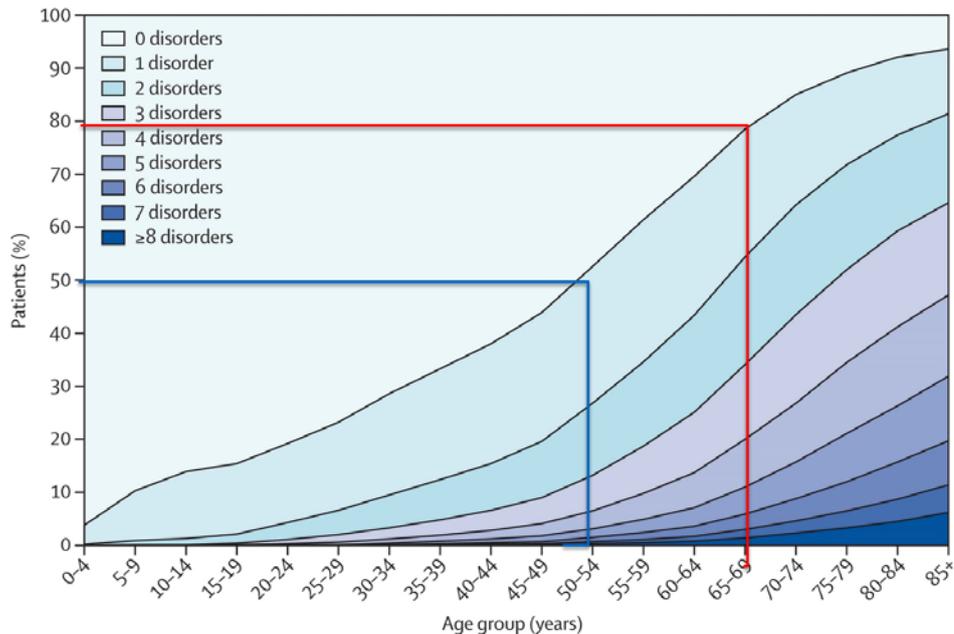
An analysis of the first fatal cases during the pandemic influenza AH1N1 in 2009 in Germany showed that the risk of death among people with at least one underlying medical condition was 10 times as high as people without any underlying medical conditions. Regarding diabetes, the risk is more than doubled (2.3) in people with diabetes compared to people without.⁷

In France, among the 275 patients admitted into an intensive care unit because of a severe H1N1 influenza infection, the risk of death was tripled (3.5) in people with diabetes compared to non-diabetic people. Similarly, the risk of death was increased in babies < 1 year old, in pregnant obese and in people with obesity or with heart failure. (13)

These 3 studies clearly showed that diabetes and more largely comorbidity are associated with a greater risk of poor outcome when people are infected by influenza. But everyone has to consider that multimorbidity is the rule rather than the exception.

In a cross-sectional study conducted among the 1.75 million people registered into one of

the 314 medical practices in Scotland in 2007, one person in 2 aged 50 to 54 years had at least one medical disorder and it reached 80% among people aged 65. On average, these latter had 2.6 medical disorders. With regard to people with diabetes only 20% had no other disorders. Conversely, the others had on average 3 comorbidities if they were < 65 years old and they double the number of comorbidities when they were > 65 years old.^{8,9}



Number of chronic disorders by age-group

The mechanisms underlying susceptibility to influenza in people with diabetes

Pathogenesis of infection in diabetes mellitus involves several mechanisms among which comorbidities, immune dysfunction, and hyperglycemia play an important role.¹⁰

The positive correlation between the mean plasma glucose levels and respiratory tract infections are possibly explained by a reduction in neutrophil degranulation; impaired complement activation; and impaired phagocytosis. Furthermore, elevated blood glucose levels can directly increase the glucose concentration in airway secretions, which in turn, in vitro, significantly increases influenza virus infection and replication.¹¹

One of the first studies to demonstrate a link between glycemic control and infection risk within people with diabetes was conducted among people registered in the CPRD (a large UK primary care database). On the 1st of January 2008, 104,717 people with diabetes were identified and matched to two age-sex-practice controls. There was an evident trend between increasing HbA1c and infection risk present in both younger (40-64 years old) and older (65-89 years old) patients with diabetes. Older patients with diabetes and HbA1c $\geq 10\%$ were approximately 5 times more likely to die as a result of infection during the follow-up period and almost 3 times as likely to be hospitalized as non-diabetic people.¹²

Conclusions

People with diabetes are at higher risk for infection, including influenza virus infections. When infected by the influenza virus, the course of the disease among people with diabetes is worse than for non-diabetic people the risks of hospitalization and of death are higher. Good glycemic control is a key factor for preventing infections – particularly influenza – in people with diabetes. Prevention through vaccination is a second key action to take.

References

1. Smith A, Poland G. Use of Influenza and Pneumococcal vaccines in people with diabetes. *Diabetes care*. 2000;23(1):14.
2. International Diabetes Federation. *IDF Diabetes Atlas*, 8th edn. Brussels, Belgium: International Diabetes Federation; 2017.
3. Gregg EW, Cheng YJ, Srinivasan M, Lin J, Geiss LS, Albright AL, et al. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data. *Lancet*. 2018;391(10138):2430-40.
4. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care*. 2003;26(2):510-3.
5. 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(4):690-8.
6. 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.
7. Wilking H, Buda S, von der Lippe E, Altmann D, Krause G, Eckmanns T, et al. Mortality of 2009 pandemic influenza A(H1N1) in Germany. *Euro Surveill*. 2010;15(49).
8. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380(9836):37-43.
9. Guthrie B, Payne K, Alderson P, McMurdo ME, Mercer SW. Adapting clinical guidelines to take account of multimorbidity. *BMJ*. 2012;345:e6341.
10. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. *Indian journal of endocrinology and metabolism*. 2012;16 Suppl 1:S27-36.
11. Hulme KD, Gallo LA, Short KR. Influenza Virus and Glycemic Variability in Diabetes: A Killer Combination? *Front Microbiol*. 2017;8:861.
12. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. *Diabetes Care*. 2018;41(10):2127-35.



INVITATION
Symposium

Why influenza is a dangerous disease for people with diabetes?

 **Wednesday
Sept 18, 2019
07:30 - 08:15**

 **PINÓS HALL
EASD 2019**

By:



DID YOU KNOW?



People with diabetes are 3-6 times more likely to be hospitalized with influenza¹⁻²



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1. Boulet, et al. Diabetes Res Clin Pract 1991;12:61-8.
2. Allard R. Diabetes Care 2010;33:1491-3



The World Health Organization recommends
YEARLY INFLUENZA VACCINATION
for people with **chronic diseases** and **healthcare professionals**

DID YOU KNOW?



- ▶ People with diabetes are 3-6 times more likely to be hospitalized with influenza¹⁻²
- ▶ X6 Increased risk of death from influenza complications³
- ▶ Influenza vaccination resulted in a 58% decrease in hospitalization among people with diabetes⁴

- ▶ People with chronic conditions such as diabetes are at higher risk of severe complications, hospitalization and death associated with influenza infection.
- ▶ Healthcare professionals are at high risk of being exposed to influenza and can unintentionally act as vectors of the disease.
- ▶ Influenza is preventable.
- ▶ Yearly vaccination is the most effective way to prevent influenza.

Learn more about influenza & diabetes, the flu vaccine and how to talk to your patients about getting vaccinated 

Protect yourself and your patients!



1. Boulet, et al. Diabetes Res Clin Pract 1991;12:61-8.
2. Allard R. Diabetes Care 2010;33:1491-3
3. <https://www.gov.uk/government/publications/influenza-the-green-book-chapter-19> (p.5)
4. <http://www.mhag-resource.org/uploads/media/default/0001/02/2800/ceb9e900192612176167b01abfab25f37.pdf>



If you have any questions about the European Scientific Working group on Influenza, please contact:

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