Università degli Studi della Campania *Luigi Vanvitelli*

Azienda Ospedaliera Universitaria *Luigi Vanvitelli*

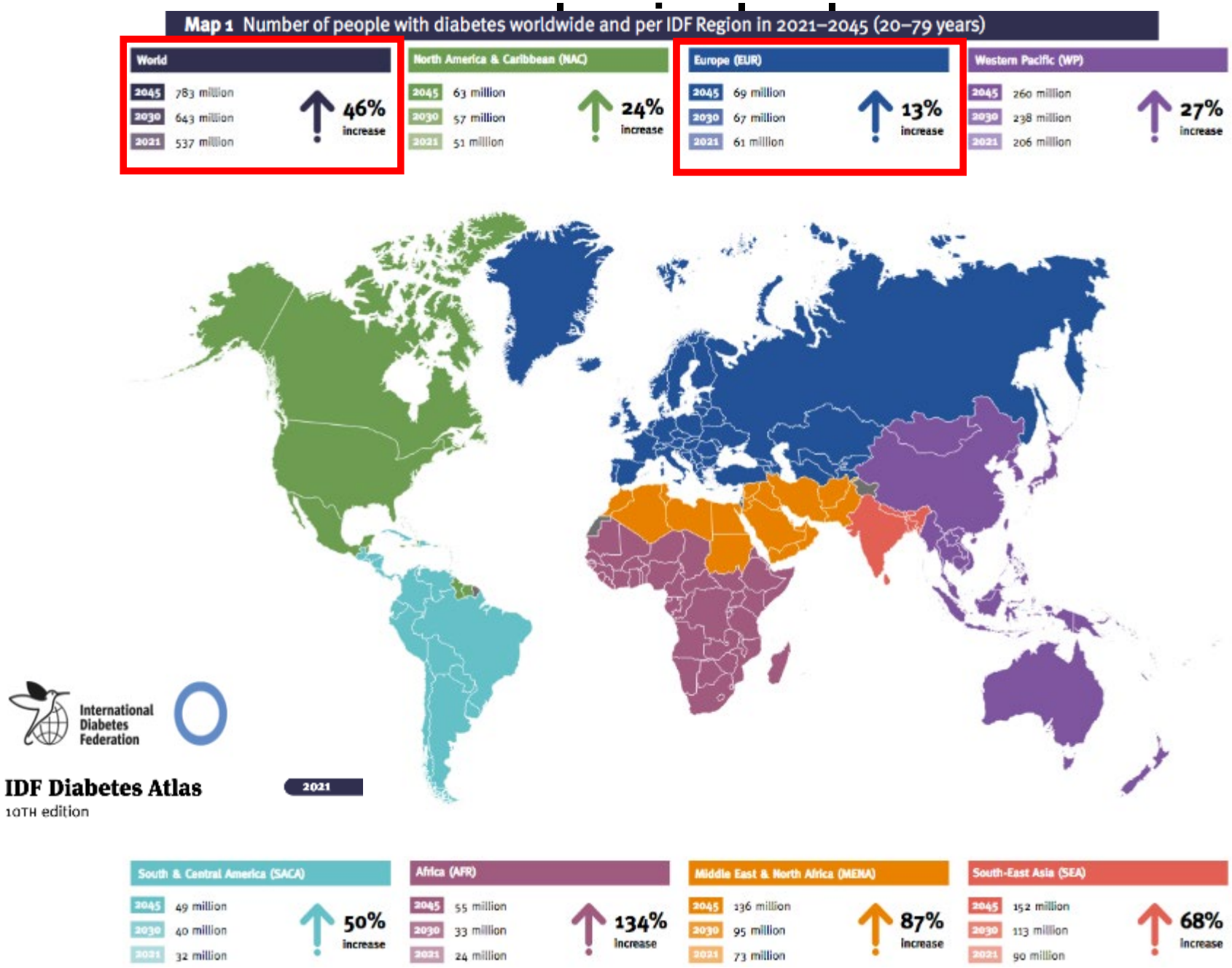
Endo-ERN

Le vaccinazionei nel paziente diabetico

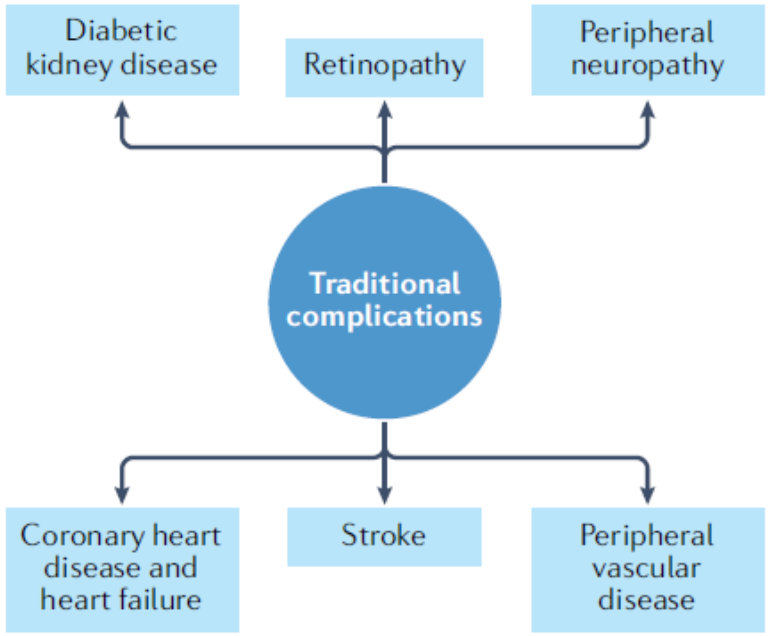
Giuseppe Bellastella

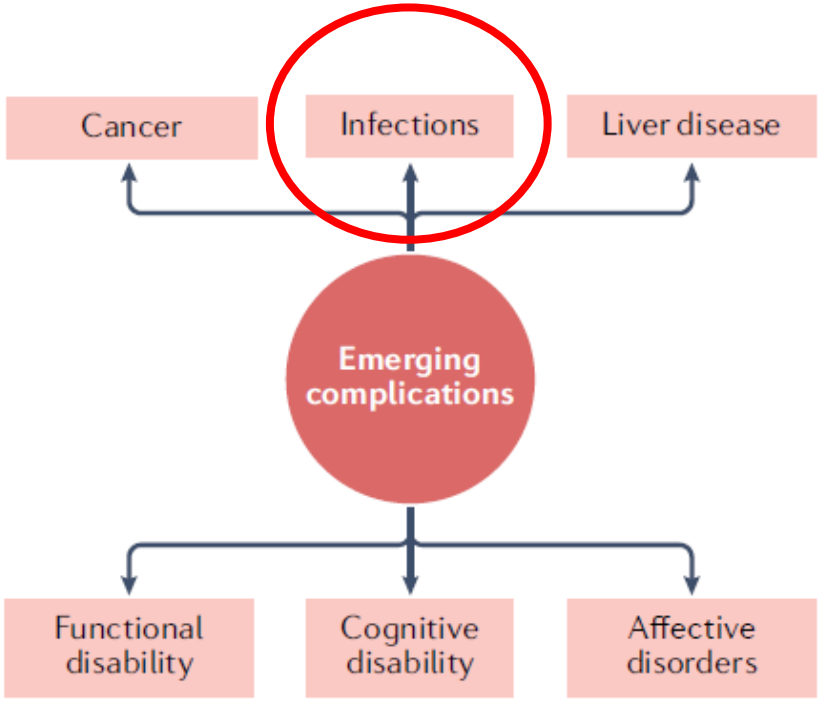
Dipartimento di Scienze Mediche e Chirurgiche Avanzate
UOC Endocrinologia e Malattie del Metabolismo
Azienda Ospedaliera Universitaria
Universita` degli Studi della Campania “Luigi Vanvitelli

Diabetes is a major health issue that has reached

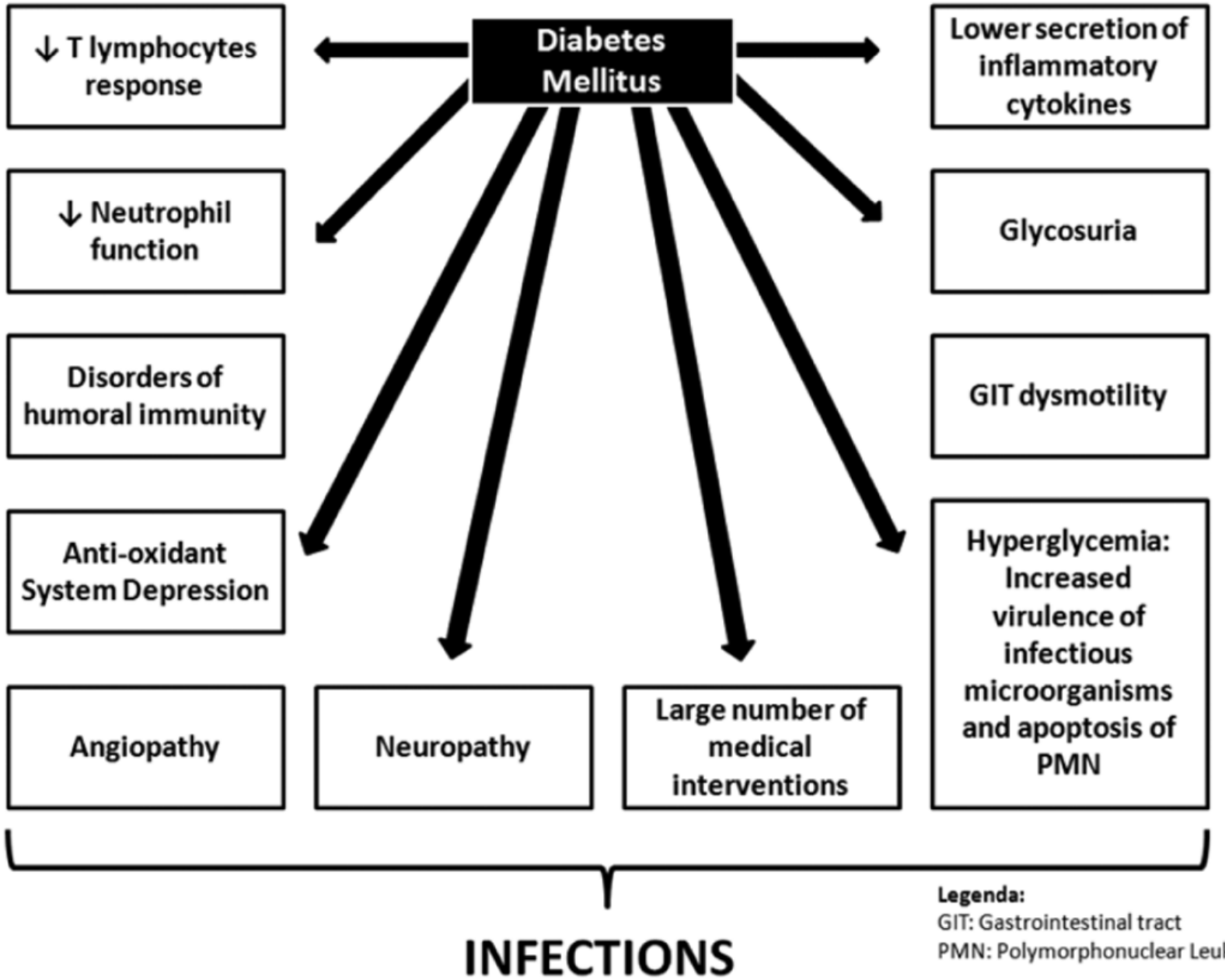


DIABETES IS A RISK FACTOR FOR INFECTION





Nat Rev Endocrinol. 2022 Sep;18(9):525-539. doi: 10.1038/s41574-022-00690-7. Epub 2022 Jun 6.



Legenda:
GIT: Gastrointestinal tract
PMN: Polymorphonuclear Leukocyte

Inflammatory cytokines

Mononuclear cells and monocytes of persons with DM secrete less interleukin-1 (IL-1) and IL-6 in response to stimulation by lipopolysaccharides.[2,4] It appears that the low production of interleukins is a consequence of an intrinsic defect in the cells of individuals with DM.[2,7] However, other studies reported that the increased glycation could inhibit the production of IL-10 by myeloid cells, as well as that of interferon gamma (IFN-γ) and tumor necrosis factor (TNF)-α by T cells. Glycation would also reduce the expression of class I major histocompatibility complex (MHC) on the surface of myeloid cells, impairing cell immunity.[8]

How diabetes affect immune system ?

Total leukocytes	Their numbers are elevated, are larger and more granular, express diminished levels of antioxidant genes but elevated levels of pro-apoptotic and pro-inflammatory genes.
Innate immunity	
Complement system	Attachment of C-type lectin proteins to mannose residues is decreased, lectin pathway is impaired, CD59 activity is reduced, MAC deposition in vascular walls is increased.
Dendritic cells (DCs)	Their numbers and activity are reduced.
Macrophages	Their cholesterol efflux is decreased, generate foam cells, have dysfunctional efferocytosis.
Neutrophils	Are activated, constitutively release NETs, produce high levels of MPO, ROS, and calprotectin (S100A8/A9), are more susceptible to apoptosis, their migration, phagocytosis and microbial killing are impaired.
NK cells	Their numbers are increased but are usually dysfunctional, express high levels of GLUT4 but decreased levels of NKG2D and NKp46, have reduced degranulation capacity, are more susceptible to apoptosis.
NKT cells	Their numbers are increased, produce high levels of IFN-γ, IL-4, and IL-17, express high levels of NKp30, NKG2D, and NKp44 but low levels of NKG2A and 158b.
Innate lymphoid cells (ILCs)	ILC1s are increased and produce high levels of IFN-γ.
Adaptive immunity	
Humoral immunity (B cells)	Germinal centers are reduced, Ab production and isotype switching is defective, Abs become glycated, Abs fail to activate complement.
Cellular immunity (T-Cells)	Pathogen-specific Th17 cells are decresed, Th1 cells are elevated, have decreased expression of perforin, GrB and CD107a.

Ab, antibody; GLUT-4, glucose transporter type 4; GrB, granzyme B; IFN, interferon; IL, interleukin; MAC, membrane attack complex; MPO, Myeloperoxidase; NET, neutrophil extracellular traps; NKG2D, the natural killer group 2d; ROS, reactive oxygen species; Th, helper T cell.

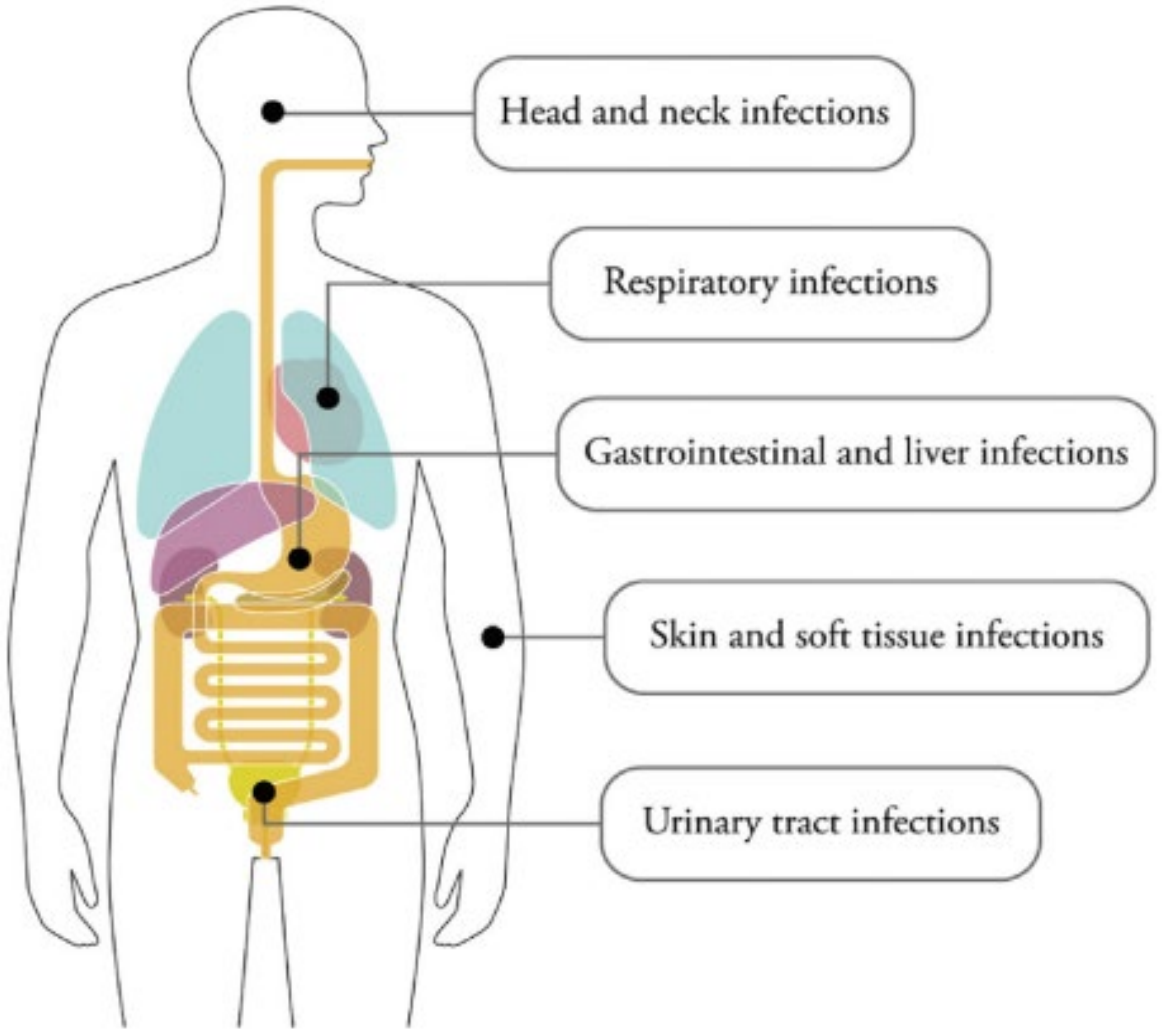
	Infectious agent	References
Dysfunctional innate immunity		
Complement system	*Candida* spp (*albicans, tropicalis, lusitaniae, lipolytica, krusei*), *Streptococcus pneumoniae, Borrelia burgdorferi, and Escherichia coli*	(130–132, 216)
NK cells	*Mycobacterium tuberculosis*	(203, 213)
Neutrophil	*Staphylococcus aureus, Klebsiella pneumoniae,* and *Burkholderia pseudomallei*	(217–221)
Macrophage	*Mycobacterium tuberculosis*	(222, 223)
ILC3	*Mycobacterium tuberculosis*	(224)
Dysfunctional adaptive immunity		
B cell (humoral immunity)	*Staphylococcus aureus, Streptococcus pneumoniae*	(199, 201)
$CD8^+$Tcells	*Mycobacterium tuberculosis*	(203, 213)

frontiers in Immunology

Daryabor et al., doi: 10.3389/fimmu.2020.01582

Table 1: Major infections associated with diabetes mellitus

Respiratory infections
Streptococcus pneumoniae
Influenza
H1N1
Tuberculosis
Urinary tract infections
Asymptomatic bacteriuria
Fungal cystitis
Emphysematous cystitis
Bacterial pyelonephritis
Emphysematous cystitis
Perinephric abscess
Gastrointestinal and liver infections
H. pylori infection
Oral and esophageal candidiasis
Emphysematous cholecystitis
Hepatitis C
Hepatitis B
Enteroviruses
Skin and soft tissue infections
Foot infection
Necrotizing fasciitis
Fournier's gangrene
Head and neck infections
Invasive external otitis
Rhinocerebral mucormycosis
Other infections
Human immunodeficiency virus



Erener S, Mol Metab 2020 Sep;39:101044

Diabetes increases risk of
hospitalization and death for infectious deseases

Already in 2003….

Quantifying the Risk of Infectious Diseases for People With Diabetes

Shah BR, Hux JE.Diabetes Care 26:510–513, 2003

A retrospective cohort study compared all people with diabetes in Ontario on 1 April 1999 to matched nondiabetic people (*n* 513,749 in each group).

The risk ratios of having an infectious disease and of death attributable to infectious disease between those with and without diabetes were calculated.

The study was repeated using a second pair of cohorts defined in 1996 to confirm stability of the estimates.

Table 2—*Risk ratios with 99% CIs for the diabetic versus the nondiabetic population for death attributable to infectious disease*

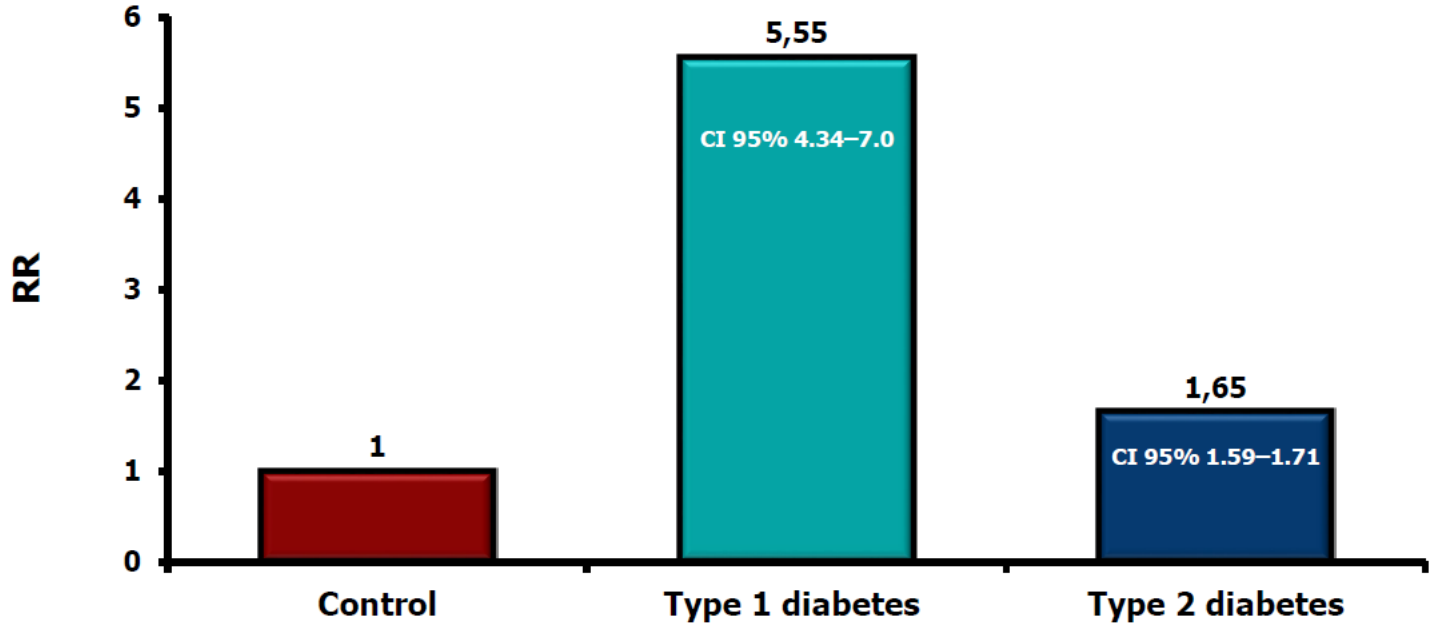
	Risk ratio (99% CI)	
	1999 Cohort	1996 Cohort
Death attributable to infectious disease among all patients	1.84 (1.73–1.95)*	1.92 (1.79–2.05)*
Death within 5 days of a physician claim for infectious disease among patients with such claims	1.38 (1.23–1.55)*	1.39 (1.23–1.57)*
Death during hospitalization with infectious disease among patients with such hospitalizations	0.95 (0.89–1.01)	0.94 (0.87–1.01)

*$P < 0.0001$.

American Diabetes Association. Diabetes Care

Diabetes, Glycemic Control, and Risk of Hospitalization With Pneumonia

A population-based, case-control study of patients with a first-time pneumonia-related hospitalization between 1997 and 2005, using health care databases in northern Denmark. The study included 34,239 patients with a pneumonia-related hospitalization and 342,390 population control subjects



Relative risk (RR) for pneumonia-related hospitalization among subjects with and without diabetes

Diabetes Care. 2008 Aug; 31(8): 1541–1545.

Risk of Infection in Type 1 and Type 2 Diabetes Compared With the General Population: A Matched Cohort Study

Diabetes Care

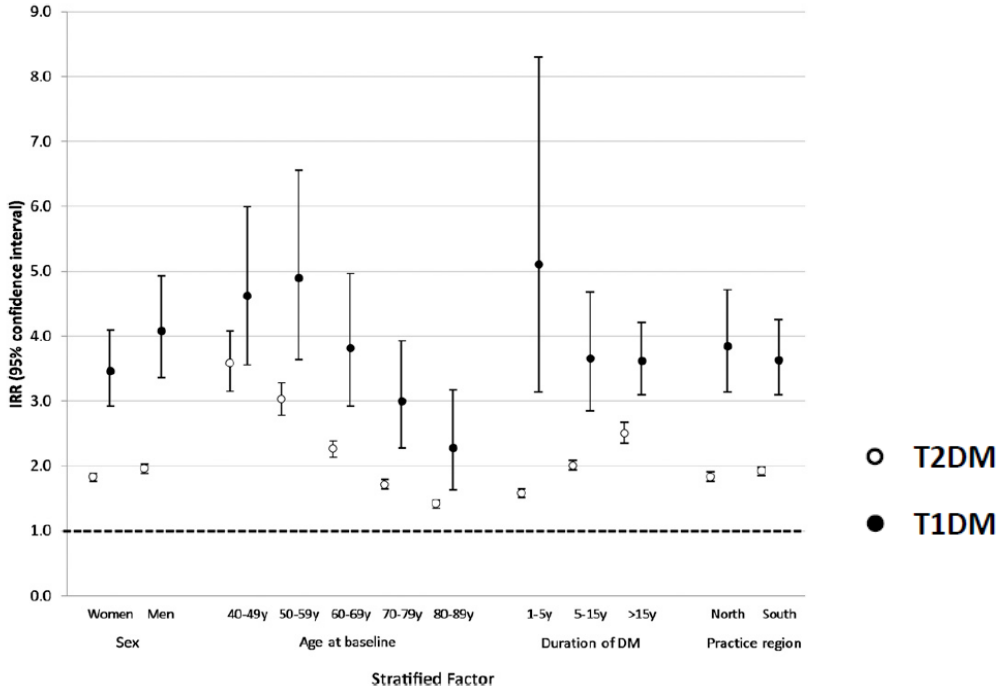
Carey IM et al, Diabetes Care 2018 Mar;41(3):513-521

RESULTS

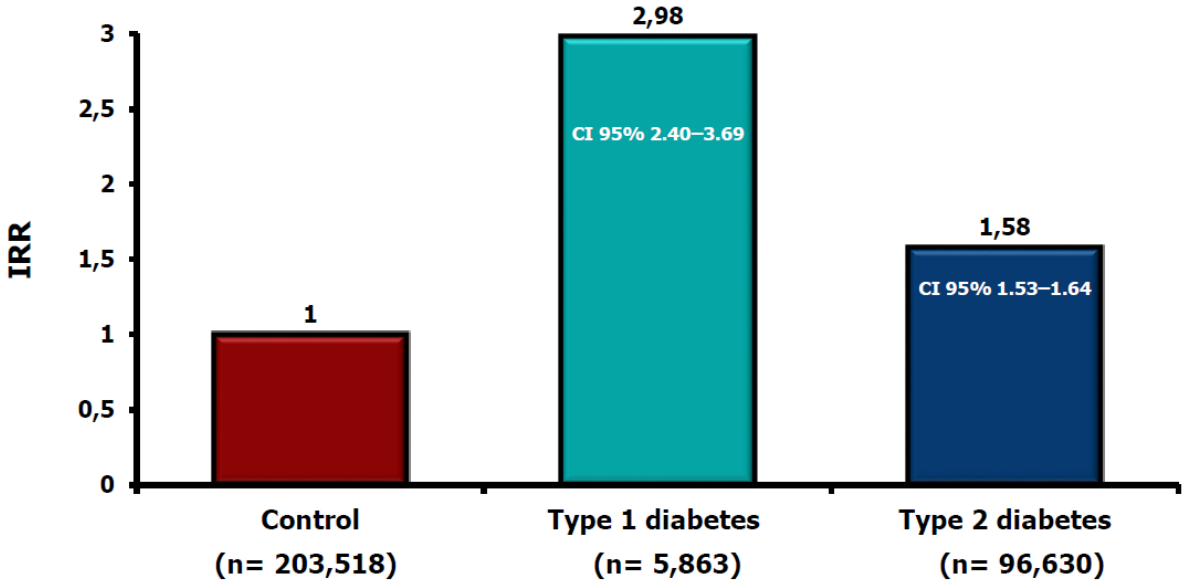
Compared with control subjects without diabetes, patients with diabetes had higher rates for all infections.

IRRs for infection-related hospitalizations were 3.71 (95% CI 3.27–4.21) for T1DM and 1.88 (95% CI 1.83–1.92) for T2DM.

A direct comparison of types confirmed higher adjusted risks for T1DM versus T2DM



IRRs for hospitalization for infection during 2008–2015 between people with diabetes and matched control subjects



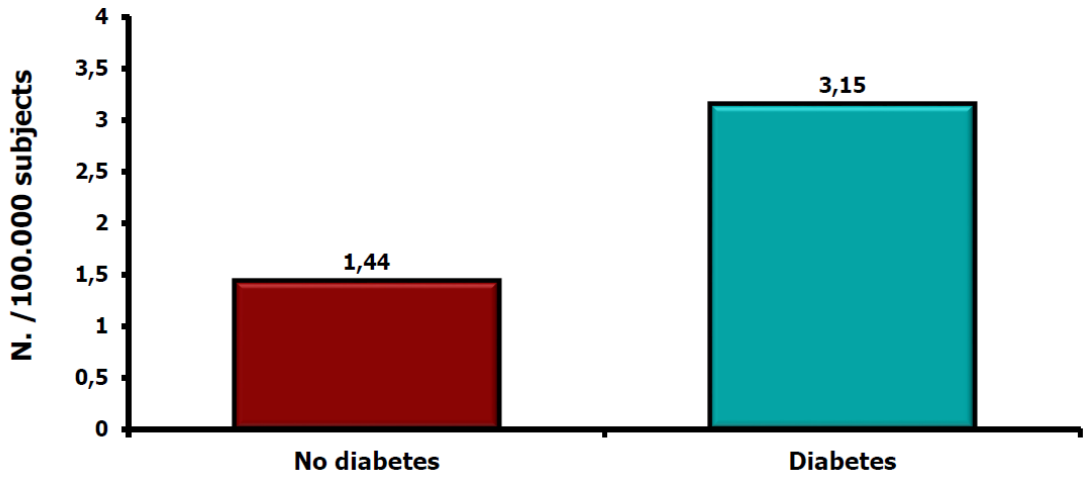
IRRs of pneumonia among people with diabetes versus matched control subjects

Bacterial meningitis

Prevalence and outcome in diabetic patients

From a nationwide, prospective cohort study , conducted in Netherland between March 2006 and October 2014.

From a single-center, prospective observational cohort study, conducted in Spain between 1982 and 2017



vanVeen KEB et al. Scientific Reports 2016

Table 3 Evolving features and outcome of bacterial meningitis in diabetic patients

Characteristics	Diabetic Patients ($n = 106$)	Other Patients ($n = 609$)	*P* value
Neurological complications	31 (29.2)	123 (20.2)	0.210
• Coma	21 (19.8)	94 (15.4)	0.254
• Seizures	18 (17)	70 (11.5)	0.148
• Focal neurological deficits	8 (7.5)	19 (3.1)	0.046
• Cranial palsies	7 (6.6)	28 (4.6)	0.337
Systemic complications	48 (45.3)	184 (30.2)	0.024
• Acute respiratory failure	28 (26.4)	103 (16.9)	0.029
• Acute kidney failure	27 (25.5)	72 (11.8)	< 0.001
• Septic shock	19 (17.9)	88 (14.4)	0.376
• Disseminated intravascular coagulation	11 (10.4)	47 (7.7)	0.677
• Rhabdomyolysis	6 (5.7)	22 (3.6)	0.286
Therapeutics			
• Adequate empiric antibiotic therapy	93 (87.7)	568 (93.3)	0.109
• Dexamethasone therapy	39 (36.8)	220 (36.1)	0.910
• Vasoactive drugs	17 (16)	77 (12.6)	0.350
• Mechanical ventilation	17 (16)	88 (14.4)	0.839
• Dialysis	3 (2.8)	15 (2.5)	0.895
Outcome			
• Neurological sequelae	8 (7.5)	19 (3.1)	0.046
• In-hospital mortality	27 (25.5)	97 (15.9)	0.025

CI confidence interval, *IQR* interquartile range, *SD* standard deviation
Values are reported as no./no. evaluated (%), unless otherwise noted

PomarV et al., . BMC InfectDis. 2020

Viral Pandemics and Diabetes

2003

Severe acute respiratory syndrome (SARS)

- Diabetes and hyperglycemia were independent risk factors for complications and death
- The percentage of patients with a known history of diabetes was significantly higher in the deceased patients than in the survivors (21.5% vs. 3.9%, $p < 0.01$)

2009

Influenza A (H1N1)

The OR for ICU admission was 4.29 among hospitalized patients with diabetes compared to those without.

2013

Middle East respiratory syndrome (MERS)

- Prevalence of diabetes was up to 51.8 in patients with Mers
- Diabetes was a clinical predictor of death (OR 1.8)

2019

Severe acute respiratory syndrome (SARS-COV -2) COVID-19

Singh et al. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020)

Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 535–545

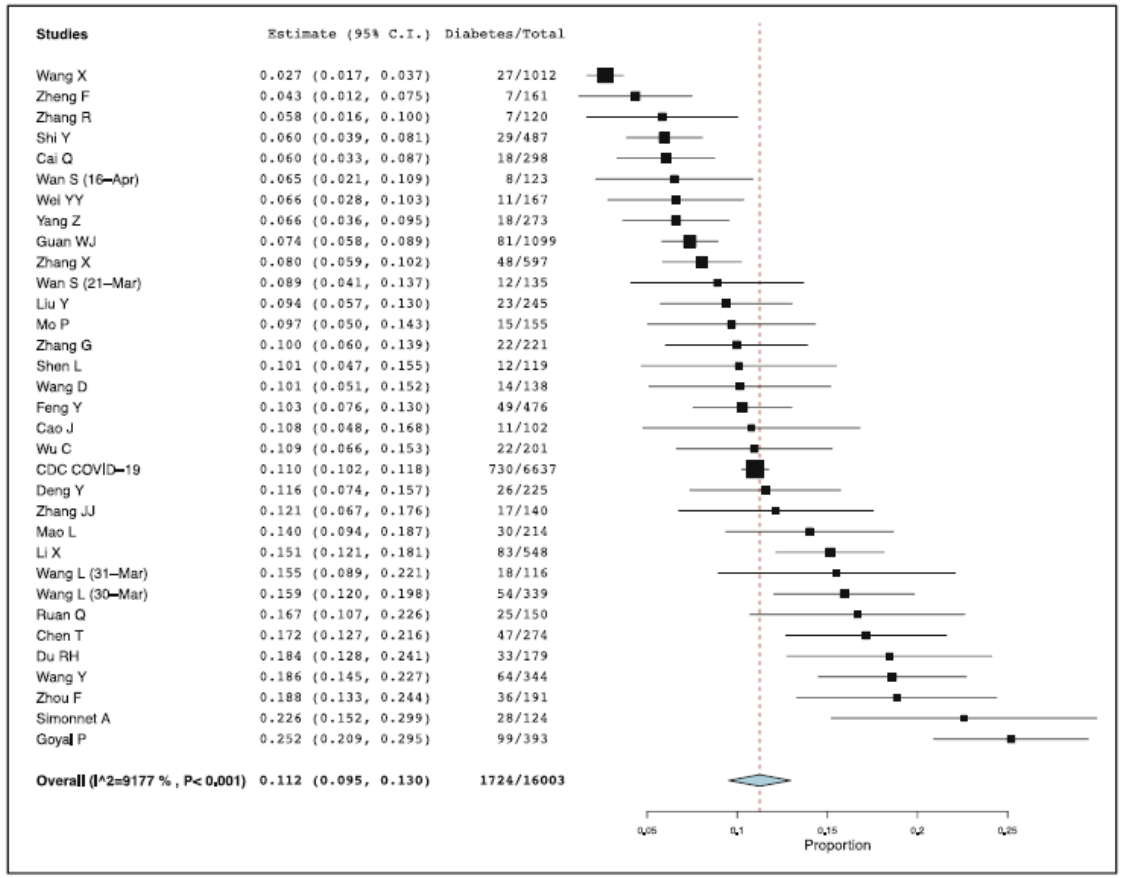


Fig. 2. Pooled proportion of diabetes mellitus in COVID-19 patients.

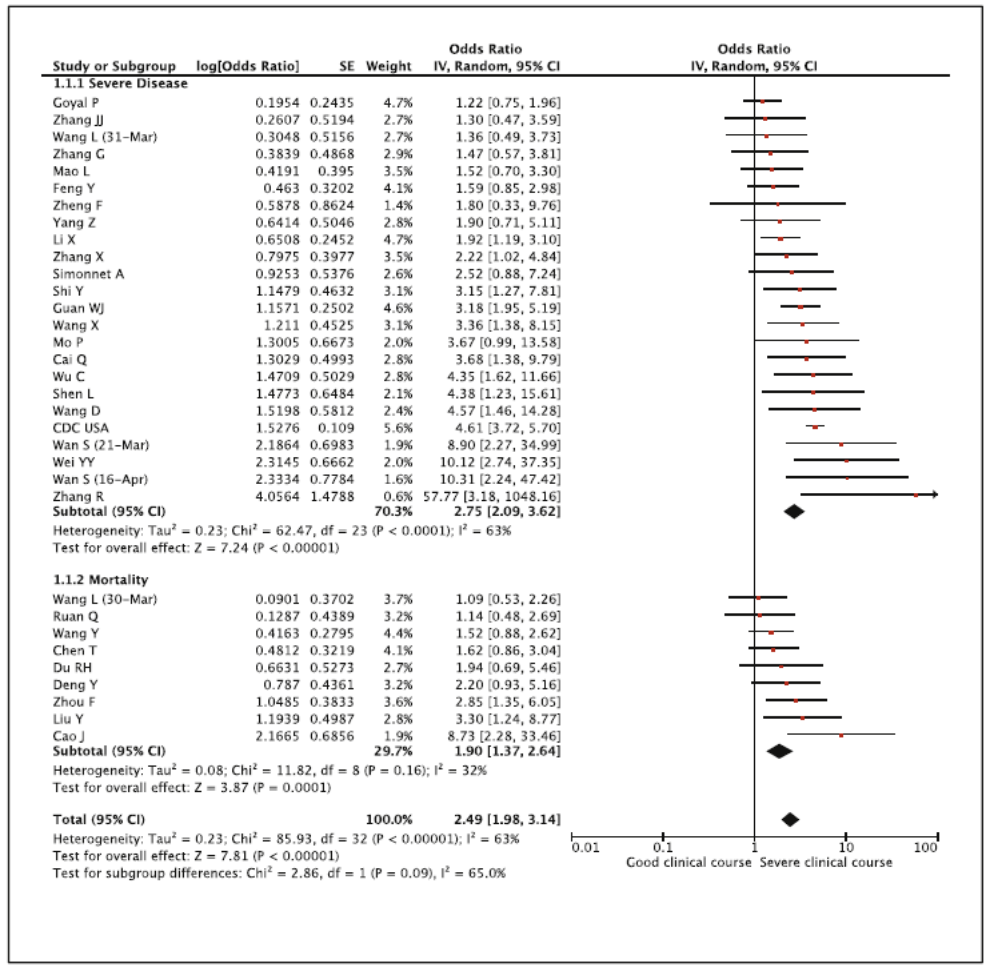


Fig. 3. Forest plot showing pooled odds ratio of diabetes mellitus associated with severe clinical course including mortality.

Do vaccines work in Diabetes?

EXPERT REVIEW OF VACCINES
https://doi.org/10.1080/14760584.2020.1760098

Taylor & Francis
Taylor & Francis Group

REVIEW

Diabetes mellitus as a vaccine-effect modifier: a review

Introduction: Diabetes mellitus (DM) is a highly prevalent, chronic condition in adults worldwide. Little is known about the potential role of diabetes as an effect modifier of vaccine protective responses.

Areas covered: We conducted a literature review of the immunogenicity, efficacy and effectiveness of immunization in individuals, in studies that compared subjects with DM (DM+) and without DM (DM-).We found few published studies, which were only for vaccines against hepatitis B, influenza, pneumococcal disease, or varicela zoster.

Except for a consistent attenuation of the immune response to hepatitis B vaccine among DM+ individuals, we found little other consistent evidence for DM as an effect modifier of vaccine responses.

Table 3. Effectiveness of influenza and pneumococcal vaccine among individuals with and without diabetes.

Reference	Vaccine	Type DM	Study design	Population	Age: median, average or range	Sample size	Outcome measured	Vaccine effectiveness (95%CI) DM+	Vaccine effectiveness (95%CI) DM-	P value
Rondy [45]	Influenza A (H1N1) pdm09	DM2	Test-negative (case-control)	65+ year old	Cases: 65–94; controls: 65–101y	DM+ N = 266 DM- N = 674	Hospitalization	58.5% (22.8–77.7)	33.9% (4.6–54.2)	NS
	Influenza B					DM+ N = 272 DM- N = 696		62.1% (5.8–84.7)	40.9% (−7.1–67.4)	NS
Lau [46]	Seasonal influenza	DM/ns	Cohort study	Working population and elderly population	Working group: 53y Elderly: 74y	DM working: 56613, DM elderly: 25092; elderly control: NR	ILI	18–65 yrs: 1% (−1-3) 65+ yrs: 13% (10–0.16)	65+: 12% (10–15)	NS
							Pneumonia and influenza hospitalization	18–65 yrs: 43% (28–54) 65+ yrs: 45% (34–53)	65+ yrs: 55% (45–63)	NS
							All-cause hospitalization	18–65 yrs: 28% (24–32) 65+ yrs: 33% (30–36)	65+ yrs: 34% (31–37)	NS
Benin [51]	PPV23	DM1 & DM2	Case-control & indirect cohort	Navajo adults, aged	>65y or <65y with underlying condition	DM+: Case N = 44, controls N = 143 DM-: Case N = 64, controls N = 187	VT-IPD	31% (−182, 83)	31% (−90, 75)	NS
Butler [52]	PPV23 (>1983) or PPV14	DM/ns	Indirect cohort analysis	General population	Vaccinated: 57y; unvaccinated: 50y	N = 2837	VT-IPD	84% (50, 95)	57% (45, 66)*	NR
Wagner [53]	PPV23	DM/ns	Retrospective case-control	LTCF residents	Cases: 82.2y, controls: 82.3y	359 cases, 718 controls, DM+: 10%	Pneumonia	OR in DM+ 2.4 compared to the DM- group		0.004
Huijts [17]	PCV13	DM/ns	RCT (post-hoc)	General population	≥ 65 years	N = 84,496	VT-CAP	89.5% (65.5, 96.8)	24.7% (−10.4; 48.7)	0.002

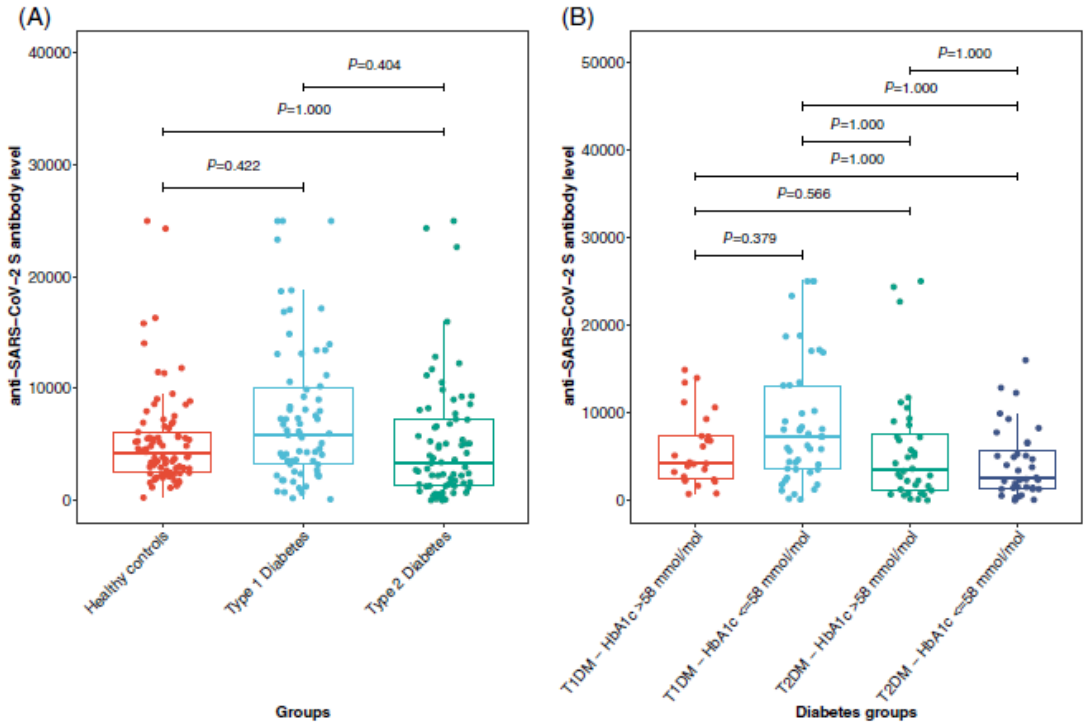
Key: DM1 = Diabetes Mellitus type 1, DM2 = Diabetes Mellitus type 2, DM/ns = Diabetes Mellitus, not further specified, DM+ and DM- refers to groups with and without diabetes, respectively, ILI = influenza-like illness, LTCF = Long-term Care Facilities, NR = not reported, NS = not significant, OR = odds ratio, PCV = pneumococcal conjugate vaccine, PPV = pneumococcal polysaccharide vaccine, RCT = Randomized Controlled Trial, VE = Vaccine Effectiveness, VT-CAP = Vaccine-Type Community-Acquired Pneumonia, VT-IPD = Vaccine-Type Invasive Pneumococcal Disease, *: overall VE.

Received: 29 October 2021 | Revised: 11 December 2021 | Accepted: 1 January 2022
DOI: 10.1111/dom.14643

Humoral immune response to COVID-19 vaccination in diabetes is age-dependent but independent of type of diabetes and glycaemic control: The prospective COVAC-DM cohort study

Aims: To investigate the seroconversion following first and second COVID-19 vaccination in people with type 1 and type 2 diabetes in relation to glycaemic control prior to vaccination and to analyse the response in comparison to individuals without diabetes.

Conclusions:Anti-SARS-CoV-2 S receptor-binding domain antibody levels after the second vaccination were comparable in healthy controls and in participants with type1 and type 2 diabetes, irrespective of glycaemic control.



(A)Comparison of anti-SARS-CoV-2-S antibodies between participants with diabetes and healthy controls after the second vaccination.
(B)Comparison of anti-SARS-CoV-2-S antibodies in people with type 1 (T1DM) and type 2 diabetes (T2DM) and a glycatedhaemoglobin (HbA1c) level of ≤58 mmol/mol or >58 mmol/mol, respectively.

Priorità della vaccinazione anti COVID-19 nelle persone con diabete: raccomandazioni di SID, AMD e SIE

Le persone con diabete presentano ad ogni età, rispetto alla popolazione non diabetica, un rischio significativamente maggiore di mortalità e gravità di malattia in caso di infezione da SARS-Cov-2. È quindi necessario e prioritario mettere in sicurezza attraverso la copertura vaccinale la popolazione diabetica, come chiaramente e giustamente indicato nelle Indicazioni Ministeriali relative alla campagna vaccinale.

Nella popolazione di soggetti con diabete con età inferiore ai 70 anni, che non rientrino nella definizione di persone estremamente vulnerabili e che abbiano ricevuto priorità di accesso alla vaccinazione con ChAdOx1 nCoV-19 (Vaccino AstraZeneca) perché appartenenti a categorie con priorità di somministrazione (i.e. Personale Scolastico e Universitario, Forze Armate e di Polizia, setting a rischio quali penitenziari e luoghi di comunità, ecc.), si dovrà valutare in prima istanza entro quale intervallo di tempo potrebbe essere realisticamente possibile offrire loro la vaccinazione con i vaccini BNT162 / PF-07302048 (Pfizer-Biontech) o mRNA-1273 (Moderna) seguendo le attuali indicazioni AIFA. Nel caso in cui la vaccinazione con questi preparati non dovesse risultare possibile in tempi molto brevi, in considerazione della possibilità di alta diffusione del virus in un contesto in cui la tempistica di vaccinazione per categorie di soggetti a rischio non è al momento prevedibile, si raccomanda di procedere in ogni modo alla vaccinazione con il vaccino più prontamente disponibile, incluso il vaccino AstraZeneca, al fine di garantire al più presto una copertura vaccinale alla persona con diabete.

Si rammenta, tuttavia, che, essendo la disponibilità dei dati scientifici in continua evoluzione, la presente raccomandazione, così come tutte le altre indicazioni, potrebbe andare incontro a modificazioni sostanziali anche nel breve periodo.

Dott. Paolo Di Bartolo	**Prof. Agostino Consoli**	**Prof. Francesco Giorgino**
Presidente AMD	*Presidente SID*	*Presidente SIE*

J PREV MED HYG 2018; 59: E249-E256

Multi-disciplinary Consensus Statement Document

Vaccinal prevention in adult patients with diabetes mellitus

ITALIAN SOCIETY OF HYGIENE, PREVENTIVE MEDICINE AND PUBLIC HEALTH (SItI)
[Prof. G. Icardi and Dr. F. Francia, on behalf of SItI board]

ITALIAN ASSOCIATION OF MEDICAL DIABETOLOGISTS (AMD)
[Dr. P. Di Bartolo and Dr. D. Mannino, on behalf of AMD board]

ITALIAN FEDERATION OF GENERAL PRACTITIONERS (FIMMG)
[Dr. E. Alti, on behalf of FIMMG board]

ITALIAN SOCIETY OF DIABETOLOGY (SID)
[Prof. F. Purrello and Prof. G. Sesti, on behalf of SID board]

ITALIAN SOCIETY OF GENERAL MEDICINE & PRIMARY CARE (SIMG)
[Dr. A. Sessa, on behalf of SIMG board]

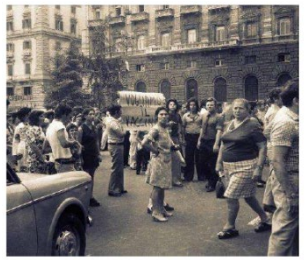
Scientific societies' recommendations about adult diabetic subject-related vaccinations

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).

Systematic vaccination counseling performed by diabetes-treating physicians, together with reporting,within either outpatient visit-associated documentation or hospital discharge-related letter (to be provided to diabetic patients) recommendations to receive the following vaccinations:

- **anti-flu;**
- **anti-pneumococcal;**
- **anti-dTp;**
- **anti-HZ;**
- **anti-meningococcal (T1DM patients).**

Piano Nazionale Prevenzione Vaccinale
PNPV 2017-2019



17 gennaio 2017

Il calendario vaccinale

Vaccino	0gg-30gg	3° mese	4° mese	5° mese	6° mese	7° mese	11° mese	13° mese	15° mese	⇨	6° anno	12°-18° anno	19-49 anni	50-64 anni	> 64 anni	Soggetti ad aumentato rischio
DTPa**		DTPa		DTPa			DTPa				DTPa***	dTpaIPV	1 dose dTpa**** ogni 10 anni			(1)
IPV		IPV		IPV			IPV				IPV					
Epatite B	EpB-EpB*	Ep B		Ep B			Ep B									(2)
Hib		Hib		Hib			Hib									(3)
Pneumococco		PCV		PCV			PCV								PCV+PPSV	(4)
MPRV								MPRV			MPRV					(6)
MPR								*oppure* MPR + V			*oppure* MPR + V					(5)
Varicella																(6)
Meningococco C								Men C§				Men ACWY coniugato				(7)
Meningococco B*^		Men B	Men B		Men B			Men B								
HPV												HPV°: 2-3 dosi (in funzione di età e vaccino)				(8)
Influenza															1 dose all'anno	(9)
Herpes Zoster															1 dose#	(10)
Rotavirus		Rotavirus## (due o tre dosi a seconda del tipo di vaccino)														
Epatite A																(11)

La categoria dei gruppi di popolazione a rischio per patologia è costituita da individui che presentano determinate caratteristiche e particolari condizioni morbose (patologie cardiovascolari, respiratorie, metaboliche, immunodepressione,etc.) che li espongono ad un aumentato rischio di contrarre malattie infettive invasive e sviluppare in tal caso complicanze gravi. La prevenzione di malattie infettive attraverso le vaccinazioni rappresenta una priorità in ambito di Sanità Pubblica, ancor di più per tali soggetti che trarrebbero beneficio da interventi vaccinali mirati e che dovrebbero quindi essere oggetto di programmi specifici

Influenza infection in patients with diabetes

Influenza infection has been shown to affect patients with diabetes to a greater extent than it does with individuals with normal glucose homeostasis.

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.

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.

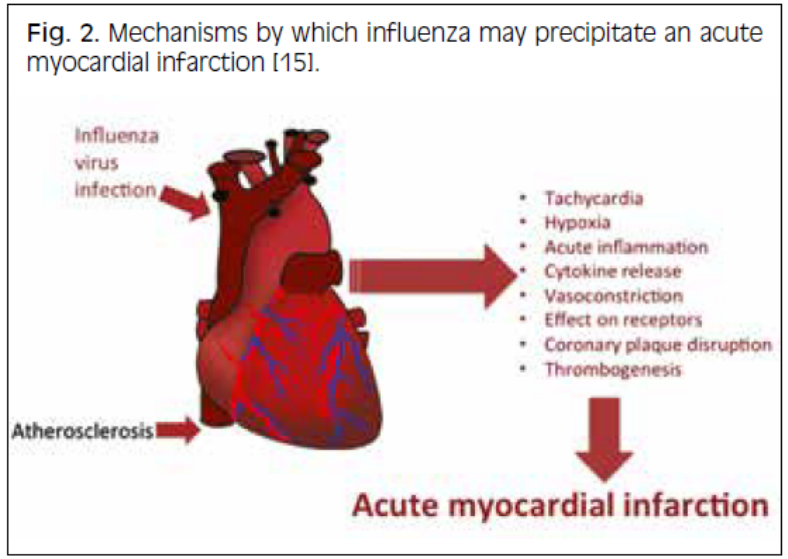


Fig. 2. Mechanisms by which influenza may precipitate an acute myocardial infarction [15].

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

Influenza e diabete

1. Diepersloot RJ, Bouter KP, Hoekstra JB. Diabetes Care. 1990 Aug;13(8):876-82

Influenza e paziente diabetico

- **I pazienti diabetici in particolare, avendo un sistema immunitario indebolito dalla malattia (tipo 1 e 2), presentano un aumentato rischio di complicanze[1]**
- **Anche se ben gestiti, l'influenza può portare a complicanze gravi (come la polmonite), ospedalizzazioni e decessi[1]**

X3 rischio di **complicanze e ospedalizzazione** rispetto a un soggetto sano[2]

1. https://www.cdc.gov/flu/diabetes/
2. https://www.cdc.gov/diabetes/managing/flu/index.html

vaccines

MDPI

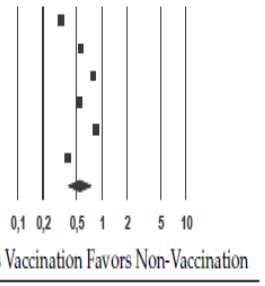
Review

Impact of Influenza Vaccination on All-Cause Mortality and Hospitalization for Pneumonia in Adults and the Elderly with Diabetes: A Meta-Analysis of Observational Studies

Vaccines **2020**, 8, 263; doi:10.3390/vaccines8020263 www.mdpi.com/journal/vaccines

Table 4. Forest plot of the meta-analysis of all cause-mortality rate.

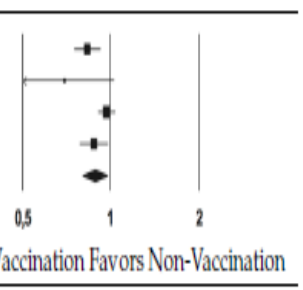
Study Name	Statistics for Each Study				
	Rate Ratio	Lower Limit	Upper Limit	Z-Value	*p*-Value
Heymann, 2004 [19]	0.33	0.25	0.43	−8.41	0.00
Looijmans, 2006 [23]	0.56	0.32	0.97	−2.06	0.04
Rodriguez-Blanco, 2012 [20]	0.78	0.53	1.15	−1.24	0.21
Shade, 2000 [21]	0.54	0.50	0.58	−16.08	0.00
Vamos, 2016 [22]	0.85	0.80	0.90	−5.13	0.00
Wang, 2013 [24]	0.39	0.32	0.48	−9.10	0.00
Overall	0.54	0.40	0.74	−3.84	0.00



ALL CAUSE-MORTALITY RATE

Table 5. Forest Plot of metanalysis of hospitalization for pneumonia rate.

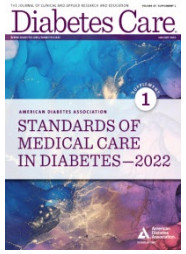
Study Name	Statistics for Each Study				
	Rate Ratio	Lower Limit	Upper Limit	Z-Value	*p*-Value
Heymann, 2004 [19]	0.83	0.75	0.92	−3.34	0.01
Looijmans, 2006 [23]	0.70	0.47	1.03	−0.80	0.072
Vamos, 2016 [22]	0.97	0.91	1.04	−0.77	0.00
Wang, 2013 [24]	0.88	0.78	0.99	−2.20	0.00
Overall	0.89	0.80	0.98	−2.36	0.00



HOSPITALIZATION FOR PNEUMONIA RATE

Guidelines

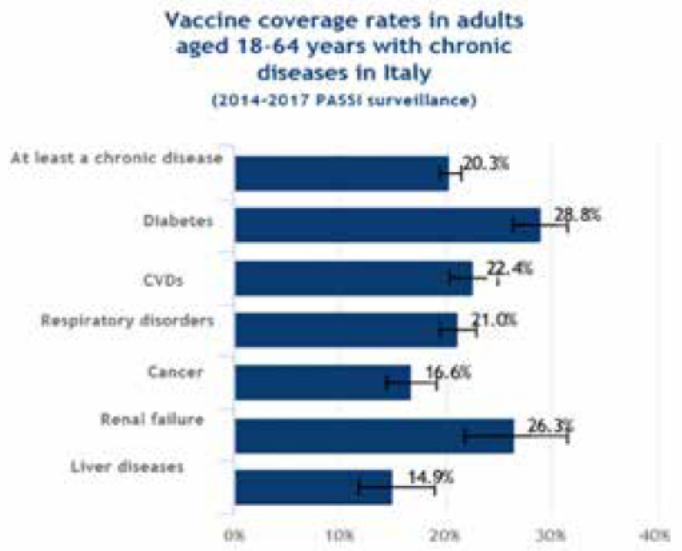
Effettuare annualmente la vaccinazione influenzale in tutti i soggetti con diabete di età superiore ai 6 mesi. *III A*



Given the benefits of the annual influenza vaccination, it is recommended for all individuals **≥6 months** of age who do not have a contraindication.

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%),

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



Pneumococcal infections in subjects with diabetes

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 .

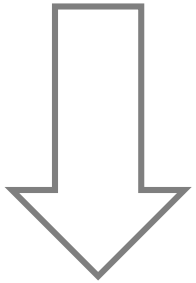
Two vaccines have been available for protection against pneumococcal infections in adults:

PPSV23

23-valent pneumococcal polysaccharide vaccine, that contains capsular polysaccharides from 23 serotypes among 83 known.

PCV13

a 13-valent conjugate vaccine that contains capsular polysaccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to genetically detoxified diphtheria toxin, CRM197, by reductive amination.



Which is indicated for diabetic patient?

Recommendations by health authorities/ scientific societies and current coverage rates

Raccomandazioni nazionali:
Piano Nazionale di Prevenzione Vaccinale
Ministero Salute

Raccomandazioni nazionali:
Consensus statement intersocietaria
AMD, SID, SIMG, SITI, FIMMG

Raccomandazioni internazionali:
CDC

Anti-influenza
Anti-pneumoccoco
Anti-Herpes Zoster

Tabella 1 | Indicazioni vaccinali per le persone con diabete.

Vaccinazione	Gruppo d'età	Frequenza
Anti-Influenzale[3,4]	Tutti i pazienti con età superiore a 6 mesi	Annuale
Anti-Pneumococcica[3,4]	Tra i 19 e i 64 anni PPSV23 Età uguale o superiore a 65 anni, effettuare una seconda dose di PPSV23, almeno dopo cinque anni dalla prima	Una dose Una dose; se era stato utilizzato PCV13, allora somministrare seconda dose di PPSV23 dopo un anno o più dal PCV13 e dopo cinque anni dalla prima dose di PPSV23 ad età inferiore a 65 anni
Anti Zoster[3,4]	Maggiore o uguale 50 anni	Due dosi preferenzialmente di vaccino ricombinante

Raccomandazioni attuali alla vaccinazione nei soggetti diabetici, JAMD July 2021, F.Tassone

Gli Standard italiani per la cura del diabete mellito AMD/SID 2018 recitano, con forza di raccomandazione III A, che "la vaccinazione contro la polmonite (pneumococcica) è raccomandata per tutte le persone con diabete fino a 64 anni, con le modalità previste dalla normativa nazionale." A pazienti di età superiore ai 65 anni, con forza di raccomandazione IIIB, si specifica di «somministrare il vaccino pneumococcico coniugato 13-valente (PCV13) almeno un anno dopo la vaccinazione con PPSV23 (vaccino pneumococcico polisaccaridico 23-valente), quindi una altra dose di PPSV23 almeno un anno dopo PCV13 ed una ulteriore dose di PPSV23 almeno 5 anni dopo l'ultimo PPSV23».[3]
Gli ADA Standards of Medical Care in Diabetes 2021 forniscono delle raccomandazioni simili[4].

La campagna vaccinale in Italia

Ministero della Salute

DIREZIONE GENERALE DELLA PREVENZIONE SANITARIA
Ufficio 5 Prevenzione delle Malattie Trasmissibili e Profilassi Internazionale

Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2022-2023

La vaccinazione anti-pneumococcica è raccomandata e gratuita per le persone di ≥65 anni.

Prevede due dosi: una prima dose di vaccino coniugato e una seconda di vaccino polisaccaridico a distanza di almeno 2 mesi, stando attenti a non invertire l'ordine delle due vaccinazioni.

Vaccino anti-pneumococcico

La presenza di patologie predisponenti può indurre un aumentato rischio di infezione pneumococcica severa e delle sue complicanze. Di conseguenza la vaccinazione anti-pneumococcica è consigliata a tutti coloro che presentino le seguenti patologie o condizioni predisponenti:

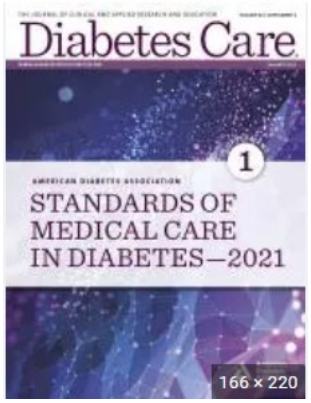
- Cardiopatie croniche
- Malattie polmonari croniche
- Diabete Mellito
- Epatopatie croniche, inclusa la cirrosi epatica e le epatopatie croniche evolutive da alcool
- Alcoolismo cronico
- Soggetti con perdite liquorali da traumi o intervento
- Presenza di impianto cocleare
- Emoglobinopatie quali anemia falciforme e talassemia
- Immunodeficienze congenite o acquisite
- Infezione da HIV
- Condizioni di asplenia anatomica o funzionale e pazienti candidati alla splenectomia
- Patologie onco-ematologiche (leucemie, linfomi e mieloma multiplo)
- Neoplasie diffuse
- Trapianto d'organo o di midollo
- Patologie richiedenti un trattamento immunosoppressivo a lungo termine
- Insufficienza renale/surrenalica cronica

La vaccinazione pneumococcica può essere offerta simultaneamente alla vaccinazione anti-influenzale (che rappresenta in tale caso una occasione opportuna), ma può pure essere somministrata indipendentemente e in qualsiasi stagione dell'anno, anche perché mentre l'anti-influenzale deve essere ripetuta ogni stagione, l'anti-pneumococcica viene somministrata secondo le attuali indicazion in dose singola una sola volta nella vita.

ANTI-DIPHTERIA-TETANUS-PERTUSSIS (DTP)

- CDC (*Centers for Disease Control and Prevention*)specifically refers to diabetics among individuals for whom such a vaccination is recommended
- 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

This vaccination is not mentioned



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Anti-Pneumococcica[3,4]	Tra i 19 e i 64 anni PPSV23 Età uguale o superiore a 65 anni, effettuare una seconda dose di PPSV23, almeno dopo cinque anni dalla prima	Una dose Una dose; se era stato utilizzato PCV13, allora somministrare seconda dose di PPSV23 dopo un anno o più dal PCV13 e dopo cinque anni dalla prima dose di PPSV23 ad età inferiore a 65 anni
Anti Zoster[3,4]	Maggiore o uguale 50 anni	Due dosi preferenzialmente di vaccino ricombinante
Anti Meningococcica[3,5]	Tutti i pazienti DMT1	Due dosi i.m.:
Anti Difterite-Pertosse-Tetano[4]	Tutti gli adulti, alle donne in gravidanza sarebbe da somministrare una dose 'extra'.	Un richiamo ogni 10 anni
Anti Epatite B[3,4]	Tutti i pazienti di età compresa tra i 19 e 60 anni, per età > 60 anni discuterne con il proprio medico	Due o tre serie di dosi
Anti Papilloma Virus[4]	≤26 anni di età; 27–45 anni di età discuterne con il proprio medico	Tre dosi in 6 mesi
Anti-morbillo / parotite / rosolia[3,4]	Tutti i pazienti	Due dosi s.c.: all'età di 12-15 mesi e, di solito, all'età di 4-6 anni.

Other vaccinations recommended in diabetic individuals

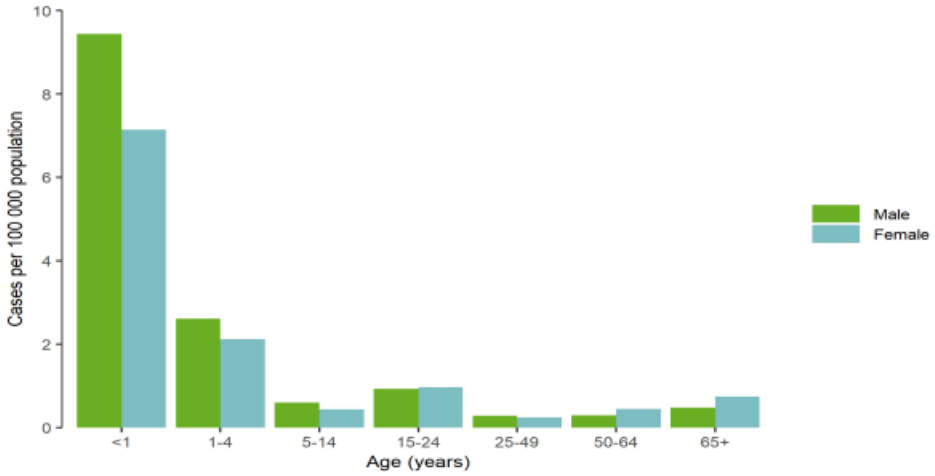
ANTI-MENINGOCOCCAL DISEASE

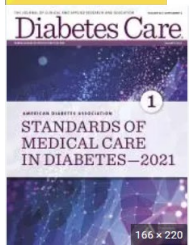
Invasive meningococcal disease

Annual Epidemiological Report for 2018

Key facts

- In 2018, 3 233 confirmed cases of invasive meningococcal disease (IMD), including 324 deaths, were reported in 30 European Union/European Economic Area (EU/EEA) Member States.
- France, Germany, Spain, and the United Kingdom accounted for 59% of all confirmed cases in 2018.
- The notification rate of IMD was 0.6 cases per 100 000 population, similar to the 2015-2017 period.
- Age-specific rates were highest in infants, followed by 1-4-year-olds, with a second peak in 15-24-year-olds.
- Serogroup B remains the major cause of IMD. It caused 51% of cases overall and was the dominating serogroup in all age groups below 65 years. Incidence remained stable between 2014 and 2018.
- The incidence of serogroups W and Y has been increasing. Serogroup W is now the second cause of IMD reported in 18% of cases.
- The continued strengthening of disease surveillance for IMD is essential to evaluate the impact of ongoing immunisation programmes and support decision-makers concerning vaccination strategies.





La vaccinazione anti-meningococcica è raccomandata in tutti i pazienti con diabete di tipo 1. *III A*

This vaccination is not mentioned

Take home messages

- Diabetes is associated with an increased likelihood of infections
- Multiple pathophysiological mechanisms appear to be involved in diabetic patients' increased risk to infections
- Infectious diseases' course is likely to be more severe in diabetics, with higher risk for hospitalization and death compared to euglycemic subjects.
- For these reasons all vaccinations are strongly recommended in diabetic people, according to PNPV and guidelines of main scientific societies.
- In order to overcome Vaccine hesintancy and to achieve Maximum vaccination coverage, Diabetologist and GPs should collaborate. They should systematically asses patient's vaccinal status regarding the following vaccination (and recommend them if necessary):
  - anti-flu;
  - anti-pneumococcal;
  - anti-diphtheria- tetanus-pertussis (dTp);
  - anti-herpes zoster (HZ);
  - anti-meningococcal (T1DM patients).