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IL DIABETE PARADIGMA DI CRONICITA'
CONIUGARE ECCELLENZA E PROSSIMITA' DELL'ASSISTENZA

Chieti - 12 novembre 2022
Auditorium Centro Studi e Tecnologie Avanzate CAST

Prevenire vuol dire anche vaccinare: la vaccinazione nel diabete

Giustino Parruti

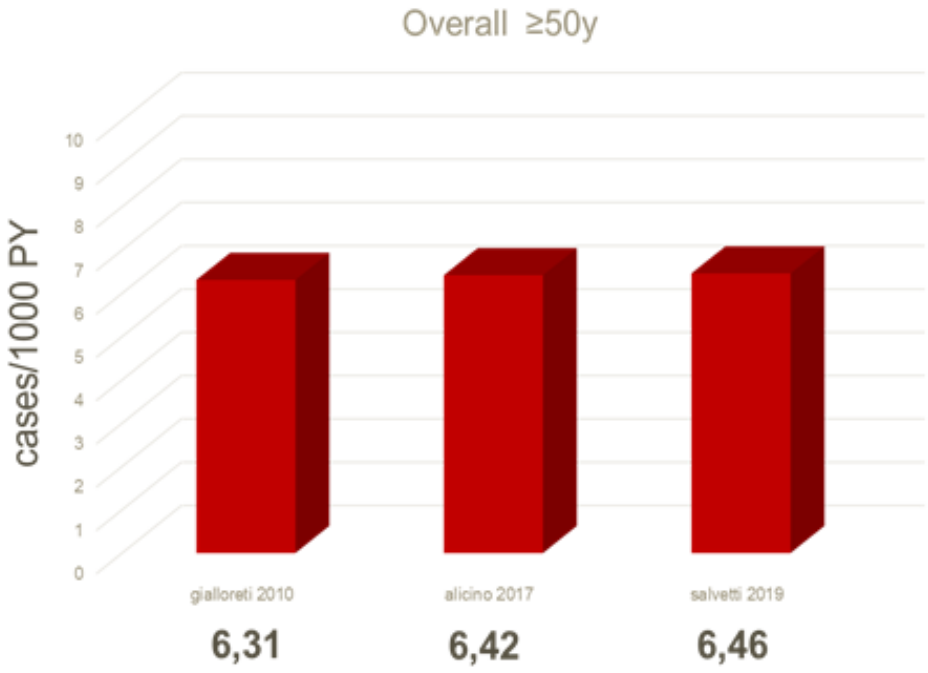
UOC Malattie Infettive

ASL Pescara

Azienda USL di pescara

Herpes Zoster

Epidemiologia in Italia: incidenza



Parruti *et al. BMC Medicine* 2010, **8**:58
http://www.biomedcentral.com/1741-7015/8/58

BMC Medicine

RESEARCH ARTICLE Open Access

Predictors of pain intensity and persistence in a prospective Italian cohort of patients with herpes zoster: relevance of smoking, trauma and antiviral therapy

Giustino Parruti[1*†], Monica Tontodonati[1†], Cristina Rebuzzi[2], Ennio Polilli[3], Federica Sozio[1], Augusta Consorte[1], Adriana Agostinone[1], Francesco Di Masi[1], Gabriele Congedo[1], Domenico D'Antonio[5], Carla Granchelli[6], Claudio D'Amario[6], Carlo Carunchio[4], Lucio Pippa[4], Lamberto Manzoli[7], Antonio Volpi[8], the VZV Pain Study Group

Abstract

Background: Herpes zoster (HZ) is a common disease, characterized by rash-associated localized pain. Its main complication, post-herpetic neuralgia (PHN), is difficult to treat and may last for months to years in the wake of rash resolution. Uncertainties remain as to the knowledge of predictors of HZ-related pain, including the role of antiviral therapy in preventing PHN in ordinary clinical practice. This prospective cohort study was aimed at investigating pain intensity at HZ presentation and its correlates, as well as the incidence of PHN and its predictors.

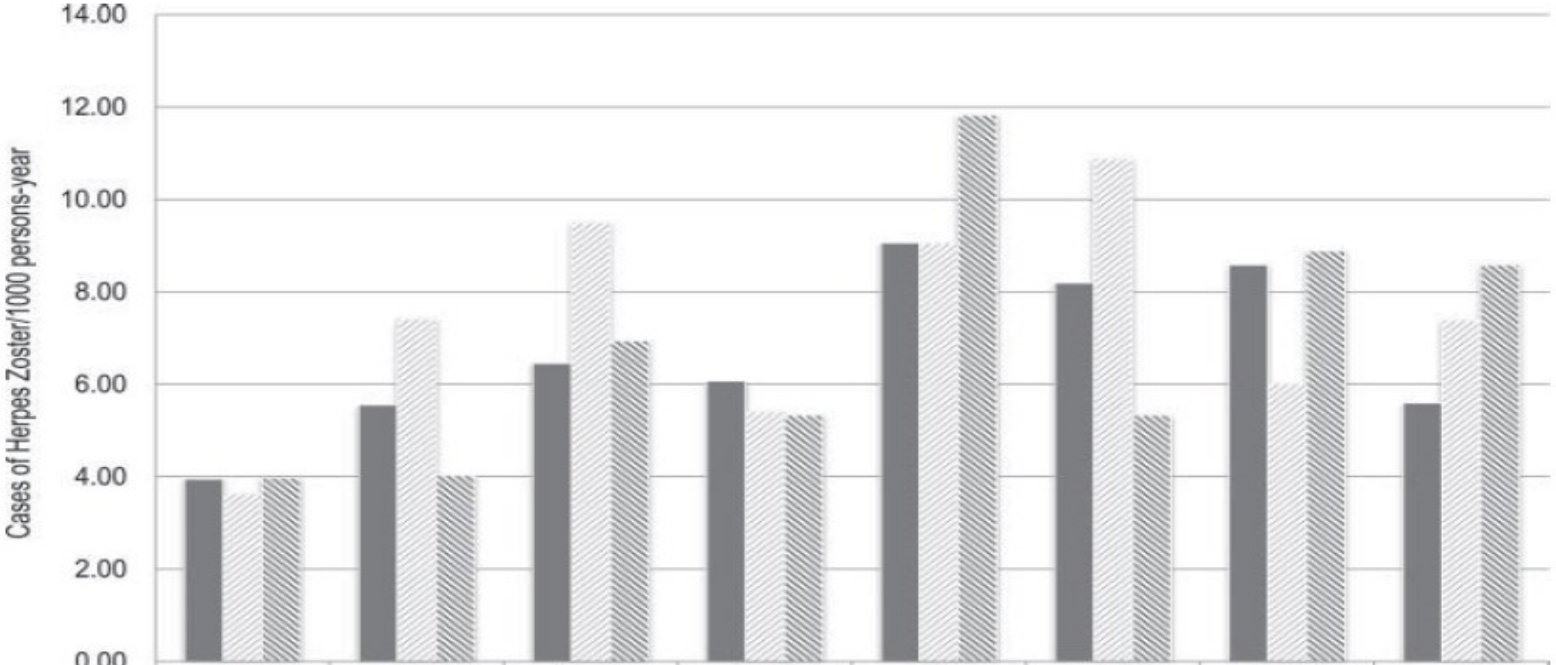
Methods: Patients diagnosed with HZ were consecutively enrolled by a network of Italian General Practitioners and Hospital Units in the health district of Pescara, Italy, over two years. Uncertain cases were referred for microbiological investigation. Data were collected through electronic case report form (e-CRFs) at enrolment and at 1, 3, 6 and 12 months after enrolment. Pain intensity was coded on a five-degree semi-quantitative scale at each time point. PHN was defined as pain of any intensity during follow-up and quantified using an area-under-the-curve (AUC) method.

Results: Four hundred and forty-one patients composed the final sample. Mean age was 58.1 years (SD = 20.4 years); 43.5% of patients were males; 7.9% did not receive prescription of antivirals. Intense/very intense pain at presentation was reported by 25.2% of patients and was significantly associated with female gender, older age, cigarette smoking, trauma and/or surgery at HZ site (logistic regression). PHN was diagnosed in 51.2% of patients at one month and in 30.0% of patients at three months. PHN was significantly associated with pain intensity at presentation, age, smoking, trauma and missed antiviral prescription (generalized estimating equations model). The same factors were also independent predictors of the overall pain burden as described by the AUC method (linear regression).

Conclusions: Smoking, traumas and surgery at the HZ site emerged as new predictors of both HZ-related pain intensity and persistence, opening new perspectives in the prevention of HZ-related pain. An independent line of evidence was provided for the efficacy of antiviral therapy in preventing PHN and reducing total pain burden.

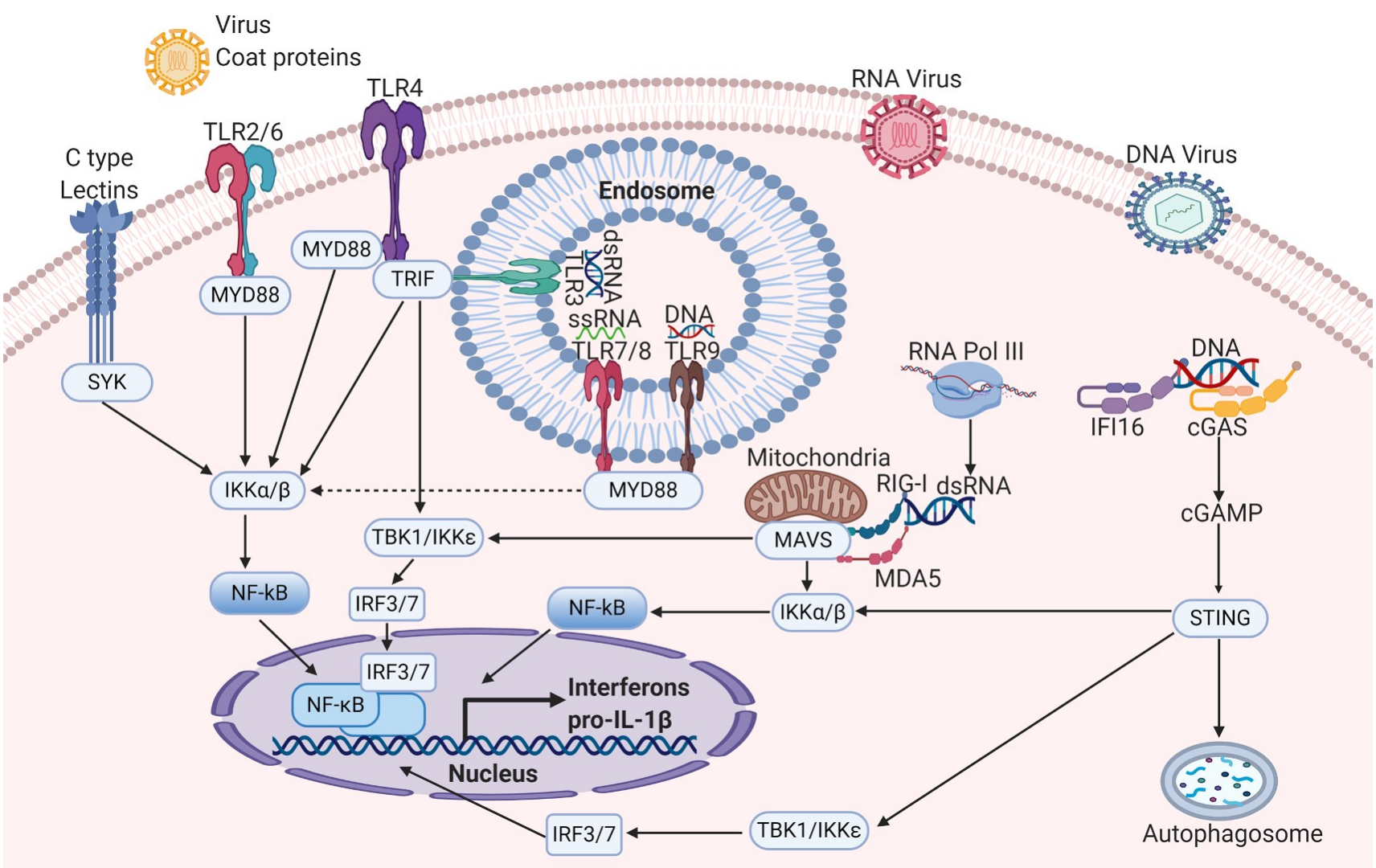
Parruti et al, BMC Medicine, 2010; Gialloreti et al. BMC Inf Diseases 2010; Alicino et al. Human Vaccines&Immunotherapeutics; Salvetti et al. Preventive Med Reports 2019

Il *disease burden* aumenta nelle fasce di età più avanzate



	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>=85
Overall	3.95	5.55	6.45	6.07	9.06	8.19	8.58	5.59
Female	3.63	7.41	9.49	5.40	9.06	10.88	6.01	7.38
Male	3.97	4.03	6.94	5.33	11.82	5.33	8.88	8.58

Alicino C, Trucchi C, Paganino C, et al. Hum Vaccin Immunother 2017; 13: 399-404


Virus
Coat proteins
TLR4
TLR2/6
C type
Lectins
RNA Virus
DNA Virus
Endosome
MYD88
TRIF
MYD88
dsRNA
TLR3
ssRNA
TLR7/8
DNA
TLR9
SYK
RNA Pol III
DNA
IFI16
cGAS
Mitochondria
RIG-I
dsRNA
cGAMP
IKKα/β
MYD88
TBK1/IKKε
MAVS
MDA5
NF-kB
IRF3/7
NF-kB
IKKα/β
STING
IRF3/7
NF-κB
Interferons
pro-IL-1β
Nucleus
IRF3/7
TBK1/IKKε
Autophagosome

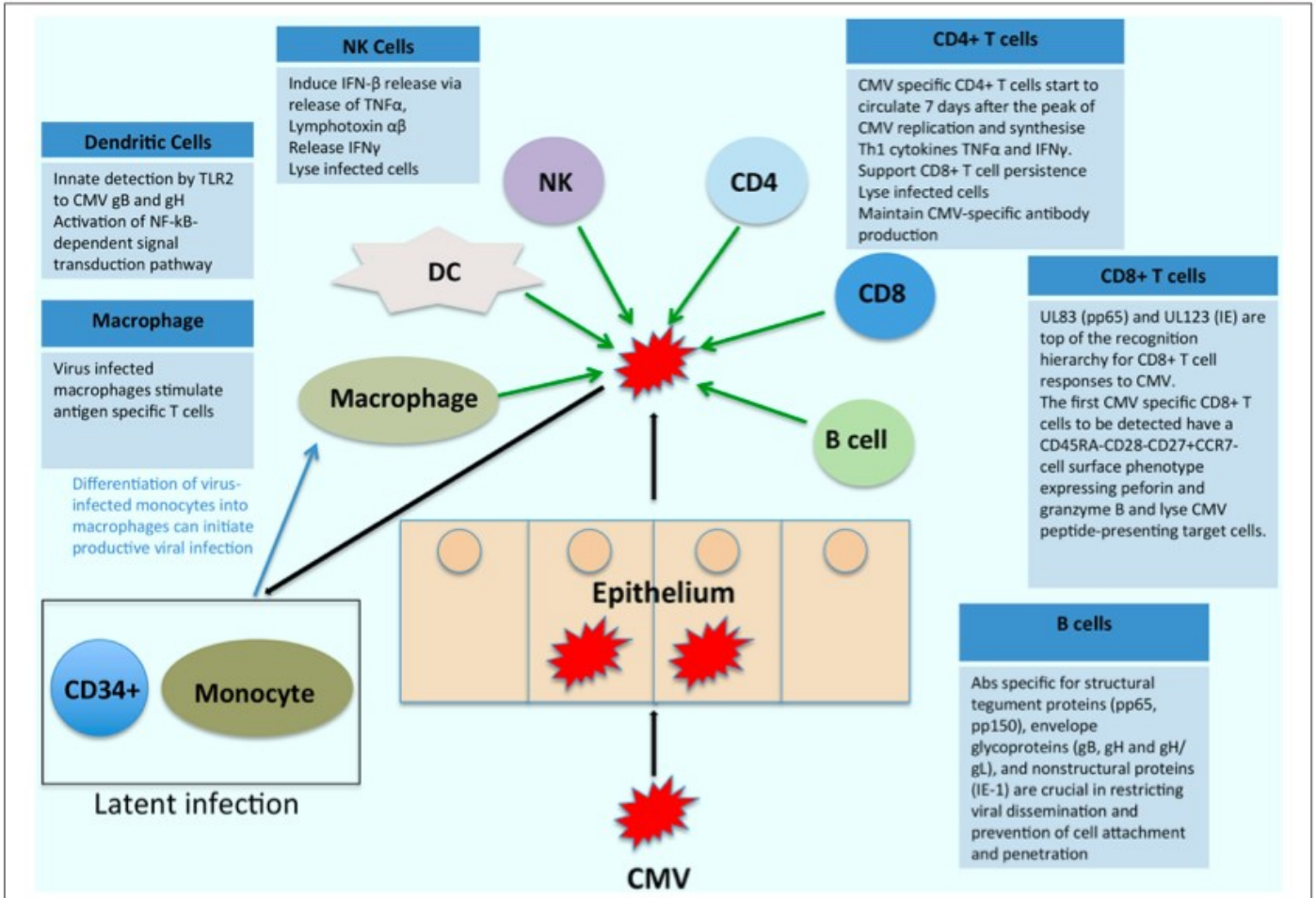
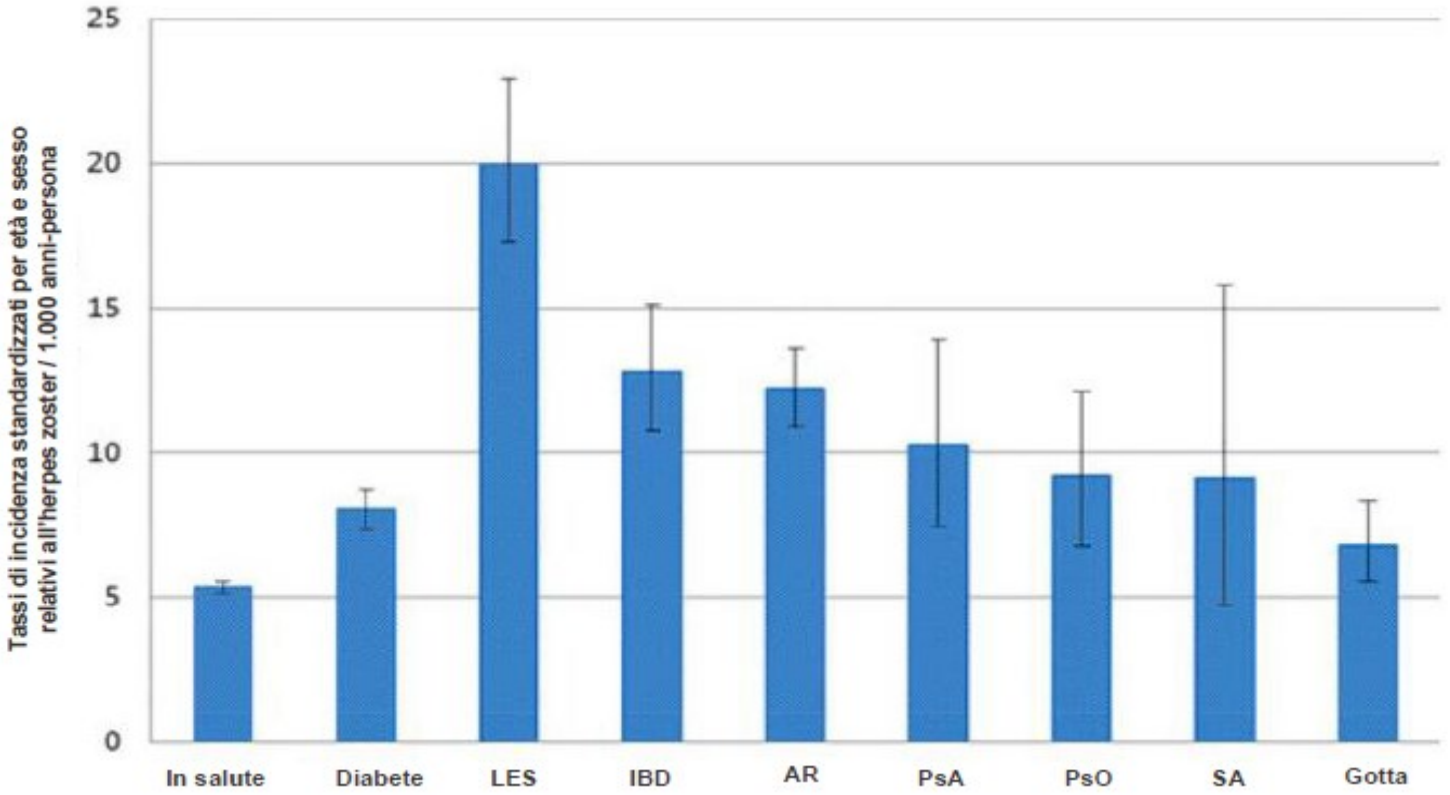


FIGURE 2 | Impact of the immune system on CMV. CMV immune control is reliant on both the innate and adaptive arms of the immune system. We have here summarized the key elements, highlighting the complex interplay of multiple limbs of the immune system in containing CMV infection.

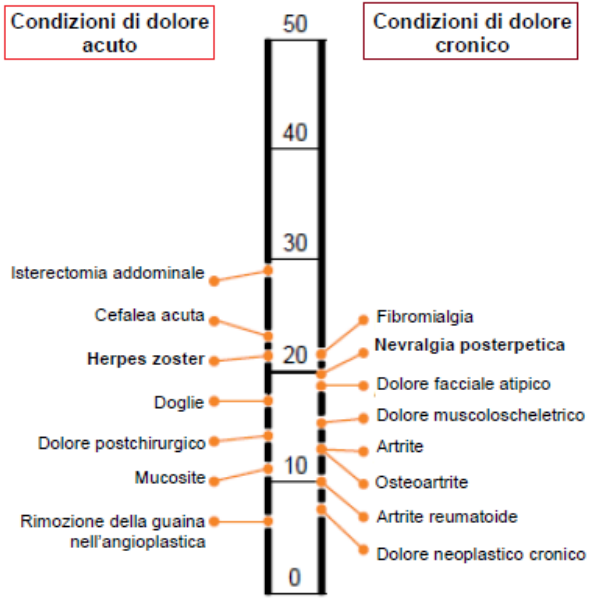
L’incidenza aumenta con l’immunocompromissione



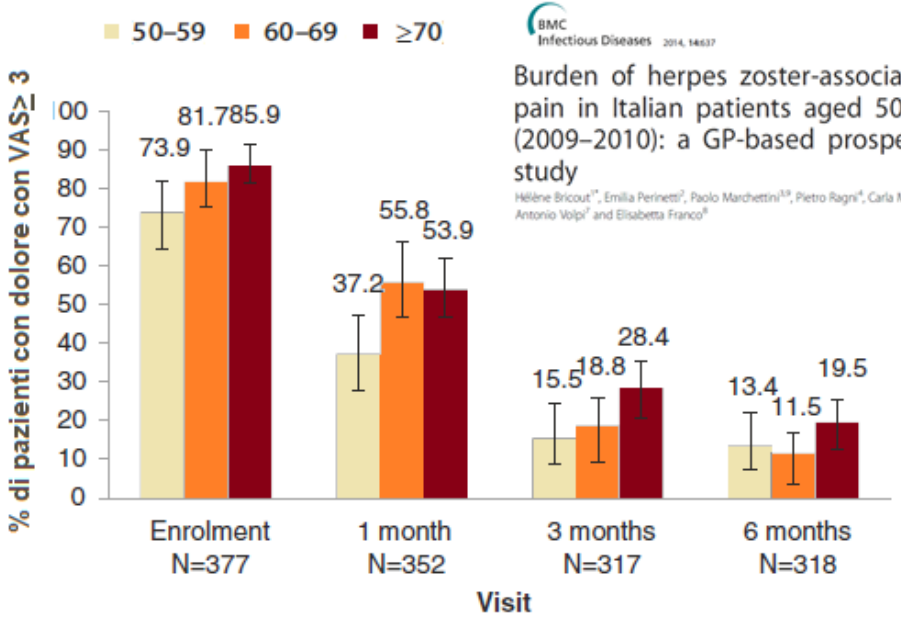
Yun H, Yang S, Chen L et al. Risk of herpes zoster in autoimmune and inflammatory diseases: Implications for vaccination. Arthritis Rheumatol 2016;68:2328-2337.

La NPE è la complicanza più frequente

Punteggi comparativi del McGill Pain Questionnaire per le condizioni di dolore acuto e cronico,



Reprinted from Katz J, Melzack R. Surg Clin N Amer(1999)

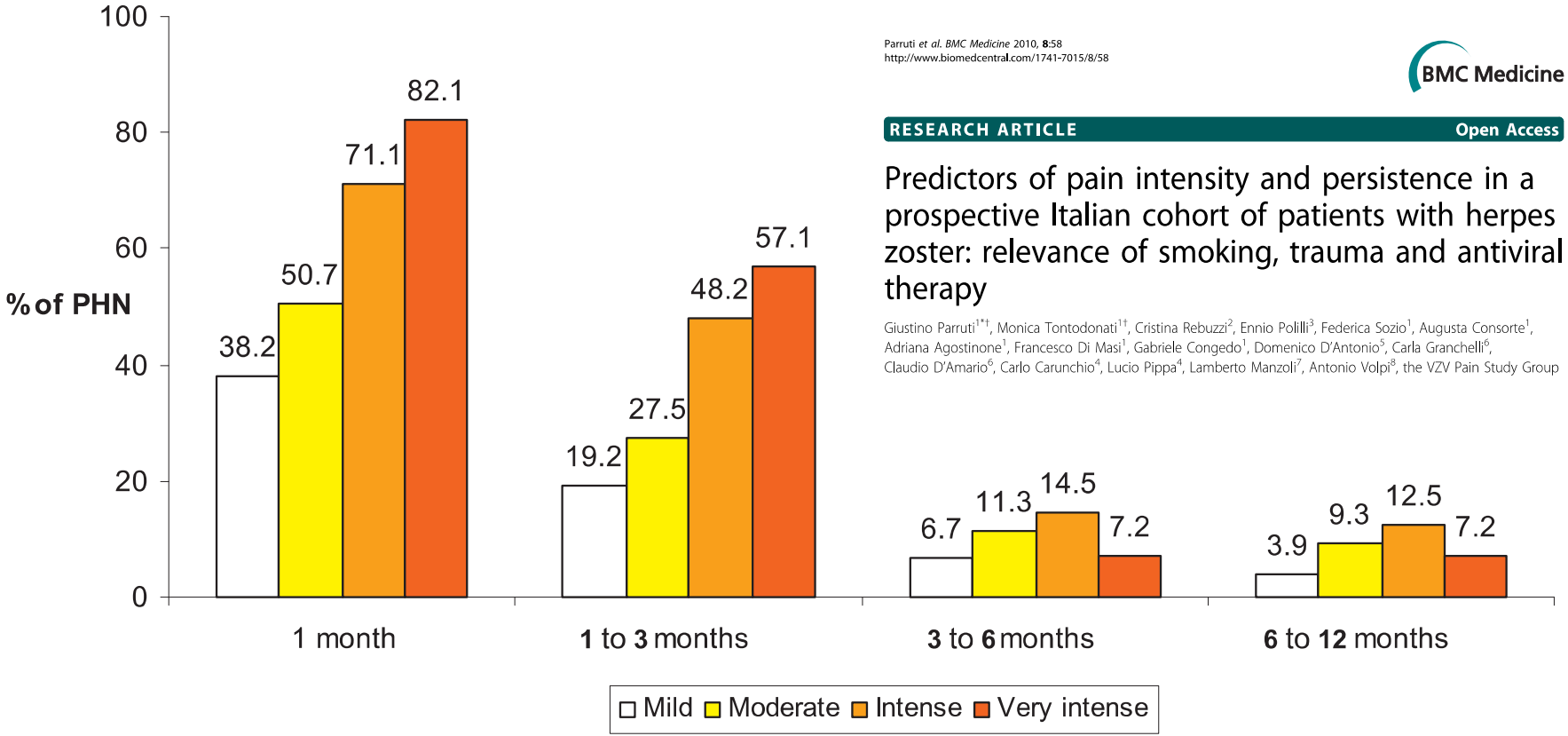


BMC Infectious Diseases 2014, 14:637

Burden of herpes zoster-associated chronic pain in Italian patients aged 50 years and over (2009–2010): a GP-based prospective cohort study

Hélène Bricout[1*], Emilia Perinetti[2], Paolo Marchettini[3,9], Pietro Ragni[4], Carla Maria Zotti[5], Giovanni Gabutti[6], Antonio Volpi[7] and Elisabetta Franco[8]

Pain intensity at presentation and risk of PHN at different time intervals



Parruti *et al. BMC Medicine* 2010, **8**:58
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BMC Medicine

RESEARCH ARTICLE Open Access

Predictors of pain intensity and persistence in a prospective Italian cohort of patients with herpes zoster: relevance of smoking, trauma and antiviral therapy

Giustino Parruti[1*†], Monica Tontodonati[1†], Cristina Rebuzzi[2], Ennio Polilli[3], Federica Sozio[1], Augusta Consorte[1], Adriana Agostinone[1], Francesco Di Masi[1], Gabriele Congedo[1], Domenico D'Antonio[5], Carla Granchelli[6], Claudio D'Amario[6], Carlo Carunchio[4], Lucio Pippa[4], Lamberto Manzoli[7], Antonio Volpi[8], the VZV Pain Study Group

Le complicanze maggiori aumentano con età ed immuno-compromissione

Complicanza	Descrizione
HZO	– HZ con interessamento oculare – Ampia gamma di complicanze, come cheratite, uveiti/iriti, ulcerazione corneale, congiuntivite, coroidite, paralisi oculomotoria, atrofia ottica, retinite, glaucoma acuto e cronico ecc.
Encefalite da VZV acuta	– Di solito si verifica pochi giorni dopo l'insorgenza del rash – Caratterizzata da delirio acuto o subacuto e pochi segni neurologici focali – Altri sintomi includono mal di testa, meningismo, febbre, atassia e convulsioni
Mielite	– A causa dell'invasione diretta da parte del VZV del midollo spinale – Più comunemente segue HZ toracico – I sintomi neurologici si sviluppano ~12 giorni dopo l'insorgenza del rash – I sintomi includono disfunzioni della vescica, debolezza degli arti inferiori, riflessi asimmetrici e disturbi sensoriali
Retinite da VZV	– Necrosi retinica acuta in pazienti immunocompetenti e immunocompromessi – Necrosi retinica esterna progressiva o RPHRN nei pazienti affetti da AIDS – La RPHRN può verificarsi dopo HZO o dopo HZ con interessamento di un dermatomo remoto
Prurito posterpetico[12]	– Può manifestarsi con o senza NPE – Può persistere dopo che il rash da HZ si è risolto – Il prurito cronico può portare a una invalidità importante dovuta all'impellente bisogno di grattarsi
Sindrome di Ramsay-Hunt	– Paralisi del nervo facciale periferico (debolezza facciale unilaterale) combinata con vescicole zoster su orecchio, palato duro o lingua – Altri sintomi includono malessere, febbre, dolore, vertigini, perdita dell'udito, sensibilità al suono, tinnito e perdita del gusto
Ictus	– La riattivazione del VZV nelle arterie cerebrali, con o senza rash da zoster, causa in modo diretto rimodellamento vascolare patologico e ictus (vasculopatia da VZV) – Può causare ictus ischemico o emorragico
Malattia cutanea disseminata	– Generalmente si verifica solo nei pazienti immunocompromessi – Non è potenzialmente fatale; tuttavia, è un marker per la viremia da VZV
Malattia viscerale disseminata (senza coinvolgimento cutaneo)	– Può verificarsi in pazienti profondamente immunocompromessi – Con il trattamento antivirale, il tasso di mortalità è del 5-15%; la polmonite è la causa di morte più comune

Kost RG, Straus SE. Postherpetic neuralgia--pathogenesis, treatment, and prevention. N Engl J Med 1996;335:32-42.

Il rischio di complicanze neurologiche e vascolari rare da VZV incrementa con la compromissione del sistema immune

Table 3 Proportion of patients with HZ with PHN, at least one HZ complication other than PHN, or vascular complications as assessed within 90 days of HZ onset, HES-CPRD, 2000–2011

	IC cohort (N=21 146)		IC-free cohort (N=18583)	
Type of complications	**n (%)**	**95% CI**	**n (%)**	**95% CI**
PHN	2253 (10.65)	10.24 to 11.08	1690 (9.09)	8.68 to 9.52
HZ complications other than PHN (overall)	623 (2.95)	2.72 to 3.18	436 (2.35)	2.13 to 2.57
Ocular	411 (1.94)	1.76 to 2.14	299 (1.61)	1.43 to 1.8
Neurological other than PHN	137 (0.65)	0.54 to 0.77	85 (0.46)	0.37 to 0.57
Disseminated	12 (0.06)	0.03 to 0.1	1 (0.01)	0 to 0.03
Other complications	69 (0.33)	0.25 to 0.41	54 (0.29)	0.22 to 0.38
Vascular complications				
Stroke	88 (0.42)	0.33 to 0.51	105 (0.57)	0.46 to 0.68
Transient ischaemic attack	52 (0.25)	0.18 to 0.32	30 (0.16)	0.11 to 0.23
Optic neuritis, vascular retinitis	9 (0.04)	0.02 to 0.08	5 (0.03)	0.01 to 0.06
Myocardial infarction	36 (0.17)	0.12 to 0.24	23 (0.12)	0.08 to 0.19

CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; N, Number of patients with HZ; n (%), number (percentage) of the patients with HZ with this complication; PHN, postherpetic neuralgia.

Yanni EA. et al et al. *BMJ open 2018*

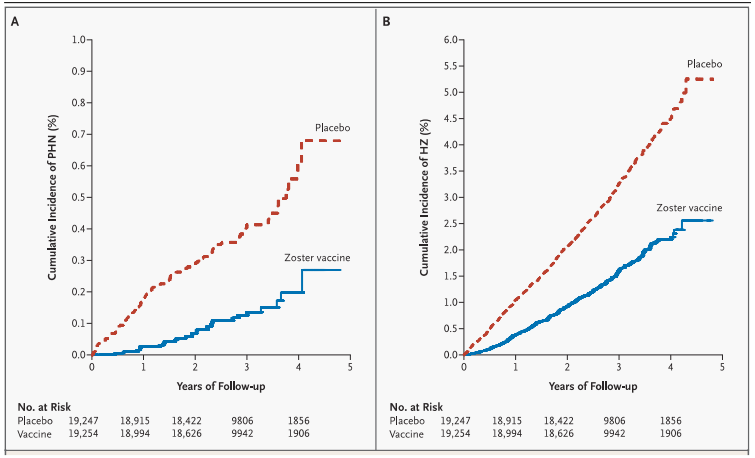
L’esperienza del vaccino vivo attenuato

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 2, 2005 VOL. 352 NO. 22

A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults

M.N. Oxman, M.D., M.J. Levin, M.D., G.R. Johnson, M.S., K.E. Schmader, M.D., S.E. Straus, M.D., L.D. Gelb, M.D., R.D. Arbeit, M.D., M.S. Simberkoff, M.D., A.A. Gershon, M.D., L.E. Davis, M.D., A. Weinberg, M.D., K.D. Boardman, R.Ph., H.M. Williams, R.N., M.S.N., J. Hongyuan Zhang, Ph.D., P.N. Peduzzi, Ph.D., C.E. Beisel, Ph.D., V.A. Morrison, M.D., J.C. Guatelli, M.D., P.A. Brooks, M.D., C.A. Kauffman, M.D., C.T. Pachucki, M.D., K.M. Neuzil, M.D., M.P.H., R.F. Betts, M.D., P.F. Wright, M.D., M.R. Griffin, M.D., M.P.H., P. Brunell, M.D., N.E. Soto, M.D., A.R. Marques, M.D., S.K. Keay, M.D., Ph.D., R.P. Goodman, M.D., D.J. Cotton, M.D., M.P.H., J.W. Gnann, Jr., M.D., J. Loutit, M.D., M. Holodniy, M.D., W.A. Keitel, M.D., G.E. Crawford, M.D., S.-S. Yeh, M.D., Ph.D., Z. Lobo, M.D., J.F. Toney, M.D., R.N. Greenberg, M.D., P.M. Keller, Ph.D., R. Harbecke, Ph.D., A.R. Hayward, M.D., Ph.D., M.R. Irwin, M.D., T.C. Kyriakides, Ph.D., C.Y. Chan, M.D., I.S.F. Chan, Ph.D., W.W.B. Wang, Ph.D., P.W. Annunziato, M.D., and J.L. Silber, M.D., for the Shingles Prevention Study Group*



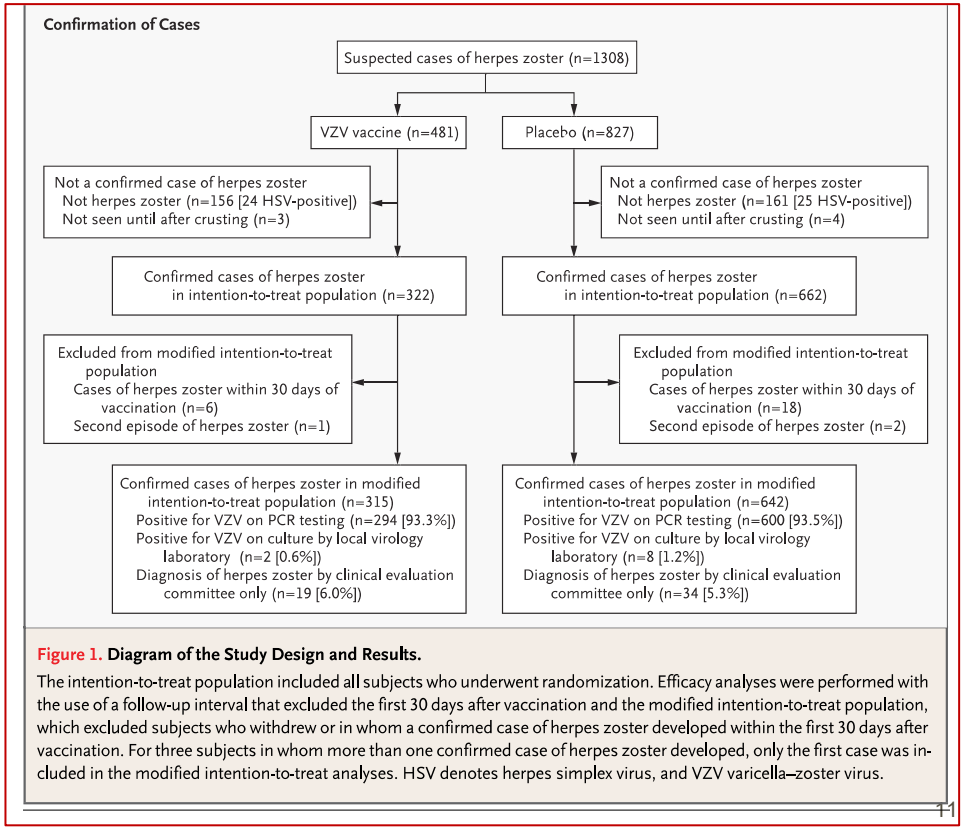


Figure 1. Diagram of the Study Design and Results.

The intention-to-treat population included all subjects who underwent randomization. Efficacy analyses were performed with the use of a follow-up interval that excluded the first 30 days after vaccination and the modified intention-to-treat population, which excluded subjects who withdrew or in whom a confirmed case of herpes zoster developed within the first 30 days after vaccination. For three subjects in whom more than one confirmed case of herpes zoster developed, only the first case was included in the modified intention-to-treat analyses. HSV denotes herpes simplex virus, and VZV varicella–zoster virus.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2016 VOL. 375 NO. 11

Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older

A.L. Cunningham, H. Lal, M. Kovac, R. Chlibek, S.-J. Hwang, J. Díez-Domingo, O. Godeaux, M.J. Levin, J.E. McElhaney, J. Puig-Barberà, C. Vanden Abeele, T. Vesikari, D. Watanabe, T. Zahaf, A. Ahonen, E. Athan, J.F. Barba-Gomez, L. Campora, F. de Looze, H.J. Downey, W. Ghesquiere, I. Gorfinkel, T. Korhonen, E. Leung, S.A. McNeil, L. Oostvogels, L. Rombo, J. Smetana, L. Weckx, W. Yeo, and T.C. Heineman, for the ZOE-70 Study Group*

ABSTRACT

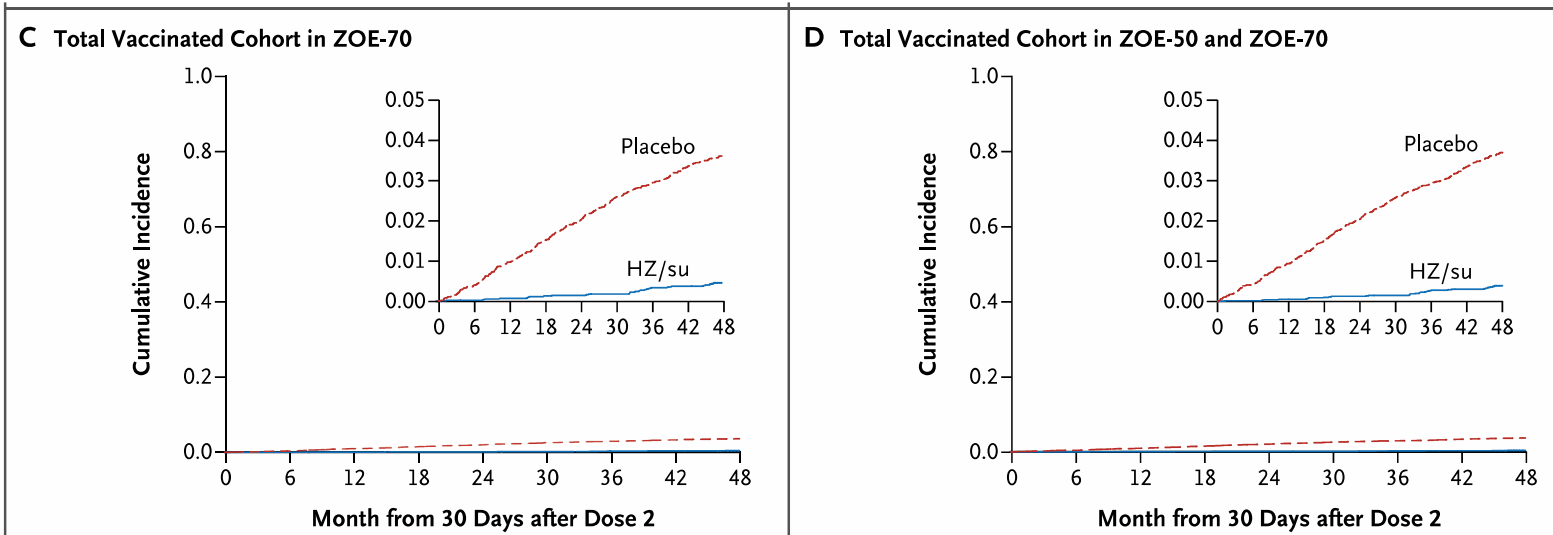


Figure 2. Risk of Development of Herpes Zoster after Vaccination.

Shown are the Kaplan–Meier estimates of the cumulative incidence (expressed as the percentage of the participants at risk) of the development of herpes zoster during the period from 30 days after receiving the second dose of HZ/su or placebo to the end of follow-up among participants 70 years of age or older. Because of the declining numbers of participants at risk, the Kaplan–Meier curves have been truncated at 48 months after the second dose of HZ/su. Some cases occurred after 48 months. In each panel, the inset shows the same data on an expanded y axis.

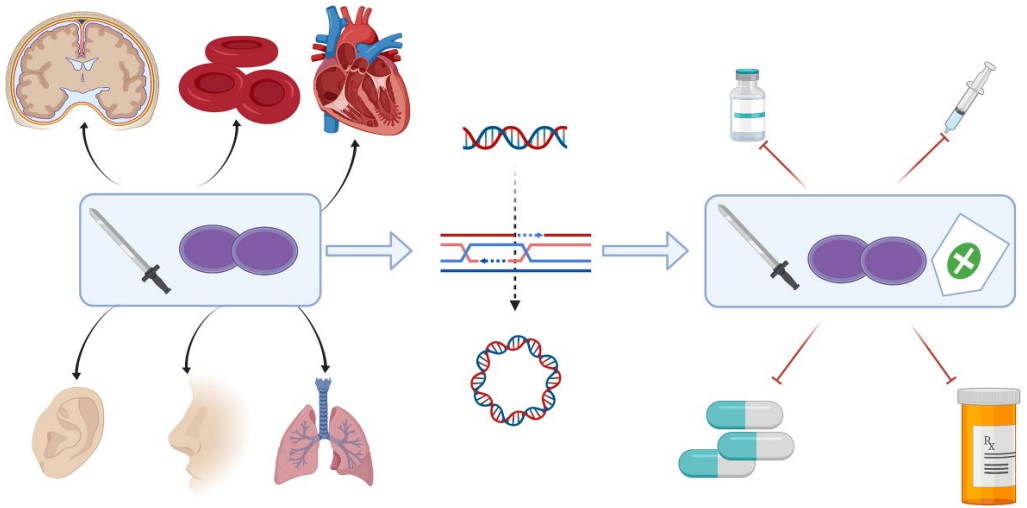
valore aggiunto della Vaccinazione per VZV?

Sarà interessante valutare come la vaccinazione con Shingrix possa impattare su di un complesso fenomeno disregolativo che nell'immune-aging impatta su:

- Frequenti riattivazioni di HSV
- Severa espressività si HSV

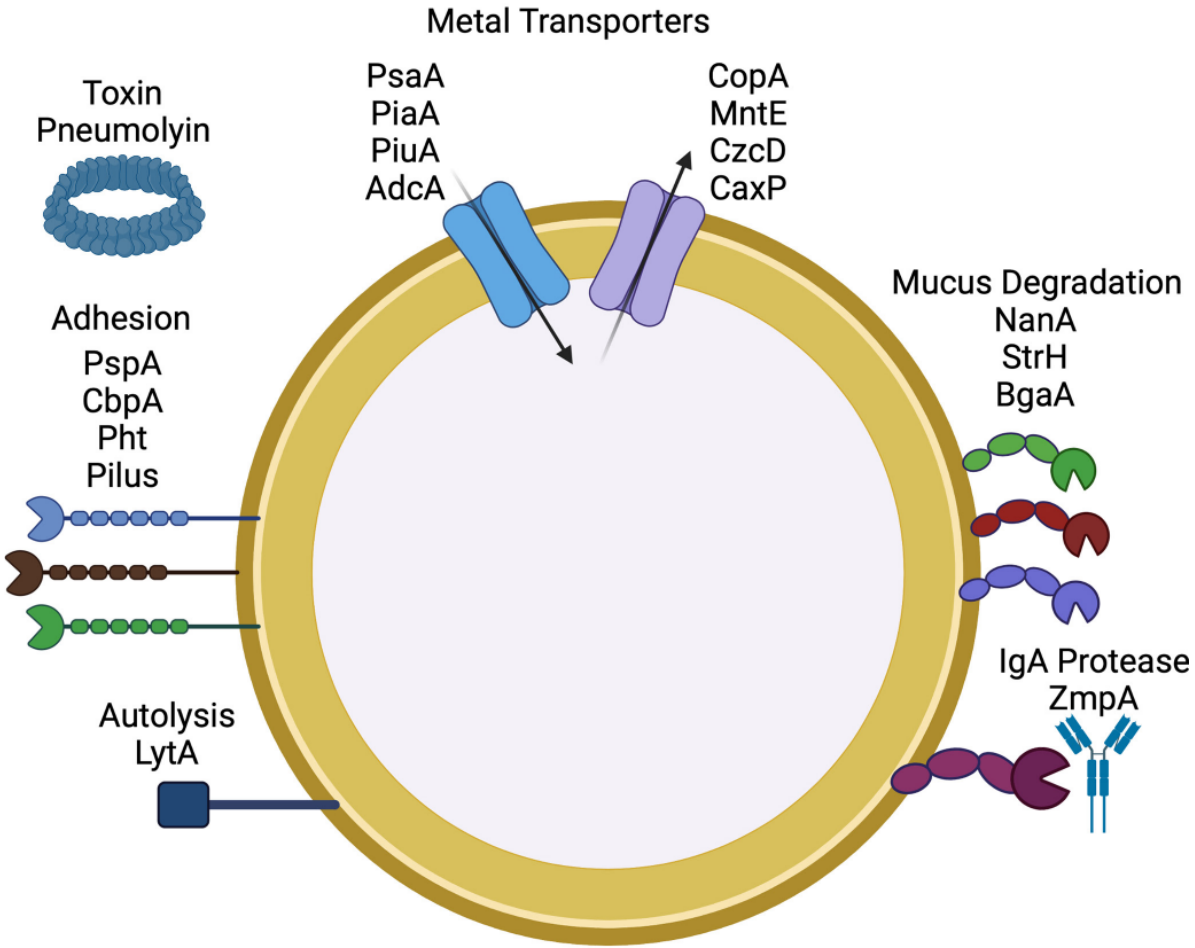
JMM Profile: *Streptococcus pneumoniae:* sugar-coated captain of the men of death

Tina H. Dao and Jason W. Rosch*

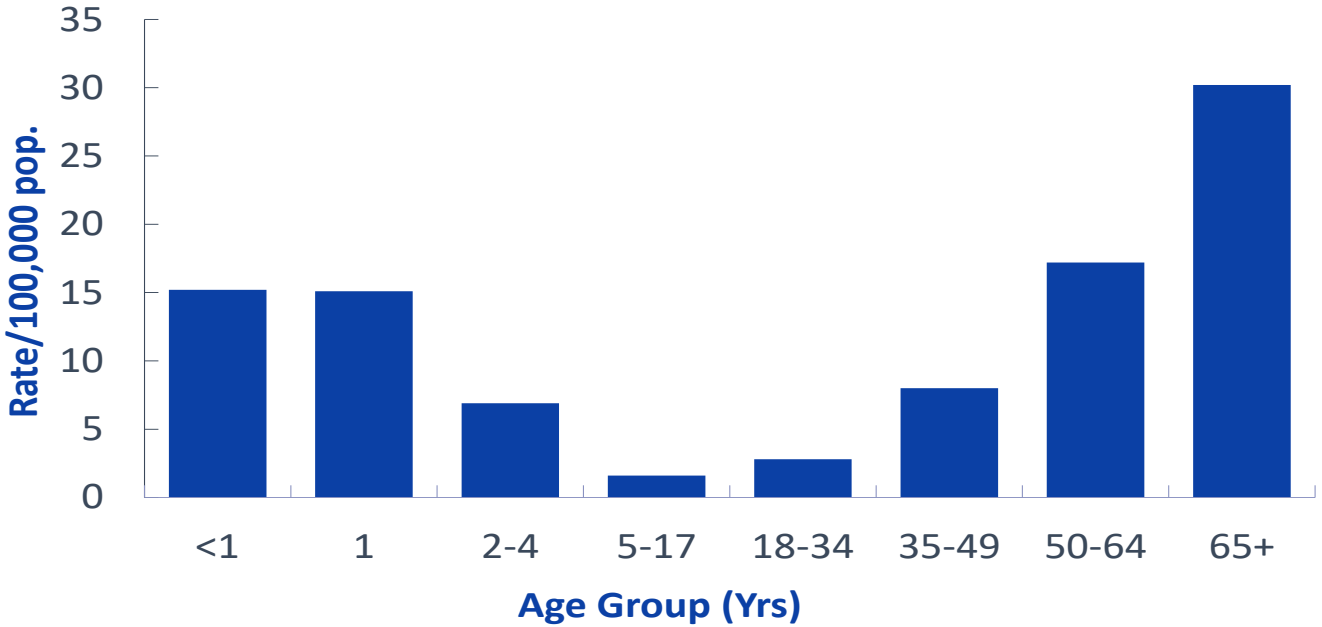


Graphical abstract

Streptococcus pneumoniae utilizes a battery of virulence factors (indicated by the sword) to cause mucosal infections, including otitis media and pneumonia, and invasive disease, including bacteremia, meningitis and cardiac lesions (left panel). In addition, a naturally competent pathogen, the pneumococcus, can rapidly acquire new genetic content (center panel) that can enable vaccine escape variants and spread antibiotic resistance (shield), allowing the pathogen to evade clinical interventions (right panel).


Metal Transporters
Toxin
Pneumolyin
PsaA
PiaA
PiuA
AdcA
CopA
MntE
CzcD
CaxP
Mucus Degradation
NanA
StrH
BgaA
Adhesion
PspA
CbpA
Pht
Pilus
IgA Protease
ZmpA
Autolysis
LytA

Invasive Pneumococcal Disease Incidence by Age Group–2013*



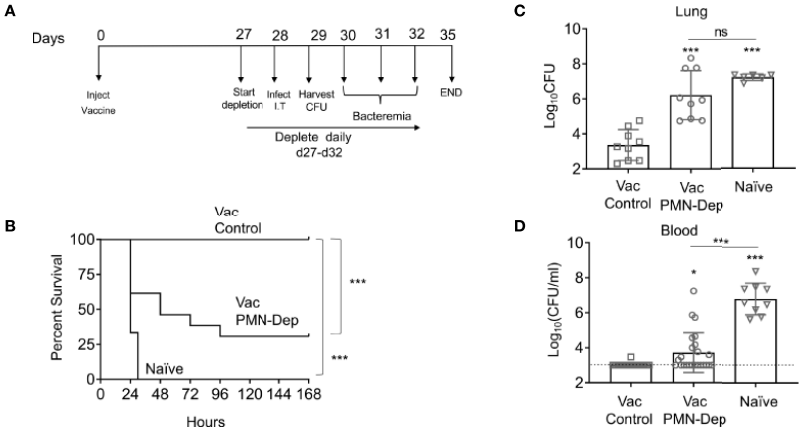
*CDC Active Bacterial Core surveillance 2009 report:
http://www.cdc.gov/abcs/reports-findings/survreports/spneu13.html

frontiers in Cellular and Infection Microbiology

ORIGINAL RESEARCH
published: 23 March 2022
doi: 10.3389/fcimb.2022.849224

The Age-Driven Decline in Neutrophil Function Contributes to the Reduced Efficacy of the Pneumococcal Conjugate Vaccine in Old Hosts

Shaunna R. Simmons, Essi Y. I. Tchalla, Manmeet Bhalla and Elsa N. Bou Ghanem *

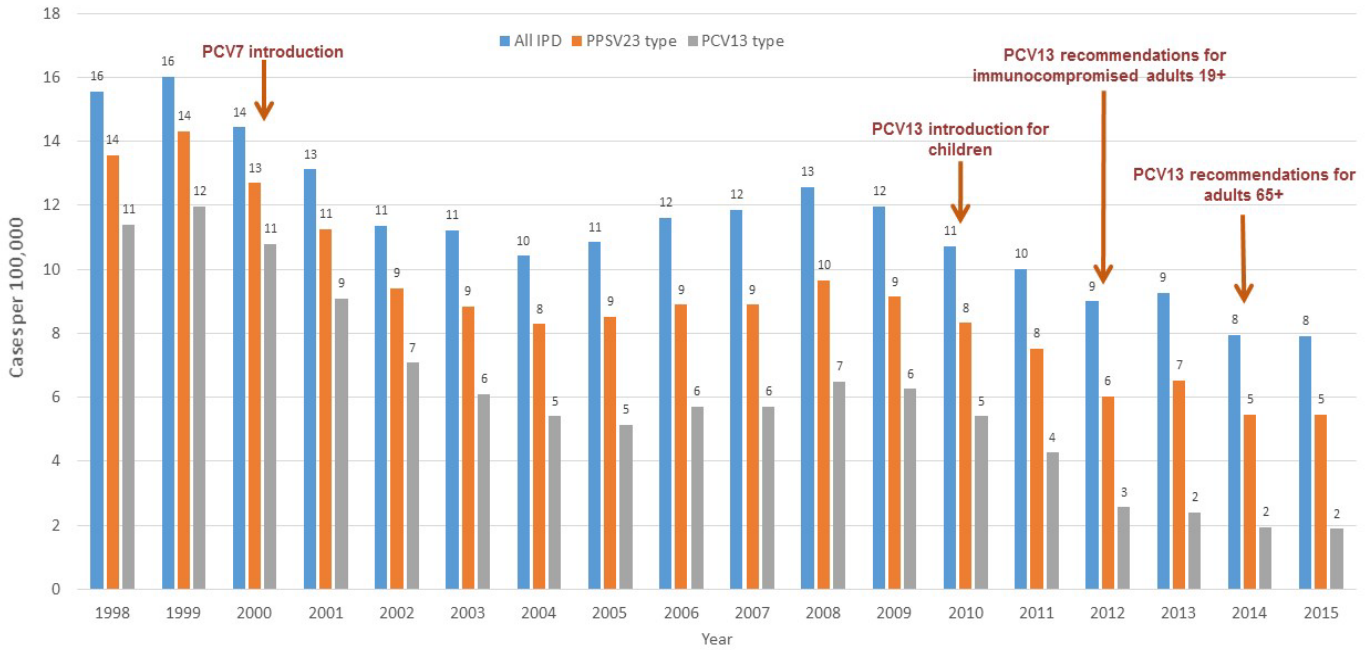


Despite the availability of vaccines, *Streptococcus pneumoniae* (pneumococcus) remains a serious cause of infections in the elderly. The efficacy of anti-pneumococcal vaccines declines with age. While age-driven changes in antibody responses are well defined, less is known about the role of innate immune cells such as polymorphonuclear leukocytes (PMNs) in the reduced vaccine protection seen in aging. Here we explored the role of PMNs in protection against *S. pneumoniae* in vaccinated hosts. We found that depletion of PMNs in pneumococcal conjugate vaccine (PCV) treated young mice prior to pulmonary challenge with *S. pneumoniae* resulted in dramatic loss of host protection against infection. Immunization boosted the ability of PMNs to kill *S. pneumoniae* and this was dependent on bacterial opsonization by antibodies. Bacterial opsonization with immune sera increased several PMN anti-microbial activities including bacterial uptake, degranulation and ROS production. As expected, PCV failed to protect old mice against *S. pneumoniae*. In probing the role of PMNs in this impaired protection, we found that aging was accompanied by an intrinsic decline in PMN function. PMNs from old mice failed to effectively kill *S. pneumoniae* even when the bacteria were opsonized with immune sera from young controls. In exploring mechanisms, we found that PMNs from old mice produced less of the antimicrobial peptide CRAMP and failed to efficiently kill engulfed pneumococci. Importantly, adoptive transfer of PMNs from young mice reversed the susceptibility of vaccinated old mice to pneumococcal infection. Overall, this study demonstrates that the age-driven decline in PMN function impairs vaccine-mediated protection against *Streptococcus pneumoniae*.

Pneumococcal Vaccines

1977	14-valent polysaccharide vaccine licensed
1983	23-valent polysaccharide vaccine licensed (PPSV23)
2000	7-valent polysaccharide conjugate vaccine licensed (PCV7)
2010	13-valent polysaccharide conjugate vaccine licensed (PCV13)

Trends in Invasive Pneumococcal Disease Among Adults 19–64 Years of Age, 1998–2015



*PPSV23 serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F
†PCV13 serotype: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Active Bacterial Core surveillance data, 1998–2015, unpublished

http://www.cdc.gov/abcs/reports-findings/survreports/spneu-types.html

JAMA Network Open

Original Investigation | Infectious Diseases

Incidence and Estimated Vaccine Effectiveness Against Hospitalizations for All-Cause Pneumonia Among Older US Adults Who Were Vaccinated and Not Vaccinated With 13-Valent Pneumococcal Conjugate Vaccine

Amber Hsiao, MPH; John Hansen, MPH; Julius Timbol, MS; Ned Lewis, MPH; Raul Isturiz, MD; Ronika Alexander-Parrish, MAEd; John M. McLaughlin, PhD; Bradford D. Gessner, MD, MPH; Nicola P. Klein, MD, PhD

Characteristics	Person-years, No.			
	All-cause pneumonia		LRTI	
	PCV13 vaccinated	Not PCV13 vaccinated	PCV13 vaccinated	Not PCV13 vaccinated
Age group				
65-69 years	110 918	128 770	110 872	128 692
70-79 years	90 271	165 632	90 168	165 332
≥80 years	505	2315	502	2308
Received PPV23 (since age 65)				
Yes	104 047	215 253	103 939	214 924
No	97 647	81 464	97 604	81 408
Prior health care use				
Low	113 851	154 875	113 791	154 702
Medium	57 328	95 585	57 285	95 473
High	30 515	46 257	30 468	46 157
Charlson score				
Low	130 502	156 980	130 477	156 945
Medium	42 370	80 586	42 332	80 518
High	28 822	59 151	28 734	58 870

Abstract

IMPORTANCE Following routine use of 13-valent pneumococcal conjugate vaccine (PCV13) in children in 2010, invasive pneumococcal disease rates have decreased substantially in children and adults. In 2014, the Advisory Committee for Immunization Practices recommended routine use of PCV13 among adults aged 65 years or older; previously only 23-valent pneumococcal polysaccharide vaccine (PPV23) was recommended.

OBJECTIVE To estimate the association between the incidence of hospitalized all-cause pneumonia and lower respiratory tract infections (LRTI) and PCV13 vaccination among older adults at Kaiser Permanente Northern California (KPNC).

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included adults at KPNC aged 65 years or older between July 1, 2015, and June 30, 2018, born after 1936 with no known history of PPV23 or PCV13 receipt before age 65. The study took place at an integrated health care system with an annual membership more than 4 million individuals, approximately 15% of whom are 65 years or older and broadly representative of the region. Data analysis took place from July 2018 to December 2021, and data collection took place from November 2016 to June 2018.

EXPOSURES PCV13 vaccination status was ascertained from the electronic medical record (EMR). Individuals were considered vaccinated 14 days following immunization.

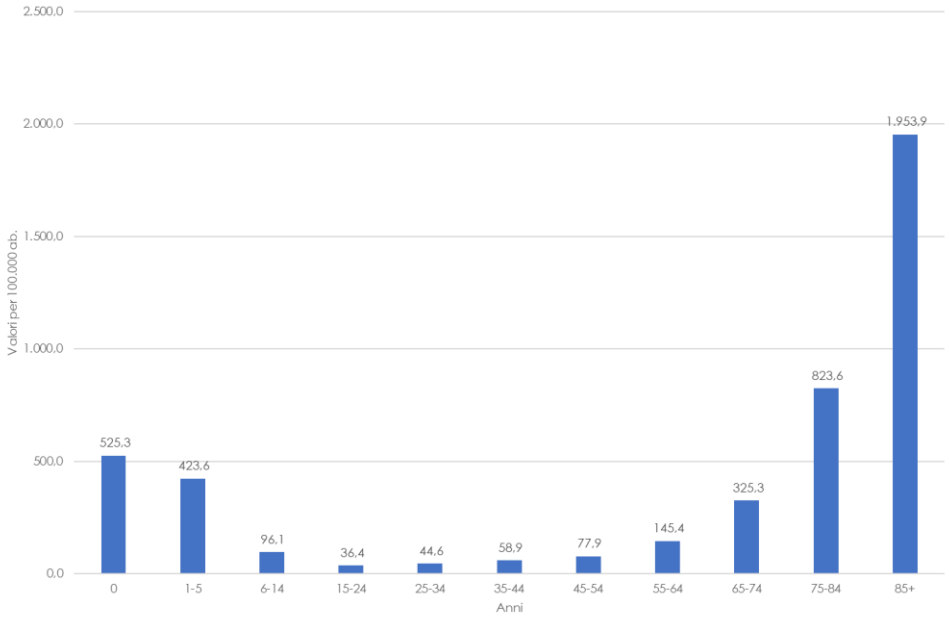
MAIN OUTCOMES AND MEASURES First hospitalized all-cause pneumonia was identified in the EMR using primary/secondary discharge diagnosis *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes. First hospitalized LRTI was identified using pneumonia codes and acute bronchitis codes. Relative risk (RR) of first pneumonia or LRTI hospitalization of individuals who were PCV13 vaccinated vs PCV13 unvaccinated was estimated using Poisson regressions adjusted for sex, race, ethnicity, age, influenza vaccine receipt, PPV23 receipt since age 65, pneumonia risk factors, health care use, and season. Vaccine effectiveness (VE) was estimated as (1−RR) × 100%.

RESULTS Of 192 061 adults, 107 957 (56%) were female and 139 024 (72%) were White individuals. PCV13 coverage increased from 0 in 2014 to 135 608 (76.9%) by 2018. There were 3488 individuals with 3766 pneumonia hospitalizations and 3846 individuals with 4173 LRTI hospitalizations. PCV13 was associated with an adjusted VE of 10.0% (95% CI, 2.4-17.0; $P = .01$) against hospitalized pneumonia and 9.4% (95% CI, 2.1-16.1; $P = .01$) against hospitalized LRTI.

Tabella 9 - Casi di malattia invasiva da pneumococco per quadro clinico, età e anno (2018-2020)

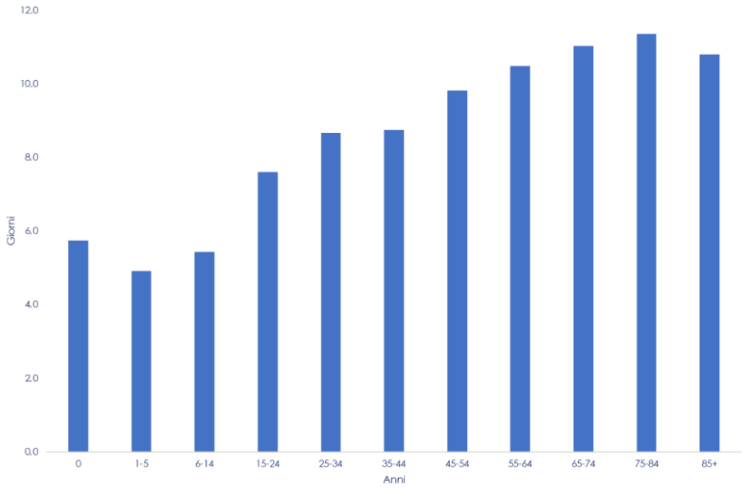
		0		1 - 4		5 - 9		10 - 14		15 - 24		25 - 64		> 64		TOTALE	
	Quadro clinico	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
2018	Meningite*	10	*43*	8	*18*	7	*41*	5	*56*	4	*24*	184	*35*	186	*20*	404	*26*
	Polmonite con Sepsi/Batteriemia	1	*4*	17	*39*	0	*0*	0	*0*	7	*41*	166	*31*	325	*36*	516	*33*
	Sepsi/Batteriemia	10	*43*	18	*41*	9	*53*	3	*33*	6	*35*	168	*32*	374	*41*	588	*38*
	Altro quadro clinico con Sepsi/Batteriemia	2	*9*	1	*2*	1	*6*	1	*11*	0	*0*	7	*1*	18	*2*	30	*2*
	Altro**	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*	2	*0*	7	*1*	9	*1*
	TOTALE 2018	**23**		**44**		**17**		**9**		**17**		**527**		**910**		**1547**	
2019	Meningite *	13	*46*	7	*21*	5	*38*	6	*67*	14	*56*	172	*31*	163	*16*	380	*23*
	Polmonite con Sepsi/Batteriemia	6	*21*	6	*18*	3	*23*	2	*22*	8	*32*	177	*31*	401	*40*	603	*36*
	Sepsi/Batteriemia	9	*32*	17	*50*	5	*38*	1	*11*	2	*8*	197	*35*	417	*41*	648	*39*
	Altro quadro clinico con Sepsi/Batteriemia	0	*0*	4	*12*	0	*0*	0	*0*	1	*4*	12	*2*	22	*2*	39	*2*
	Altro**	0	*0*	0	*0*	0	*0*	0	*0*	0	*0*	4	*1*	5	*0*	9	*1*
	TOTALE 2019	**28**		**34**		**13**		**9**		**25**		**562**		**1008**		**1679**	
2020	Meningite *	2	*18*	2	*13*	5	*63*	3	*100*	2	*50*	62	*35*	47	*17*	123	*25*
	Polmonite con Sepsi/Batteriemia	1	*9*	2	*13*	0	*0*	0	*0*	1	*25*	53	*30*	107	*38*	164	*33*
	Sepsi/Batteriemia	8	*73*	10	*67*	3	*38*	0	*0*	1	*25*	54	*31*	111	*39*	187	*37*
	Altro quadro clinico con Sepsi/Batteriemia	0	*0*	1	*7*	0	*0*	0	*0*	0	*0*	5	*3*	6	*2*	12	*2*

Figura 6. Tasso di ospedalizzazione in acuzie per polmonite Per età - Anno 2019



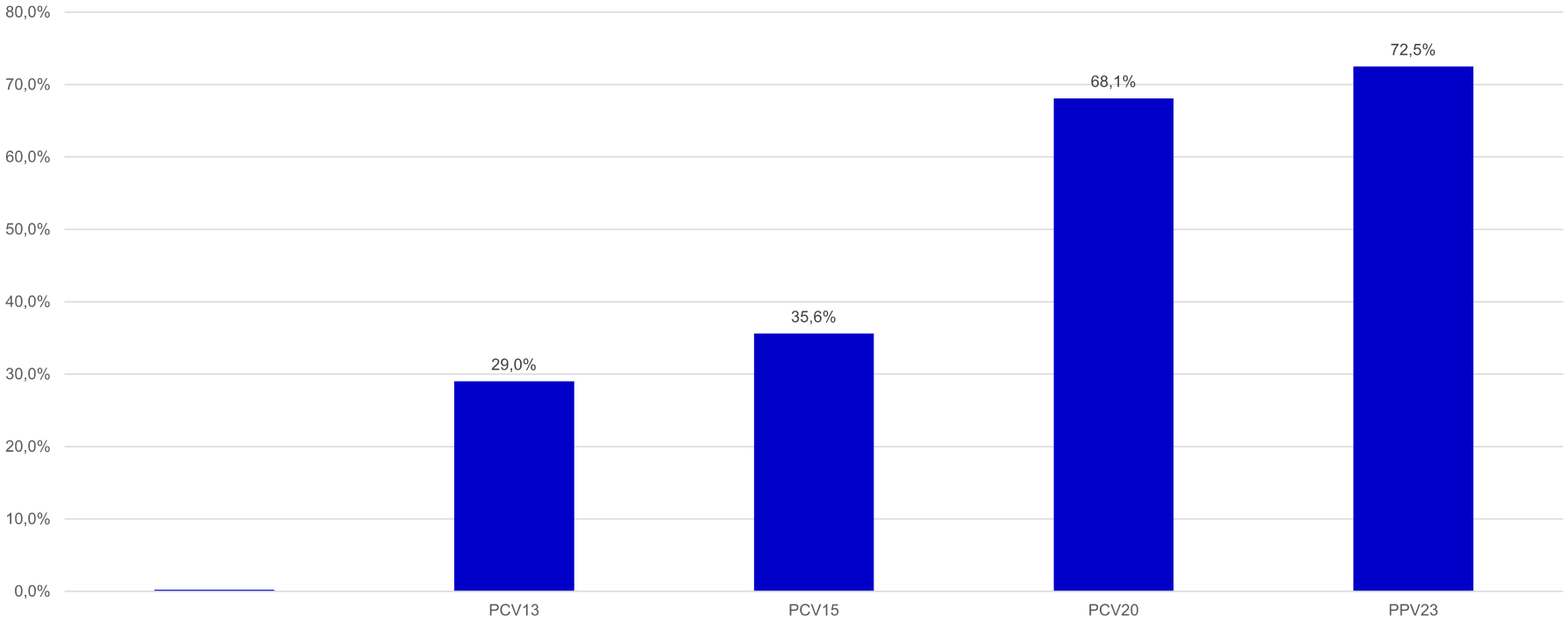
Fonte: Elaborazione C.R.E.A. Sanità© su dati SDO, Ministero della Salute

Figura 10. Degenza media per ricoveri ordinari in acuzie per età - Anno 2019



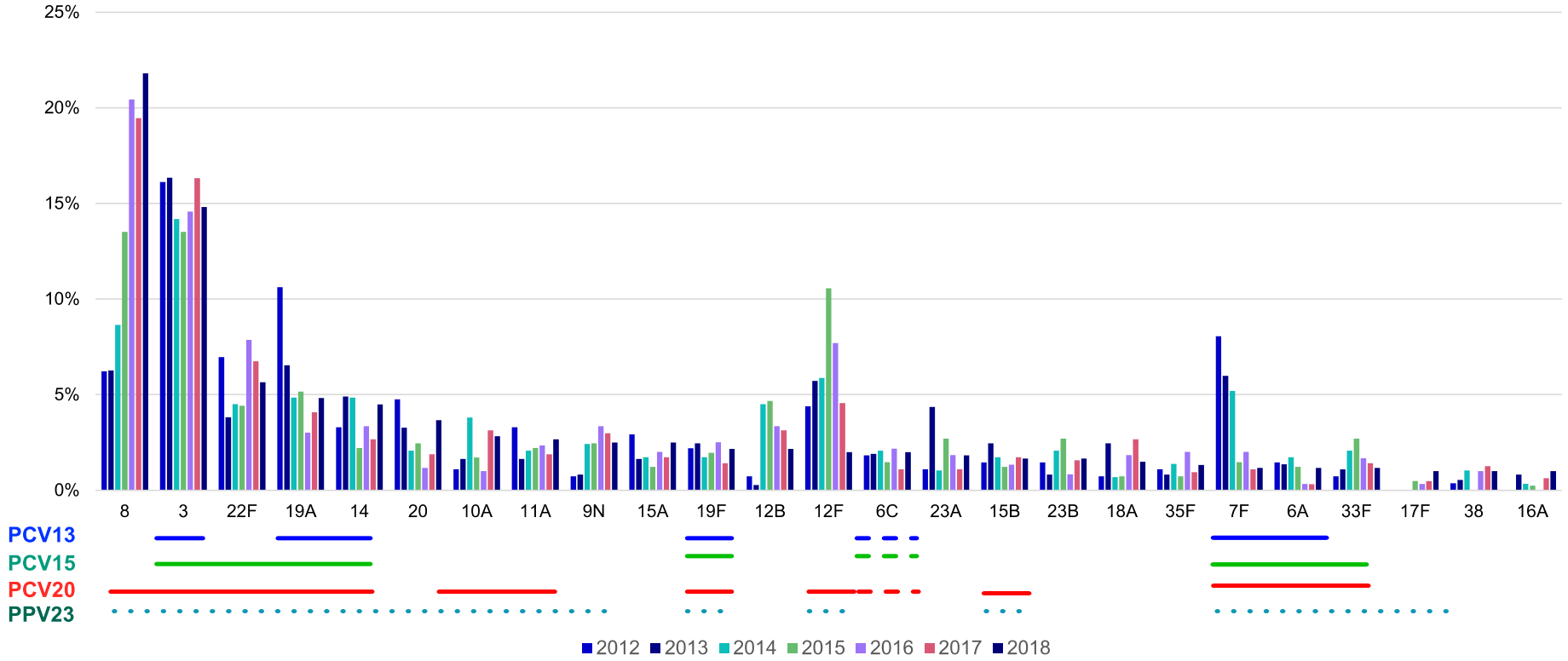
Fonte: Elaborazione C.R.E.A. Sanità© su dati SDO, Ministero della Salute

Dati di copertura in tutte le età (1671 casi tipizzati) - anno 2019



I sierotipi prevalenti che causano IPD negli adulti di età ≥ 65 anni in Italia

ECDC Sorveglianza pneumococcica 2018



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https://doi.org/10.1186/s12879-019-4214-x

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Self-reported diabetes and herpes zoster are associated with a weak humoral response to the seasonal influenza A H1N1 vaccine antigen among the elderly

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Table 4 Risk factors associated with a weak humoral response to each of the three vaccine antigens contained in the adjuvanted influenza vaccine Fluad® among individuals ≥65 years of age[d]

Variables	A H1N1		A H3N2		B	
	UOR & 95% CI	AOR & 95% CI	UOR & 95% CI	AOR & 95% CI	UOR & 95% CI	AOR & 95% CI
Female vs. male	1.21 (0.69–2.13)	1.36 (0.73–2.50)	0.52 (0.22–1.26)	0.48 (0.19–1.20)	0.74 (0.41–1.32)	0.78 (0.42–1.46)
Age (change per year)	1.06 (0.99–1.13)	1.08 (0.99–1.16)	0.99 (0.90–1.09)	1.01 (0.91–1.12)	1.05 (0.98–1.12)	1.03 (0.96–1.11)
BMI (change per unit)[a]	1.02 (0.96–1.08)	1.01 (0.94–1.08)	1.00 (0.91–1.10)	0.99 (0.89–1.09)	0.96 (0.90–1.03)	0.98 (0.91–1.05)
Hypertension[b]	0.73 (0.42–1.28)	0.67 (0.36–1.23)	0.82 (0.37–1.86)	0.94 (0.40–2.19)	1.05 (0.59–1.87)	0.94 (0.51–1.72)
Diabetes[c]	5.11 (1.40–18.53)	4.64 (1.16–18.54)	1.53 (0.41–5.76)	1.16 (0.24–5.65)	0.37 (0.10–1.35)	0.58 (0.14–2.29)
Cancer[c]	1.39 (0.69–2.79)	1.26 (0.58–2.69)	0.88 (0.31–2.50)	0.73 (0.24–2.25)	1.74 (0.86–3.52)	1.57 (0.74–3.31)
Heart attack[c]	3.41 (0.89–13.01)	2.78 (0.64–12.15)	3.54 (0.99–12.71)	3.39 (0.80–14.40)	0.32 (0.07–1.49)	0.44 (0.09–2.21)
Herpes zoster[c]	1.99 (0.94–4.23)	2.27 (1.01–5.10)	2.71 (1.10–6.69)	3.12 (1.18–8.23)	1.03 (0.48–2.20)	0.96 (0.43–2.12)
CMV (change per unit)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.00)	1.00 (0.99–1.00)

BMI Body mass index, *CMV* Cytomegalovirus, *UOR* Unadjusted odds ratio, *AOR* Adjusted odds ratio, *CI* Confidence intervals
[a]Weight and height were measured at the study center (see Methods). BMI was calculated using the formula "weight/height^2" (kg/m^2)
[b]Blood pressure was measured at the study center (see Methods). Hypertension was defined as a systolic or diastolic blood pressure ≥ 140 mmHg and/or 90 mmHg, respectively
[c]Self-reported information
[d]Results of fractional polynomial regression. Robust independent risk factors (underlined) were defined as those with lower bound 95% CI of AOR not crossing below 1

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ORIGINAL ARTICLE

Impact of diabetes status on immunogenicity of trivalent inactivated influenza vaccine in older adults

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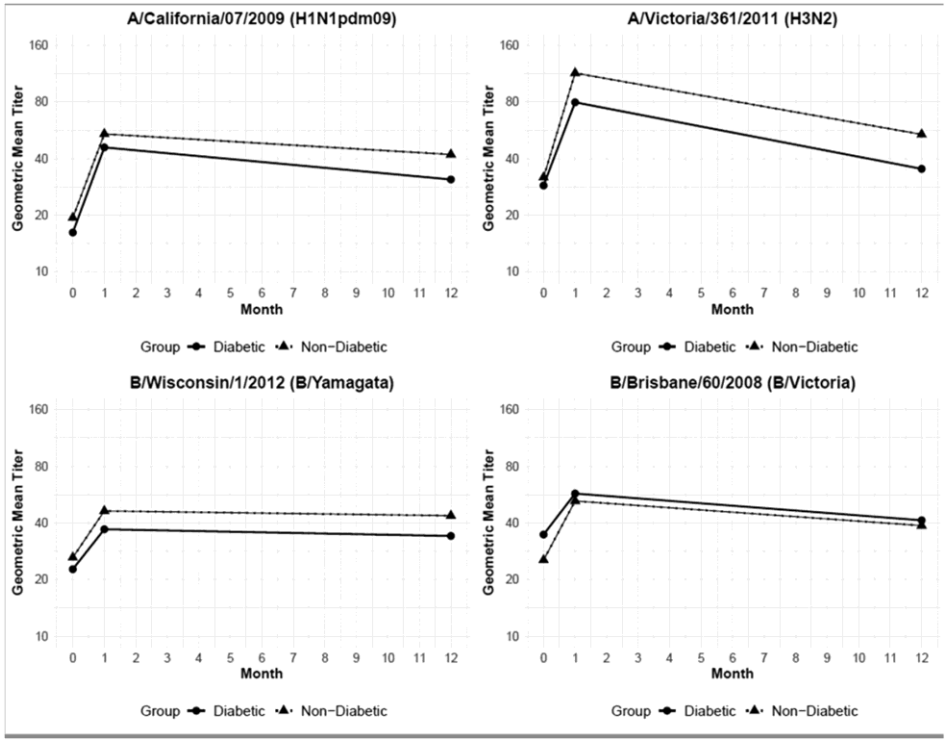
Abstract

Individuals with type 2 diabetes mellitus experience high rates of influenza virus infection and complications. We compared the magnitude and duration of serologic response to trivalent influenza vaccine in adults aged 50–80 with and without type 2 diabetes mellitus. Serologic response to influenza vaccination was similar in both groups: greater fold-increases in antibody titer occurred among participants with lower pre-vaccination antibody titers. Waning of antibody titers was not influenced by diabetes status.



Effectiveness of the influenza vaccine in preventing admission to hospital and death in people with type 2 diabetes

Eszter P. Vamos MD PhD, Utz J. Pape PhD, Vasa Curcin MSc PhD, Matthew J. Harris DPhil, Jonathan Valabhji MD, Azeem Majeed MD, Christopher Millett PhD

Competing interests: None declared.

This article has been peer reviewed.

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CMAJ 2016. DOI:10.1503/cmaj.151059

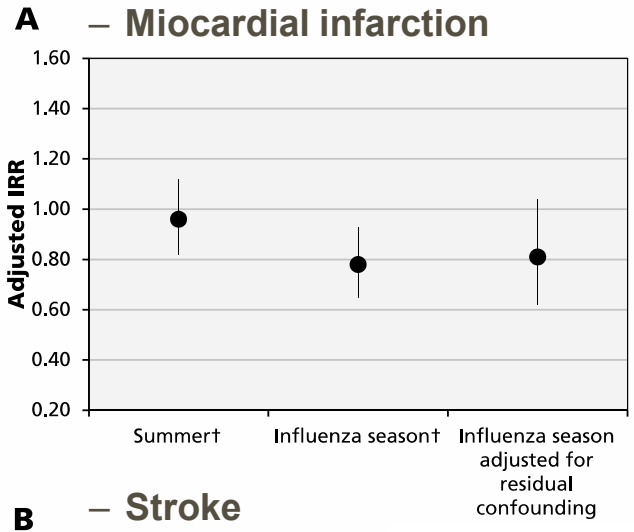
Abstract

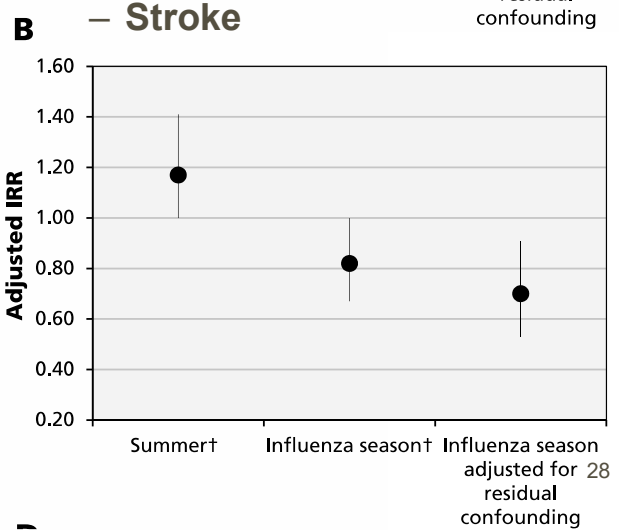
Background: The health burden caused by seasonal influenza is substantial. We sought to examine the effectiveness of influenza vaccination against admission to hospital for acute cardiovascular and respiratory conditions and all-cause death in people with type 2 diabetes.

Methods: We conducted a retrospective cohort study using primary and secondary care data from the Clinical Practice Research Datalink in England, over a 7-year period between 2003/04 and 2009/10. We enrolled 124 503 adults with type 2 diabetes. Outcome measures included admission to hospital for acute myocardial infarction (MI), stroke, heart failure or pneumonia/influenza, and death. We fitted Poisson regression models for influenza and off-season periods to estimate incidence rate ratios (IRR) for cohorts who had and had not received the vaccine. We used estimates for the summer, when influenza activity is low, to adjust for residual confounding.

Results: Study participants contributed to 623 591 person-years of observation during the 7-year study period. Vaccine recipients were older and had more comorbid conditions compared with nonrecipients. After we adjusted for covariates and residual confounding, vaccination was associated with significantly lower admission rates for stroke (IRR 0.70, 95% confidence interval [CI] 0.53–0.91), heart failure (IRR 0.78, 95% CI 0.65–0.92) and pneumonia or influenza (IRR 0.85, 95% CI 0.74–0.99), as well as all-cause death (IRR 0.76, 95% CI 0.65–0.83), and a nonsignificant change for acute MI (IRR 0.81, 95% CI 0.62–1.04) during the influenza seasons.

Interpretation: In this cohort of patients with type 2 diabetes, influenza vaccination was associated with reductions in rates of admission to hospital for specific cardiovascular events. Efforts should be focused on improvements in vaccine uptake in this important target group as part of comprehensive secondary prevention.





Journal of
Clinical Medicine

MDPI

Article

Effect of Influenza Vaccination on the Reduction of the Incidence of Chronic Kidney Disease and Dialysis in Patients with Type 2 Diabetes Mellitus

Li-Chin Sung [1,2,3,4,†], Chun-Chao Chen [1,2,3,5], Shih-Hao Liu [4,†], Chun-Chih Chiu [1,2], Tsung-Yeh Yang [1,2], Cheng-Hsin Lin [2,6,7], Yu-Ann Fan [1,2], William Jian [8], Meng-Huan Lei [9], Hsien-Tang Yeh [10], Min-Huei Hsu [11,12], Wen-Rui Hao [1,2,3,*] and Ju-Chi Liu [1,2,3,*]

CKD in the vaccinated and unvaccinated patients. The study population comprised 48,017 eligible patients with DM; 23,839 (49.7%) received influenza vaccination and the remaining 24,178 (50.3%) did not. The adjusted HRs (aHRs) for CKD/dialysis decreased in the vaccinated patients compared with the unvaccinated patients (influenza season, noninfluenza season, and all seasons: aHRs: 0.47/0.47, 0.48/0.49, and 0.48/0.48, respectively, all $p < 0.0001$). We observed similar protective effects against CKD during the influenza and noninfluenza seasons. Regardless of comorbidities or drug use, influenza vaccination was an independent protective factor. Furthermore, aHRs for CKD/dialysis were 0.71 (0.65–0.77)/0.77 (0.68–0.87), 0.57 (0.52–0.61)/0.69 (0.56–0.70), and 0.30 (0.28–0.33)/0.28 (0.24–0.31) in the patients who received 1, 2–3, and ≥4 vaccinations during the follow-up period, respectively. This population-based cohort study demonstrated that influenza vaccination exerts

Table 5. Sensitivity Analysis of Adjusted HRs for Vaccination in the Risk Reduction of Dialysis in All Seasons.

	Unvaccinated	Vaccinated			*p*-Value for Trend
		1	2–3	≥4	
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	
Main model †	1.00	0.77 (0.68, 0.87) ***	0.63 (0.56, 0.70) ***	0.28 (0.24, 0.31) ***	<0.001
Subgroup effects					
Age, years					
<65	1.00	0.63 (0.52, 0.77) ***	0.47 (0.38, 0.58) ***	0.29 (0.23, 0.36) ***	<0.001
≥65	1.00	0.82 (0.70, 0.97) *	0.66 (0.58, 0.77) ***	0.25 (0.21, 0.29) ***	<0.001
Sex					
Female	1.00	0.73 (0.62, 0.87) ***	0.59 (0.51, 0.69) ***	0.28 (0.23, 0.33) ***	<0.001
Male	1.00	0.82 (0.68, 0.98) *	0.68 (0.57, 0.80) ***	0.28 (0.23, 0.33) ***	<0.001
Hypertension					
No	1.00	0.64 (0.51, 0.81) ***	0.63 (0.51, 0.76) ***	0.27 (0.21, 0.34) ***	<0.001
Yes	1.00	0.82 (0.71, 0.95) **	0.62 (0.54, 0.71) ***	0.28 (0.24, 0.32) ***	<0.001
Cerebrovascular diseases					
No	1.00	0.75 (0.66, 0.87) ***	0.65 (0.57, 0.73) ***	0.29 (0.25, 0.33) ***	<0.001
Yes	1.00	0.80 (0.61, 1.05)	0.54 (0.41, 0.70) ***	0.22 (0.16, 0.30) ***	<0.001
Dyslipidemia					
No	1.00	0.72 (0.62, 0.83) ***	0.63 (0.55, 0.72) ***	0.28 (0.24, 0.32) ***	<0.001
Yes	1.00	0.90 (0.72, 1.11)	0.63 (0.51, 0.78) ***	0.28 (0.23, 0.36) ***	<0.001
Heart diseases					
No	1.00	0.74 (0.63, 0.86) ***	0.62 (0.53, 0.71) ***	0.28 (0.24, 0.33) ***	<0.001
Yes	1.00	0.82 (0.67, 1.01)	0.64 (0.53, 0.78) ***	0.27 (0.22, 0.33) ***	<0.001

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]

Keywords

Diabetic patients • Vaccinations

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

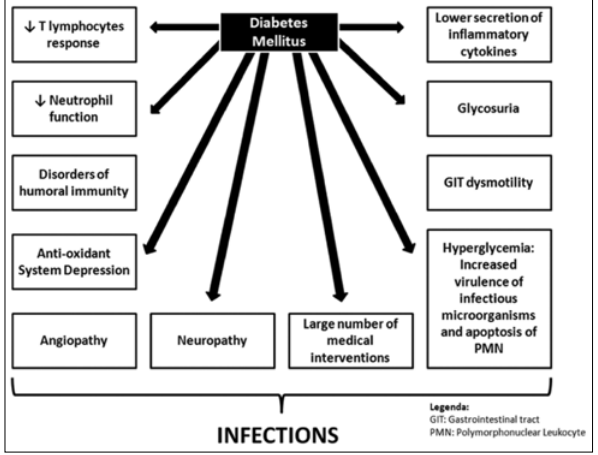
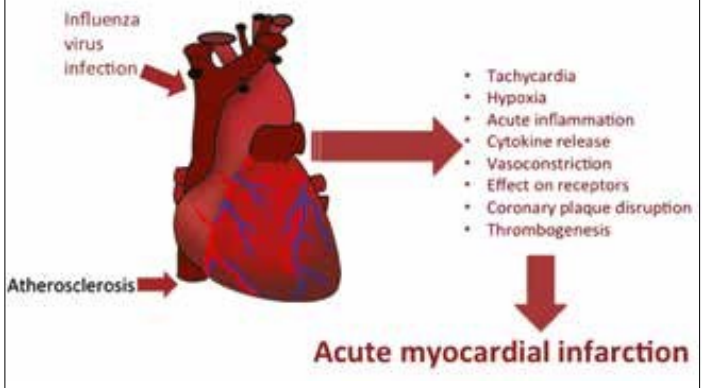


Fig. 2. Mechanisms by which influenza may precipitate an acute myocardial infarction [15].



Published in final edited form as:
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Influenza vaccination coverage among adults with diabetes, United States, 2007–08 through 2017–18 seasons

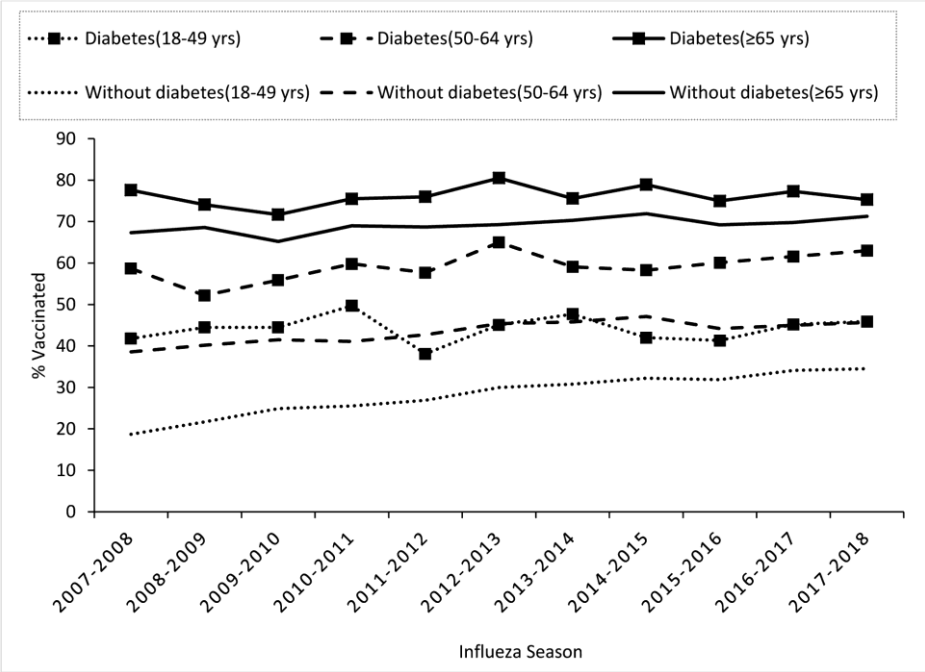
Mei-chuan Hung[a,b], **Peng-jun Lu**[a], **Anup Srivastav**[a,b], **Yiling J Cheng**[c], **Walter W. Williams**[a]

[a]Immunization Services Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[b]Leidos, Incorporated, Atlanta, Georgia, USA

[c]Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Results: During the 2007–08 through 2017–18 influenza seasons, influenza vaccination coverage among adults aged ≥18 years with diabetes ranged from 62.6% to 64.8%. In the 2017–18 influenza season, coverage was significantly higher among adults with diabetes (64.8%) compared with those without diabetes (43.9%). Having diabetes was independently associated with an increased prevalence of vaccination after controlling for other factors. Among adults with diabetes, living at or above poverty level, having more physician contacts, having usual place for health care, and being unemployed were independently associated with increased prevalence of vaccination; being 18–64 years and non-Hispanic black were independently associated with decreased prevalence of vaccination.



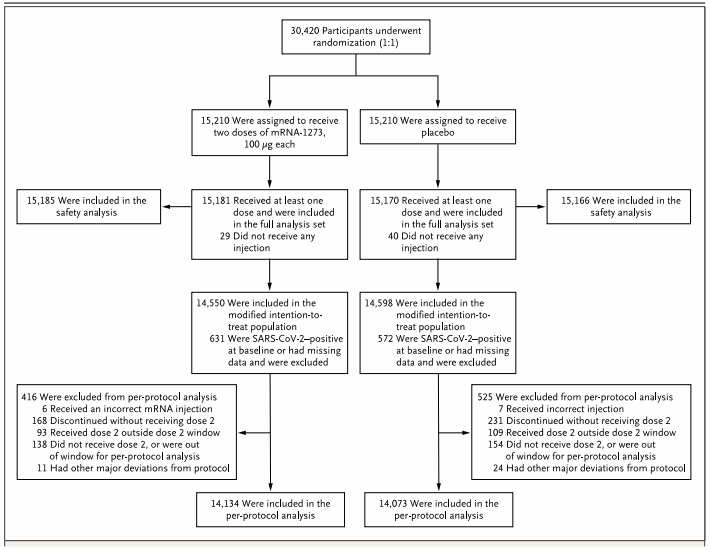
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

ABSTRACT



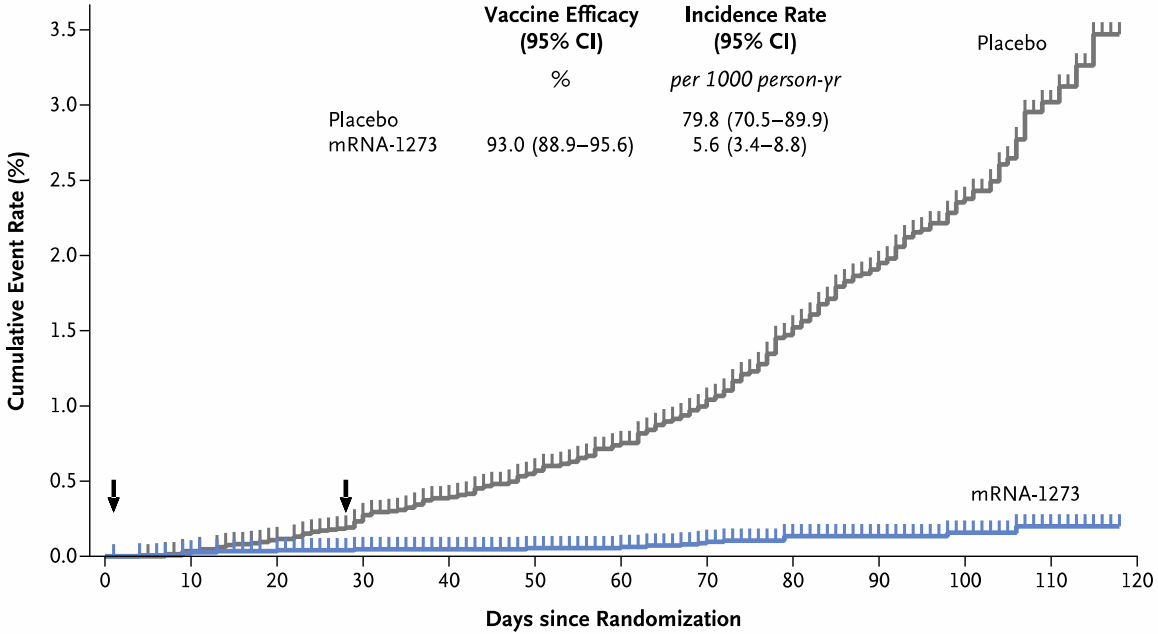
RESULTS

The trial enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). More than 96% of participants received both injections, and 2.2% had evidence (serologic, virologic, or both) of SARS-CoV-2 infection at baseline. Symptomatic Covid-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001). Efficacy was similar across key secondary analyses, including assessment 14 days after the first dose, analyses that included participants who had evidence of SARS-CoV-2 infection at baseline, and analyses in participants 65 years of age or older. Severe Covid-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Moderate, transient reactogenicity after vaccination occurred more frequently in the mRNA-1273 group. Serious adverse events were rare, and the incidence was similar in the two groups.

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Sex — no. of participants (%)			
Male	8,062 (53.1)	7,923 (52.2)	15,985 (52.7)
Female	7,108 (46.9)	7,258 (47.8)	14,366 (47.3)
Mean age (range) — yr	51.3 (18–95)	51.4 (18–95)	51.4 (18–95)
Age category and risk for severe Covid-19 — no. of participants (%)†			
18 to <65 yr, no			
18 to <65 yr, at			
≥65 yr			
Hispanic or Latino			
Hispanic or La			
Not Hispanic o			
Not reported a			
Race or ethnic gro			
White			
Black or Africa			
Asian	731 (4.8)	651 (4.3)	1,382 (4.6)
American Indian or Alaska Native	121 (0.8)	112 (0.7)	233 (0.8)
Native Hawaiian or Other Pacific Islander	32 (0.2)	35 (0.2)	67 (0.2)
Multiracial	321 (2.1)	315 (2.1)	636 (2.1)
Other	316 (2.1)	321 (2.1)	637 (2.1)
Not reported and unknown	127 (0.8)	155 (1.0)	282 (0.9)
Baseline SARS-CoV-2 status — no. of participants (%)§			
Negative	14,598 (96.2)	14,550 (95.8)	29,148 (96.0)
Positive	337 (2.2)	343 (2.3)	680 (2.2)
Missing data	235 (1.5)	288 (1.9)	523 (1.7)
Risk factor for severe Covid-19 — no. of participants (%)			
Chronic lung disease	744 (4.9)	710 (4.7)	1,454 (4.8)
Significant cardiac disease	744 (4.9)	752 (5.0)	1,496 (4.9)
Severe obesity	1,021 (6.7)	1,025 (6.8)	2,046 (6.7)
Diabetes	1,440 (9.5)	1,435 (9.5)	2,875 (9.5)
Liver disease	96 (0.6)	100 (0.7)	196 (0.6)
Human immunodeficiency virus infection	87 (0.6)	92 (0.6)	179 (0.6)

B Modified Intention-to-Treat Analysis

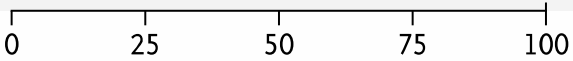


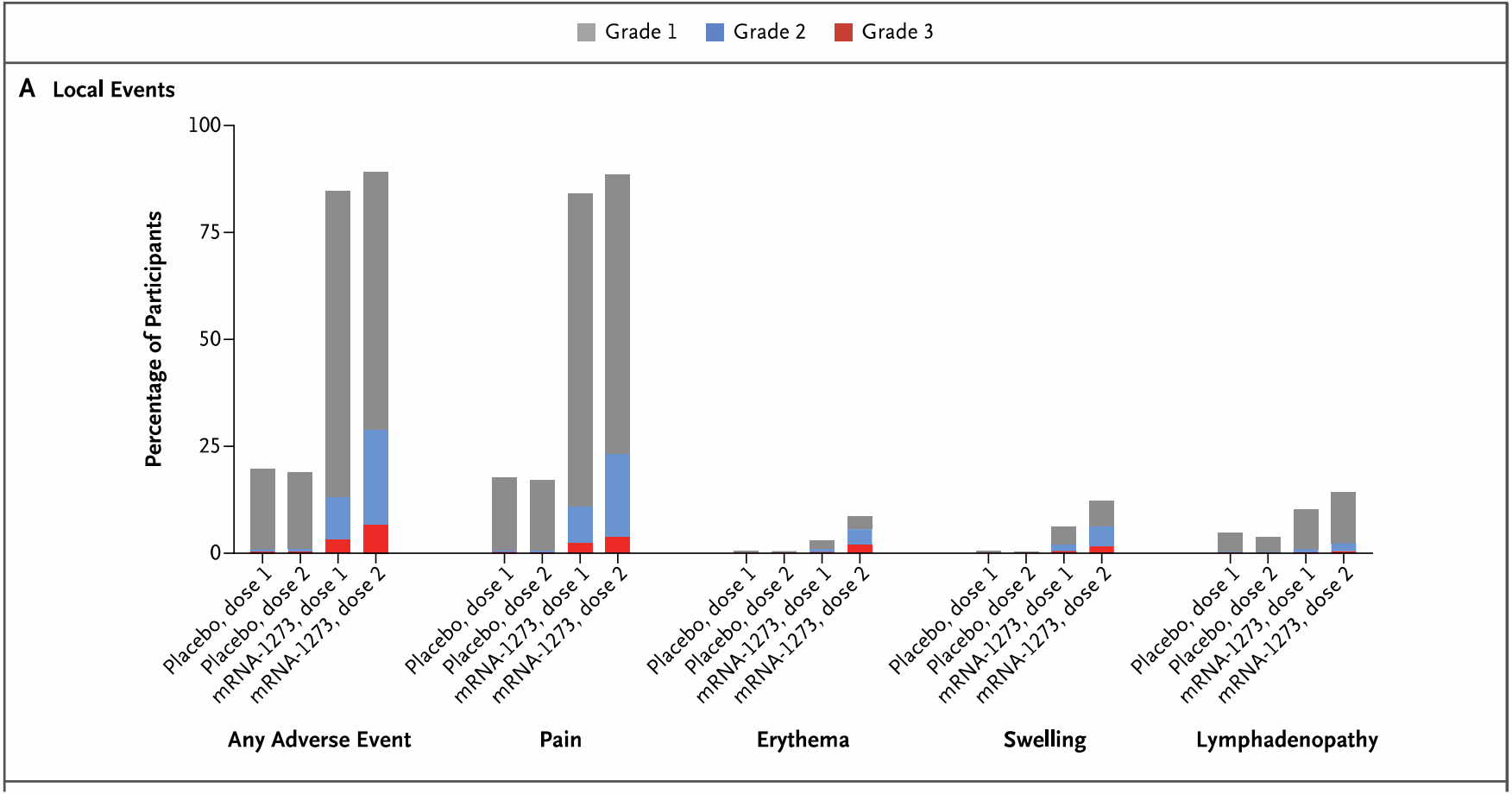
No. at Risk

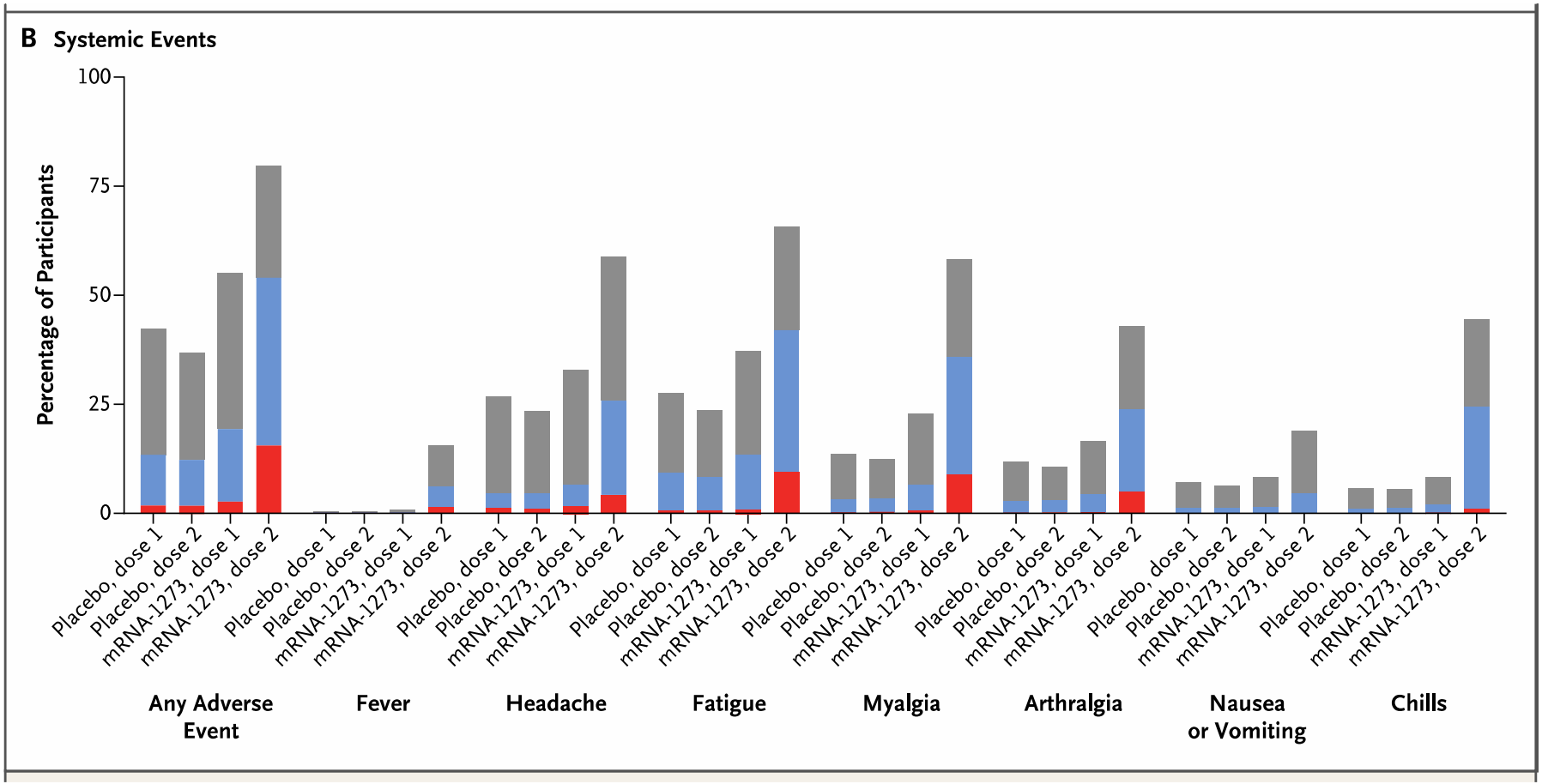
Placebo	14,598	14,590	14,567	14,515	13,806	12,352	12,694	11,450	9736	6729	4067	1200	0
mRNA-1273	14,550	14,543	14,532	14,504	13,825	13,398	12,791	11,573	9911	6871	4179	1238	0

Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

Subgroup	Placebo (N=14,073)	mRNA-1273 (N=14,134)	Vaccine Efficacy (95% CI)
	no. of events/total no.		
All patients	185/14,073	11/14,134	94.1 (89.3–96.8)
Age			
≥18 to <65 yr	156/10,521	7/10,551	95.6 (90.6–97.9)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Age, risk for severe Covid-19			
18 to <65 yr, not at risk	121/8403	5/8396	95.9 (90.0–98.3)
18 to <65 yr, at risk	35/2118	2/2155	94.4 (76.9–98.7)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Sex			
Male	87/7462	4/7366	95.4 (87.4–98.3)
Female	98/6611	7/6768	93.1 (85.2–96.8)
At risk for severe Covid-19			
Yes	43/3167	4/3206	90.9 (74.7–96.7)
No	142/10,906	7/10,928	95.1 (89.6–97.7)
Race and ethnic group			
White	144/8916	10/9023	93.2 (87.1–96.4)
Communities of color	41/5132	1/5088	97.5 (82.2–99.7)




Grade 1
Grade 2
Grade 3
A Local Events
Percentage of Participants
100
75
50
25
0
Placebo, dose 1
Placebo, dose 2
mRNA-1273, dose 1
mRNA-1273, dose 2
Any Adverse Event
Pain
Erythema
Swelling
Lymphadenopathy


B Systemic Events
Percentage of Participants
100
75
50
25
0
Placebo, dose 1
Placebo, dose 2
mRNA-1273, dose 1
mRNA-1273, dose 2
Any Adverse Event
Fever
Headache
Fatigue
Myalgia
Arthralgia
Nausea or Vomiting
Chills

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MINI-REVIEW

The role of vaccines in fighting antimicrobial resistance (AMR)

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ABSTRACT

The problem of antimicrobial resistance (AMR) and the associated morbidity and mortality due to antibiotic resistant bacterial pathogens is not new. However, AMR has been increasing at an alarming rate with appearances of diseases caused by bacteria exhibiting resistance to not just one but multiple classes of antibiotics. The World Health Organization (WHO) supported by governments, health ministries and health agencies has formulated global action plans to combat the rise in AMR, supporting a number of proven initiatives such as antimicrobial stewardship, investments in development of new classes of antibiotics, and educational programs designed to eliminate inappropriate antibiotic use. Vaccines as tools to reduce AMR have historically been under-recognized, yet the positive effect in reducing AMR has been well established. For example *Haemophilus influenzae* type B (Hib) as well as *Streptococcus pneumoniae* (pneumococcal) conjugate vaccines have impressive track records in not only preventing life threatening diseases caused by these bacteria, but also reducing antibiotic use and AMR. This paper will describe the drivers of antibiotic use and subsequent development of AMR; it will make the case how existing vaccines are already participating in combatting AMR, describe future prospects for the role of new vaccines in development to reduce AMR, and highlight challenges associated with future vaccine development to combat AMR.

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KEYWORDS
antimicrobial resistance; vaccines; *Streptococcus pneumoniae*; *Staphylococcus aureus*; *Clostridium difficile*; Group B streptococcus

What is the clinical relevance of drug-resistant pneumococcus?

Catia Cillóniz[a], *Carmen Ardanuy*[b,c], *Jordi Vila*[d,e], *and Antoni Torres*[a]

Purpose of review
Pneumococcal infections are a major cause of morbidity and mortality worldwide. In recent years, *Streptococcus pneumoniae* has shown increasing resistance to a several antibiotics, becoming a worldwide problem. The impact of antibiotic resistance of *S. pneumoniae* on clinical outcomes is still controversial. The principal reason for this controversy is the existence of several factors related to the patients and to the pathogen that may influence how antibiotic resistance patterns affect clinical outcomes. The aim of this review is to discuss current knowledge of the epidemiological data on antibiotic resistance; we also discuss mechanisms and risk factors for antibiotic resistance.

Recent findings
The phenomenon of serotype replacement after the introduction of conjugate pneumococcal vaccinations and the escalation of antibiotic resistance worldwide remains an important issue in terms of their impact on clinical outcomes in pneumococcal disease. Antimicrobial resistance of pneumococcus leads to changes in the clinical presentation of pneumococcal disease, making it more difficult to diagnose and to treat. Consumption of antibiotics in the community is directly proportional to antimicrobial resistance. Carriage of *S. pneumoniae* and infection with antibiotic-resistant pneumococcus is associated with prior antibiotic therapy, extremes of age, presence of comorbidities (i.e. COPD), attendance at child day care centers, crowded conditions, intra-familial transmission, and nursing home residence.

Summary
Antibiotic-resistant *S. pneumoniae* is a worldwide problem. The implementation of several strategies including vaccine campaigns, prudent use of current antibiotics, and programs for the surveillance of pneumococcal infections, could limit the increasing resistance of this pathogen to antimicrobials.

Keywords
antimicrobial resistance, pneumococcus, *Streptococcus pneumoniae*

Other studies have also examined the association between antibiotic-resistant IPD and clinical outcomes, with differing results, although no recent studies have been reported. Moroney et al. compared persons with bacteremic pneumonia with MICs of cefotaxime of ≥0.25 μg/ml with persons with less resistant bacteremic pneumonia; they found that the proportions of those who died did not differ significantly between the two groups (32). This finding was also documented by Plouffe et al. among pneumococcal bacteremia cases in 10 adult care hospitals in Franklin County, OH, but those authors found that the duration of hospitalization was significantly longer for patients with penicillin-nonsusceptible *S. pneumoniae* (PNSP) than for those with penicillin-susceptible disease (15.8 days versus 12.1 days; $P = 0.05$) (33). In contrast to previous studies that found no difference in mortality, both Metlay et al. and Feiken et al. demonstrated that there was an increased risk of mortality among persons infected with nonsusceptible and resistant *S. pneumoniae* (34, 35). Metlay et al. found that in-hospital mortality was significantly increased among cases with PNSP bacteremic pneumonia compared to those with penicillin-susceptible *S. pneumoniae* (relative risk, 2.1; 95% confidence interval, 1.0 to 4.3) (34), while in the study by Feiken et al., mortality was significantly increased in U.S. persons infected with pneumococci with penicillin MICs of ≥4.0 μg/ml after the fourth day of hospitalization (35).

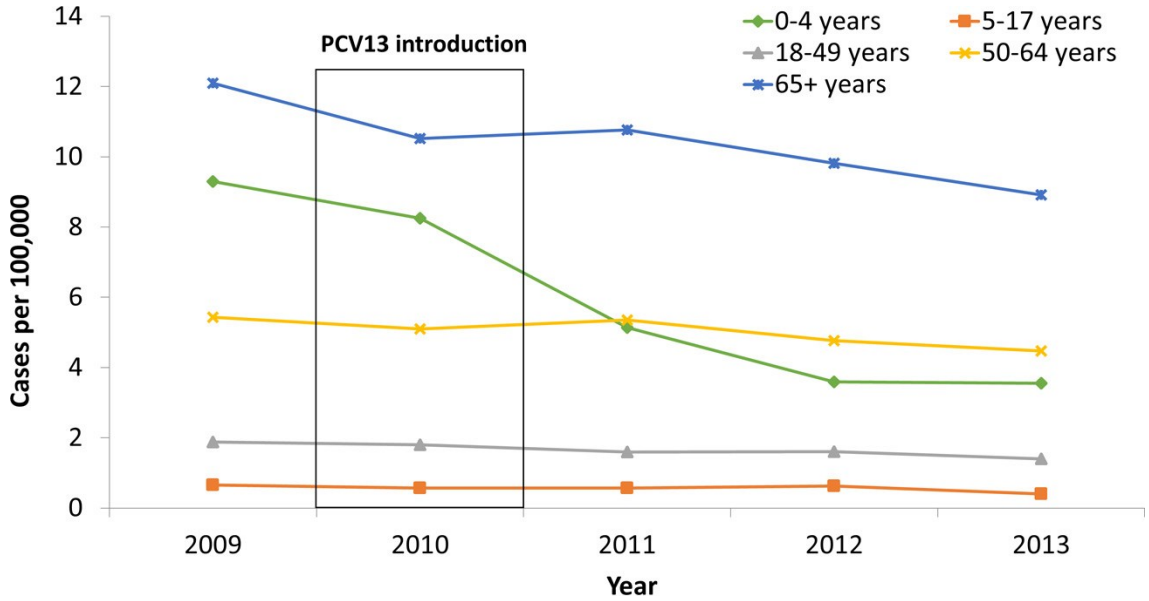

FIG 3 Incidences (number of cases per 100,000 individuals) of antimicrobial-nonsusceptible (nonsusceptible to one or more classes of antimicrobials, including macrolides, cephalosporins, tetracyclines, penicillins, fluoroquinolones, and glycopeptides) IPD. (Data from Active Bacterial Core surveillance, 2009 to 2013.)

Review article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

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Impact of vaccination on carriage of and infection by antibiotic-resistant bacteria: a systematic review and meta-analysis

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This systematic review and meta-analysis aims to quantify the impact of vaccination on the incidence and prevalence of nonsusceptible infections and investigates the impact of vaccination programs on serotype replacement. We searched a comprehensive set of databases. Identified studies were assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach and resulting evidence was analyzed using random-effect meta-analyses. Nineteen studies on pneumococcal conjugate vaccines (PCV) met our inclusion criteria. PCV decreases the incidence of nonsusceptible pneumococcal infections (PIs) by 56.91% (95% confidence interval [CI], -50.90% to -62.91%) and the probability of carriage of nonsusceptible pneumococcal bacteria by 28.10% (95% CI, -13.25% to -42.95%). The effect of PCV on PIs becomes higher when only serotypes specifically targeted by the vaccine are taken into account (-80.98%; 95% CI, -70.34% to -91.52%), while it becomes lower when all the PIs, including both susceptible and nonsusceptible PIs, are considered (-48.30%; 95% CI, -31.55% to -65.08%). The effect of PCV is found greater in populations with high prevalence of human immunodeficiency virus and for PCV covering a higher number of serotypes. Findings from this study suggest that vaccination programs may be an effective tool to prevent the spread of PIs and may play a significant role in tackling antimicrobial resistance.

Keywords: Streptococcus pneumoniae, Drug resistance, Vaccination, Systematic review, Meta-analysis

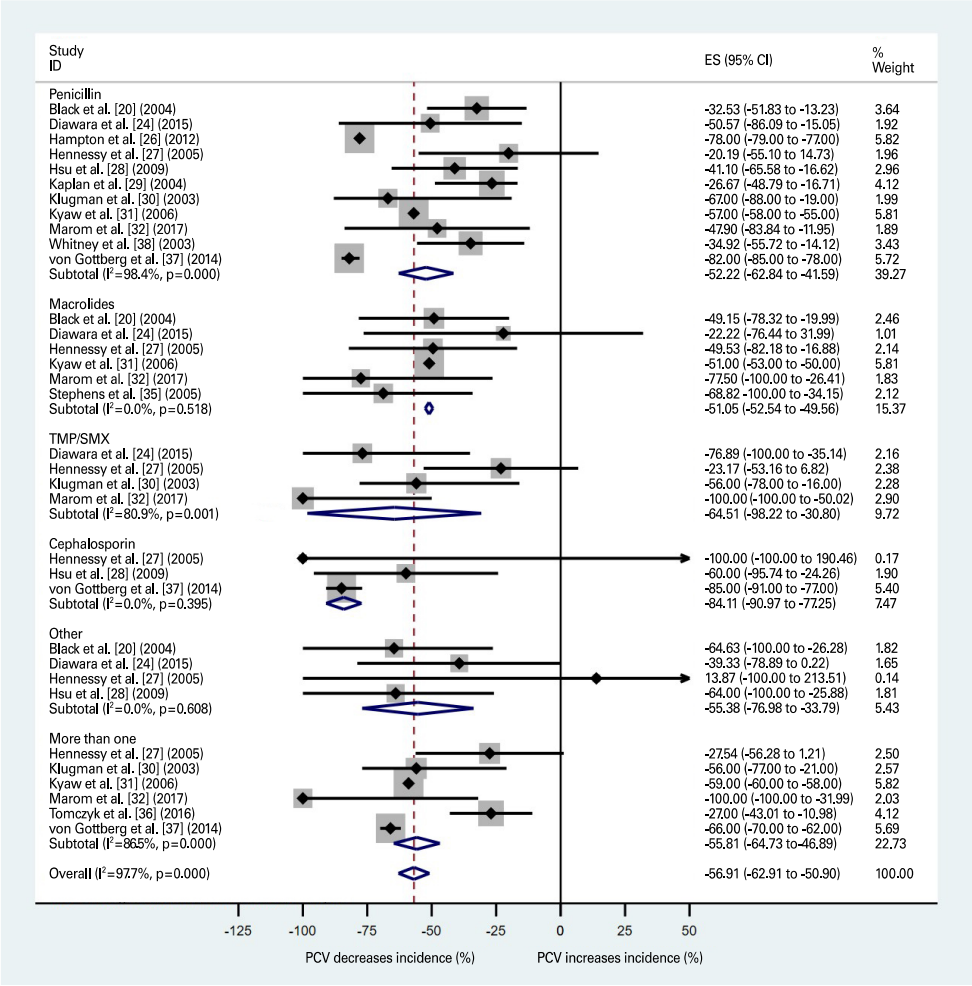

Fig. 2. Forest plot for effect of pneumococcal conjugate vaccine (PCV) on the incidence of nonsusceptible pneumococcal infections. Weights are from random effects analysis. ES, estimates; CI, confidence interval.

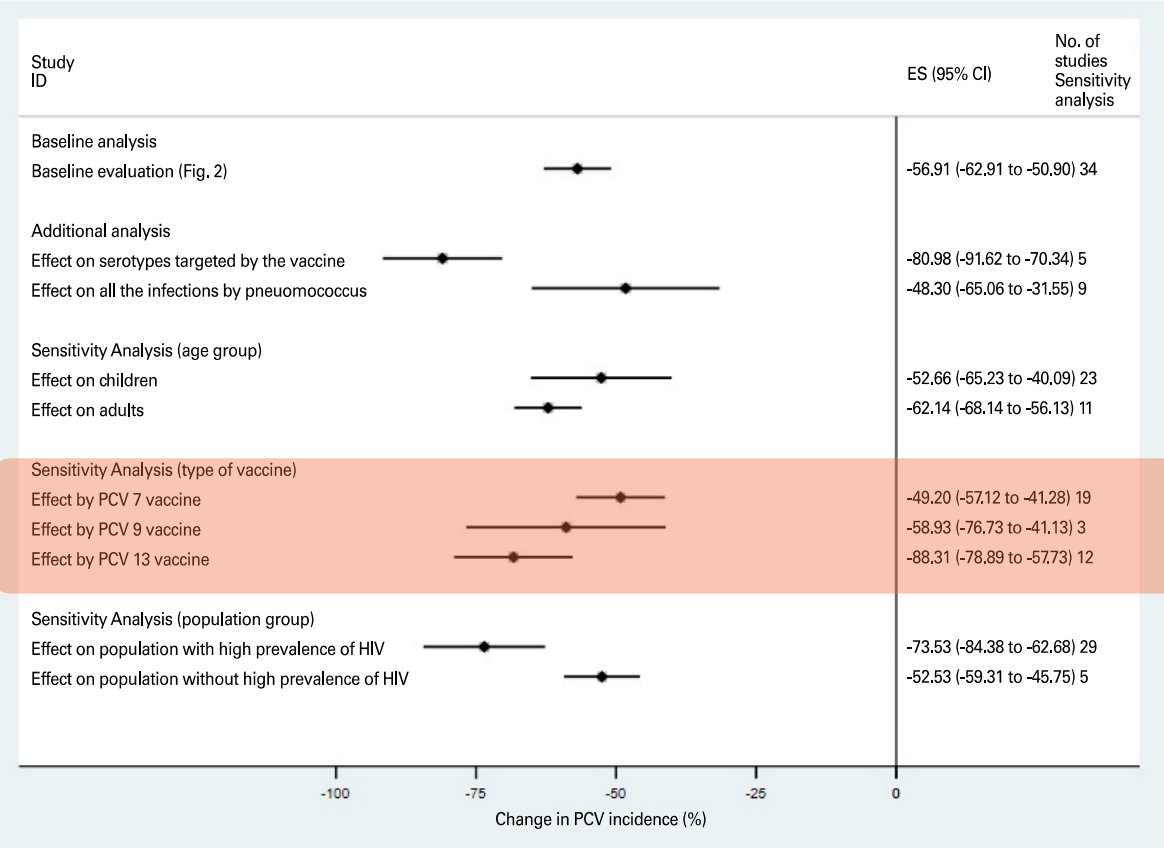

Fig. 4. Forest plot for effect of pneumococcal conjugate vaccine (PCV) on the incidence of nonsusceptible pneumococcal infections: additional analyses and sensitivity analysis. Weights are from random effects analysis. ES, estimates; CI, confidence interval; HIV, human immunodeficiency virus.

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Biological and Epidemiological Features of Antibiotic-Resistant *Streptococcus pneumoniae* in Pre- and Post-Conjugate Vaccine Eras: a United States Perspective

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Epidemiology Section[a] and Streptococcus Laboratory,[b] Respiratory Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Antimicrobial-resistant pneumococcal infections were documented as early as 1912, when optochin resistance in experimental mice was described (9). Acquired optochin resistance was seen in humans 5 years later (10). In 1939, treatment-acquired sulfonamide resistance was reported in a human case of pneumococcal meningitis (11). Penicillin-resistant pneumococci were also selected in laboratories (12, 13); however, it was not until 1965 that the first clinical isolate with reduced penicillin susceptibility was reported (14). During the 1970s and 1980s, pneumococci resistant to penicillin (MIC of ≥0.1 μg/ml), erythromycin, and trimethoprim-sulfamethoxazole (TMP-SMX) spread rapidly globally, including to Australia, Papua New Guinea, Israel, Spain, Poland, South Africa, and the United States (15–19). Tetracycline and chloramphenicol resistances were also identified, with rates varying by region and population (20). Finally, fluoroquinolone resistance has been documented at relatively low levels compared to those for the above-mentioned antibiotics (21).

Multidrug-resistant pneumococci, defined as strains resistant to three or more classes of antimicrobials, were first identified in children (22) via nosocomial transmission and are predominantly associated with pediatric serotypes, or serotypes associated with carriage and disease among the pediatric population (i.e., serotypes 6A, 6B, 9V, 14, 19A, 19F, and 23F) (20, 23–25). Among 21 European Union and European Economic Activity countries, multidrug resistance was observed among isolates of serotypes 19A, 14, 1, 19F, and 23F (26). In the United States, residual mul-

IMPACT OF ANTIMICROBIAL RESISTANCE

In 2013, the U.S. Centers for Disease Control and Prevention (CDC) released the first national report on antibiotic resistance threats in the United States, underscoring their increasing importance (27). The CDC estimated that at least 2 million people acquired serious infections from pathogens that were antimicrobial resistant and that at least 23,000 people died as a result of antimicrobial-resistant infections annually in the United States (27). Antimicrobial resistance complicates treatment and can result in additional antibiotic courses and outpatient visits, excess hospitalizations, and work loss (27).

Specific to antibiotic-resistant pneumococcal pneumonia, a study by Reynolds et al. found that resistance led to 32,398 additional outpatient visits and 19,336 additional hospitalizations, accounting for $91 million (4%) in direct medical costs and $233 million (5%) in total costs, including work and productivity losses (28). A Canadian study found that increased costs associated with penicillin-resistant IPD in children ≤18 years of age admitted to two hospitals was due mainly to antibiotic choice (29). In adults, increased costs due to penicillin-nonsusceptible pneumonia and bacteremia were due to prolonged hospitalization and the use of more expensive antibiotics (30, 31).

TABLE 1 Molecular mechanisms responsible for most observed cases of pneumococcal antibiotic resistance

Antibiotic	Mechanism(s)
β-Lactams (penicillin and cephalosporins)	Mutations in penicillin-binding (transpeptidase) domains of *pbp* genes (primarily *pbp2x*, *pbp2b*, and *pbp1a*); mutations in aminoacyl-tRNA ligase gene (*murM*); mutations in other genes, including *pdgA*, *ciaH-ciaR*, and *stkP*
Macrolides	*erm* (23S rRNA methyltransferases) (*ermB* and rarely *ermTR*), *mef*-mediated efflux [*mef*(A) or *mef*(E)], mutations in 23S rRNA genes or L4 or L22 ribosomal protein genes (*rplD* and *rplV*, respectively)
Fluoroquinolones	Mutations in DNA gyrase (primarily *gyrA*) and/or topoisomerase IV genes (primarily *parC*), PmrA-mediated efflux
Tetracycline	Ribosomal protection proteins, primarily Tet(M) and rarely Tet(O)
Rifampin	Mutations in *rpoB* encoding the β-subunit of RNA polymerase
Chloramphenicol	Inactivation of chloramphenicol by *cat*-encoded chloramphenicol acetyltransferase
Trimethoprim-sulfamethoxazole	Mutations in the dihydrofolate reductase gene (*folA*) and dihydropteroate synthetase gene (*folP*)
Ketolides	Mutations in 23S rRNA or L4 or L22 ribosomal protein genes (*rplD* and *rplV*), *ermB* with deletion or mutation in leader sequence
Oxazolidinones	Mutations in 23S rRNA genes, deletions in L4 ribosomal protein gene *rplD*

In this environment, microbial species are often subjected to various, and often nonlethal, concentrations of β-lactams. Pneumococci are naturally transformable by the uptake and chromosomal integration of DNA from other pneumococcal strains and other related nonpathogenic mitis group species. Compatible with the importance of recombination in the evolution of β-lactam-resistant pneumococci is the fact that even within neutral housekeeping genes, the majority of observed allelic changes have occurred through horizontal recombination events rather than through intrachromosomal mutation events (146). There is irrefutable observational evidence that β-lactam resistance in pneumococci has repeatedly occurred in nature through recombination events with highly related nonpathogenic fellow members of the *Streptococcus mitis* group. Since colonization with closely related nonpneumococcal species occurs in all humans, it is logical that β-lactam nonsusceptibility would arise first in such strains prior to its appearance in pneumococci. This prediction is supported by the remarkable observation that virtually all clinical isolates that display reduced penicillin susceptibility (MICs of >0.5 μg/ml) are characterized by one or more mosaic PBP1a, -2b, and -2x genes. Within these PBP genes, there are clearly discernible regions of sequence that clearly originated within nonpneumococcal mitis group species (96–100). In contrast, within basally

Streptococcus mitis and *Streptococcus oralis* have been identified as PBP gene sequence donors for variant PBP2x, -2b, -1a, and -2a (108, 147, 148) found in certain PNSP strains. The observation of mosaic pneumococcal PBP genes is consistent with the finding that commensal mitis group nonpneumococcal species, which are also normally β-lactam susceptible, exhibit high β-lactam MICs in areas where rates of pneumococcal resistance are also high (149). It follows that optimal pneumococcal recipients for the development of β-lactam resistance would have optimal exposure to penicillin-nonsusceptible resistant DNA donors in the human URT. The pneumococcal recipient strain would be an efficient long-term colonizer and also highly transformable. These features, while obviously conducive for the development of the β-lactam nonsusceptible (NS) phenotype, are also conducive for the acquisition of other resistance determinants through horizontal transfer events.

Intrapneumococcal Exchange of β-Lactam Resistance Loci

Interspecies recombination events involving pneumococcal recipients result in the cotransformation of multiple unlinked genes, some of which are intrinsically required for resistance and some of which may or may not provide compensatory mutations that relieve deleterious effects on cell fitness (115). Although many different mosaic pneumococcal PBP genes have been associated with β-lactam resistance (48), existing multilocus sequence typing (MLST) data for genes that are under neutral selection indicate that most recombinant pneumococcal alleles reflect intraspecies recombination events. It is insightful that of the seven MLST targets used for typing of pneumococci, only one (*ddl*) is frequently associated with sequences of a nonpneumococcal origin and is due to its proximity to *pbp2b* causing it to be frequently cotransferred into pneumococci (154). Not coincidentally, nearly all such divergent *ddl* alleles are associated with a β-lactam NS phenotype.

Recombinational exchange events at the *cps* loci have been shown to have occurred often between pneumococcal strains (49, 98, 155, 156), providing a mechanism of immune escape from serotype-specific antibody. The first account of pneumococcal serotype switching was described in 1928 (157), leading to the discovery of the transforming substance in 1944 (158). Through transforming a sensitive strain with chromosomal DNA from a resistant strain and selecting for β-lactam resistance, another hitchhiking effect was observed: the cotransfer of the large *cps* locus and the closely flanking *pbp1a* and *pbp2x* genes (159). This experiment demonstrated the potential for the appearance of serotype-switching events through selection for β-lactam resistance. It logically follows that the reverse is also possible through immune selection of serotype-switching events. Soon after the implementation of PCV7, genotyping results from a set of invasive serotype 19A isolates suggested that a cotransformation event of this nature had occurred within a serotype 4 recipient strain, where an intermediately penicillin-resistant non-PCV7 strain served as a donor of the *cps19A cps* locus along with the flanking *pbp1a* and *pbp2x* alleles (160). This single cotransfer of both cap-

Aumentano gli ospiti con deficit immune

prematuri / naïve

ridotta immunocompetenza

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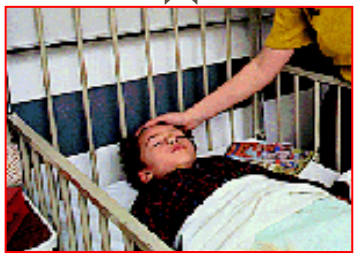

condizioni croniche

immunodeficienza

Vaccines in early stages of development with potential to reduce AMR

Streptococcus agalactiae, also known as Group B streptococcus (GBS) is an encapsulated Gram-positive bacterium that asymptomatically colonizes the vagina (women) and rectum (women and men) of approximately 25% of the population and can cause serious invasive infections including pneumonia, meningitis, bacteremia and sepsis across all age groups. Pregnant women and their babies are vulnerable to disease as asymptomatic maternal carriage is a prime risk factor for diseases in the mother, and the baby. Infant disease as a result of GBS infection presenting within the first 90 days of life is particularly devastating. In the US and some other high-income countries, GBS related disease incidence has been reduced by screening pregnant women for GBS recto-vaginal colonization and then treating carriers with antibiotics during labor, a process known as intrapartum antibiotic prophylaxis (IAP). In the US, hurdle for a long time. Attitudes have changed over the last 10 years due to the demonstration that tetanus, pertussis and flu vaccines can be safely administered to pregnant women and have had measurable positive effects on infant mortality and morbidity.[60-62] Today, Tdap and influenza vaccines are successful maternal vaccines and are routinely recommended in pregnant women.[63] Given these developments, GBS vaccines for use in maternal immunization are now under development. Current GBS vaccine development is focused on capsular polysaccharide conjugate vaccines (NCT03170609),[64-66] as capsular serotype specific antibodies have been shown to kill GBS via complement mediated phagocytosis.

Vaccines as powerful tools to fight AMR

There are a number of well-established tools to reduce the global burden of AMR such as sanitation and hygiene, funding mechanisms to develop new classes of antibiotics, antibiotic stewardship, education to avoid inappropriate antibiotic use to treat viral infections for example and elimination of routine antibiotic use in livestock production. These interventions all have shown benefit when implemented (Box 1). However, it is less well known that prophylactic vaccines also are highly effective and valuable tools in the tool chest to fight AMR. Vaccines work by training the immune system to recognize and respond to a pathogen by mounting a rapid and effective immune defense, preventing the establishment of an infection/disease or decreasing disease severity.[21] Many vaccines have an added

Staphylococcus aureus

S. aureus is a major cause of invasive disease including bacteremia, infectious endocarditis, osteomyelitis, pneumonia and various skin and soft tissue infections in hospital and community settings.[44] Infections caused by MRSA are harder to treat than methicillin sensitive strains and associated with prolonged hospital stays and increased morbidity and mortality. MRSA contributes to over 70,000 cases of invasive disease per year in the US alone.[45] Both the CDC and the WHO have recently

The most advanced vaccine candidate, a 4 antigen *S. aureus* vaccine, SA4Ag is being evaluated in a phase 2/3 efficacy study for the prevention of invasive *S. aureus* disease in elective spinal surgery patients.[52,53] SA4Ag was shown to be safe, well tolerated in early stage clinical trials, and induced high levels of bacterial killing antibodies in healthy adults, leading to a fast-track designation by the U.S. FDA.[54] In addition, a separate 4 component *S. aureus* vaccine (4C-Staph) formulated with a TLR7-dependent adjuvant is under development.[55]

Respiratory Syncytial Virus

Respiratory syncytial virus entry and how to block it

Michael B. Battles[1] *and Jason S. McLellan*[2]*

Abstract | Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract disease in young children and elderly people. Although the virus was isolated in 1955, an effective RSV vaccine has not been developed, and the only licensed intervention is passive immunoprophylaxis of high-risk infants with a humanized monoclonal antibody. During the past 5 years, however, there has been substantial progress in our understanding of the structure and function of the RSV glycoproteins and their interactions with host cell factors that mediate entry. This period has coincided with renewed interest in developing effective interventions, including the isolation of potent monoclonal antibodies and small molecules and the design of novel vaccine candidates. In this Review, we summarize the recent findings that have begun to elucidate RSV entry mechanisms, describe progress on the development of new interventions and conclude with a perspective on gaps in our knowledge that require further investigation.

CYPRESS: Ad26.RSV.preF-Based Vaccine Against RSV-Mediated Infections

- Although RSV is viewed primarily as a pediatric pathogen, it is a major cause of respiratory infections in older adults and persons with medical comorbidities
  - Estimated to cause 177,000 hospitalizations and 14,000 deaths annually among adults ≥65 yr

- No licensed vaccine currently available
- RSV F protein stabilized as preF conformation is strong immunogen
  - Vaccine candidate: **Ad26.RSV.preF + RSV preF** (adenovirus vector encoding RSV F protein from A2 strain + RSV preF soluble protein)

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CYPRESS: Efficacy, Immunogenicity, and Safety Against RSV-Mediated Infections

- Randomized, double-blind placebo-controlled phase IIb study

Vaccination prior to RSV season

US adults ≥65 yr in stable health ± preexisting medical conditions that predispose to a higher risk of severe disease (N = 5800)

Ad26.RSV.preF + RSV preF Protein
(n = 2900)

Placebo
(n = 2900)

Stratified by increased risk of severe disease and age

Follow-up for 3 RSV seasons (~2.6 yr)

- Blood samples collected Days 1 and 15 after injection and during ARI episodes
- Active surveillance for ARI every 2 wk until end of RSV season
- Serious adverse events assessed for 6 mo or until end of RSV season

– Primary endpoint: RT-PCR–confirmed RSV infection from nasal swab/sputum *plus* ≥3 LRTI symptoms or ≥2 LRTI symptoms new/worsening or (≥2 LRTI symptoms or ≥1 LRTI symptoms combined with ≥1 systemic symptoms new/worsening)

Falsey. IDWeek 2021. Abstr LB14.

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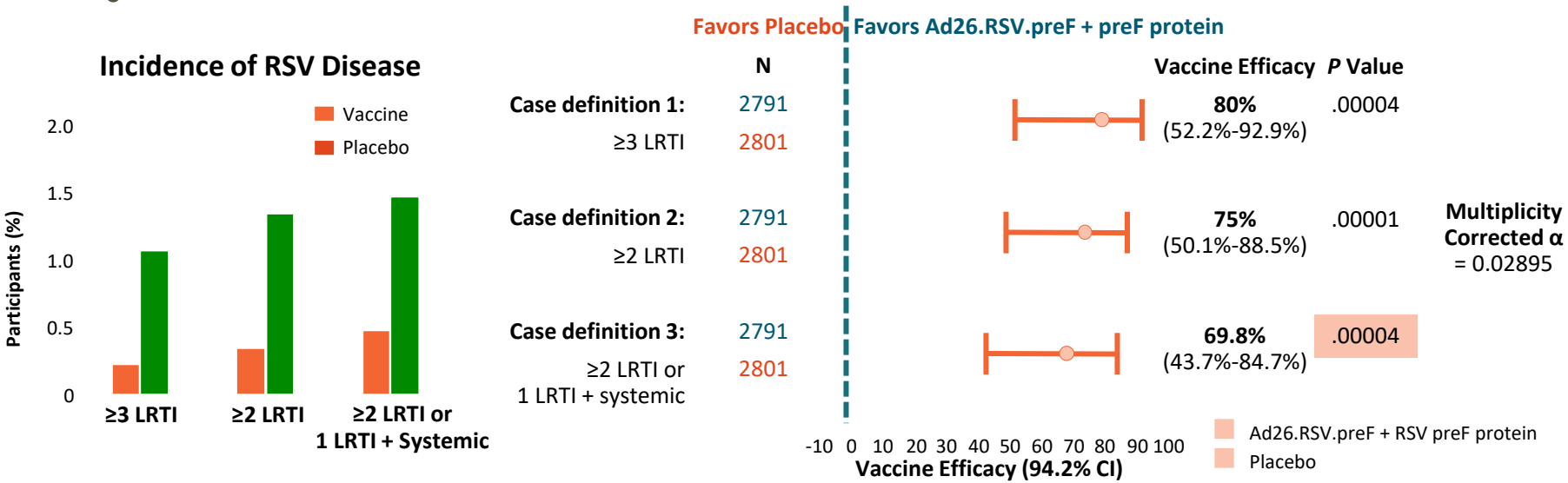
CYPRESS: Efficacy Against RSV Disease

Slide credit: clinicaloptions.com

- Vaccine was highly effective against RSV-mediated LRTD
  - **Higher efficacy seen with increasing severity of LRTD case definitions**
- Vaccine elicited robust and durable humoral and cell-mediated immune responses at Day 15 and Mo 6



Falsey. IDWeek 2021. Abstr LB14.

conclusioni

- L’offerta vaccinale aumenterà, sempre di migliore qualità
- Restare fuori da questo flusso di protezione negli anni della globalizzazione, dell’invecchiamento e dell’immunodeficit potrà riprodurre un mondo a due velocità, con più disuguaglianze
- Decisivo il ruolo della cultura del medico: alcune cose importanti sui vaccini devono essere condivise da tutti gli operatori, non solo dagli esperti
- Occorrerà migliorare il ruolo della farmacovigilanza, proattiva e reale: solo in un sistema monitorato l’utente potrà avere piena fiducia sul livello di sicurezza