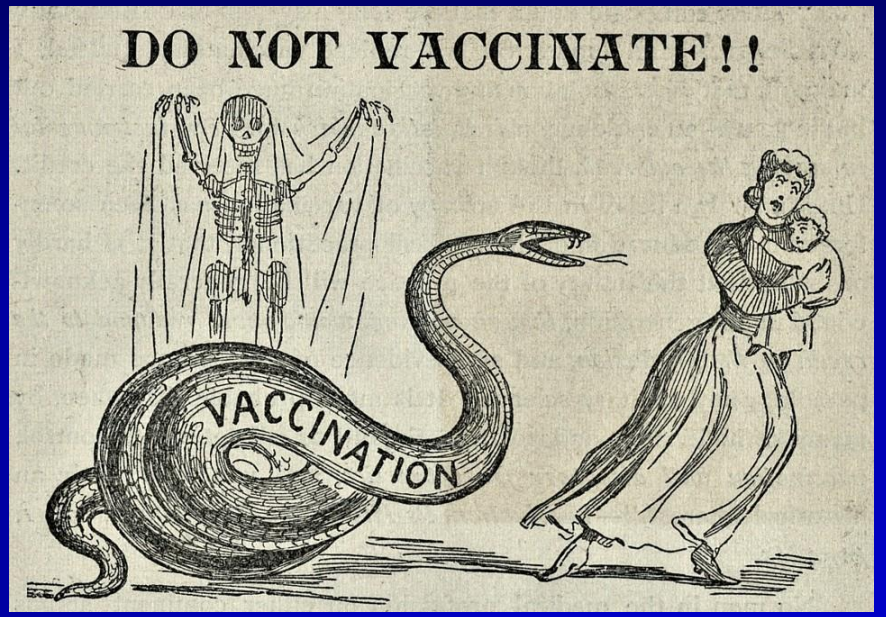
Burden of Vaccine Preventable Infections in Immunocompromised Individuals



Per Ljungman, MD, PhD
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Stockholm, Sweden

Disclosures and caveats

Speaker, investigator, scientific expert	MSD
Speaker	Pfizer
Speaker, expert	Moderna

I’m a hematologist and mainly these days doing allogeneic stem cell transplants and CAR T cell treatments so my views and this presentation reflect these facts.

Number of immunocompromised individuals

Estimated in the USA to be 2.7% of the adult population (7 million individuals)
Source – AMA

Estimated number in the UK – 500.000 individuals

Estimated number in the EU – approximately 8 million individuals

The numbers are constantly increasing!

General concepts

A heterogeneous group

Different causes of the immunocompromised state

Inherited (also in adults), infections (HIV), malignancies, treatments

A long list of therapeutic drugs and strategies

Immunosuppressed status varies over time

General concepts

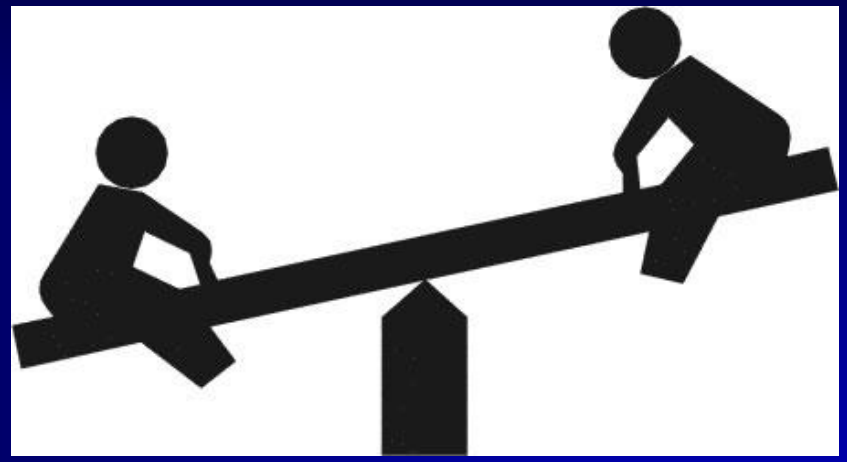
There is an increased risk for contracting certain infections (pneumococci)

There is an increased risk for reactivating latent infections

Many (but not all) patients are at an increased risk for severe infections

The balance regarding vaccinations

Benefit



Risk

What's the risk for severe disease?

What's the potential benefit (will the patient respond)?

Will an immune response have the same protective effect as in healthy individuals?

What are the risks?

Study data: Caveat!

(Almost) no true efficacy data exist

Toxicity data quite robust for many vaccines

”All” efficacy data is on surrugate endpoints e.g immune responses!

but

Absence of Evidence is not Evidence of Absence

Risks with inactivated vaccines

No evident major risks for direct side effects

- Local side effects
- Systemic side effects

Is there a risk for immune activation complications (rejection, GVHD, autoimmune phenomena)?

- Existing data suggest the risks are very low
- However, an exception is mRNA vaccines against COVID-19

Increased risk with adjuvanted vaccines?

Risks with live vaccines

Possibility for vaccine induced disease especially in patients with suppressed T-cell immunity

Local or disseminated side effects

Risks for immune activation complications (rejection, GVHD, autoimmune phenomena)?

Existing data suggest that the risks are low although deaths after varicella-zoster vaccinations were reported

Which are the most important infections?

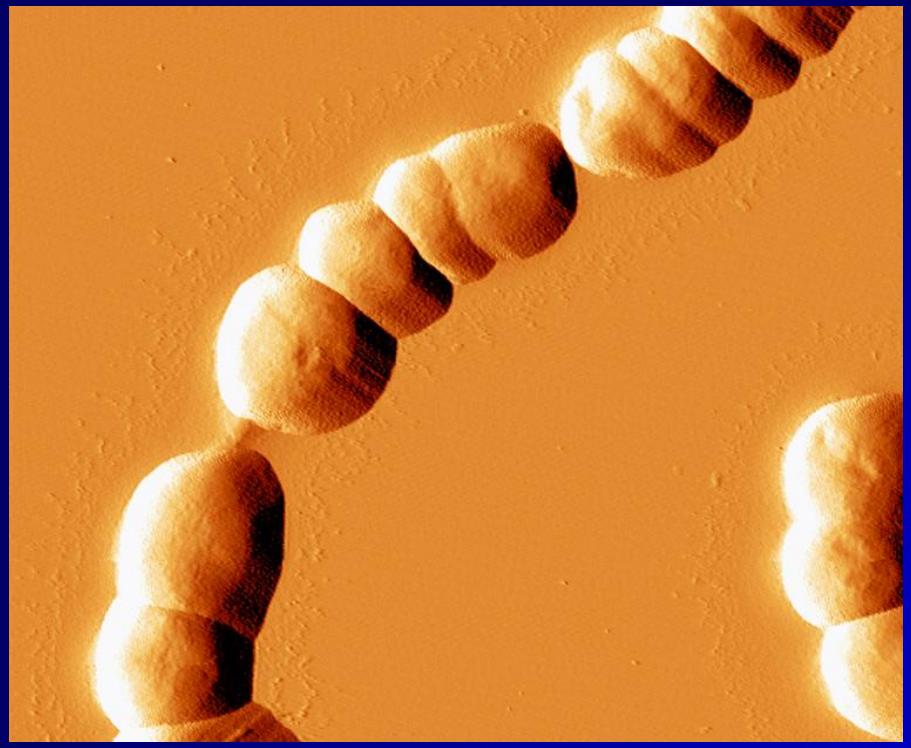
Pneumococci

Influenza

SARS-CoV-2

VZV

HPV



Incidence of invasive pneumococcal disease (IPD) in immunocompromised hosts

Adults, ABCs database on 7 american states, 1999-2000

Group	Incidence (CI 95%) / 100 000 persons
Healthy subjects	*8.8 (8.5-9)*
Diabetes	51.4 (49.2-53.9)
Chronic respiratory failure	62.9 (59.8-66.3)
Chronic heart disease	93.7 (87.4-100.9)
Alcoholism	100.4 (94.1-107.7)
Solid tumor	**300.4 (272.6-334.6)**
HIV infection	**422.9 (378.3-479.4)**
Hematological malignancy	**503.1 (422.2-622.3)**

Kyaw MH et al. J Infect Dis 2005

Risks for Invasive Pneumococcal Infections

Table 2. Annual Incidence of Invasive Pneumococcal Disease and Incidence Rate Ratio for Persons With Selected Immunocompromising Conditions Relative to the Immunocompetent Population, 2010/2011, Toronto/Peel Region, Ontario

	Population	Age Group (in Years)					
		All		<15 y		≥15 y	
	N	Incidence[a]	IRR (95% CI)	Incidence[a]	IRR (95% CI)	Incidence[a]	IRR (95% CI)
Immunocompetent	3 973 048	4.8		4.9		4.8	
Immunocompromised (all)	112 439	56	12 (8.7–15)	199	41 (18–91)	53	11 (8.0–15)
Chronic renal failure requiring dialysis[b]	2798	89	19 (5.3–65)	. . .		107	22 (6.4–78)
HIV infection	19 274	56	11 (6.1–21)	294	60 (3.7–986)	52	11 (5.8–21)
Hematological malignancy[c]	9038	266	55 (36–84)	914	188 (67–531)	233	48 (30–77)
Acute leukemia	850	647	134 (58–313)	1122	231 (77–694)	371	77 (19–312)
Chronic leukemia	1818	220	46 (17–124)	. . .		220	46 (17–124)
Lymphoma	5184	106	22 (9.4–51)	398	82 (5.0–1337)	99	21 (8.4–50)
Multiple myeloma	945	847	176 (87–358)	. . .		847	176 (87–358)
Solid organ/bone marrow transplant	4377	217	45 (24–86)	555	114 (22–585)	195	41 (20–83)
Sickle cell disease	1226	122	25 (5.1–127)	248	51 (3.1–833)	98	20 (2.8–145)
Systemic autoimmune disease[d]	20 427	20	4.1 (1.5–11)	. . .		18	3.7 (1.2–12)
Immunosuppressive therapy[e]	55 300	19	3.9 (2.1–7.3)	. . .		20	4.2 (2.2–7.8)

Shigayeva et al, CID 2016

Increased risk for Invasive Pneumococcal Infections

	≥15 y	
	Incidence[a]	IRR (95% CI)
Immunocompetent	4.8	
Immunocompromised (all)	53	11 (8.0–15)
Chronic renal failure requiring dialysis[b]	107	22 (6.4–78)
HIV infection	52	11 (5.8–21)
Hematological malignancy[c]	233	48 (30–77)
Acute leukemia	371	77 (19–312)
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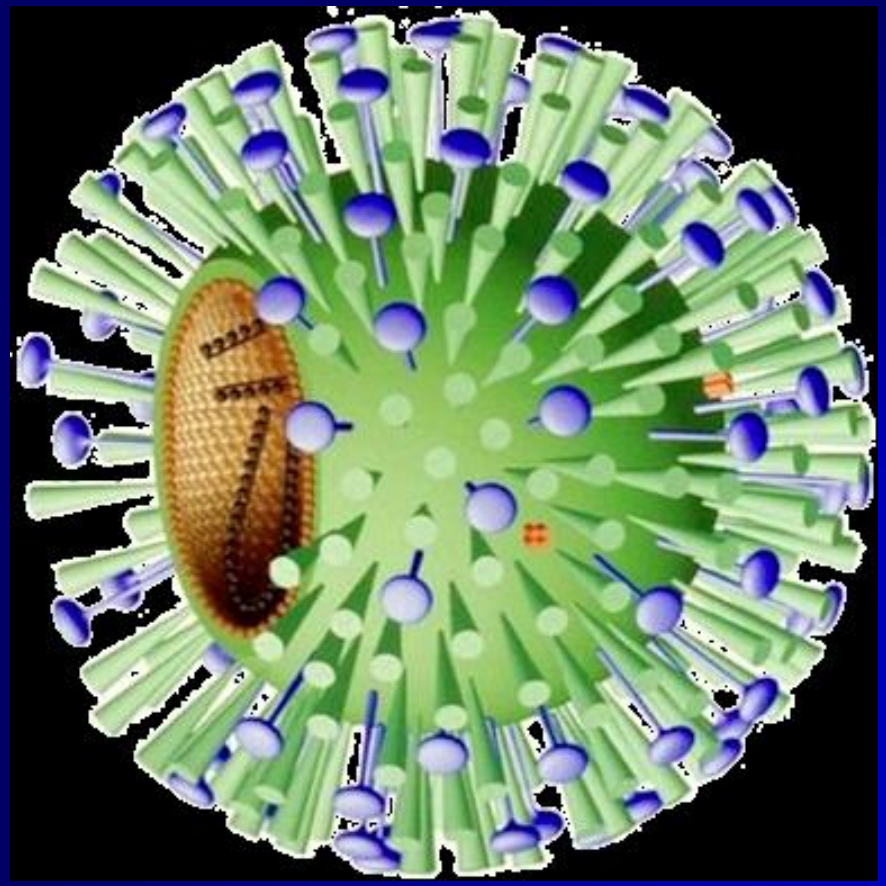
All > 4-fold increased risk

Many > 20-fold increased risk

Shigayeva et al, CID 2016

Influenza



Karolinska Institutet

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Outcomes of Immunocompromised Adults Hospitalized With Laboratory-confirmed Influenza in the United States, 2011–2015

Jennifer P. Collins,[1,2] Angela P. Campbell,[3] Kyle Openo,[2] Monica M. Farley,[2,4] Charisse Nitura Cummings,[3] Mary Hill,[5] William Schaffner,[6] Mary Lou Lindegren,[6] Ann Thomas,[7] Laurie Billing,[8] Nancy Bennett,[9] Nancy Spina,[10] Marisa Bargsten,[11] Ruth Lynfield,[12] Seth Eckel,[13] Patricia Ryan,[14] Kimberly Yousey-Hindes,[15] Rachel Herlihy,[16] Pam Daily Kirley,[17] Shikha Garg,[3] and Evan J. Anderson[1,2,4]

35348 adults; 10% immuncompromised

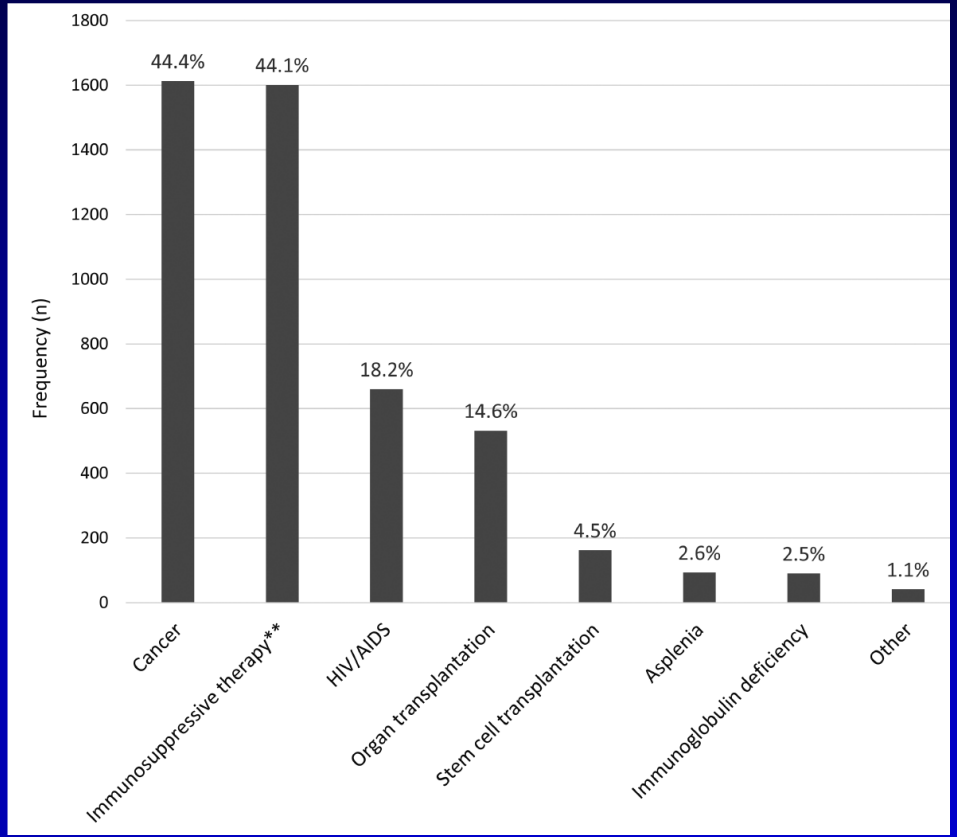
Higher proportion were vaccinated (53% vs 46%)

IC patients had a higher mortality

IC patients > 65 years had a higher need for ICU care

IC patients were more likely to need mechanical ventilation

IC patients had longer hospital stays



Influenza vaccination – clinical results in transplant patients

No randomized study vs placebo or no vaccination (difficult from an ethical point of view to perform)

Cohort studies and ”compliance” studies have been reported

Vaccination can reduce the risk for influenza in HCT patients and severity in HCT and SOT patients

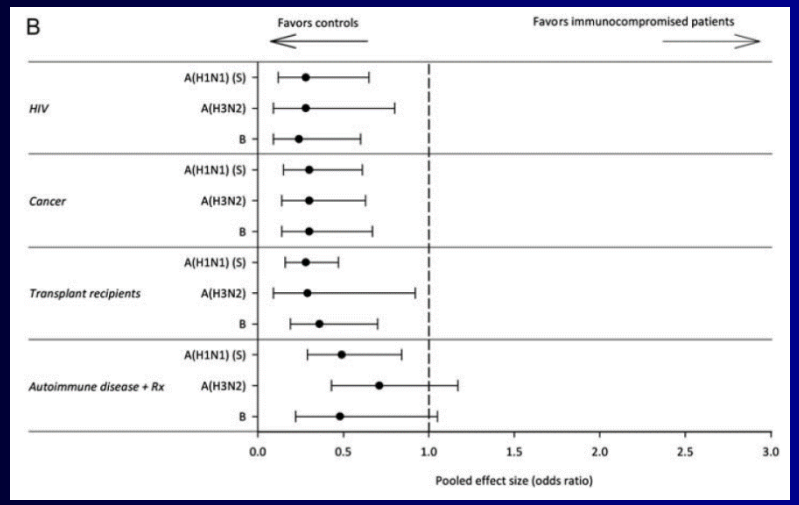
(Machado et al; Bone Marrow Transplant 2005; 36; 897-900; Piñana et al; Clin Infect Dis 2019; 68: 1894-1902; Kumar et al, Clin Infect Dis 2018; 67: 1322-29)

MAJOR ARTICLE

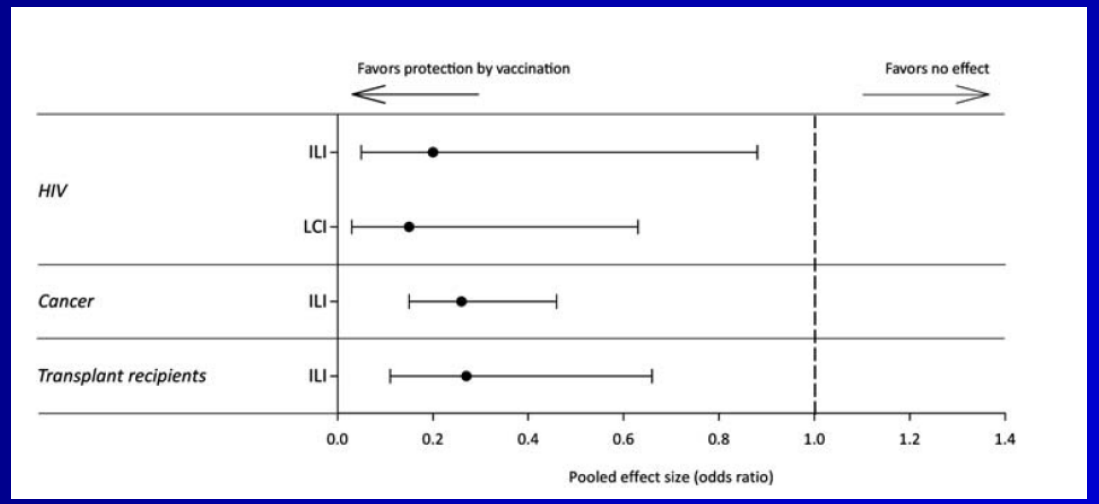
Influenza Vaccination for Immunocompromised Patients: Systematic Review and Meta-analysis by Etiology

Charles R. Beck,[1] Bruce C. McKenzie,[1] Ahmed B. Hashim,[1] Rebecca C. Harris,[2] University of Nottingham Influenza and the ImmunoCompromised (UNIIC) Study Group,[a] and Jonathan S. Nguyen-Van-Tam[1]

[1]Division of Epidemiology and Public Health, University of Nottingham, United Kingdom; and [2]Global Influenza Programme, World Health Organization, Geneva, Switzerland



Seroprotection



Clinical protection

Influenza vaccination and severity of disease

Vaccination can reduce the risk for progression to influenza pneumonia

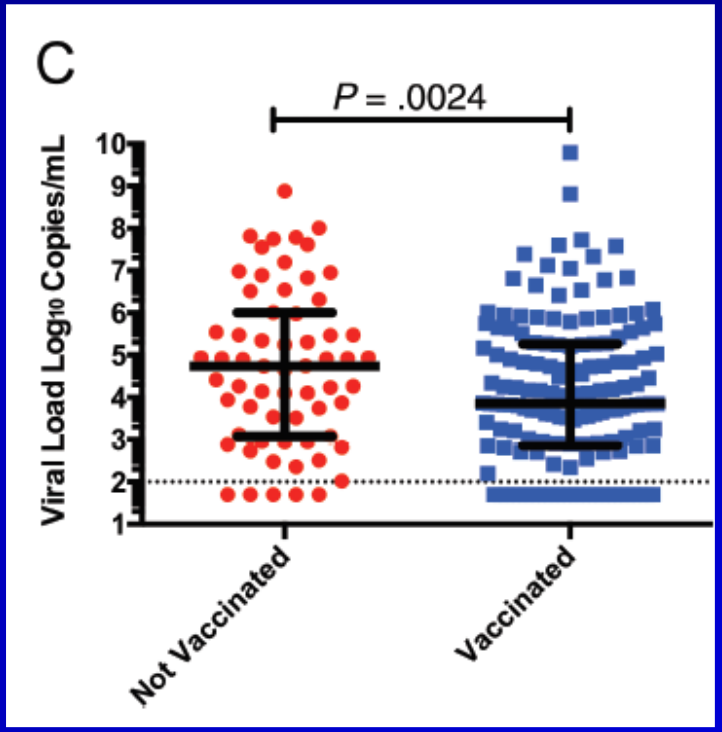
(Piñana et al; Clin Infect Dis 2019; 68: 1894-1902; Kumar et al, Clin Infect Dis 2018; 67: 1322-29)

Vaccination can reduce the risk for ICU admission due to influenza

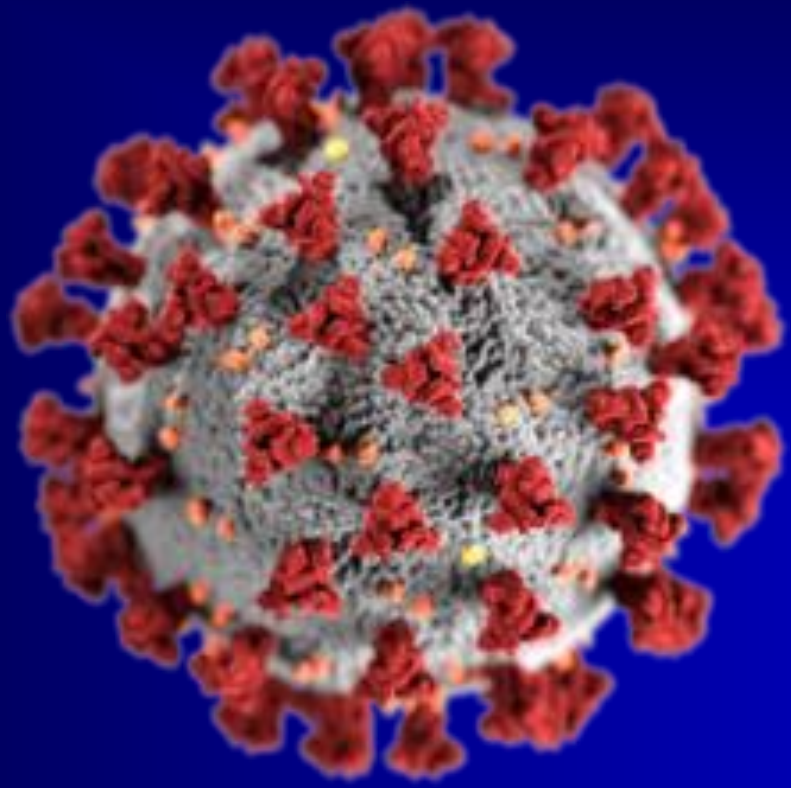
(Kumar et al, Clin Infect Dis 2018; 67: 1322-29)

Viral loads were higher in patients with pneumonia and those requiring ICU. Vaccinated patients had lower viral loads

(Kumar et al, Clin Infect Dis 2018; 67: 1322-29)



SARS-CoV-2/Covid-19



General comments

Severly immuncompromised patients had a high mortality early in the pandemic.

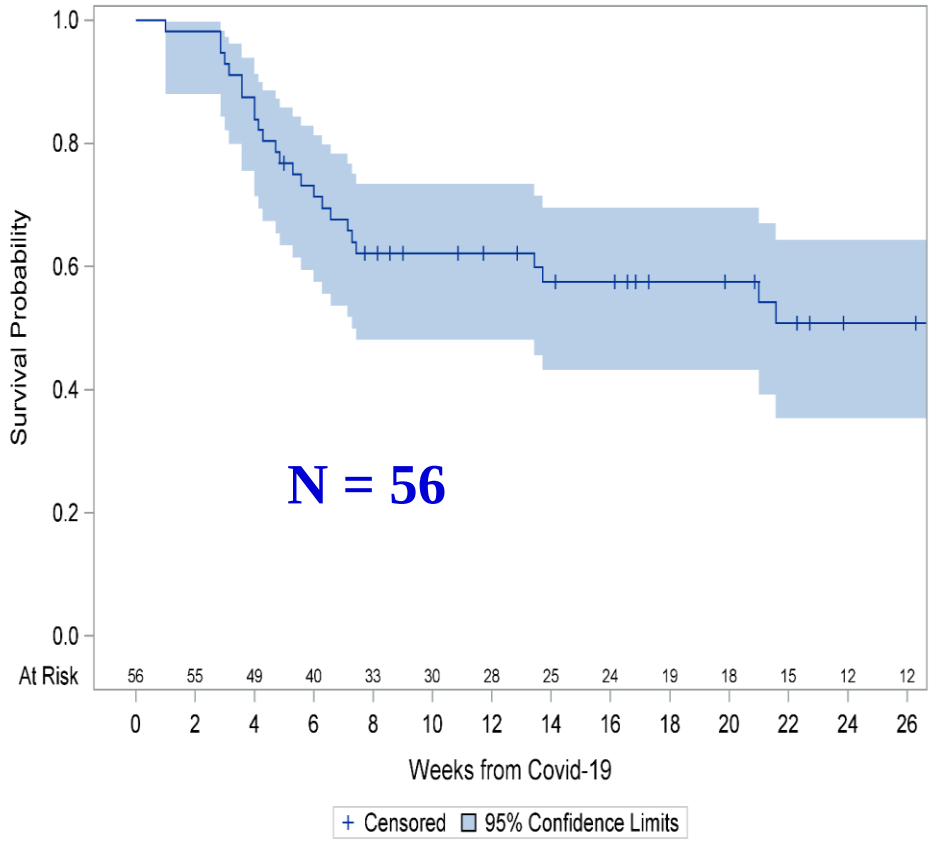
Major variations were found between different patient groups and given therapies

When the vaccines were introduced, these groups had a high priority for vaccination.

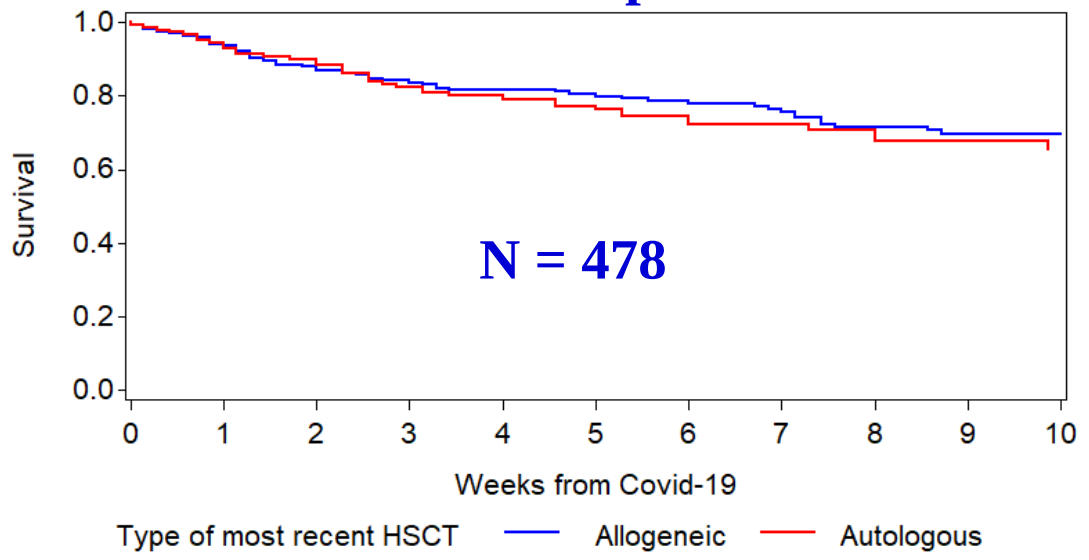
However, very few formal clinical trials were performed in IS populatations

This is where we were

CAR T cell treated



Stem cell transplants



Spanjaart, et al; Leukemia 2021

Ljungman et al, Leukemia 2021

General comments - continued

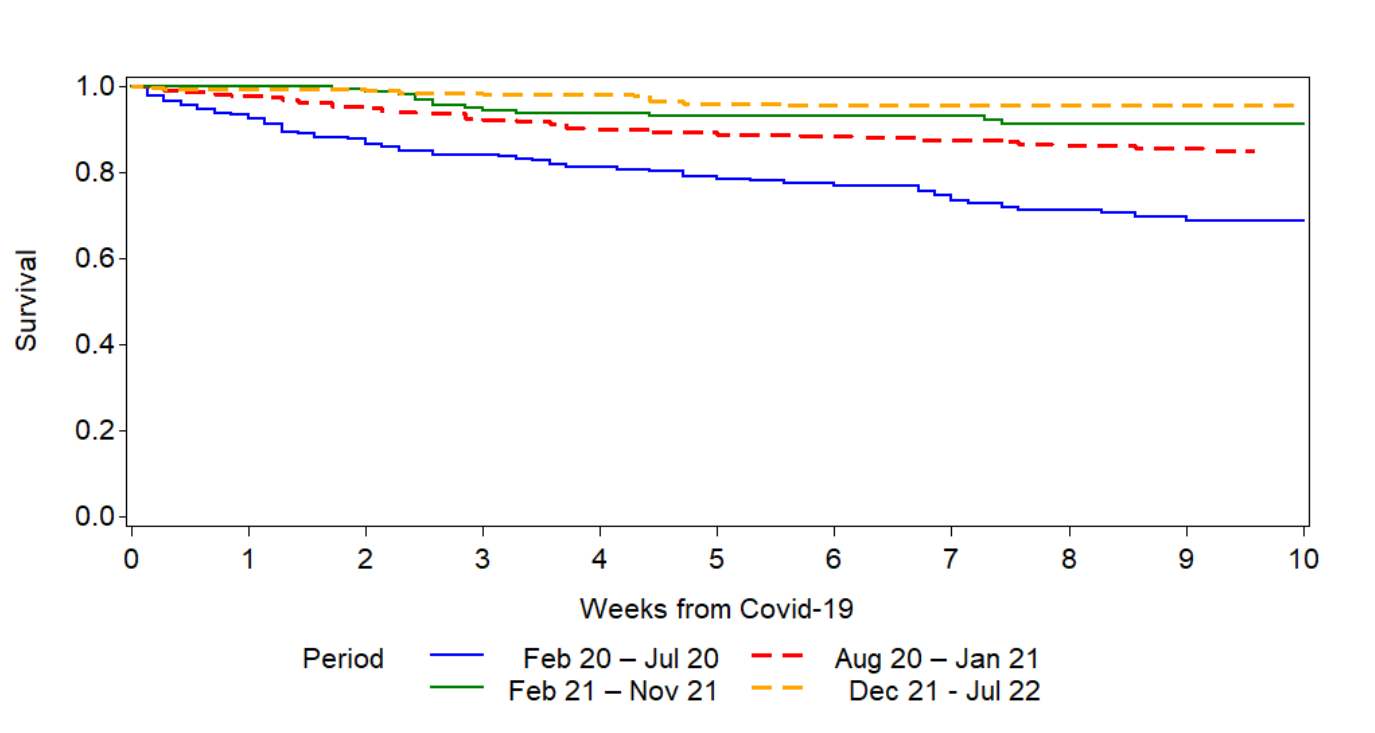
Cohort studies and retrospective analyses showed decreased antibody responses in IS patients. T cell responses can usually be elicited

Morbidity and mortality have decreased in these populations probably due to several factors (variants, vaccination, therapeutic interventions)

Repeated doses of especially mRNA vaccines were (and are) recommended by several national authorities

No safety (or efficacy) analysis has been performed on 5 – 6 – 7 or more doses of mRNA vaccine.

Where are we now?



Results from the EBMT registry

986 allogeneic HCT recipients

Improved survival

Decreased hospitalization

Decreased risk for LRTD

Mortality in fully vaccinated patients

2/207 patients (1%)

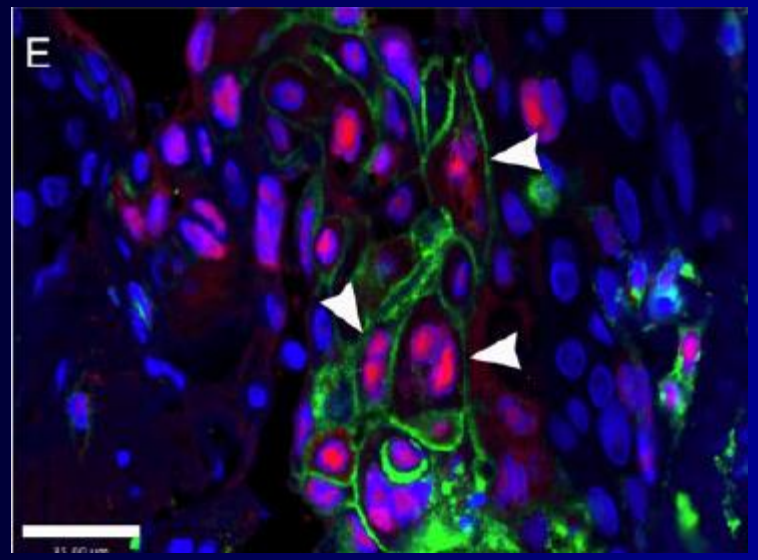
Ljungman et al; Frontiers Immunol 2023

Varicella-zoster virus (VZV)

Safety of live vaccines – example VZV

Disseminated, Persistent, and Fatal Infection Due to the Vaccine Strain of Varicella-Zoster Virus in an Adult Following Stem Cell Transplantation

Preeti Bhalla,[1,a] Graeme N. Forrest,[1,2] Michael Gershon,[3] Yan Zhou,[3,b] Jason Chen,[3] Philip LaRussa,[4] Sharon Steinberg,[4] and Anne A. Gershon[4]



Age, Sex	Underlying Condition	Complication
Reactions resembling varicella within 42 d after vaccination (n = 11)		
13 mo, M	ADA deficiency	Hepatitis, respiratory distress
13 mo, M	Di George syndrome	Pneumonia
15 mo, F	Possible undiagnosed immunodeficiency disease	Severe rash, respiratory compromise, steroids, died
16 mo, M	Human immunodeficiency virus, 8 CD4 cells/mm^3	Severe rash, encephalopathy
18 mo, F	Unidentified cell-mediated immune deficit	Severe rash, pneumonia
4 yr, F	Leukemia, remission 5 mo	Pneumonia, multiorgan failure; died
5 yr, M	Asthma, cerebral palsy, steroid therapy	Pneumonia
6 yr, M	iNK cell deficiency	Severe rash, pneumonia
11 yr, F	iNK cell deficiency	Severe rash, pneumonia
14 yr, M	Severe combined immunodeficiency	Severe rash, hepatitis
48 yr, M	Down's syndrome	Pneumonia

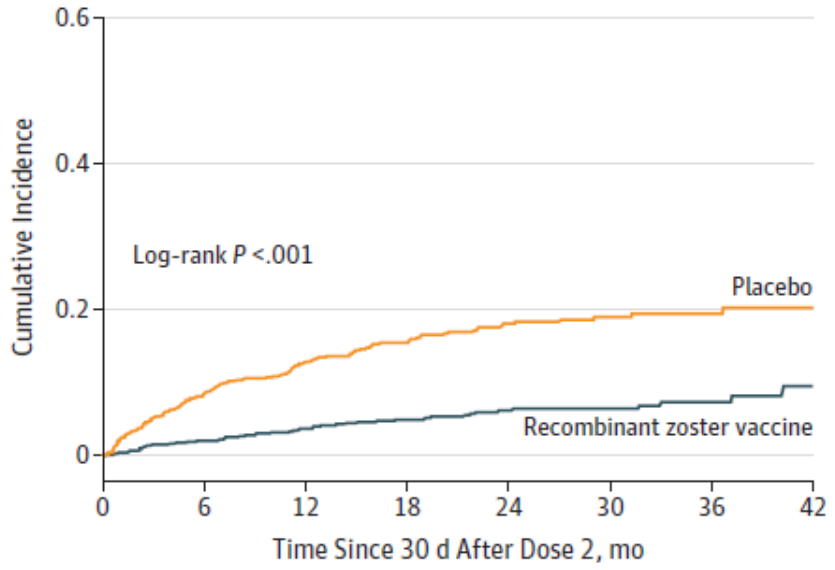
Recombinant zoster vaccine (Shingrix)

JAMA | Original Investigation

Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation
A Randomized Clinical Trial

Adriana Bastidas, MD; Javier de la Serna, MD; Mohamed El Idrissi, MSc; Lidia Oostvogels, MD; Philippe Quittet, MD; Javier López-Jiménez, MD, PhD; Filiz Vural, MD; David Pohlreich, MD; Tsila Zuckerman, MD; Nicolas C. Issa, MD; Gianluca Gaidano, MD, PhD; Je-Jung Lee, MD; Sunil Abhyankar, MD; Carlos Solano, MD, PhD; Jaime Perez de Oteyza, MD, PhD; Michael J. Satlin, MD; Stefan Schwartz, MD; Magda Campins, MD, PhD; Alberto Rocci, MD, PhD; Carlos Vallejo Llamas, MD, PhD; Dong-Gun Lee, MD, PhD; Sen Mui Tan, MD; Anna M. Johnston, MBBS; Andrew Grigg, MBBS, FRACP, MD; Michael J. Boeckh, MD, PhD; Laura Campora, MD; Marta Lopez-Fauqued, PhD; Thomas C. Heineman, MD, PhD; Edward A. Stadtmauer, MD; Keith M. Sullivan, MD; for the ZOE-HSCT Study Group Collaborators

Figure 2. Cumulative Incidence of Herpes Zoster Overall (Modified Total Vaccinated Cohort)



Bastidas et al; JAMA 2019

Another intriguing possibility

Can we prevent secondary malignancies by vaccination?

The logical vaccine to use would then be HPV vaccine

HPV vaccine is today recommended to children to decrease the risk for HPV infection and subsequent development of malignancies.

Transplant patients have an increased risk for HPV associated cancers

It is unclear if HPV is cleared after primary infection or becomes persistent/latent

Compliance to recommendations?

Patients and doctors!

663 HSCT recipients reviewed between December 2010 through February 2013 revealed that:
252 (38%) patients had received the first series of recommended vaccinations by 6 months
398 (60%) had received them by 1 year after HSCT

Ariza-Heredia EJ et al, Transplant Infect Dis 2014

We checked the situation ”at home” and were moderately better but far from 100% compliant
The reasons for not vaccinating varied a lot but were usually non based on the SOP

Vaccination compliance

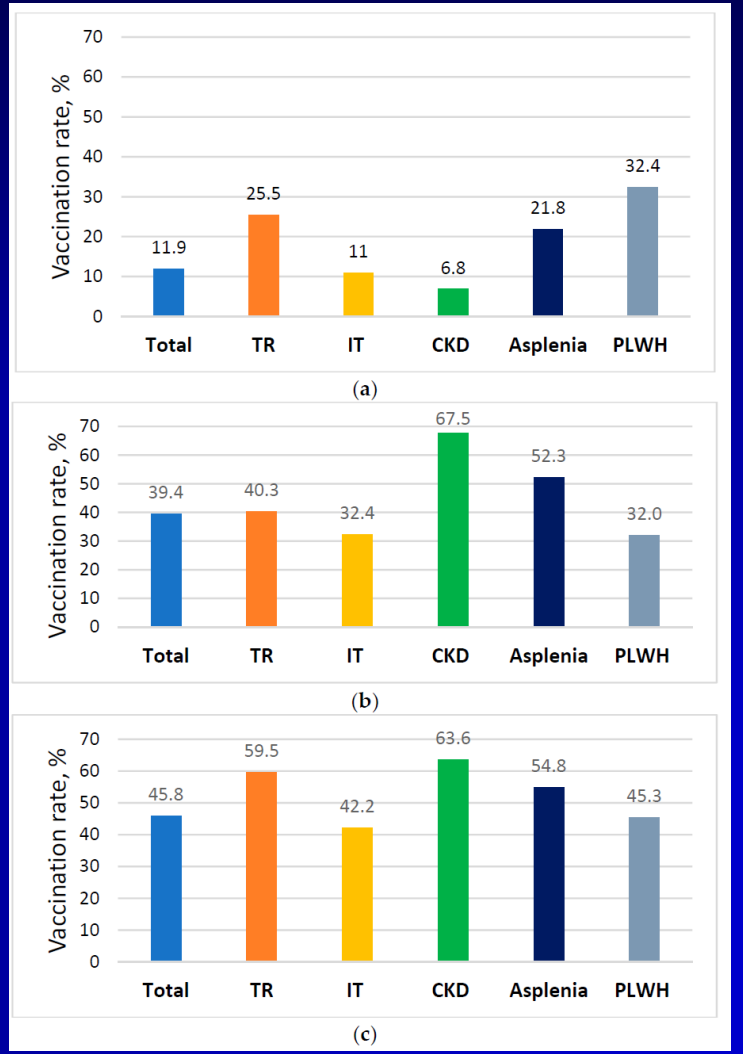
vaccines

MDPI

Article

Vaccination Coverage among Immunocompromised Patients in a Large Health Maintenance Organization: Findings from a Novel Computerized Registry

Shirley Shapiro Ben David [1,2,*], Iris Goren [1], Vered Mourad [1] and Amos Cahan [3]



PCV

PPSV23

Influenza

Vaccines 2022

Vaccine coverage; pneumococci and influenza

Vaccine 40 (2022) 4911–4921

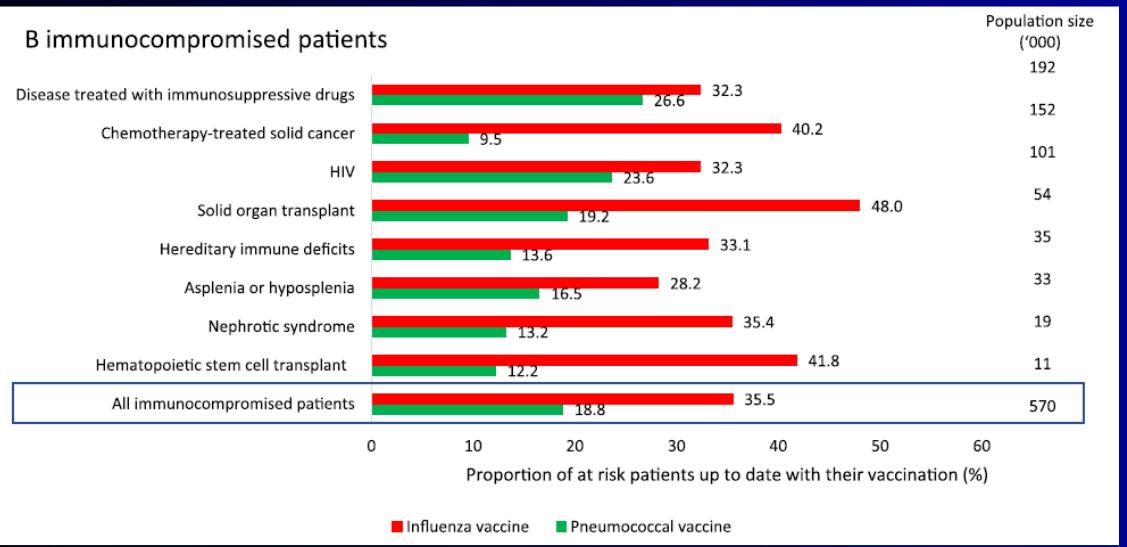
Contents lists available at ScienceDirect

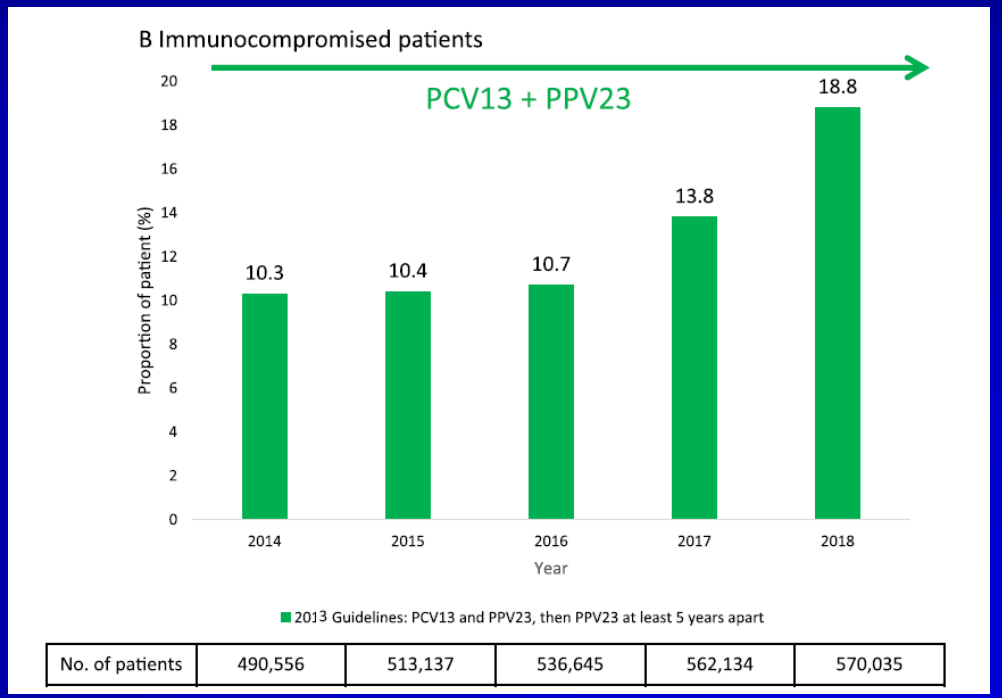
Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Pneumococcal and influenza vaccination coverage among at-risk adults: A 5-year French national observational study

Benjamin Wyplosz [a,*], Jérôme Fernandes [b], Ariane Sultan [c], Nicolas Roche [d], François Roubille [e], Paul Loubet [f], Bertrand Fougère [g], Bruno Moulin [h], Didier Duhot [i], Alexandre Vainchtock [j], Fanny Raguideau [j], Joannie Lortet-Tieulent [j], Emmanuelle Blanc [k], Jennifer Moïsi [k], Gwenaël Goussiaume [k]





No. of patients	490,556	513,137	536,645	562,134	570,035

Summary

IS patients are many and the numbers are increasing.

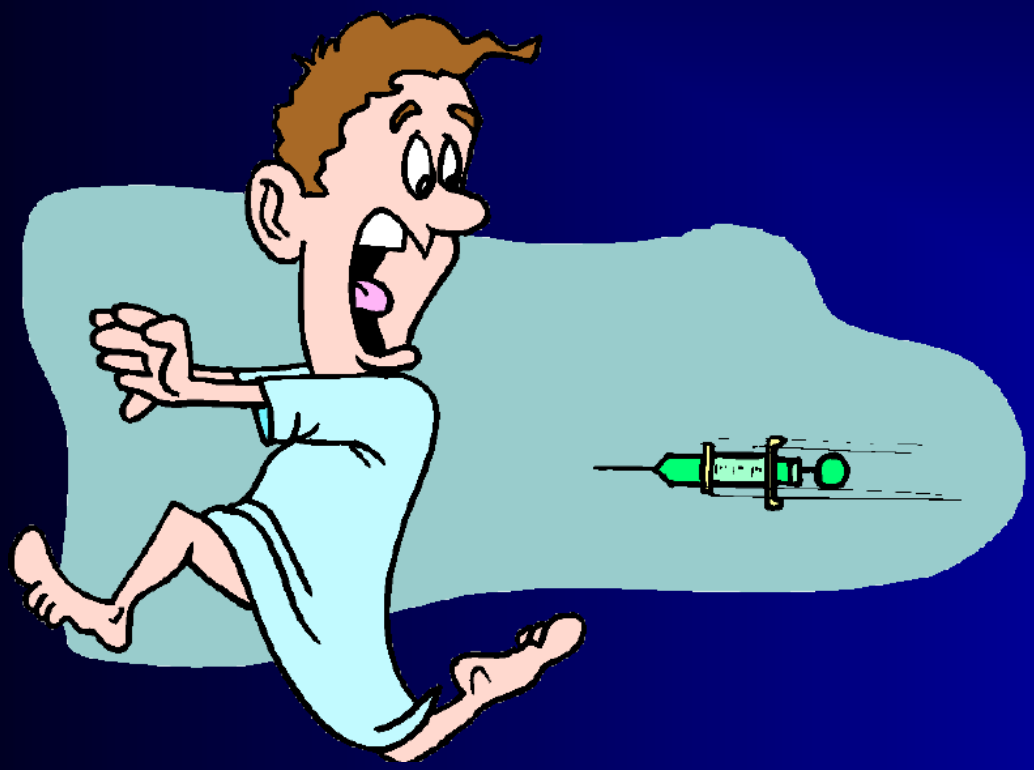
Many patients are at risk for severe VPI

Few well-designed studies have been targeted to these populations

The compliance/vaccine coverage needs to be improved.

Thus, this should be an important part of the AIBs agenda

Thank you for your attention!



Questions?