Vaccine responses in the elder…in older adults

John M Kelso, MD

Division of Allergy, Asthma and Immunology
Scripps Clinic
San Diego CA

Clinical Professor of Pediatrics and Internal Medicine
University of California, San Diego
School of Medicine

Burton Zweiman, MD

Faculty Disclosure Information

- I have not had a financial interest or other relationship with the manufacturers of the products that will be discussed in my presentation.
- This presentation will not include discussion of pharmaceuticals or devices that have not been approved by the FDA.
- I will not be discussing unapproved or "off-label" uses of pharmaceuticals or devices.

Objectives

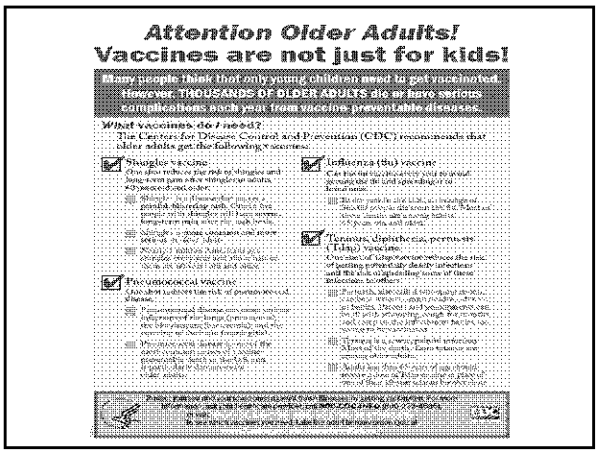
- Review current vaccine recommendations for adults 60 years and older including the rationale for these recommendations

Immunosenescence

- ↓ # plasmacytoid DC (pDC)
- ↓ capacity of pDC to make TNF- α and IFN-α after TLR7/9 stimulation
- ↓ capacity of myeloid DC (mDC) to make TNF- α, IL-6 and IL-12 after TLR2/4 stimulation
- ↓ # CD19+CD27+IgD- "switched" memory B cells
- ↓ amount and affinity of Ab responses

Immunosenescence

- ↑ # Treg
- ↑ Treg production of IL-10 and TGF-β (immunosuppressive)
- ↓# Th17 (↓ recruitment and activation of neutrophils)



Influenza: CDC

- Hospitalization rates highest for adults aged ≥65 years; among persons aged ≥65 years with high-risk underlying medical conditions, 560 influenza-associated hospitalizations per 100,000 persons
- Yearly average of 21,098 influenza-related deaths occurred among adults aged ≥65 years (90% of all influenza deaths)

MMWR 2013;62(RR-7)

Age group (years)

Cause of death (based on ICD-10, 2004) and year	All ages[1]	Under 1 year[2]	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85 and over
Influenza and pneumonia (J09-J18)	per 100,000											
2010	16.2	4.9	0.6	0.2	0.4	0.9	1.9	4.5	9.9	27.9	102.4	426.2
2009[4]	17.6	6.5	0.9	0.3	0.5	1.0	2.0	3.2	6.5	11.7	20.5	107.0	430.8
2008[3]	18.5	5.6	0.9	0.2	0.5	0.9	2.1	5.1	10.9	30.6	119.8	512.3
2007[3]	17.5	5.4	0.7	0.3	0.4	0.8	1.8	4.3	9.5	26.2	113.5	500.7
2006[3]	16.9	6.5	0.8	0.2	0.4	0.9	1.9	4.6	9.9	24.6	127.3	547.0
2005[3]	21.3	8.8	0.7	0.3	0.4	0.9	2.1	5.1	11.2	36.1	142.9	644.9
2004[3]	20.4	8.9	0.8	0.2	0.4	0.8	2.0	4.6	10.8	34.2	139.1	622.8
2003[3]	22.5	8.1	1.0	0.4	0.5	1.0	2.2	5.2	11.2	38.9	150.8	709.0
2002[3]	22.8	6.7	0.7	0.2	0.4	0.9	2.2	4.8	11.2	37.2	166.6	732.4
2001[3]	21.8	7.5	0.7	0.2	0.5	0.9	2.2	4.6	10.8	36.2	148.3	706.1
2000	23.2	7.9	0.7	0.2	0.5	0.9	2.4	4.7	11.9	39.1	160.3	744.1
1999	22.8	6.4	0.8	0.2	0.5	0.9	2.4	4.6	11.0	37.2	157.8	751.8

Murphy SL, et al. National vital statistics reports 2013;61(4)

Influenza vaccine

RDBPCT ≥ 60 years old

Table 5.—Relative Risks (RRs) and 95% Confidence Intervals (CIs) of Vaccinated Participants Compared With Nonvaccinated Participants in Relation to Serological Influenza and Clinical Influenza

Influenza		Vaccine Group, n (n=927)	Placebo Group, n (n=911)	RR (95% CI)
Clinical[a]	Serological			
No	No	753	694	. . .
Yes	No	107	115	0.92 (0.72-1.17)
No	Yes	25	42	0.59 (0.36-0.96)
Yes	Yes	16	38	0.42 (0.23-0.74)
Dropouts		26	22	. . .

[a]Clinical influenza if any of the criteria (family physician, Sentinel Stations, or *International Classification of Health Problems in Primary Care*[40] criteria) were met.

Govaert TM, et al. JAMA 1994;272:1661-5.

Influenza vaccine responses elderly vs young adults

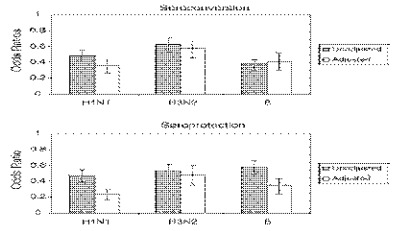


Fig. 1. Comparison of influenza vaccine adjusted and unadjusted weighted responses in the elderly vs. young adults, measured as unadjusted and adjusted odds-ratio, by outcome and vaccine component. An odds-ratio below 1 indicates that the vaccine response is better in young adults than in the elderly. Adjusted odds-ratios (ORs) for age derived from stratified multiple regression models that controlled for other demographic and vaccine-specific factors that also affecting the outcome. The bars indicate the OR point estimate and the ranges the 95% confidence limits.

Seroconversion: % subjects with 4X ↑ titers
Seroprotection: % subjects with titers ≥1:40

Goodwin K, et al. Vaccine 2006;24:1159-69

Influenza vaccine: HD vs SD

Response, by antigen	HAI GMT ratio for HD and SD vaccine, (95% CI)
GMT	
A/H1N1	
Day 0	. . .
Day 28	1.7 (1.6 – 1.8)
A/H3N2	
Day 0	. . .
Day 28	1.8 (1.7 – 2.0)
B	
Day 0	. . .
Day 28	1.3 (1.2 – 1.4)
Seroprotection[a]	Percentage difference in rate (95% CI)
A/H1N1	25.4 (22.4 – 28.5)
A/H3N2	16.4 (13.1 – 21.7)
B	11.8 (8.6 – 15.0)
Seroprotection[b]	
A/H1N1	13.1 (10.6 – 15.8)
A/H3N2	2.8 (1.7 – 3.9)
B	11.7 (8.7 – 14.7)

Falsey AR, et al. J Infect Dis 2009;200:172-80.

Influenza vaccine: CDC

- The desire to improve responses among adults aged ≥65 years led to the development of a vaccine with more antigen than standard-dose IIV.
- High-dose IIV among persons aged ≥65 years elicited substantially higher titers
- Whether the higher postvaccination immune responses observed among High-Dose vaccine recipients will result in greater protection against influenza illness is under study.
- No preferential recommendation is made for high-dose IIV over standard dose IIV for persons aged ≥65 years.

MMWR 2013;62(RR-7)

Pneumococcal vaccine: CDC

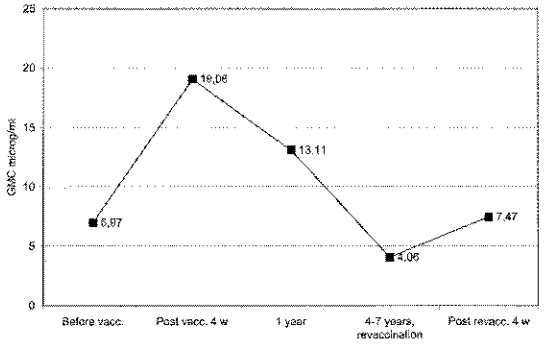
- The incidence of invasive pneumococcal disease ranges from 3.8 per 100,000 among persons aged 18–34 years to 36.4 per 100,000 among those aged ≥65 years
- PPSV23 effectiveness is 50% to 80% for prevention of IPD among immunocompetent older adults and adults with various underlying illnesses

MMWR 2010;59(34), 2012;61(40)

Pneumococcal vaccines

•PPSV23 contains 12 of the serotypes included in PCV13, plus 11 additional serotypes, i.e., PCV13 contains one serotype not included in PPSV23.

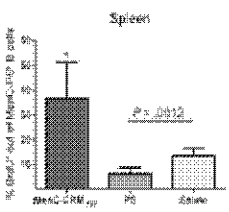
Antibody response to initial and booster PPSV23



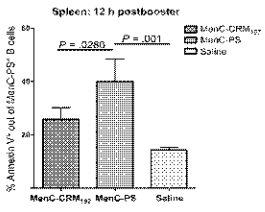
J. Törling et al. Vaccine 2003;22:96–103

Mice primed with conjugate vaccine and boosted with conjugate, polysaccharide or saline have…

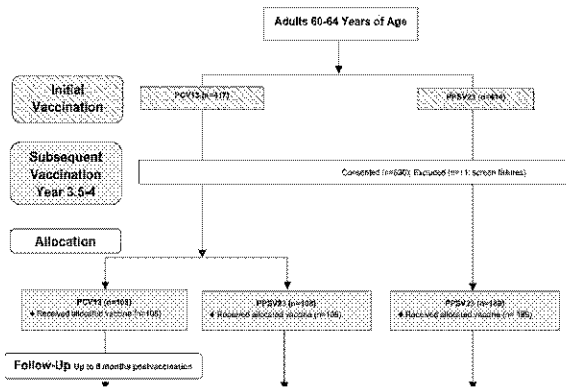
fewer specific B cells



more apoptotic specific B cells



Brynjolfsson et al. JID 2012:205:422-30



L.A. Jackson et al. Vaccine 2013;31:3594-3602.

Serotype	PPSV23/PPSV23 vs PPSV23 (Adults 60–64 years of age)		
	PPSV23/PPSV23 n[a] = (57–181) GMT[b]	PPSV23 n[a] = (57–181) GMT[b]	Ratio GMT ratio[c] (95% CI)
1	95	115	0.8 (0.68–1.02)
3	53	109	0.5 (0.44–0.59)
4	725	1437	0.5 (0.48–0.54)
5	71	152	0.5 (0.39–0.56)
6A*	133	286	0.5 (0.35–0.62)
6B	915	1133	0.8 (0.62–1.04)
7F	466	448	1.1 (0.81–1.37)
9V	181	369	0.5 (0.38–0.41)
14	619	823	0.8 (0.69–0.95)
18C	822	1098	0.8 (0.69–0.94)
19A	381	374	1.0 (0.83–1.12)
19F	485	696	0.7 (0.57–0.81)
23F	58	91	0.6 (0.50–0.76)

L.A. Jackson et al. Vaccine 2013;31:3594-3602.

PCV13/PPSV23 vs. PPSV23/PPSV23 (Adults 60–64 years of age)		
PCV13/PPSV23 n[a] = 99–107 GMT[b]	PPSV23/PPSV23 n[a] = 174–186 GMT[b]	Ratio GMT ratio[c] (95% CI)
398	95	4.2 (2.87–6.08)
184	53	3.4 (2.26–4.30)
1875	733	2.6 (1.72–3.80)
476	74	6.5 (4.09–10.10)
932	123	5.8 (3.72–12.33)
2670	916	2.6 (1.83–4.67)
1895	497	3.8 (2.41–6.83)
1069	187	5.8 (3.13–10.82)
1268	661	1.9 (1.30–2.86)
2450	862	2.1 (2.02–4.78)
905	364	2.7 (1.87–3.76)
1653	374	4.4 (2.97–6.98)
259	54	5.5 (3.20–9.41)

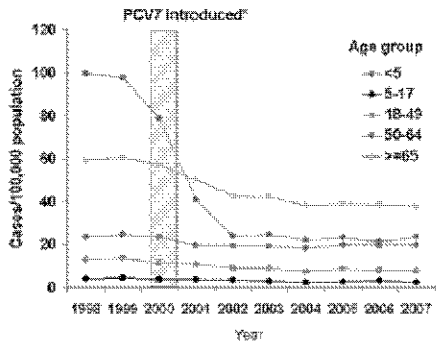
L.A. Jackson et al. Vaccine 2013;31:3594-3602.

PCV13/PCV13 vs. PPSV23/PPSV23 (Adults 60–64 years of age)		
PCV13/PCV13 n[a] = 100–104 GMT[b]	PPSV23/PPSV23 n[a] = 174–186 GMT[b]	Ratio GMT ratio[c] (95% CI)
334	95	3.5 (2.39–5.14)
82	53	1.6 (1.19–2.28)
1155	733	1.6 (1.05–2.44)
226	74	3.7 (2.32–6.04)
2694	123	10.8 (8.45–20.87)
4184	916	4.6 (2.62–7.15)
1203	497	2.5 (1.56–3.89)
770	187	4.1 (2.22–7.65)
1023	661	1.6 (1.07–2.26)
1918	802	2.4 (1.64–3.72)
780	364	2.2 (1.52–3.08)
958	374	2.6 (1.68–3.62)
867	54	15.9 (9.33–27.10)

L.A. Jackson et al. Vaccine 2013;31:3594-3602.

- "Potential advantage of initial PCV administration, which permits the establishment of an immune state that results in appropriate recall responses upon subsequent immunization with either PCV13 or PPSV23."

L.A. Jackson et al. Vaccine 2013;31:3594-3602.

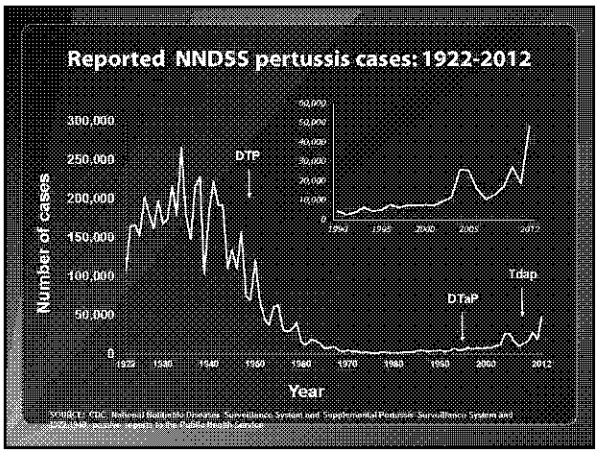


Pilishvili et al. JID 2010:201:32-41.

Pneumococcal vaccine: CDC

- All persons should be vaccinated with PPSV23 at age 65 years.
- Those who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years or later if at least 5 years have passed since their previous dose.
- Those who receive PPSV23 at or after age 65 years should receive only a single dose.

MMWR 2010;59(34)



Pertussis

Reported Case Profiles, 2012
By Age, Weeks 1-52

Age	No. of Cases	%	Age Inc /100,000
< 1 yr	4994	10.3	126.7
1-6 yrs	8280	17.2	34.1
7-10 yrs	5532	19.8	58.5
11-19 yrs	14440	29.9	38.0
20+ yrs	10436	21.6	4.5
Unknown	595	(1.2)	N/A
Total	48277	100.0	15.2

2012 Reported Pertussis Deaths

Age	Deaths
Infants, aged < 3 months:	15
Infants, aged 3-11 months:	1
Children, 1-4 years:	2
Adults, aged 55+ years:	2
Total	20

CDC

Tdap vaccine: CDC

•To reduce pertussis morbidity among adults and maintain the standard of care for tetanus and diphtheria prevention and to reduce the transmission of pertussis to infants

MMWR 2006;55(RR17)

Interval between Td and Tdap

- The recommended interval between doses of Td had been 10 years, with shorter intervals thought to be associated with increased rates of Arthus reactions.

Table 1: Guide to Use of Tetanus and Diphtheria Toxoids Adsorbed (Td) and Tetanus Immune Globulin (TIG) (Human) for Tetanus Prophylaxis in Routine Wound Management for Persons 7 Years of Age and Older

History of Adsorbed Tetanus Toxoid (doses)	Clean, Minor Wounds		All Other Wounds[a]	
	Td	TIG	Td	TIG
Unknown or <three	Yes	No	Yes	Yes
≥three[b]	No[c]	No	No[d]	No

[a] Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.
[b] If only three doses of fluid tetanus toxoid have been received, then a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.
[c] Yes, if ≥10 years since the last tetanus toxoid-containing vaccine dose.
[d] Yes, if ≥5 years since the last tetanus toxoid-containing vaccine dose. (More frequent boosters are not needed and can accentuate side effects.)

Interval between Td and Tdap

- However, in a recent study, the rates of injection site reactions to Tdap were no different in those vaccinated less than 2 years than in those vaccinated more than 2 years after previous Td.
- Another study found no higher rates of injection site reactions whether a Tdap-containing vaccine was administered one month after a Td-containing vaccine or placebo.

Interval between Td and Tdap

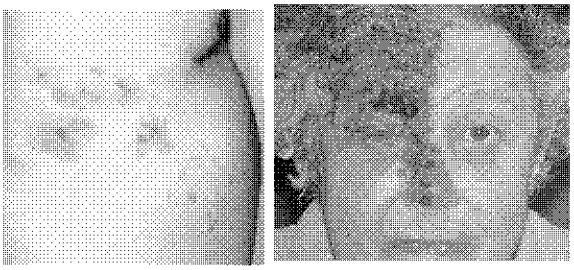
- Thus, with the pertussis disease burden continuing to be substantial, it is now recommended that Tdap be given to all adolescents and adults regardless of interval since the last Td
- This includes those 65 years of age and older in whom the vaccine has been found to be equally safe and immunogenic.

Zoster

- Occurs most frequently among older adults
- 1/3 will develop zoster during their lifetime
- 1 million episodes in the US annually
- Common complications:
  - Postherpetic neuralgia (PHN) chronic, often debilitating pain 10%–18%.
  - Eye involvement that can result in loss of vision

MMWR 2008;57(RR-5)

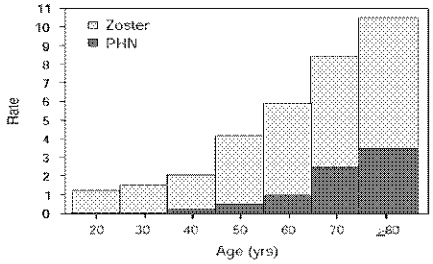
Zoster



MMWR 2008;57(RR-5)

Zoster

FIGURE 3. Rate* of zoster and postherpetic neuralgia (PHN)†, by age — United States



*Per 1,000 person-years.
†Defined as ≥30 days of pain.

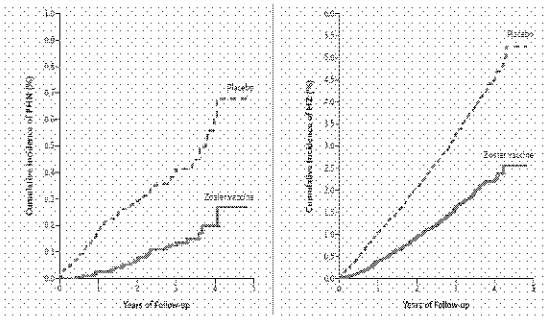
MMWR 2008;57(RR-5)

Zoster vaccine

- VARIVAX, Each 0.5-mL dose contains 1350 plaque-forming units (PFU) of Oka/Merck strain of varicella virus (VZV)
- ZOSTAVAX, Each 0.65-mL dose contains 19,400 PFU of Oka/Merck VZV

MMWR 2008;57(RR-5)

Zoster vaccine: efficacy in prevention of HZ and PHN



Oxman, et al. N Engl J Med 2005;352:2271-84.

Zoster vaccine: prior history of zoster

Table 2. Comparison of Incidence of Recurrent Herpes Zoster Between the Vaccinated and the Unvaccinated Cohorts

Characteristic	Vaccinated Cohort: Cases/ Vaccinees, No.	Person-Years, No.	Incidence* (95% CI)	Unvaccinated Cohort: Cases/ Nonvaccinees, No.	Person-Years, No.	Incidence* (95% CI)	RR (95% CI)	P
Confirmed case†								
Age, years								
<70	1/633	1009.96	0.99 (.02–5.54)	14/2965	5969.35	2.20 (1.16–3.83)	0.45 (.06–3.51)	.45
≥70	3/603	1099.41	2.73 (.56–7.99)	14/2516	5349.41	2.62 (1.43–4.39)	1.05 (.30–3.69)	.94

* No. of cases per 1000 person-years.

Tseng, et al. J Inf Dis 2012;206:190-6.

Zoster vaccine: CDC

- Repeated zoster has been confirmed in immunocompetent persons after a previous episode
- The risk for zoster following an earlier episode is unknown
- Reported diagnosis or history might be erroneous
- No laboratory evaluations exist to test for the previous occurrence of zoster

MMWR 2008;57(RR-5)

Zoster vaccine: CDC

- Routine vaccination of all immunocompetent persons aged >60 years with 1 dose
- Persons who report a previous episode of zoster can be vaccinated
- Not indicated to treat acute zoster, to prevent persons with acute zoster from developing PHN, or to treat ongoing PHN

MMWR 2008;57(RR-5)

Changes you may wish to make in practice

- Make assessment of immunization status a routine part of allergy / immunology visits for older adults
- Don't assume they are receiving their vaccinations elsewhere
- Administer IIV, PPSV23, Tdap and Zoster vaccines to all eligible recipients