

SAFETY AND EFFECTIVENESS OF VARICELLA AND ZOSTER VACCINATION

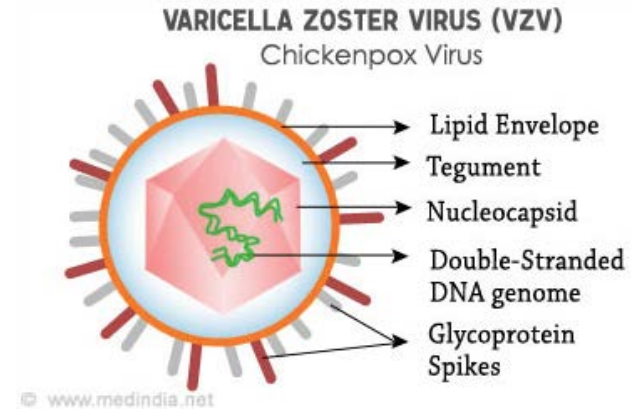
Steven Black, MD
Division of Infectious
Diseases
Cincinnati Children's Hospital
Cincinnati USA

OVERVIEW

- The Varicella Zoster virus (VZV)
- Nature of the diseases caused by VZV
- Varicella and Zoster epidemiology
- VZV Vaccines
- VZV vaccine safety
- VZV vaccine effectiveness
- Future prospects
- Recommendations for use of varicella vaccine in the US

VARICELLA ZOSTER VIRUS

- Herpesvirus (DNA)
- Primary infection results in varicella (chickenpox)
- Reactivation of infection results in herpes zoster (shingles)
- Virus has short survival in environment
- In populated areas prior to introduction of vaccine, infection was virtually universal.



VARICELLA PATHOGENESIS

- Virus is transmitted via respiratory droplets.
- Replication in nasopharynx and regional lymph nodes
- Repeated episodes of viremia during illness
- Illness is usually self limited but not always.
- Multiple tissues, including sensory ganglia, infected during viremia
- Infection of the sensory ganglia is life long.

VARICELLA CLINICAL FEATURES

- Incubation period 14-16 days (range 10-21 days)
- Mild prodrome for 1-2 days
- Rash generally appears first on head; most concentrated on trunk
- Successive crops over several days with lesions present in several stages of development



EPIDEMIOLOGY: VZV INCIDENCE PRIOR TO VACCINE USA

TABLE 1 Average Historical Incidence Rates of Varicella From Published Population-based Studies of Unvaccinated Children (Prevaccine Era) per 1000 PY

Age Group	NHIS ¹		Kentucky ²	
	Unadjusted Rate	Susceptibility-adjusted Rate ^a	Unadjusted Rate	Susceptibility-adjusted Rate ^a
1–4 y	82.1	97	99.4	120
5–9 y	90.3	197	80.7	231
10–15 y	17.5	116	13.5	117
Weighted average historical rate ^b		140.1		158.9

NHIS, National Health Interview Survey.

^a From Vessey et al, 2001.³⁰


^b Historical incidence rate of varicella expected to be observed in the study cohort at the end of the 14-year follow-up.



VARICELLA COMPLICATIONS

- Bacterial infection of skin lesions
- Pneumonia (viral or bacterial)
- Central nervous system manifestations (eg cerebellar ataxia)
- Reye syndrome
- Hospitalization: 2-3 per 1,000 cases
- Death: 1 per 60,000 cases
- Post-herpetic neuralgia (complication of zoster)

GROUPS AT INCREASED RISK OF COMPLICATIONS OF VARICELLA

- Persons older than 15 years 
- Infants younger than 1 year
- Immunocompromised persons
- Newborns of women with rash onset within 5 days before to 48 hours after delivery

NEONATAL VARICELLA



NECROTIZING FASCIITIS



HERPES ZOSTER (SHINGLES)

- Reactivation of varicella zoster virus
- Can occur years or even decades after illness with chickenpox
- Generally associated with normal aging and with anything that causes reduced immunocompetence
- Lifetime risk of 20 percent in the United States
- Estimated 500,000- 1 million cases of zoster diagnosed annually in the U.S
- 50% of persons living until age 85 years will develop zoster
- Herpetic neuralgia can be very painful and debilitating

VACCINES



- Live attenuated varicella vaccine (Merck) licensed in the US in 1995
- Combination MMR-V (Merck) licensed in the US subsequently
- GSK also makes varicella and MMR-V vaccines
- Live attenuated zoster vaccine licensed in the US in 2006.
- GSK recombinant zoster vaccine is currently still under IND

LIVE ATTENUATED VARICELLA VACCINE FOR CHILDREN

- Merck vaccine licensed in 1995 in the US.
- Single dose vial containing > 1350 PFU of virus.
- Two doses given at least 4 weeks apart for children less than 12 years of age and two months apart for older individuals.
- Also available at MMR-V with this vaccine having a varicella titer of >9300
- Reactogenicity of MMR-V has been higher than MMR and V given separately.
- Increased risk of febrile seizures after dose one of MMRV (but not dose two)

	Odds ratio	95% Confidence Interval	P-value
MMRV versus MMR + Varicella*	2.3	1.6, 3.2	<0.0001
	Attributable Risk	95% Confidence Interval	
MMRV versus MMR + Varicella*	5.2 / 10,000	2.2, 8.1	

WHY TWO DOSES FOR CHILDREN?

- Enhanced immunogenicity of a 2 dose regimen in children 1-12 yo was known pre-licensure
- Breakthrough rates for a one dose schedule were estimated to be 1-3%/year after 1 dose.
- Just as for measles, a second dose is needed to address the problem of primary vaccine failure
- Mean gpELISA titers after one dose was 10-15 units – barely above the protective threshold of 5 units
- Following two doses, the mean titer was 469 units with seroconversion in 99% children.
- Two doses was considered necessary to avoid developing a cohort of older susceptibles.

ZOSTER VACCINE FOR ADULTS— THE LIVE ATTENUATED VACCINE

- Same Oka strain as the pediatric vaccine except the adult vaccine contains not less than 19,400 plaque-forming units [PFU] per 0.65 mL dose when reconstituted to a suspension.
- Goal is to boost T-cell immunity which wanes after 50 years of age.
- Target outcomes are
 - Shingles rash
 - Ophthalmic zoster
 - Zoster Neuralgia

ZOSTER VACCINE FOR ADULTS— LIVE ATTENUATED EFFECTIVENESS (US MEDICARE DATABASE)

Year of Follow-up	Outpatient Herpes Zoster (No. Outcomes = 56,939)	Hospitalized Herpes Zoster ^b (No. Outcomes = 614)	Outpatient Ophthalmic Zoster (No. Outcomes = 5,282)	Postherpetic Neuralgia (No. Outcomes = 2,033)
	VE (95% CI)	VE (95% CI)	VE (95% CI)	VE (95% CI)
Primary Model				
First 3 Years	33%** (32%, 35%)	74%** (67%, 79%)	31%** (27%, 36%)	57%** (52%, 61%)
4 or More Years	19%** (17%, 22%)	55%** (39%, 67%)	21%** (12%, 29%)	45%** (36%, 53%)
Yearly Model				
1	38%** (37%, 40%)	77%** (68%, 84%)	38%** (32%, 44%)	70%** (63%, 76%)
2	32%** (29%, 34%)	68%** (55%, 78%)	28%** (20%, 36%)	49%** (39%, 57%)
3	25%** (22%, 28%)	75%** (60%, 84%)	22%** (11%, 32%)	50%** (39%, 59%)
4	21%** (17%, 25%)	45%* (11%, 66%)	19%** (6%, 31%)	44%** (28%, 56%)
5	17%** (12%, 22%)	52%* (15%, 73%)	21%* (4%, 34%)	40%** (21%, 54%)
6	17%** (10%, 23%)	66%** (30%, 83%)	19% (-3%, 37%)	52%** (31%, 66%)
7+	21%** (11%, 31%)	70%* (25%, 88%)	33% (-1%, 55%)	60%** (28%, 78%)

Izurieta et al in *Clinical Infectious Diseases*, Volume 64, Issue 6, 15 March 2017, Pages 785–793,

RECOMBINANT ZOSTER VACCINE FOR ADULTS (INVESTIGATIONAL VACCINE)

- GSK has developed an investigational recombinant subunit vaccine containing
 - VZV glycoprotein E
 - E was selected as a candidate vaccine antigen because it is essential for viral replication and cell-to-cell spread and is a primary target of VZV-specific immune responses.
 - The AS01 adjuvant system
 - The antigen was combined with AS01 because this adjuvant system promotes strong CD4+ T-cell and humoral immune responses against recombinant proteins.

RECOMBINANT ZOSTER VACCINE EFFICACY (INVESTIGATIONAL)

Table 2. Vaccine Efficacy against the First or Only Episode of Herpes Zoster Infection.*

Cohort and Age Group	HZ/su Group				Placebo Group				Vaccine Efficacy†
	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period‡ person-yr	Rate of Herpes Zoster no./1000 person-yr	No. of Participants	No. of Confirmed Cases	Cumulative Follow-up Period‡ person-yr	Rate of Herpes Zoster no./1000 person-yr	
Modified vaccinated cohort									
All participants in cohort	7344	6	23,297.0	0.3	7415	210	23,170.5	9.1	97.2 (93.7–99.0)
50–59 yr	3492	3	11,161.3	0.3	3525	87	11,134.7	7.8	96.6 (89.6–99.3)
60–69 yr	2141	2	7,007.9	0.3	2166	75	6,952.7	10.8	97.4 (90.1–99.7)
70 yr or older	1711	1	5,127.9	0.2	1724	48	5,083.0	9.4	97.9 (87.9–100.0)
Total vaccinated cohort									
All participants in cohort	7698	9	25,584.5	0.4	7713	235	25,359.9	9.3	96.2 (92.7–98.3)
50–59 yr	3645	3	12,244.9	0.2	3644	95	12,162.5	7.8	96.9 (90.6–99.4)
60–69 yr	2244	5	7,674.1	0.7	2246	83	7,581.8	10.9	94.1 (85.6–98.1)
70 yr or older	1809	1	5,665.5	0.2	1823	57	5,615.6	10.2	98.3 (89.9–100.0)

n engl j med 372;22 may 28, 2015



WHAT HAS BEEN THE IMPACT OF VARICELLA VACCINE PROGRAMS ??

DISEASE EPIDEMIOLOGY PRE AND POST VACCINE

TABLE 2 Incidence of HZ According to Age Group and Compared With Historical Rates

Age Group ^a	PY ^b	Expected		Observed			RR Observed/ Expected	
		Historical Rate ^{c,d}	No. of Expected Cases ^c	Observed Cases	Observed Rate ^d	95% CI	RR	95% CI
<5 y	25 313	1.10	27.8	4	0.16	0.04–0.40	0.14	0.05–0.35
5–9 y	37 176	0.51	19.0	17	0.46	0.27–0.73	0.89	0.54–1.40
10–15 y	40 609	0.69	28.0	25	0.62	0.40–0.91	0.89	0.52–1.53
All ages (1–15 y)	103 098	0.73	74.8	46	0.45	0.33–0.60	0.61	0.43–0.89

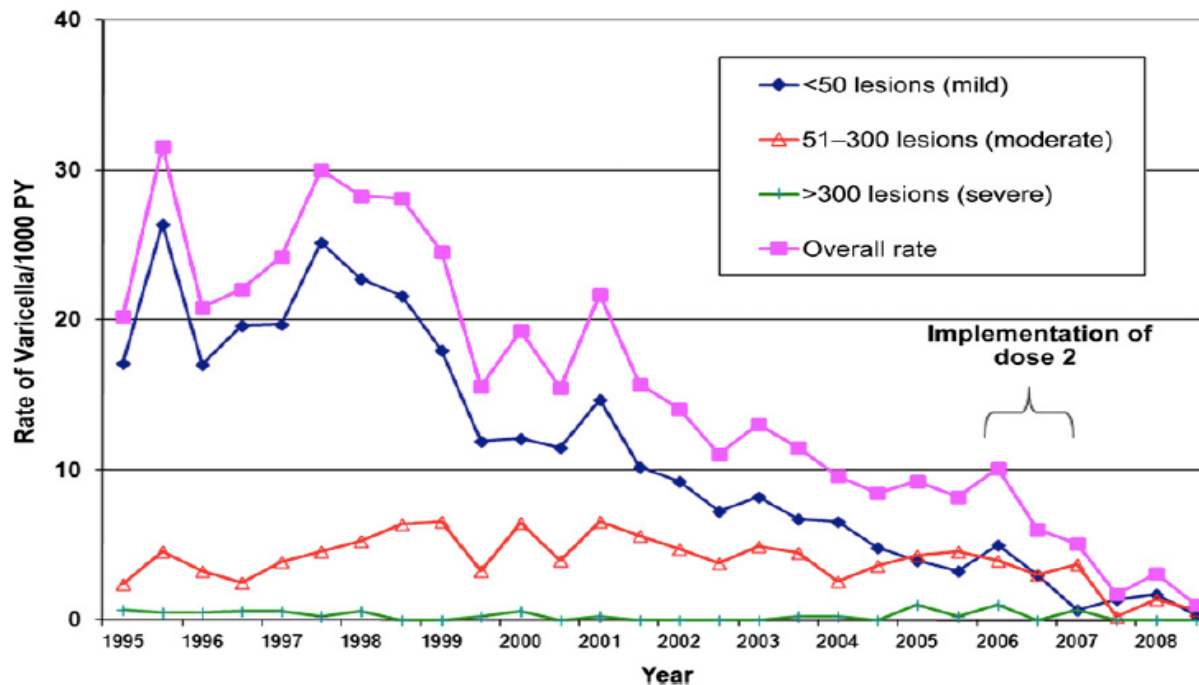
^a Age was estimated on interview cycle since vaccination, assuming that all children were vaccinated at 18 months of age.

^b Person-time denominators were based on the total follow-up time since the last interview by subjects with completed interviews for that phase.

^c Age-specific population-based rates in individuals with a history of varicella were obtained from Guess et al, 1986.⁶

^d Rate per 1000 PYs.

INCIDENCE RATES OF BREAKTHROUGH VARICELLA PER 1000 PY (FIRST EPISODE ONLY), ACCORDING TO CALENDAR YEAR, SINCE VACCINATION IN 1995



DECREASED INCIDENCE OF ZOSTER IN VACCINATED CHILDREN

From 2000 to 2006, the incidence of herpes zoster among children 10 years of age declined by 55%,

- 74.8/100,000 persons; (95% CI 55.3–101.2) to 33.3/100,000; 95% CI: 20.9 – 52.8; P 0.001.
- During the same period, the incidence of herpes zoster among 10- to 19-year-olds increased by 63%

Therefore, among children aged 10 years, those with a history of varicella vaccination had a 4 to 12 times lower risk of developing herpes zoster than those with a history of varicella disease.

US ACIP RECOMMENDATIONS

Routine Vaccination

Persons Aged 12 Months--12 Years

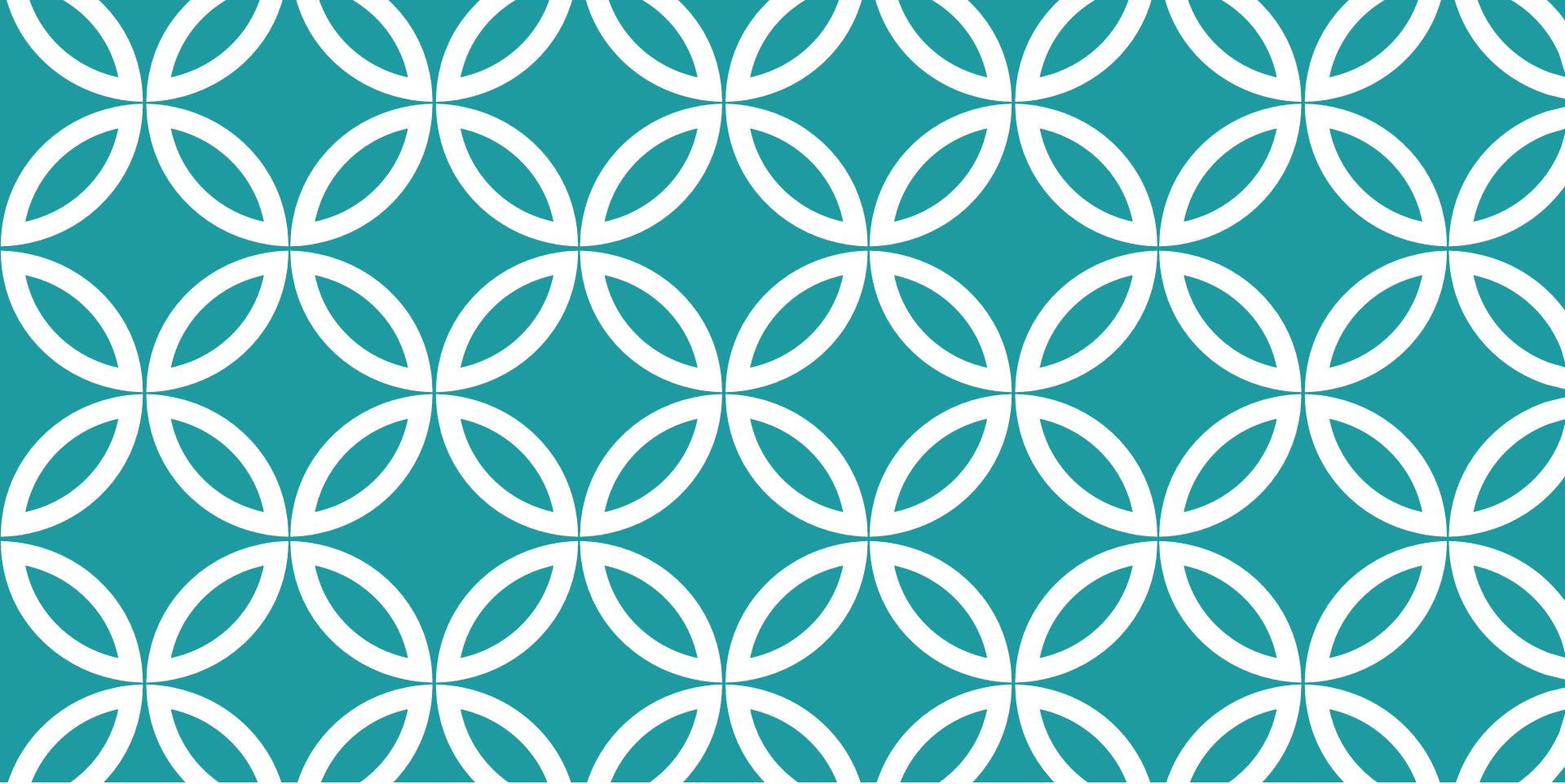
- First dose 12-15 mo of age
- Second dose to be given to children 4-6 years of age

Persons Aged >13 Years

Persons aged >13 years without evidence of varicella immunity should receive two 0.5-mL doses of single-antigen varicella vaccine administered subcutaneously, 4--8 weeks apart. If >8 weeks elapse after the first dose, the second dose may be administered without restarting the schedule. Only single-antigen varicella vaccine may be used for vaccination of persons in this age group

Other Adults

All healthy adults should be assessed for varicella immunity, and those who do not have evidence of immunity should receive 2 doses of single-antigen varicella vaccine 4--8 weeks apart.



THANK YOU |



BACKUP SLIDES

BREAKTHROUGH VARICELLA IN 15 YEAR F/U STUDY

TABLE 3 Incidence Rate of Breakthrough Varicella (First Episode Only) According to Year Since Vaccination (Rate per 1000 PYs): KPNC, 1996–2009

Years Since Vaccination	Follow-up in PY	Any Lesions			Mild (1–50 Lesions)			Moderate (51–299 Lesions)			Severe (>300 Lesions)		
		N	Rate	95% CI	n	Rate	95% CI	n	Rate	95% CI	n	Rate	95% CI
1	6531	174	26.6	22.9–31.0	150	23.0	19.5–27.0	20	3.1	1.9–4.8	4	0.6	0.2–1.7
2	7311	157	21.5	18.3–25.1	136	18.6	15.7–22.0	17	2.3	1.4–3.8	4	0.5	0.2–1.5
3	7044	191	27.1	23.5–31.3	161	22.9	19.6–26.7	27	3.8	2.6–5.7	3	0.4	0.1–1.4
4	6841	193	28.2	24.5–32.5	153	22.4	19.1–26.2	38	5.6	4.0–7.7	2	0.3	0.1–1.2
5	6671	134	20.1	16.9–23.8	101	15.1	12.4–18.4	32	4.8	3.3–6.9	1	0.1	0.0–1.0
6	6505	113	17.4	14.3–20.9	79	12.1	9.7–15.2	32	4.9	3.4–7.0	2	0.3	0.1–1.2
7	6425	120	12.6	15.6–22.4	81	12.6	10.1–15.7	38	5.9	4.2–8.2	1	0.2	0.0–1.0
8	6273	79	18.7	10.1–15.8	52	8.3	6.3–10.9	27	4.3	2.9–6.3	0	0.0	0.0–0.8
9	6172	76	12.3	9.8–15.5	47	7.6	5.7–10.2	28	4.5	3.1–6.6	1	0.2	0.0–1.1
10	6096	55	9.0	6.9–11.8	36	5.9	4.2–8.3	18	3.0	1.8–4.8	1	0.2	0.0–1.1
11	6058	53	8.7	6.6–11.5	26	4.3	2.9–6.4	23	3.8	2.5–5.8	4	0.7	0.2–1.8
12	5937	48	8.1	6.0–10.8	27	4.5	3.1–6.7	18	3.0	1.9–4.9	3	0.5	0.1–1.6
13	5945	20	3.4	2.1–5.3	8	1.3	0.6–2.8	10	1.7	0.9–3.2	2	0.3	0.1–1.4
14	5886	12	2.0	1.1–3.7	6	1.0	0.4–2.3	6	1.0	0.4–2.3	0	0.0	0.0–0.8
All years (0–14)	89 695	1425	15.9	15.1–16.7	1063	11.9	11.2–12.6	334	3.7	3.3–4.2	28	0.3	0.2–0.5

Breakthrough episodes were defined as any reported varicella with onset of symptoms occurring >6 weeks after vaccination. *Baxter R. PEDIATRICS Volume 131, Number 5, May 2013*