Update on varicella vaccine safety 1995-2005

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Varicella Vaccination Program

- Routine childhood varicella vaccination program implemented in 1995
  - Varivax® - Varicella virus vaccine live (Oka/Merck)

- Documented impact
  - Disease burden ↓90%
  - Mortality rate ↓74% (persons <50yo) from 1990-94 to 1999-2001
  - Health care utilization
    - Hospitalization ↓88%
    - Ambulatory visits ↓60%
    - Medical expenditures ↓74% ($84.9 million in 1994 to $22.1 million in 2002

[Guris et al., JID 2008 (in press); Nguyen et al, NEJM, 2005; and Zhou et al., JAMA, 2005]

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Early post-marketing vaccine safety data

1995-1998: (data from health maintenance organizations and VAERS)

- Most common - non-serious adverse events
  - Fever, varicella-like rash (localized and generalized), injection site reaction *(also seen in pre-licensure clinical trials)*

- Rare - serious adverse events
  - Confirmed through identification of vaccine Oka strain
    - Pneumonitis and hepatitis (immunodeficient hosts)
    - Herpes zoster
    - Secondary transmission
    - Severe rash post-vaccination

  Not lab confirmed: encephalitis, ataxia, thrombocytopenia, vasculitis

k5

[Wise et al., JAMA, 2000; Sharrar et al., Vaccine, 2001 Black et al.,PIDJ, 1999.]

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Slide 3

k5 Not confirmed as an adverse event temportally related to vaccine or not confirmed as a vaccine-related Oka strain AE? Can't tell

krb2, 10/17/2007

Rationale for further analysis

1. Since 1998, 5-fold increase in varicella vaccine doses distributed allowing for detection of rare adverse events

   (from ~11 million doses in 1998 to ~50 million in 2005)

2. New adverse events described in the literature

   (case reports of stroke, urticaria, severe herpes zoster presentation in vaccinees)

3. Late reactivation of latent varicella vaccine virus

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Methods

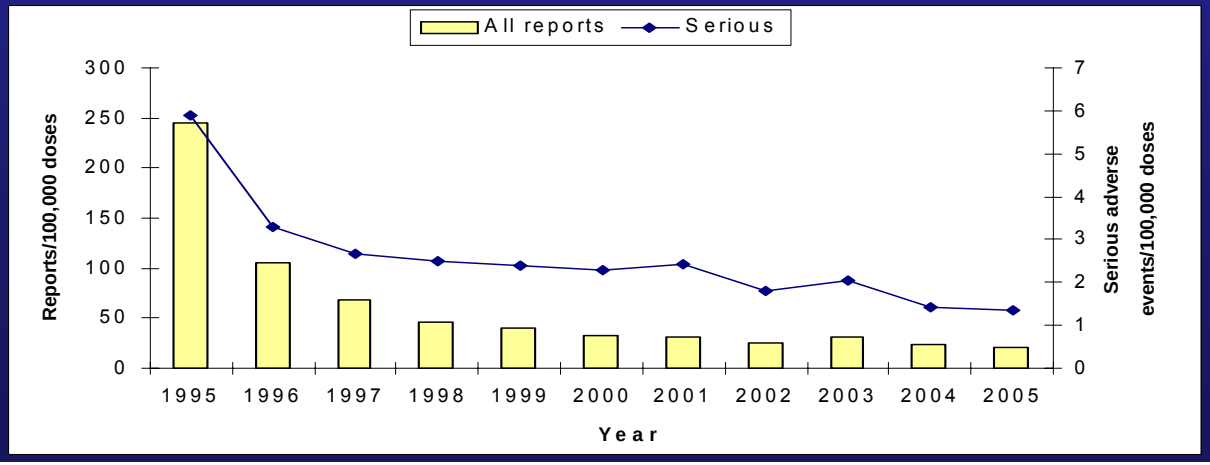
- **VAERS** - Passive reports submitted by clinicians, manufacturers, patients/parents, others from May 23, 1995 to December 31, 2005
  - Reports were classified based on signs and symptoms into COSTART* codes
    - Some COSTART codes were grouped (e.g., ataxia was combined with cerebellar ataxia)
  - Search text field for 'herpes zoster' and "meningitis"
  - Serious reports defined as hospitalization, death, "life-threatening" or "disabling" illness
  - Reporting rate based on no. doses distributed

**Coding Symbols for a Thesaurus of Adverse Reaction Terms*

Results
Overview

- VAERS reports during 1995 -2005:
  - Overall reporting rate 52.7/100,000 doses distributed
  - Serious adverse event reporting rate 2.6/100,000 doses distributed
  - 58% (14,780) followed varicella vaccine administered alone

Annual reporting rates for overall and serious adverse events, VAERS, 1995-2005



Most commonly reported adverse events

N = 25,306

- Rash (any) 32.6% (17.3/100,000)
- Fever 21.5% (11.4/100,000)

- Injection site reactions 13.0% (6.9/100,000)

- Urticaria 4.1% (2.2/100,000)
- Herpes Zoster 3.9% (2.1/100,000)

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Reported deaths

- 60 deaths total - Reporting rate 0.1/100,000 doses distributed
  - Majority had alternative diagnoses or very little data to be judged as vaccine related
- 4 cases with possible associations:
  - Vaccine strain VZV as a contributing factor in a death of a child with varicella pneumonitis and natural killer T cell deficiency *[Levy et al., JID, 2003]*
  - Two cases of encephalopathy due to ornithine transcarbamylase (OTC) deficiency could be associated with vaccine virus
  - One case of hemophagocytic lymphohistiocytosis (HLH) could be associated with vaccine virus.
- Further investigations needed to confirm the role of varicella vaccine virus in activating diseases linked with genetic proclivity.

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Other selected serious adverse events: Herpes Zoster

- **981 reports of herpes zoster (HZ)**
  - Reporting rate 2.1/100,000 doses distributed
- **47/981 hospitalized (~ 5%)**
  - Median age 2.5 years (12 mo -12 yr)
  - Median interval from vaccination to HZ 7.3 months (3 days-4.3 years)
  - Most frequent HZ location was face (21/43)
    - 2 Ramsay Hunt syndrome
    - 10 Herpes zoster ophthalmicus
  - 12 HZ and meningitis concomitantly

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Hospitalized herpes zoster cases

N = 47

- **PCR VZV+ 28**
  - Vaccine Oka 10
  - Wild-type 7
  - Not typed 11
- **Tzanck + 2**
- **DFA+ 1**
- **No lab 16**

- **7/47 immunosuppressed**

- **12/47 with meningitis**
  9/12 PCR VZV+ in CSF
  2/12 no CSF test
  1/12 EV

PCR confirmed herpes zoster and meningitis

Age (Yrs)	Interval vacc'n to HZ	Laboratory results		Interval HZ to meningitis	Comments
		CSF	Skin		
4	8 d	PCR VZV+	PCR VZV+	1-2 days	Healthy. Treated with IV acyclovir. Recovered.
3	19 mo	PCR VZV+ Vaccine strain	PCR VZV+ Vaccine strain	No information	Maintenance chemotherapy for ALL (Vaccinated while healthy). Treated with IV acyclovir. Recovered.
4	3 y	PCR VZV+ Vaccine strain	PCR VZV+	3 days	Healthy. Treated with IV acyclovir with rapid improvement.
6	5 y	IgM VZV negative. IgG VZV+. PCR negative for VZV, enterovirus, HSV, Epstein Barr	PCR VZV+ Vaccine strain	6 days	Asthma but otherwise healthy / HZ rash in the injection site. Treated with IV acyclovir with complete recovery.
5	1 y	PCR VZV+	DFA VZV+	3 days	Healthy. Treated with IV acyclovir. Recovered.
3	14 mo	PCR VZV+	PCR VZV+	10 days	Healthy. Treated with IV acyclovir. Recovered.
1	3 mo	PCR VZV+ Vaccine strain	PCR VZV+ Vaccine strain	~ 4 months	Vaccinated just prior to diagnosis of neuroblastoma. VZV acyclovir resistent. Case published JID 2003 (Levin et al).
10	9 y	PCR VZV+	DFA VZV+	3 days	Healthy. Treated with IV acyclovir. Recovered.
12	11 y	PCR VZV+	Not performed	No information	Healthy. Treated with IV acyclovir. Recovered.

NOTE: Another case reported in 2007 – Healthy, 8 yo, vaccinated at age 4, HZ followed by Meningitis 4 days later, CSF and skin PCR+ VZV/Vaccine Oka Strain

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Limitations - VAERS

- Underreporting – not all events reported
- More likely to capture events soon after vaccination
- Overreporting – many reports temporally related to vaccine but caused by something else
  - » (e.g., bacterial meningitis, other viral diseases common in childhood)
- Multiple vaccines administered simultaneously
- Most reports not verified PLUS limited clinical and lab information
- Greater reporting enthusiasm soon after introduction of a new vaccine ("Weber effect")
- Lack of denominator on doses administered by age

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Discussion

- Extensive post-licensure experience (~ 50 million doses)
  - » Majority are non-serious events (rash, fever, injection site reaction)
  - » Convulsion, cellulitis, otitis media, diarrhea, vomiting/nausea, pharyngitis, thrombocytopenia, arthritis and other may be biologically plausible
- Limited data available from immunocompromised and healthy children indicate lower rate of HZ in vaccine recipients; longer follow up is needed
  - » Rate of HZ following wild VZV infection in children <10 years ~30-70/100,000 persons (not corrected for children NOT at risk)
- Rate of rare complications of HZ is unknown; although European studies have shown neurological complication associated with HZ to be more common than previously thought

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Conclusions

- Overall, serious adverse events reported after varicella vaccination continue to be rare, and must be considered relative to the substantial benefits of varicella vaccination
- Vaccine strain VZV may be a contributing factor in activating diseases in patients with genetic predispositions
- Vaccine strain VZV reactivation can rarely cause severe herpes zoster (e.g., hospitalization) and neurological complications (e.g., meningitis) among healthy children
- Healthcare providers should be reminded to report adverse events after varicella vaccination to VAERS and to send viral specimens to state health departments for forwarding to CDC for laboratory testing and genotyping

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Next Steps

- **Communication of findings**
  - Journal of Infectious Diseases supplement will be published in January 2008
  - Additional communication materials to be developed to educate healthcare providers on the need for laboratory confirmation of suspected adverse events following varicella vaccine

- **Analytic studies to assess risk of VZV reactivation (using Vaccine Safety Datalink)**
  - To better define risks in vaccinated compared to following wild VZV infection
  - To investigate rate of rare neurological complications in vaccinated persons

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Thank you!

EXTRA SLIDES

Description of fatal events, VAERS, 1995-2005

Characteristic	N (%)
Vaccines	
Varicella vaccine administered alone	23 (38.3)
Description of fatal events	
Septicemia and multi-organ failure *	11 (18.3)
Crib death	10 (16.7)
Bacterial pneumonia	4 (6.7)
Breakthrough varicella (*Wild type VZV*)	3 (5.0)
Encephalopathy	3 (5.0)
Thrombocytopenia	2 (3.3)
Meningoencephalitis	2 (3.3)
Bacterial meningitis	2 (3.3)
Viral myocarditis (*other than VZV*)	2 (3.3)
Varicella pneumonitis	1 (1.7)
Viral infection with hepatomegaly	1 (1.7)
Hemaphagocytic lymphohistiocytosis	1 (1.7)
Anaphylaxis and thrombocitopenia	1 (1.7)
Others†	17 (28.3)
Total	**60 (100.0)**

Death reporting rate:

0.1/100,000 doses

*All were in individuals with severe congenital abnormalities or with disorders that affect their immune system

†Limited information available

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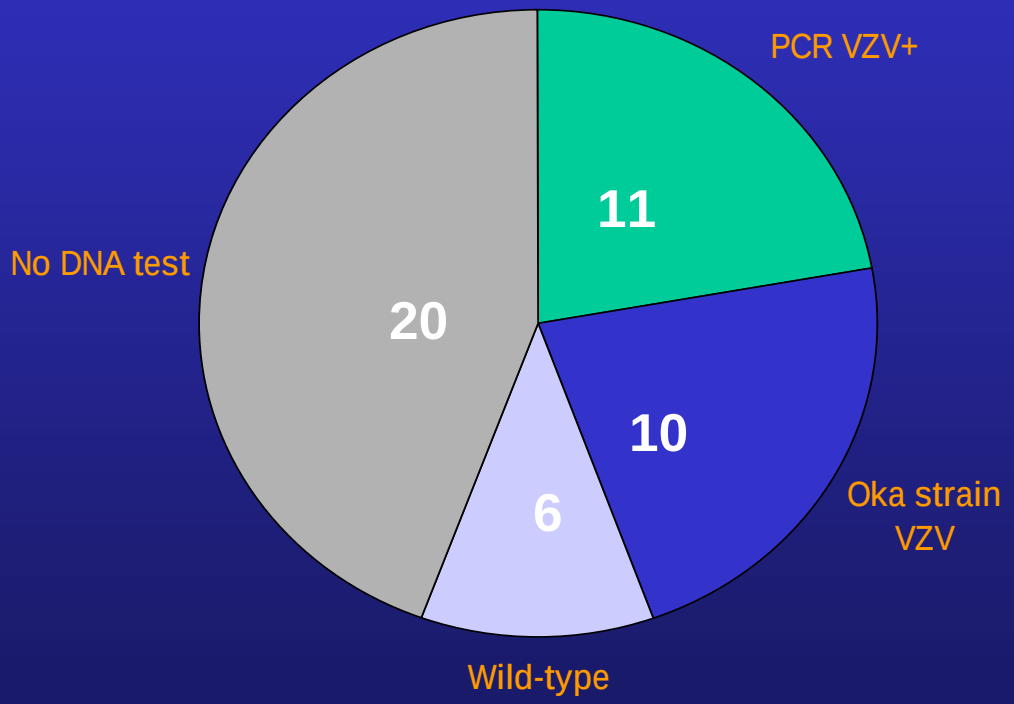
Hospitalized herpes zoster cases VAERS, 1995-2005



Selected conditions reported to VAERS, 1995-2005

Condition	Varicella alone		Serious		Total		Reporting[†]
	N	%	N	%	N	%	Rate
Rash	5288	64.0	197	2.4	8262	32.6	17.3
Fever	2474	45.4	464	8.5	5451	21.5	11.4
Injection site reaction	1235	37.5	76	2.3	3291	13.0	6.9
Urticaria	375	35.8	44	4.2	1047	4.1	2.2
Herpes zoster	696	71.0	52	5.0	981	3.9	2.1
Convulsion	155	18.2	313	36.7	852	3.4	1.8
Cellulitis	113	36.3	56	18.0	311	1.2	0.7
Diahrrea	102	34.0	56	18.7	300	1.2	0.6
Otitis media	87	31.0	51	18.1	282	1.1	0.6
Ataxia	66	41.5	64	40.3	159	0.6	0.3
Erythema multiforme	55	36.2	15	9.9	152	0.6	0.3
Thrombocytopenia	50	33.6	95	63.8	149	0.6	0.3
Pneumonia	51	49.5	55	53.4	103	0.4	0.2
Arthralgia	68	71.0	13	13.5	96	0.4	0.2
Meningitis	22	56.0	36	92.3	39	0.2	0.1
Hepatic pathology	18	56.0	23	71.9	32	0.1	0.1
Anaphylaxis	10	37.0	20	74.0	27	0.1	0.1
Renal pathology	11	61.0	14	77.8	18	0.1	0.0
Encephalopathy	4	25.0	14	87.5	16	0.1	0.0

[†]Reporting rate calculated per 100,000 doses of varicella vaccine distributed in the US

Note: Conditions coded based on signs and symptoms, not necessarily confirmed diagnoses

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