

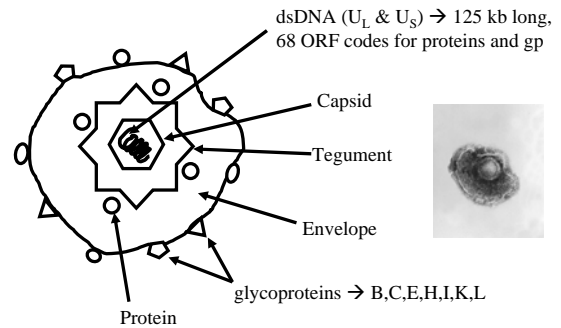
What's Happening with Chickenpox?

Public Health WORKS – 17 October 2006

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Varicella zoster virion (cartoon)



Objectives

- Review varicella/zoster in the pre- versus post-vaccine eras:
 - Disease management issues (prevention vs treatment).
 - Epidemiology of chickenpox and shingles.
 - Benefits of varicella immunization.
 - Vaccine-modified (“breakthrough”) disease → blessing or problem?
- Challenges in Canada:
 - Vaccine coverage.
 - Surveillance, disease control by Public Health?
- Zoster vaccine + MMRV on the horizon.

Declarations

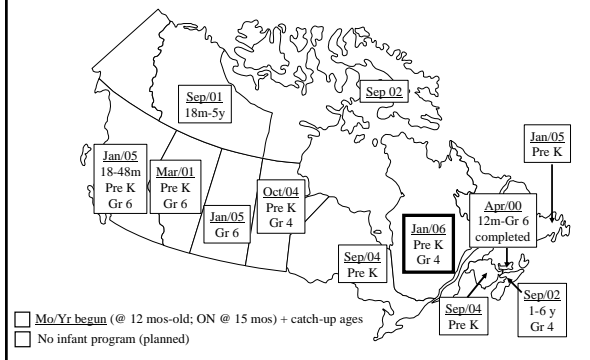
- This talk is sponsored by Public Health WORKS.
- I have spoken at meetings sponsored by vaccine manufacturers → last in 2004 (i.e. air travel & hotel; no honorarium).
- I do not speak on behalf of the National Advisory Committee on Immunizations (NACI) → although reflecting NACI recommendations.

Varicella immunization in Canada

- Fridge-stable Varivax™-III or Varilrix™.
- Dosing schedule:
 - Age 12 mos to 12 years → single dose.
 - Age 13 years → 2 doses.
- Catch-up recommended, targeting especially high-risk individuals.

Varicella vaccination programs in Canada

From: CNCI/PHAC (as of Jul 2006)



Before availability of varicella vaccine (≤ 1998)

	Healthy persons	High risk persons - Immunocompromised - Pregnant women
Prevention	• Nil.	• VZIG. • \pm Acyclovir.
Treatment	• Symptomatic only (antiviral not indicated).	• Acyclovir IV.

After availability of varicella vaccine ($> Dec 98$)

	Healthy persons	High risk persons - Immunocompromised - Pregnant women
Prevention	• Vaccinate (pre-exposure preferred; post-exposure also effective if within 3-5 days).	• Vaccinate healthy contacts. • VZIG (<u>not</u> vaccination; may only vaccinate selected high-risk groups pre-exposure).
Treatment	• Nil; vaccine-modified disease (breakthrough) usually mild, but may transmit.	• Acyclovir IV.

VZV-exposure management

- Is the person susceptible?
- Did significant exposure occur?
- Is the person at risk for complications of varicella?
- Is it effective and/or safe to vaccinate post-exposure?

Immunity to VZV

- Hx of varicella or zoster illness (parent, older patient, MD-diagnosed, lab confirmed).
 - Reliability may \downarrow w/ widespread immunization \rightarrow less wild-type virus circulation, plus vaccine-modified disease.
 - Reliable in children, less reliable in adults (70-90% immune even if cannot recall illness \rightarrow screen).
- Hx of age-appropriate varicella vaccination.
 - U.S. now requires 2 doses in children, versus 1 in Canada.
- Lab evidence of immunity (i.e. VZV-IgG +ve).

Varicella "significant exposure"

- Household contact (living in the same dwelling) with a person with varicella.
- Being indoors for more than 1 hour with a case of varicella.
- Being in the same hospital room for more than 1 hour, or more than 15 minutes of face-to-face contact with a patient with varicella.
- Touching the lesions of a person with chickenpox or shingles.

Varicella complications (healthy children)

- Secondary infections (in 5-10%):
 - Skin & soft tissue, including nec fasciitis from Gp A Strept
 - Otitis media, pneumonia.
 - Bacteremia, sepsis.
 - Osteomyelitis, septic joints.
- Hospitalization = 1 in 200-500 cases.
- Hepatitis.
- Thrombocytopenia.
- Cerebellar ataxia (1 in 4,000).
- Encephalitis (1 in 5,000).
- Death (rare, 5-10/yr in Canada).



Severe varicella disease



Varicella in the immunocompromised

- Visceral dissemination in 30%.
- Death in 7-10%.
- However, immunocompromised persons make up only 30-50% of hospital admissions due to chickenpox (i.e. the majority are previously healthy persons).

Varicella in adults

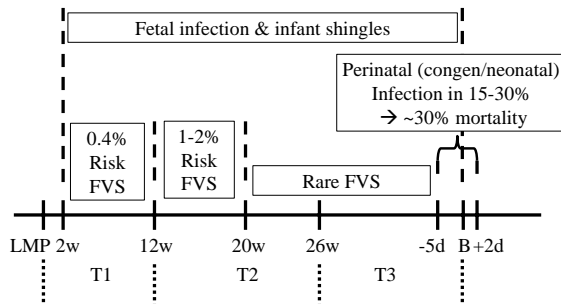
- More severe as compared to children:
 - Hospitalization risk → 3-18 fold higher.
 - Pneumonia → 11-20 fold higher.
 - Encephalitis → 1-2.5 fold higher.
- Varicella pneumonia:
 - Smoking significant co-factor increasing severity.
 - Pregnancy – debated whether it is a co-factor for severity.

Varicella in pregnant women

- Varicella pneumonia:
 - 3.5-9.5% of preg women develop pneumonia (similar to non-preg adults).
 - Of 418 pregnant women with varicella, 1 died.
- No statistically-significant increase in spontaneous abortions, stillbirths or premature delivery; however, anecdotal reports of fetal deaths reported in the literature.

Varicella risks for the fetus

Modified from: Nathwani et al. J Infect 1998;36(supp1):59-71
 FVS = Fetal (Congenital) Varicella Syndrome



Varicella immunity in tropical countries

Lee. Trop Med & Int Health 1999;3:886-90.

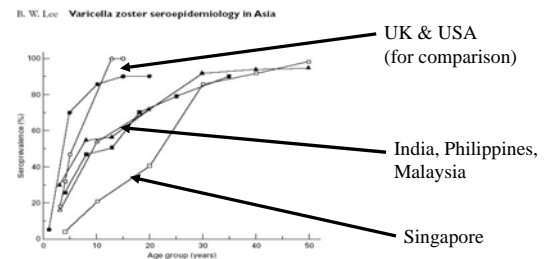


Figure 1 Age-related VZV seroprevalence in SE Asia, UK and USA. □ Singapore (Coi et al. 1992); ■ Malaysia (Malik & Baharin 1995); △ India (Venkataraman et al. 1986); ▲ Philippines (Barzaga et al. 1994); ● UK (Fairley & Miller 1996); ○ USA (Moench et al. 1986).

Exposure management

- No preventive measure (i.e. no vaccine, no VZIG) → accepts the risk(s) of complications, hospitalization, mortality.
- Post-exposure vaccination → up to 95% effective if within 3-5 days of exposure (for non-immunocompromised only).
- VZIG IM (for high risk groups; if within 96 hrs of exposure).
- Outside prevention “window” → acyclovir prophylaxis used by some specialists; may also use acyclovir to treat illness occurring in the immunocompromised.

VariZIG replaces VZIG in 2006

- In Oct 2004, Massachusetts Biologics Lab ceases manufacture of VZIG because of declining varicella disease (from vaccination).
- By 2006, last lots of VZIG will run out in Canada.
- CanGene (Winnipeg) has started producing VariZIG, which has same VZV Ab titer.
 - Studied and approved in pregnant women.
 - Can use for other VZIG indications based on expert opinion → prems, immunocompromised patients.

VariZIG effectiveness in pregnancy

Koren, et al. J Clin Pharmacol 2002;42:267-74.

- In 57 susceptible pregnant women exposed to chickenpox:
 - 17 recd IM VariZIG → 5 (29%) developed mild chickenpox.
 - 21 recd IV VariZIG → 6 (29%) developed mild chickenpox.
 - 19 recd IM VZIG (the Massachusetts product) → 8 (42%) developed mild chickenpox.
- VariZIG and VZIG do not necessarily prevent clinical infection, but ameliorates the disease; study too small to determine if it protects the fetus.

Reasons for varicella immunization

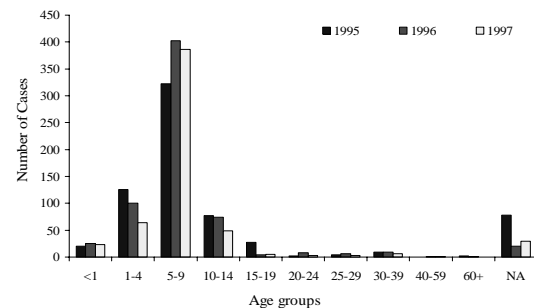
- Decrease morbidity and mortality in healthy children (albeit at low baseline rates) → “disease not as mild as is thought”.
- Ensures immunity before any immunocompromising condition strikes (e.g. autoimmune diseases, malignancy, adulthood).
- Provide herd immunity for surrounding immunocompromised neighbours, daycare- and schoolmates.
- Reduce risk for zoster (at least short-term).
- Less disruptive to daycare/school, parents’ schedules (economic).

Limitations to immunization

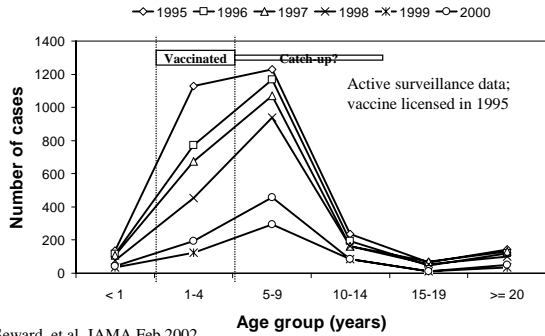
- Vaccine only 70-90% effective against disease of any severity (*but* 95% effective against severe varicella):
 - 10-30% risk for vaccine-modified (breakthrough) disease; ∴ vaccine coverage of > 95% cannot prevent “outbreaks”.
 - Vaccine-modified disease (if mod/severe) can transmit (cause “outbreaks”).
 - Parental faith in vaccination dashed (too high expectations).
 - Unknown duration of immunity.
 - Affect on adult shingles unknown (↑ for the short-term??).

Chickenpox cases in Newfoundland, 1995-97

Personal communication: S. Ratnam, MD



Age-group of varicella cases, Antelope Valley, CA (popn 300,000) 1995-2000

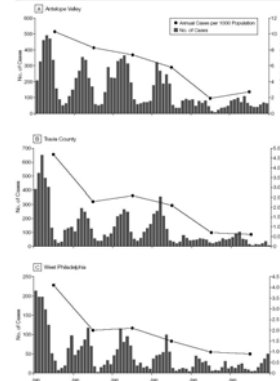


Seward, et al. JAMA Feb 2002

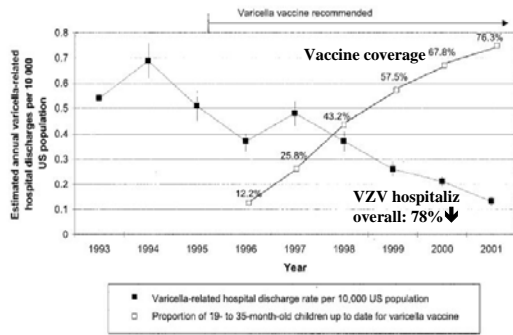
Single-dose effect on VZV, U.S.

- Active surveillance for varicella by local public health and the CDC in 3 counties, 1995-2000 (Seward, et al. JAMA Feb 2002).
- Vaccine coverage and decline in varicella cases:
 - Antelope Valley, CA → coverage 82%, decline 71%.
 - Travis County, TX → coverage 74%, decline 84%.
 - West Philadelphia, PA → coverage 84%, decline 79%.

Figure. Reported Varicella Cases by Month and Annual Rates of Reported Cases per 1000 Population in 3 Surveillance Areas, 1995-2000



Single-dose effect on VZV-hosp, U.S.



Davis, Peds Sep 2004; Nationwide Inpatient Sample, 17 → 33 states, 800-1000 hosp

Single-dose effect on VZV-hosp by age, U.S.

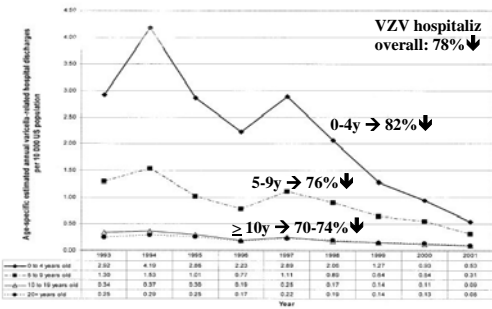


Fig 2. Estimated population-adjusted varicella-related hospitalization rates for specific age groups, 1993-2001. Weighted point estimates for rates in each year are shown, standardized to the year-specific population for each age group.

Davis, Peds Sep 2004; Nationwide Inpatient Sample, 17 → 33 states, 800-1000 hosp

Single-dose effect on VZV-hosp by age, U.S.

Figure 1. Varicella-Related Hospitalization Rates, 1994-2002

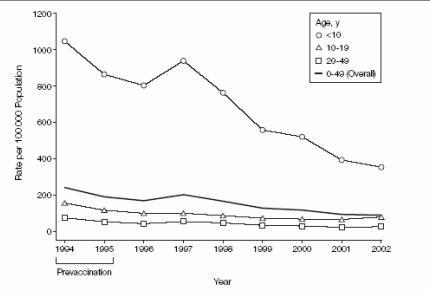


Varicella was the primary diagnosis code for data shown.

Zhou, JAMA 2005;294:797-802 – MarketScan database of 100 health insurance plans

Single-dose effect on VZV-amb visits by age, U.S.

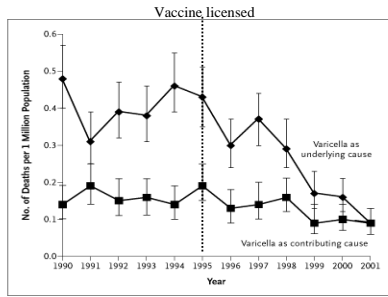
Figure 2. Varicella-Related Ambulatory Visit Rates, 1994-2002



Varicella was the primary diagnosis code for data shown.

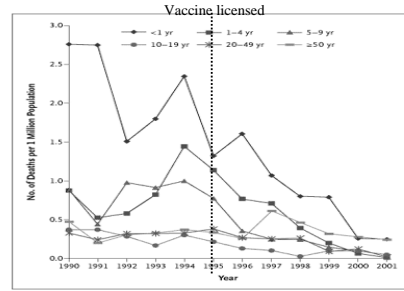
Zhou, JAMA 2005;294:797-802 – MarketScan database of 100 health insurance plans

Single-dose effect on VZV-mortality, U.S.



Nguyen HQ, Jumaan A, Seward JF. NEJM Feb 2005;352:450-8

Single-dose effect on VZV-mortal by age, U.S.



Nguyen HQ, Jumaan A, Seward JF. NEJM Feb 2005;352:450-8

Varicella vaccination strategies

Brisson & Edmunds. Vaccine 2002;20:1113-25

Assume 90% coverage	Infant only strategy (12 mos)	Catch-up strategy (12 mos + 5 yr + 11 yrs x 5 yrs)	Pre-teen only strategy (12 yrs)
Reduce cases by	72%	87%	12%
Reduce MD visits by	63%	81%	
Reduce hospitaliz by	71%	83%	15%
Reduce deaths by	52%	67%	12%

Single-dose effect on invasive Gp A Strep

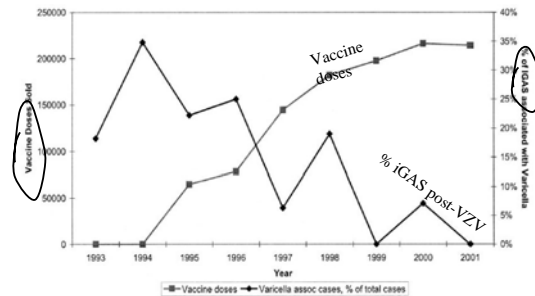
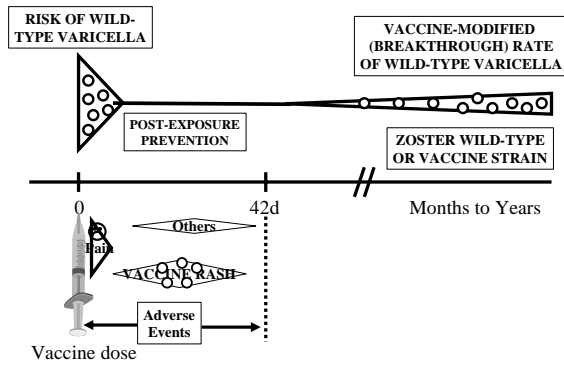


Fig 2. Vaccine doses sold versus varicella-associated IGAS. An inverse relation is demonstrated between number of varicella vaccine doses distributed in Illinois and the percent of IGAS cases in a given year that were associated with varicella (Spearman correlation coefficient, $n = 8$, $r = -0.697$, $P = .037$).

Patel RA, et al. J Pediatr Jan 2004;144:68-74

Terminology – post-vaccine timelines



Contagiousness of vaccine-modified disease

Seward J, et al. JAMA Aug 2004 – Antelope Valley, CA

Primary cases	N	# lesions	Secondary attack rate
Unvaccinated	654	≥ 50	74% (669/907 contacts)
	434	< 50	68% (402/592 contacts)
Vaccinated	15	≥ 50	65% (15/23 contacts)
	39	< 50	23% (11/47 contacts)

VE disease all severity = 79% (95% CI = 70-85%)

VE mod/severe disease = 92-100%

Vaccine strain transmission

Vaccinee (w/ rash)	Susceptible contact	Transmission
Healthy	Healthy	Rare → 3 in > 20 million doses (MMWR 1999;48:1-5).
Healthy	Immuno-compromised	Unknown, likely very low → ∴ can vaccinate household contacts.
Immuno-compromised	Healthy	More common, but still < 25% of that seen after wild-type infection (Tsolia et al. J Pediatr 1990;116:184).
Immuno-compromised	Immuno-compromised	Unknown (assume common, and hope we never find out!).

Differentiating wild-type vs vaccine strain PCR test available through NML, Winnipeg

- When an unanticipated severe post-vaccine rash occurs.
- When vaccine-modified illness requires admission to hospital.
- When a varicella-like illness occurs in an immunized HCW with subsequent spread in the health care setting.
- When zoster occurs in a previously immunized (especially immunocompromised) individual.
- When a varicella-like illness develops in a pregnant or immunocompromised contact of a vaccinee with a varicella-like rash.

Varicella outbreaks in the U.S.A. The early years post-vaccine → 1995-99

Study	Vaccine Effectiveness (95% CI)		Setting/Design
	Any severity	Mod/severe dis	
Izurieta, JAMA, 1997	86% (73-92%)	100% (96-100%)	GA daycare, 96
Clements, PIDJ, 1999	83% (67-90%)	-	NC 11 daycare, 96-97
Buchholz, Ped, 1999	71% (38-86%) 100% (67-100%)	93% (33-99%) 100% (0-100%)	LA, CA 2 daycare, 98

Varicella outbreaks in the U.S.A. The latter years → 2000-03

Study	Vaccine Effectiveness (95% CI)		Setting/Design
	All disease	Mod/severe dis	
Seward, JAMA, 2004	79% (70-85%)	92-100%	Antelope Val, CA 97-01
Galil, JID, 2002	79% (66-88%)	95% (84-98%)	PA daycare, 00
Galil, NEJM, 2002	44% (7-66%)	86% (39-97%)	NH daycares, 01
Dworkin, CID, 2002	88% (-)	-	IL elem school, 01
Tugwell, Ped, 2004	72% (3-87%)	-	OR elem school, 01
Lee, JID, 2004	56% (-)	90% (-)	MN elem school, 02
Renas, MMWR, 2004	85% (78-90%)	98% (95-99%)	MI elem school, 03
Miron, PIDJ, 2005	20% (0-40%)	93% (75-98%)	ISRAEL daycare, 03
Haddad, Ped, 2005	87% (71-94%)	90-99% (76-99%)	UT elem schools, 02-03

Studies of: time from, & age at vaccination

Study	Time since vaccination	Age at vaccination
Lee, JID, 2004 MINN sch	≥ 5 yrs RR 2.6 (1.3-2.4)	12-15 mos RR 2.1 (1.1-4.1)
Renas, MMWR, 2004 MICH sch	≥ 4 yrs RR 4.7 (1.5-15)	NS
Tugwell, Peds, 2004 OREG sch	≥ 5 yrs RR 6.7 (2.2-22)	NS
Verstraeten, Ped, 2003 HMO-A(west) day care	N/A	12-14 mos RR 1.4 (1.1-1.9)
Dworkin, CID, 2002 ILL sch	N/A	12-14 mos RR 3.7 (1.1-13.1)
Galil, NEJM, 2002 NH daycare	≥ 3 yrs RR 2.6 (1.3-5.3)	NS
Galil, JID, 2002 PENN daycare	N/A	12-14 mos RR 3.0 (0.9-9.9)

One dose does not prevent school outbreaks Lopez, Ped Jun 2006;117:1070-77

- Arkansas elementary school, 545 students, school entry VZV vaccination requirement started in 2000.
- Varicella outbreak Sep 24 – Nov 19, 2003 → 3/6 confirmed by PCR as wild-type.
- Past Hx of varicella range from 7% to 57% by age/class.
- Vaccine coverage 96% → med age at vaccination 18 mos (4-99 mos); med time since vaccination 59 mos (0-101 mos).
– 14 students had received 2 vaccine doses.

One dose does not prevent school outbreaks

Lopez, Ped Jun 2006;117:1070-77

- Varicella cases, susceptible immunocompromised and pregnant teachers excluded during outbreak.
- Total 49 varicella cases → med age 6 yrs, range 5-11 yrs.
 - 48 students, 1 teacher.
 - 43 were vaccinated (42 w/ 1 dose, 1 w/ 2 doses 3 mos apart), 6 unvaccinated.
- First case was Gr 2 vaccinated student, 15 lesions, no fever.

One dose does not prevent school outbreaks

Lopez, Ped Jun 2006;117:1070-77

- East Wing = 275 students (K → Gr 2), vaccine coverage 99%.
 - 44 varicella cases → med age at vaccination of cases 18.5 mos, vs of non-cases 14 mos.
 - AR highest in Gr 1 (26%), then Gr 2 (19%).
 - AR vaccinated 18%.
 - AR unvaccinated 100%.
 - ∴ VE any severity 82%, mod/severe disease 97%.
- West Wing = 270 students (one K class + Gr 3-5) → 4 cases.
 - Separate ventilation system from East Wing.

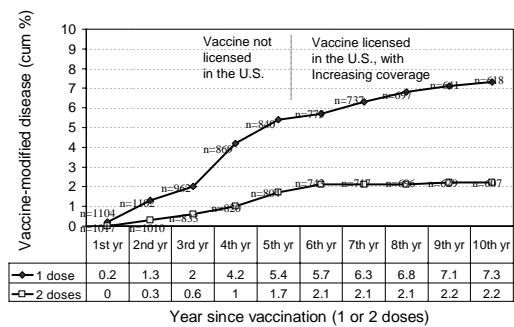
One dose does not prevent school outbreaks

Lopez, Ped Jun 2006;117:1070-77

- Disease severity:
 - Vaccinated → 89% were mild, 94% “did not look ill”, missed median 2 days of school, 2 had secondary skin infections, none hospitalized.
- Secondary transmission:
 - 2 vaccinated cases w/ mild/mod disease → infected their vaccinated siblings (aged 3 & 4 yrs).
 - None in West Wing.
- Risk factors for vaccine failure → none proved statistically significant (age at vaccin, time since vaccin, asthma/steroid inhalers).

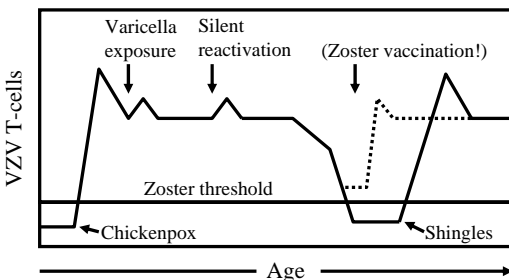
Vaccine-modified varicella, prospective 1993-03

Kuter B, et al. PIDJ Feb 2004;23:132-37



Zoster and Cell-Mediated Immunity

Modified from: Arvin A. NEJM 2 Jun 2005;352:2266-7

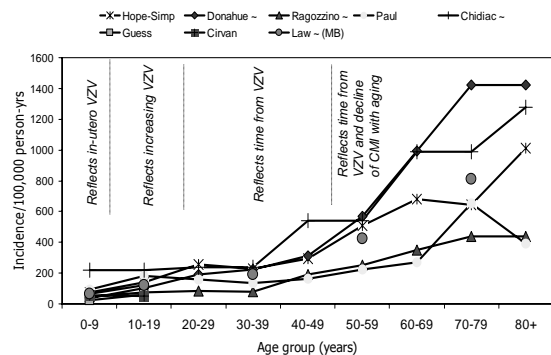


Zoster incidence



- In vaccinees:
 - 14 to 16/100,000 person-years in pre-licensure studies.
 - 2.6/100,000 doses based on U.S. VAERS data.
 - May be vaccine strain or wild-type strain (?50-50).
- In (unvaccinated) healthy children < 20 yrs = 68/100,000.
 - For all ages combined = 215/100,000.
- In seniors = 400 to 1,400 per 100,000 person-years.
- In the immunocompromised = 2,500 to 9,150/100,000 person-years.

Zoster incidence in healthy, unimmunized



Zoster vaccine → shingles prevention Oxman, et al. NEJM 2005;352:2272-84

- Randomized, double-blind, placebo-controlled:
 - 22 US centers; from Nov 1998 to Apr 2004.
- Subjects → total 38,546:
 - Age ≥ 60 yrs; median 69 yrs, about 7% > 80 yrs.
 - Healthy 51%, mild-health problems 39%.
 - Hx of varicella, or resided in USA > 30 yrs.
- Oka Merck vaccine (higher potency than ped vaccine):
 - Single 0.5 ml sc dose.
 - 12 lots → 18,700-60,000 PFU (median 24,600 PFU; > 90% received ≤ 32,300 PFU).
- Follow-up for zoster occurrence and pain score (3-10):
 - Range = 1 day– 4.9 yrs (mean = 3.13 yrs; median = 3.12 yrs)
 - > 95% followed to completion; 0.6% withdrew, 4% died.

Zoster vaccine → shingles prevention Oxman, et al. NEJM 2005;352:2272-84

- Conclusions:
 - Zoster incidence (per 1,000 person-yrs) → VE = 51%:
 - Placebo gp → 11.1; Vaccinated gp → 5.4.
 - Zoster burden → VE for all age groups = 61%:
 - VE for age 60-69 yrs → 66%.
 - VE for age ≥ 70 yrs → 55%.
 - Post-herpetic neuralgia incidence (per 1,000 person-yrs) → VE = 67%:
 - Placebo gp → 1.4; Vaccinated gp → 0.5.
 - VE ranges from 57-69% for persistent PHN.

Varicella and public health (Canada)

	Prevaccine era	Postvaccine era
Management goal(s)?	Prevent illness in high risk persons	Prevent illness in all (reduce morbid & mortal, ?elimination)
Surveillance for VZV & zoster?	Passive under-reporting; hospital data, MD billings	No change – how to improve?
Daycare/school entry vaccination?	Vaccine not available	No (not yet?)
Daycare/school exclusion?	No (some prov/terr exclude until lesions scab)	No change?
Post-exposure management?	VZIG for high risk persons	VZIG for high risk persons; vaccinate healthy susceptibles?

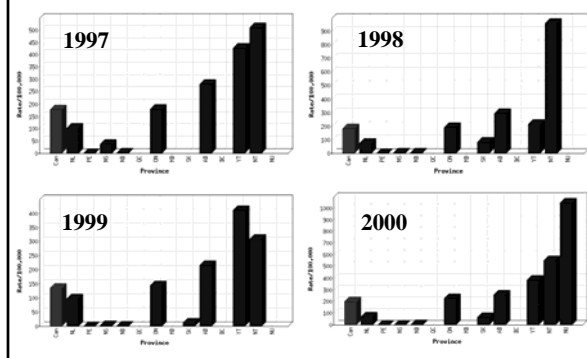
Monitoring varicella – Canada and the U.S.

Issues	Canada	U.S.A.
Surveillance	Passive reporting. IMPACT (hosp children). Hosp Discharge Data. Physician billings for zoster.	Passive reporting. VASP sites. Hospitalization data. Shingles surveillance.
Vaccine & indications	1998 (Dec). Varivax™ III, Varilrix™. Single dose - young children. Healthy, some immunocomp. Coverage u/k (just starting).	1995. Varivax™. Two doses (Aug 2006). Healthy. Coverage ~85-90%.
Daycare, school entry vaccin.	No requirement. No action for outbreaks.	Most states (44) require. Manage, study outbreaks.

Challenges monitoring varicella in Canada

- Surveillance:
 - Passive (NDRS) → unreliable (under-reporting).
 - Active → only children admitted to ped hosp (IMPACT).
- Coverage:
 - Most varicella programs in place by 2005.
 - Alberta monitoring; no info from PEI or NS.
- Vaccine-modified cases:
 - No mandate from Public Health to manage/investigate.

Varicella reported cases, Canada 1997-00



Varicella and vaccination in Alberta

Personal communication – E. Sartisan, RN (Edmonton)

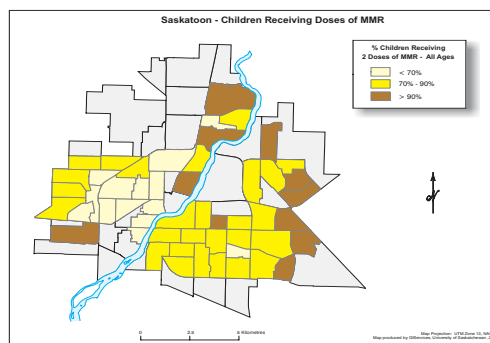
- Apr 2001 → catch-up pre-school and Gr 5, then routine at 12 mos.
- Varicella passive reporting by PHNs; shingles is notifiable.
- Coverage:
 - 2002 → 79% at 1 yr, & 93% at Gr 5.
 - 2003 → 75% at 1 yr, & 93% at Gr 5.

	Varicella		Zoster	
	#	Rate	#	Rate
1998	8649	303	71	3
1999	6417	219	62	2
2000	7767	262	36	1
2001	4176	138	25	0.8
2002	3739	121	26	0.8
2003	2379	76	27	0.8

IMPACT varicella admissions, 1999-04

Center\Yr	1999	2000	2001	2002	2003	2004
Van	25	35	27	27	29	29
Cal	6	25	17	18	13	9
Edm	21	17	27	23	9	5
Sas	-	10	16	17	12	8
Win	19	45	33	36	46	30
Tor	49	76	57	54	50	81
Ott	28	50	18	39	27	28
MonCH	23	40	38	24	17	27
MonSJ	63	98	54	95	65	57
Que	13	29	26	23	15	17
Hal	11	24	18	16	7	1
StJ	12	6	11	16	15	8
Total	270	455	342	388	305	300

2-dose MMR coverage rates by 2 years of age, Saskatoon, SK 1999-2002 (K. Avis, MSC)



MMRV

- Developed by both MerckFrosst and GlaxoSmithKline.
- MerckFrosst's MMRV (ProQuad) currently licensed in the U.S.; freezer-stable.
- Need MMRV which is fridge-stable in Canada, may be available in the near future?
- No recommendations as yet in Canada for single or 2-dose schedule.

Conclusions

- Varicella vaccination is effective, though not perfect.
- Fridge-stable vaccines are essential in Canada.
- Better population-based surveillance would be ideal for both chickenpox and shingles (but likely to be very costly).
- Canada's disease control goal differs from the U.S., which explains current dosing strategy; unclear whether availability of MMRV will create impetus to have common goals.
- Zoster vaccine appears effective; will create challenges re cost-effectiveness and implementation.

