Western Canadian Immunization Forum
Vancouver – Dec 8, 2011

Varicella vaccine – 2-dose rationale

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Objectives

- About varicella & vaccine programs across Canada.
- Timeline of varicella-related studies.
- Benefits and limitations from 1- and 2-dose schedules in children.
- Modelling (to predict) the future.
- Conclude with what's known & unknown (for further research!).

Live vaccines ↑ from 1- to 2-dose sched

- Canadian response to vaccine-preventable disease (VPD) outbreaks → usually adolescents and young adults:
  - Measles in 1980s to 1992 → consensus conf Dec 1992 → 2-dose recommendation.
  - Mumps in 2004-07) → NACI 2-dose recommendation in 2007.
  - Administered as MMR @ 12 & 18 mos, or @ 12 mos & preschool.

- Does varicella require the same aproach?

Varicella in Canada

- Considered an endemic (occasionally severe) disease:
  - No school-entry requirement, no daycare/school outbreak management.
  - Manage exposure among susceptibles, e.g. pregnancy, the immunocompromised, school exclusion (controversial).

- Goal for vaccine program = ↓ morbidity & mortality from the disease.
  - Surveillance via passive case reporting (under-reported), MD billing (zoster), & hospital data (ICD9/10, IMPACT).
  - Vaccine coverage variably measured, incomplete in many Prov/Terr.

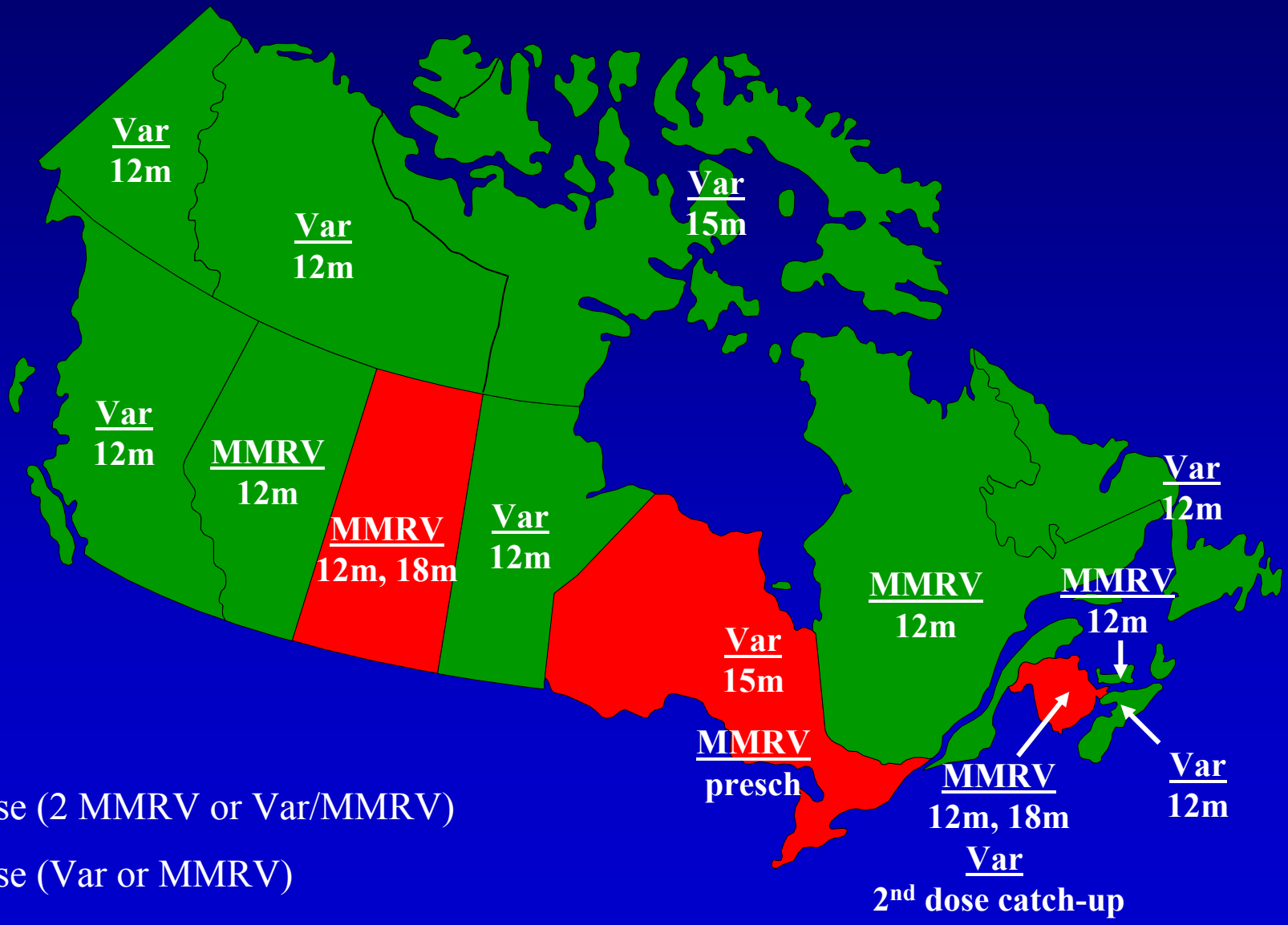
Varicella vaccines in Canada

- Univalent vaccines first approved in 1998:
  - 1-dose for children 12 mos – 12 yrs.
  - 2-doses for susceptible persons 13 yrs and older.

- Combination vaccine (MMRV-GSK) approved in 2007:
  - 2-doses for children 12 mos – 12 yrs.

- Accurate test for “protective Ab levels” not readily available in clinical settings (e.g. manufacturer’s gpELISA or IFA):
  - Restricted to NML in Winnipeg or hosp/research labs.

Var vaccine programs – CNCI, Sep 2011



Varicella vaccination – eras/studies

USA 1995; Can 1998 **USA 2006; Can 2010**

Pre-approval or -licensure | 1-dose | 2-dose

Studies of:
Var vaccine effectiveness (VE), safety

Studies estimating VE:
Outbreaks: daycare/school
Retrospective: case-control
Prospective cohort: 1- & 2-dose recip.

Studies on:
MMRV
VE, safety

Studies estimating VE:
School: 1- & 2-dose recip.

Studies on trends over time:
Disease incidence: USA Var active surveillance project (VASP)
Hospitalization/Resources: IMPACT, Ontario; USA databases
Mortality (deaths): USA databases

Studies on what the future holds:
Wait-and-see, or Modelling trends

Var hosp case 2009 – polling ID/pub health

Vaccinated, or

✗ ✗

Unable to predict!

Not Vaccinated?

✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓

Correctly predicted

Single-dose vaccine in children – benefits

- Reduced varicella (sources):
  - Disease incidence (VASP-USA).
  - Physician visits (Ontario data).
  - Hospitalizations (USA, Ontario, IMPACT).
  - Deaths (USA).

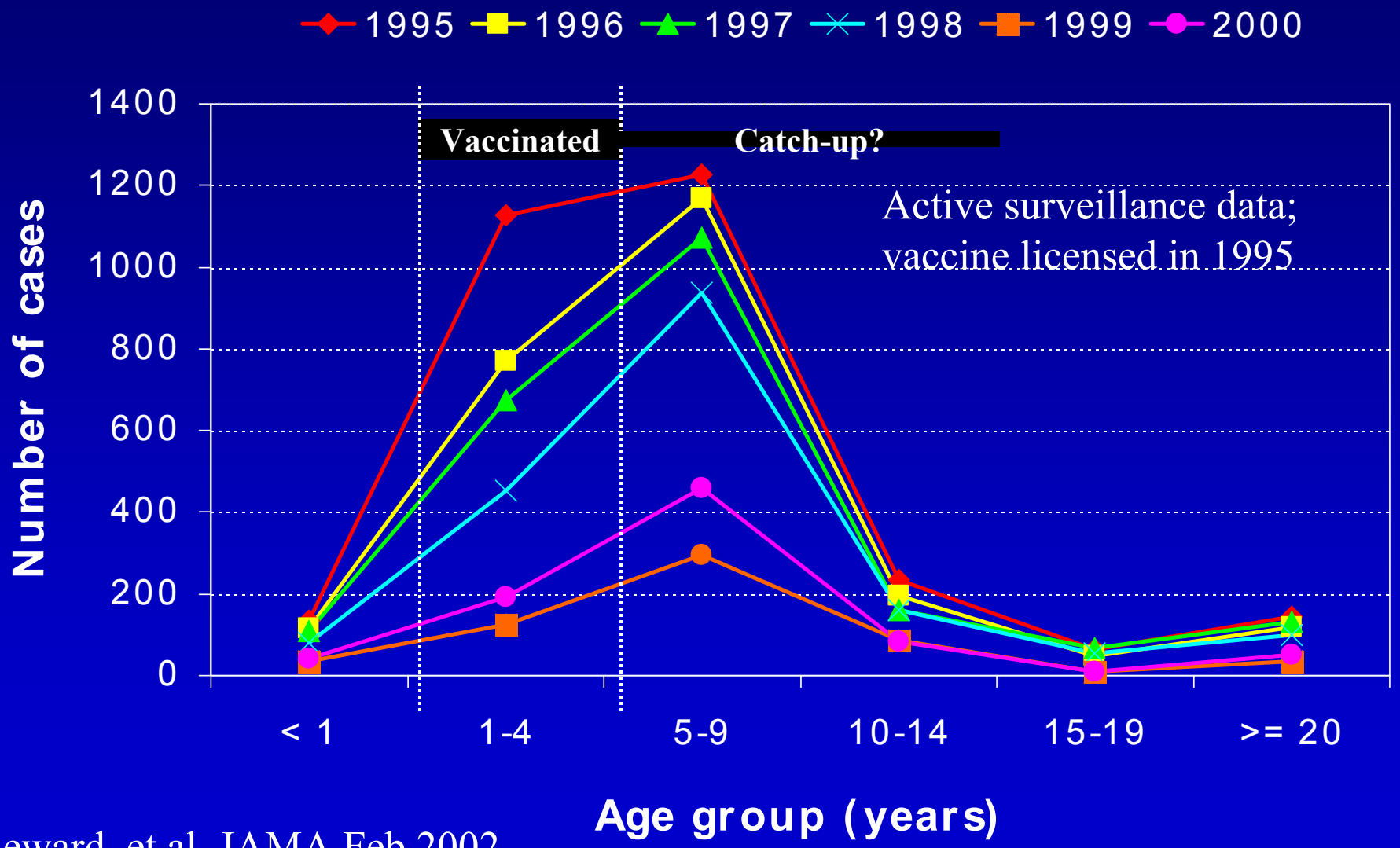
Guris D, Jumaan AO, Mascola L et al.

JID 2008 Mar;197(suppl2):S71-5

Guris D, Jumaan AO, Mascola L et al.

JID 2008 Mar;197(suppl2):S71-5

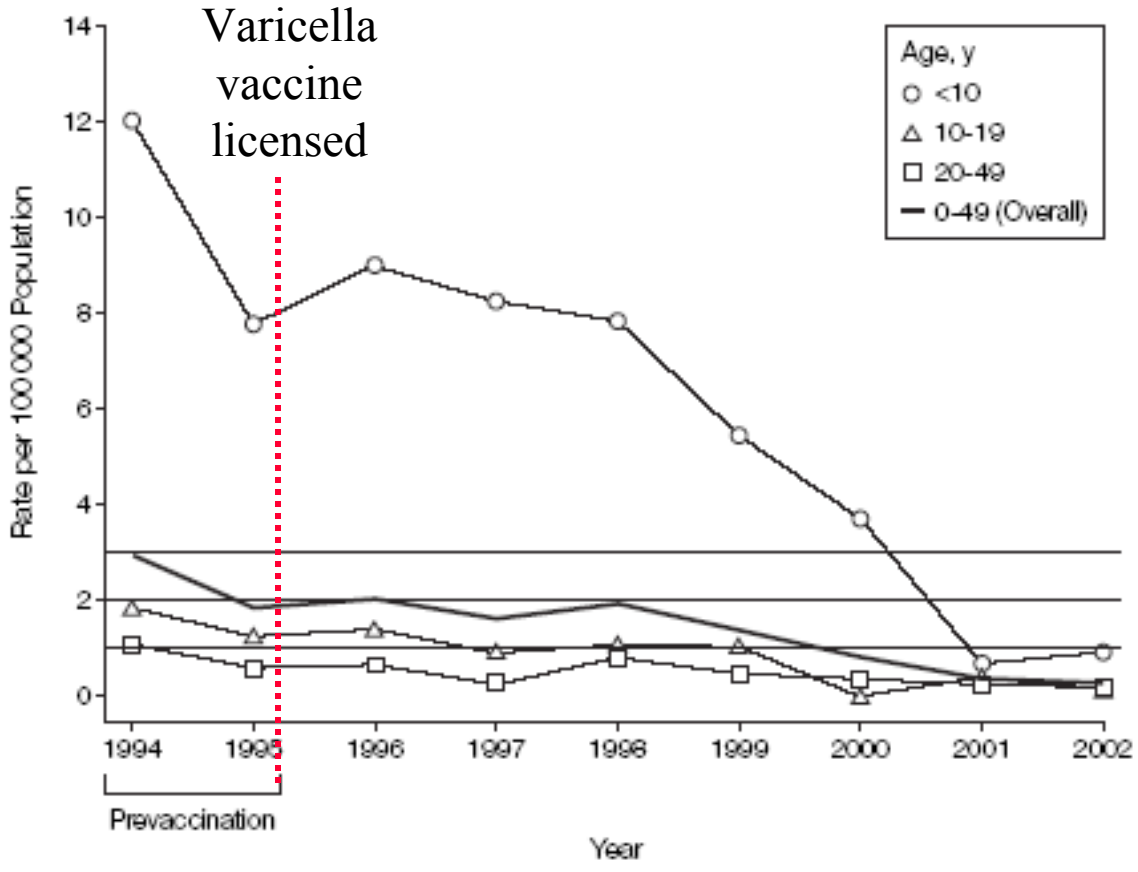
Age-group of varicella cases, Antelope Valley, CA (popn 300,000) – 1995-2000



Seward, et al. JAMA Feb 2002

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

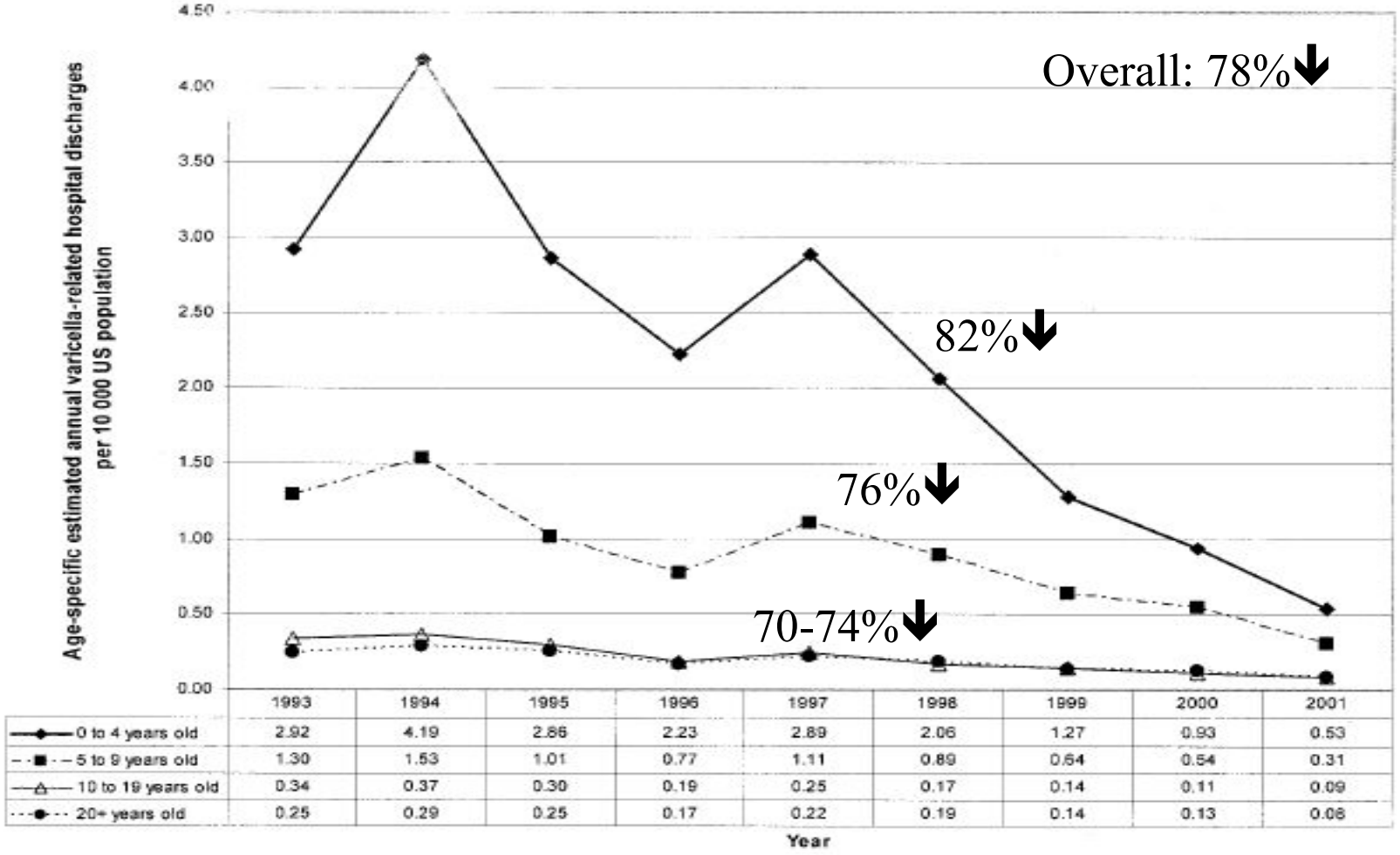
Figure 1. Varicella-Related Hospitalization Rates, 1994-2002



Varicella was the primary diagnosis code for data shown.

Zhou, JAMA Aug 2005 – MarketScan database of > 100 HMOs of 40 employers

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



	1993	1994	1995	1996	1997	1998	1999	2000	2001
0 to 4 years old	2.92	4.19	2.86	2.23	2.89	2.06	1.27	0.93	0.53
5 to 9 years old	1.30	1.53	1.01	0.77	1.11	0.89	0.64	0.54	0.31
10 to 19 years old	0.34	0.37	0.30	0.19	0.25	0.17	0.14	0.11	0.09
20+ years old	0.25	0.29	0.25	0.17	0.22	0.19	0.14	0.13	0.08

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

Varicella-related deaths, USA – 1990-2007

Marin et al. Pediatrics Aug 2011;128(2):214-20

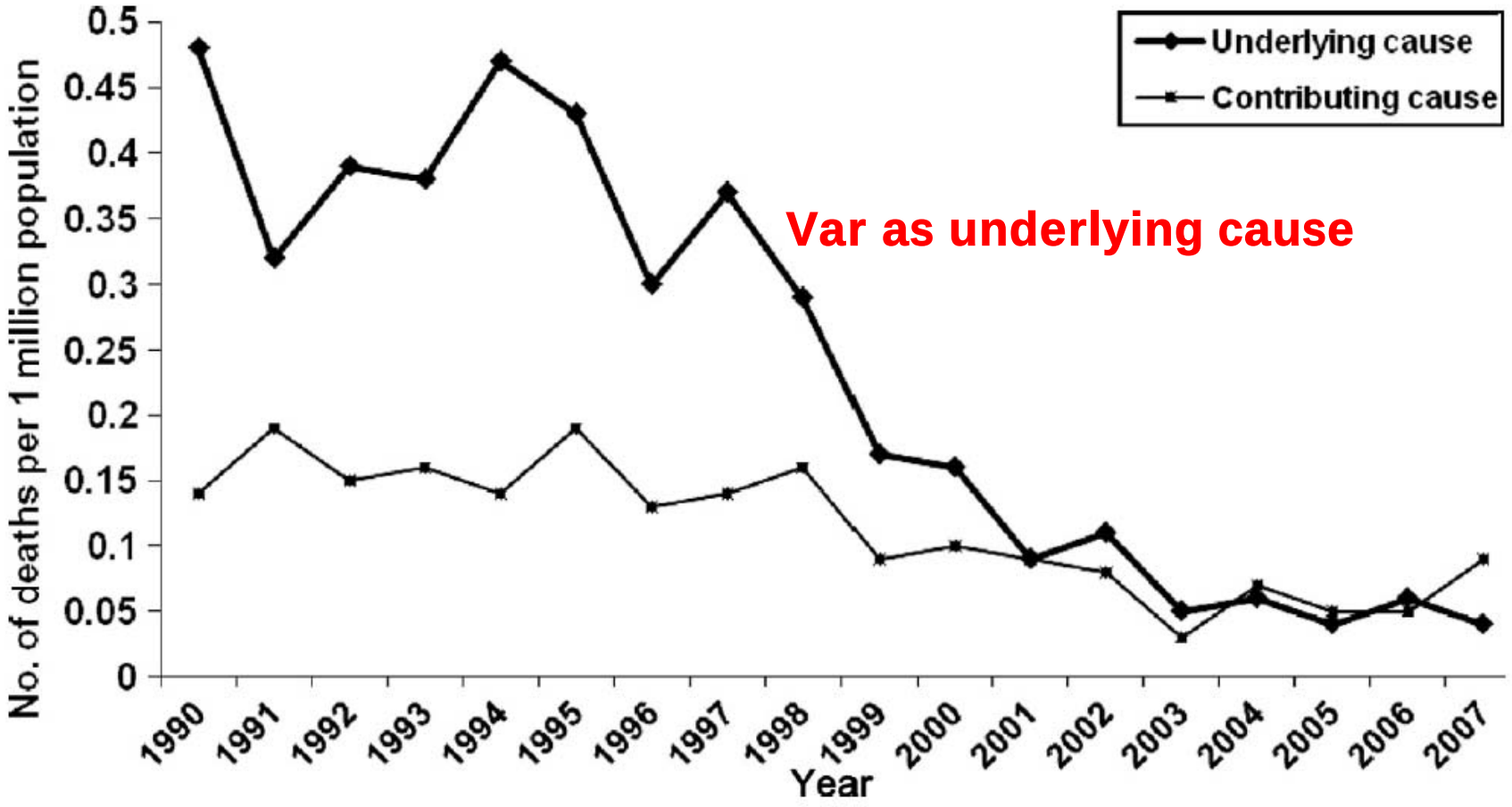


FIGURE 1

Varicella-related mortality rates in the United States, 1990–2007 (age adjusted to the 2000 US population).

Varicella-related deaths, USA – 1990-2007

Marin et al. Pediatr Aug 2011;128(2):214-20

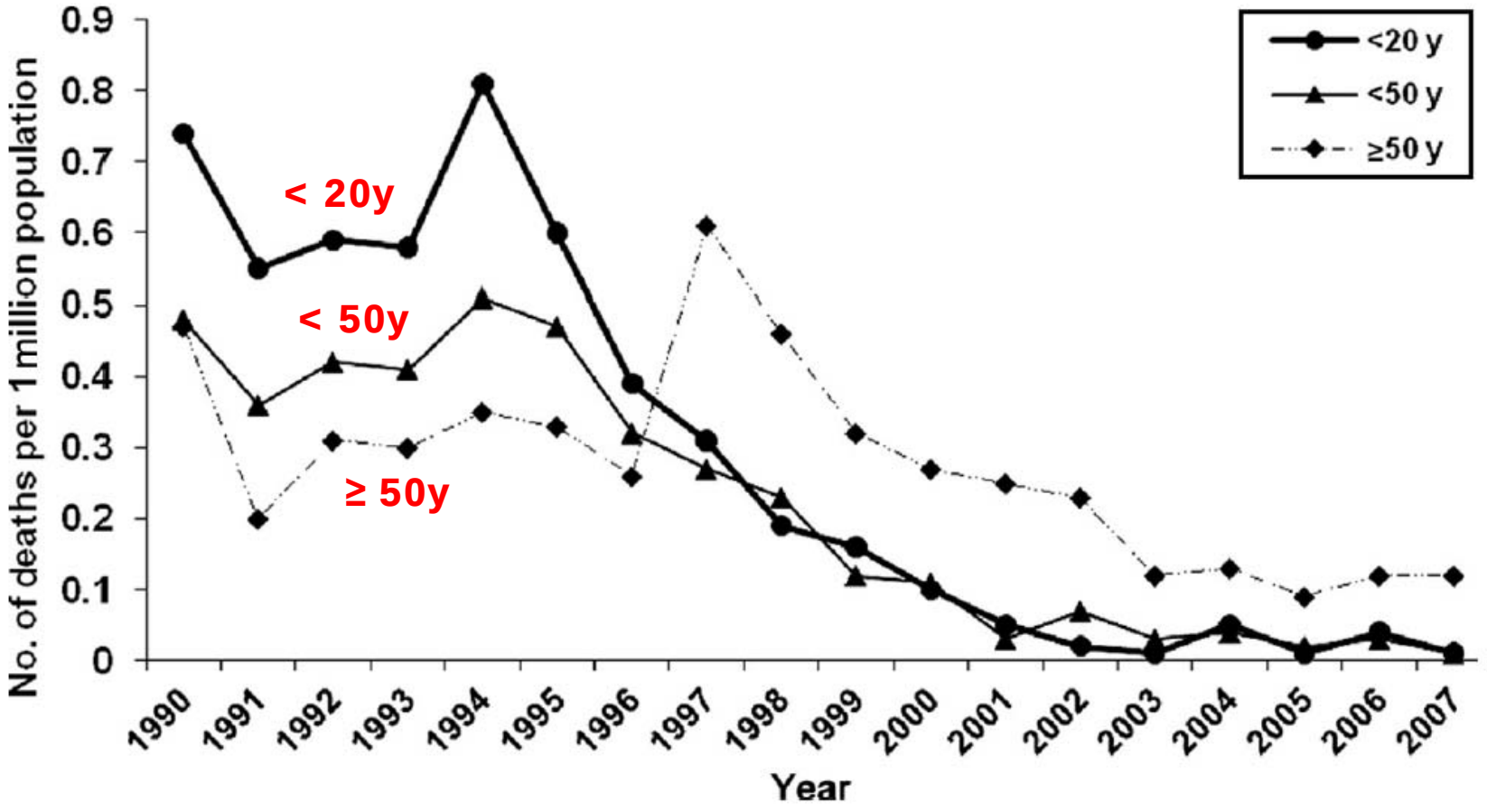


FIGURE 2

Annual age-specific mortality rates for varicella listed as the underlying cause, United States, 1990–2007.

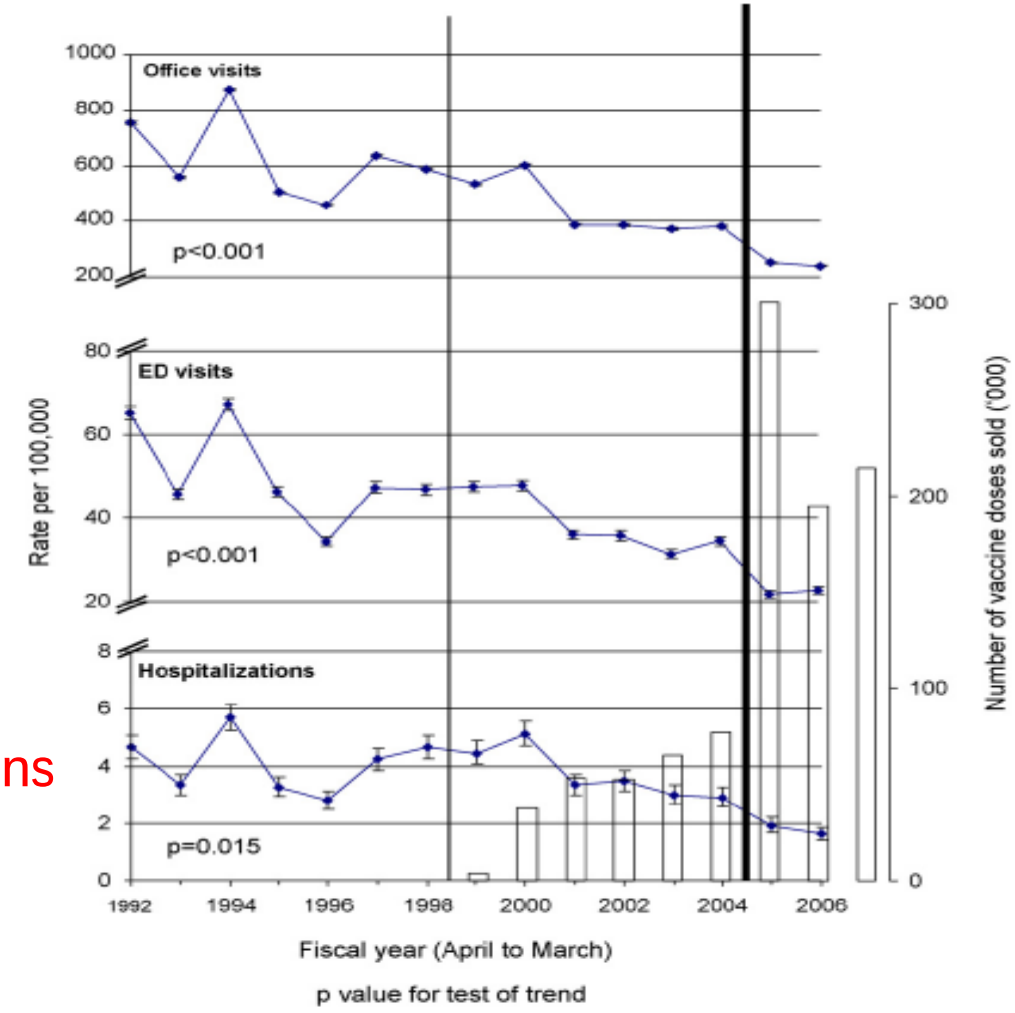
Kwong JC, Tanuseputro P, Zagorski B et al.

Vaccine. Nov 2008;26(47):6006-12

Office visits

ER visits

Hospitalizations



Province of Ontario, 1992-2007 (1-dose era)

Fig. 1. Age-standardized varicella-related outcomes for the overall population, Ontario, 1992–2007, with vaccine sales data. The thin vertical line indicates the start of private availability of varicella vaccines and the thick vertical line indicates publicly funded immunization program introduction.

Kwong JC, Tanuseputro P, Zagorski B et al.

Vaccine. Nov 20085;26(47):6006-12

Periods	1992-98	1999-2004	2005-06	1st transition Rel Risk	2nd transition Rel Risk	Overall transition RR
Hospitaliz per 100,000	4.0 (3.9-4.2)	3.7 (3.5-3.8)	1.7 (1.6-1.9)	0.91 (0.86-0.96)	0.47 (0.42-0.52)	0.43 (0.38-0.47)
ER visits per 100,000	50.3 (49.8-50.8)	38.9 (38.4-39.3)	22.3 (21.7-22.9)	0.77 (0.76-0.78)	0.57 (0.56-0.59)	0.44 (0.43-0.46)
MD visits per 100,000	624.7 (622.9-626.4)	445.3 (443.7-446.9)	246.0 (243.9-248.1)	0.71 (0.71-0.72)	0.55 (0.55-0.56)	0.39 (0.39-0.40)

Greatest ↓s during the 2nd transition were in the 1-4 yr age-group, w/ RR of 0.38 for hospitaliz, 0.50 for ER visits and 0.45 for MD visits.
Smaller ↓s under 1 yr and 5-9 yr age-groups.

PHAC/CPS - IMPACT pediatric centers

Varicella publicly-funded programs, Canada

- Five P/T with earlier programs (EP, 2000-02):
  - PEI, NS, AB, NW, NU [15% of Canadian popn].
  - IMPACT (ped tertiary care hosp) surveillance in 3 sites = Halifax, Calgary and Edmonton.

- Eight P/T with later programs (LP, 2004-07):
  - NL, NB, QC, ON, MB, SK, BC, YT [85% of popn].
  - Remaining 9 IMPACT sites = St. John's, Quebec City, Montreal (2), Ottawa, Toronto, Winnipeg, Saskatoon, Vancouver.

- Hospitalized cases reflect the most severe cases of varicella (zoster removed).

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Decreasing admissions over time at IMPACT centers monitoring early programs (EP)

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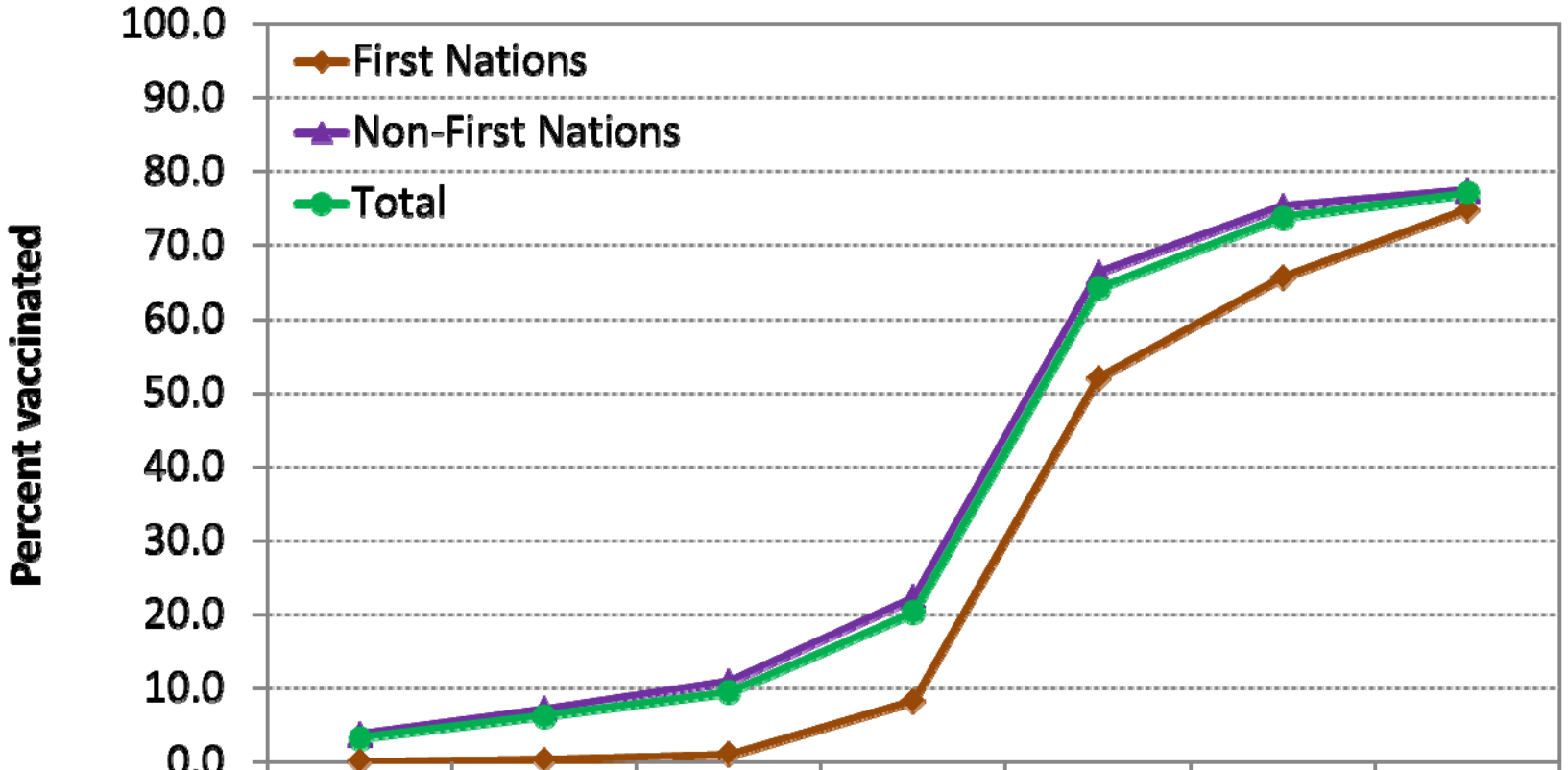
Decreasing admissions over time, at IMPACT centers monitoring later programs (LP)

Manitoba (MIMS data) – Varicella vaccine single-dose coverage by the 2nd birthday, 2002-08



	2002	2003	2004	2005	2006	2007	2008
First Nations	0.0	0.2	1.0	8.2	52.0	65.6	74.8
Non-First Nations	3.7	7.1	10.9	22.3	66.3	75.3	77.4
Total	3.2	6.2	9.5	20.3	64.2	73.8	77.0

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Decreasing admissions at all IMPACT centers over time, by age-groups

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Decreasing seasonal trends for admissions at IMPACT centers over time

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Decreasing admissions at IMPACT centers over time, by underlying health status

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Increasing proportion of breakthrough cases among admissions at IMPACT centers over time

Single-dose in children – limitations 1

- 10-30% breakthrough (vaccine-modified) disease:
  - Resetting "seroconversion" (Merck's) gpELISA titer to 5.0 (from pre-approval 0.6).
  - Too low threshold led to high "primary failure" rate.

- Secondary vaccine failure (waning immunity) also likely, although data difficult to interpret:
  - Higher odds ratios for increased time since vaccination in many, but not all studies.
  - But when coverage still low, boosting of Ab was occurring.

Single-dose in children – limitations 2

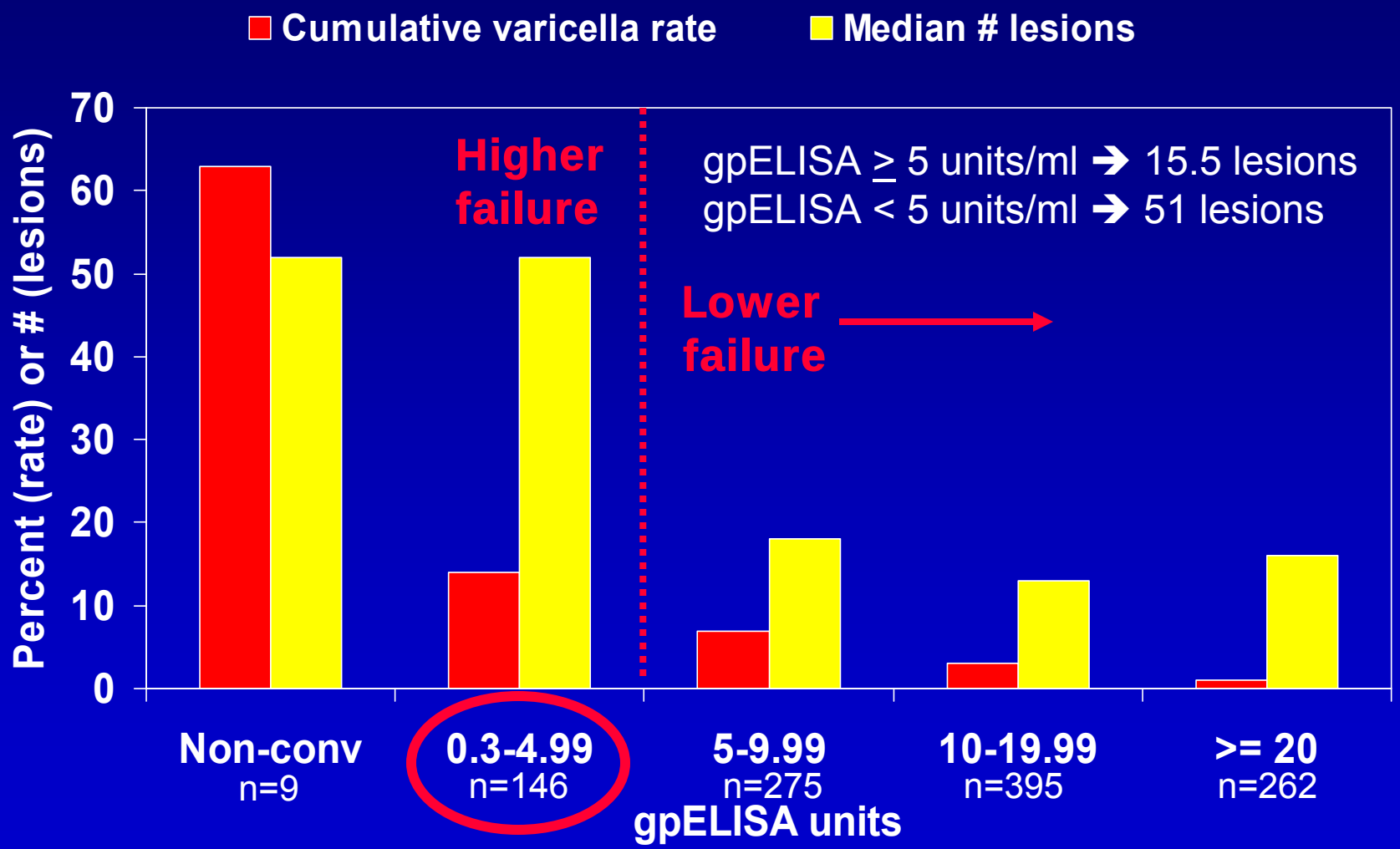
- Breakthrough disease is mild in 75-80%, but the remainder are mod-severe and can initiate or propagate "outbreaks":
  - Public Health manage outbreaks in USA, not in Canada.

- Decline in disease incidence has plateau'd, seemingly shifted to an older age-group, unknown if this will eventually lead to higher complications in adolescents/adults.

- Brisson's (and others) modelling predicts large wave of breakthrough disease in 10-20 years after a honeymoon period (at older ages) ??

Varicella – 6 wk gpELISA & breakthrough

Li S, et al. PIDJ Apr 2002;21:337-42



Prospective study, same study group as Kuter et al but with 7 yr follow-up

Marin M, Meissner HC, Seward JF.

Pediatrics 2008 Sep;122(3):e744-51

Humoral and cell-mediated responses to 1 and 2 doses of Var-containing vaccines among children 12 mos to 12 yrs

Immune response	6w after dose 1		6w after dose 2 (w/ 3m between doses)		6w after dose 2 (given at 4-6y)	
	Var	MMRV	Var	MMRV	Var	MMRV
VZV IgG gpELISA ≥ 5 U/ml	85.7%	91.2%	99.6%	99.2%	99.4%	98.9%
VZV IgG gpELISA GMT U/ml	12.5	13.0	142.6	588.0	212.4	317.0
Mean Stim Index (SI)	28.6 ± 6.2		36.9 ± 9.1		58.6 ± 6.5	

Guris D, Jumaan AO, Mascola L et al.

JID 2008 Mar;197(suppl2):S71-5

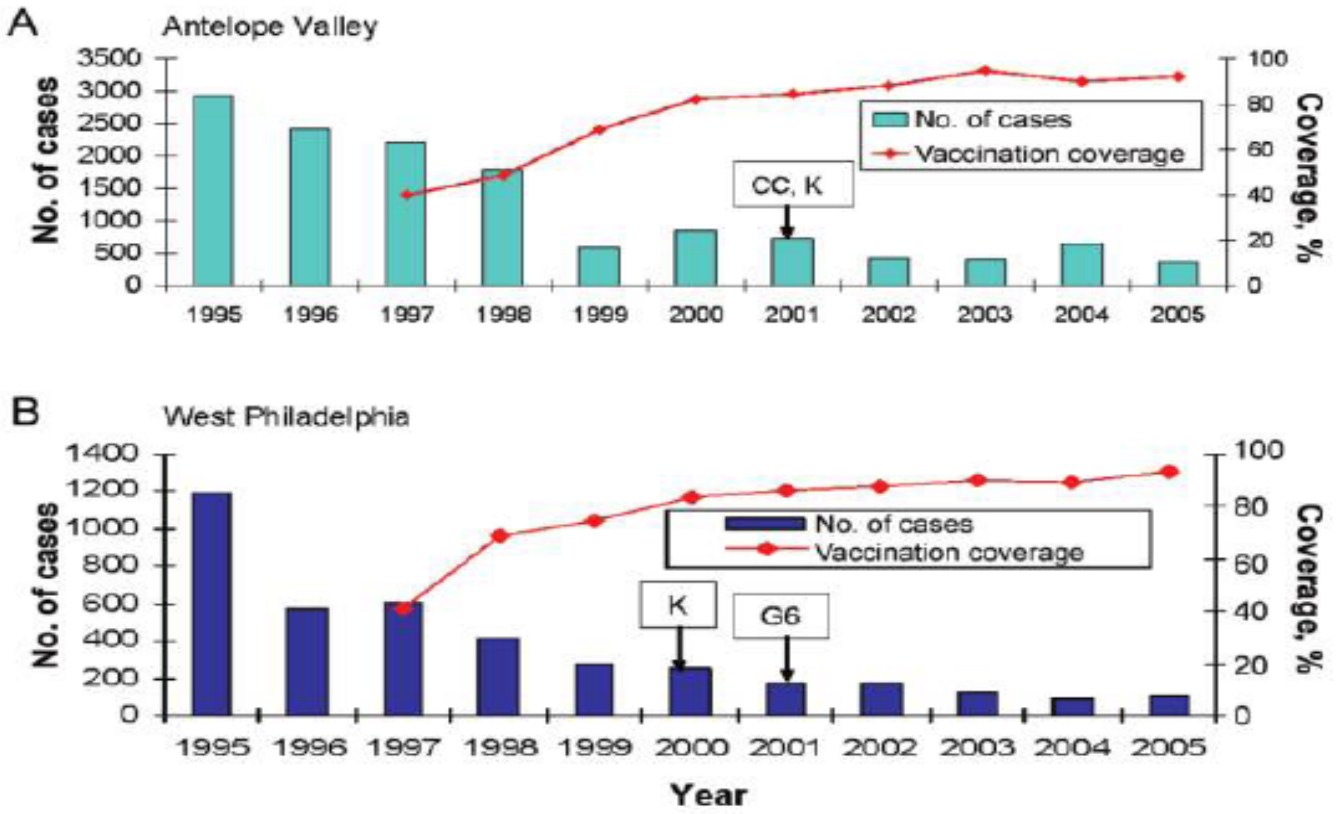


Figure 1. No. of cases and vaccination coverage, Antelope Valley, California *(A)*, and West Philadelphia, Pennsylvania *(B)*, 1995–2005. Boxes with arrows indicate when varicella vaccination requirements for child care (CC), kindergarten (K), and sixth grade (G6) entry went into effect.

Guris D, Jumaan AO, Mascola L et al.

JID 2008 Mar;197(suppl2):S71-5

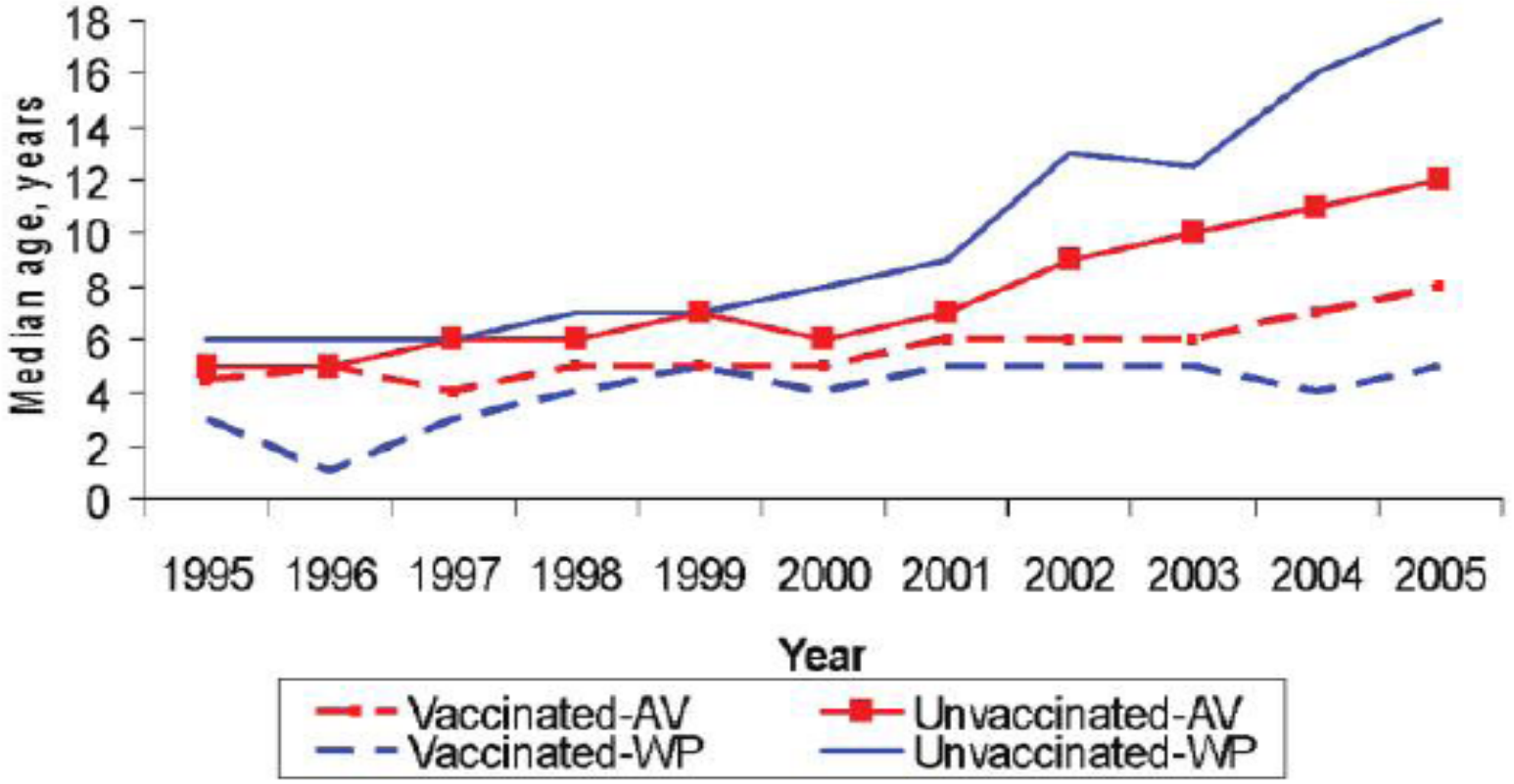


Figure 3. Median ages of both vaccinated and unvaccinated case patients, Antelope Valley, California (AV), and West Philadelphia, Pennsylvania (WP), 1995–2005.

Varicella outbreaks in the USA, 1997-2004

Study	Vaccine Effectiveness (VE)		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 daycare, 01
Dworkin, CID, 2002	88% (-)	-	IL elem school, 01
Tugwell, Peds, 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%)	Israeli daycare, 03
Huebner, mmwr, 2006	81% (66-89%)	93% (82-97%)	NE elem school, 04

Other unpublished studies from schools or daycare centers in Maine, NH, CA (LA) and Utah ➔ VE against any severity = 73-90%

Contagiousness & severity of breakthrough

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

	Secondary attack rate		
Index case	Unvaccinated	Vaccinated	Previous VZV hx
Unvaccinated	71% (1071/1499) 25% mild	15% (25/166) 75% mild	7% (44/620) 20% mild
Vaccinated	37% (26/70) 40% mild	22% (21/94) 90% mild	3% (1/38) 100% mild
Previous VZV hx	45% (29/65) 30% mild	0 (0/19) 0	16% (26/161) 25% mild

From 1997-2001 ➔ 6,316 cases in 1,602 households with 5,912 contacts

Contagiousness of breakthrough 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 overall = 79% (95% CI = 70-85%)

VE mod/severe disease = 92-100%

Varicella outbreaks – breakthrough factors

Study	Time since vaccination	Age at vaccination
Lee, JID, 2004 MN sch	≥ 5 yrs Rel Risk (RR) 2.6 (1.3-2.4)	12-15 mos RR 2.1 (1.1-4.1)
Renas, MMWR, 2004 MI sch	≥ 4 yrs RR 4.7 (1.5-15)	Not Signif
Tugwell, Peds, 2004 OR sch	≥ 5 yrs RR 6.7 (2.2-22)	NS
Verstraeten, Ped, 2003 HMO-A(west) day care	Not available (N/A)	12-14 mos RR 1.4 (1.1-1.9)
Dworkin, CID, 2002 IL 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 PA daycare	N/A	12-14 mos RR 3.0 (0.9-9.9)

Oka/Merck vaccine at 12-14 vs 15-23 moa

Silber et al. PIDJ, Jul 2007;26:572-76

Age (mos)	N	% ≥ 5 gpELISA units/ml (95%CI)	GMT gpELISA units/ml (95%CI)
12-14	3133	93.8 (92.9-94.6)	15.1 (14.6-15.5)
15-17	479	90.8 (87.9-93.2)	13.5 (12.4-14.7)
18-23	159	93.1 (88.0-96.5)	13.7 (11.9-15.8)
Total	**3771**	**93.4 (92.6-94.2)**	**14.8 (14.4-15.2)**

P = 0.08 comparing % ≥ 5 gpELISA units/ml across the 3 age-groups

P = 0.02 comparing GMTs across the 3 age-groups

Oka/Merck vaccine at 12-14 vs 15-23 moa

Silber et al. PIDJ, Jul 2007;26:572-76

Initial serostatus (by gpELISA)	N	% ≥ 5 gpELISA units/ml (95%CI)	GMT gpELISA units/ml (95%CI)
Seronegative, gpELISA < 0.6	2388	93.6 (92.5-94.5)	15.2 (14.7-15.7)
Seropositive, gpELISA 0.6-1.24	558	95.0 (92.8-96.6)	14.2 (13.3-15.2)
Seropositive, gpELISA ≥ 1.25	187	93.6 (89.1-96.6)	16.5 (13.9-19.6)
Total	**3133**	**93.7 (92.9-94.6)**	**15.1 (14.7-15.7)**

P = 0.46 comparing % ≥ 5 gpELISA units/ml across the 3 age-groups

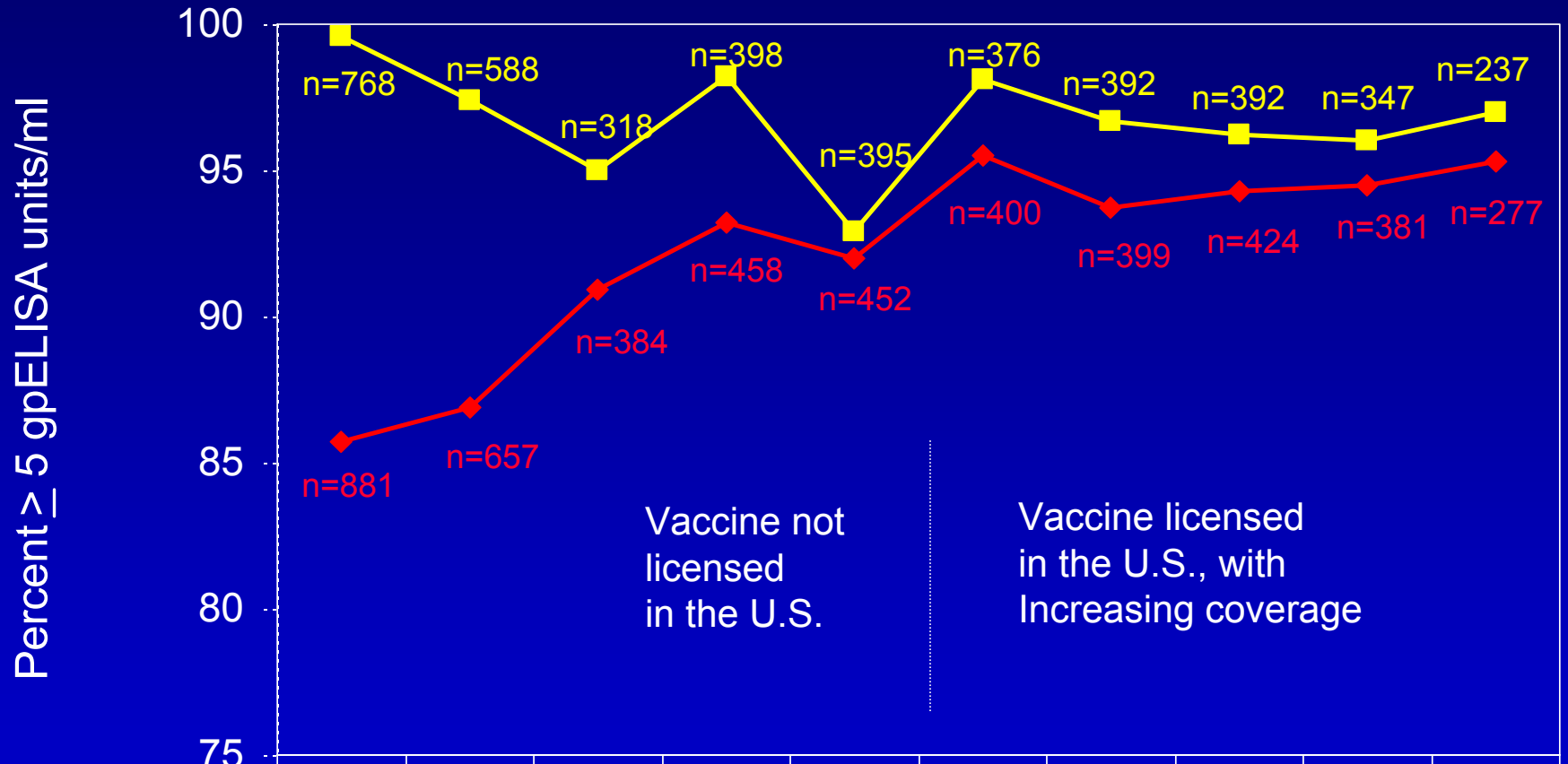
P = 0.83 comparing GMTs across the 3 age-groups

Two-doses in children – benefits

- Close to 100% over the "true" protective level, much higher GMT → anticipate longer-lasting.
- Lower cumulative attack rate (2.2%) in children who got two-doses compared with single-dose (7.3%) in prospective study by Kuter et al.
- Modelling predicts lesser wave of breakthrough & wild-type cases into the future.
- Able to use MMRV in two-dose program.

Varicella gpELISA ≥ 5.0 (10-yr Follow-Up)

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

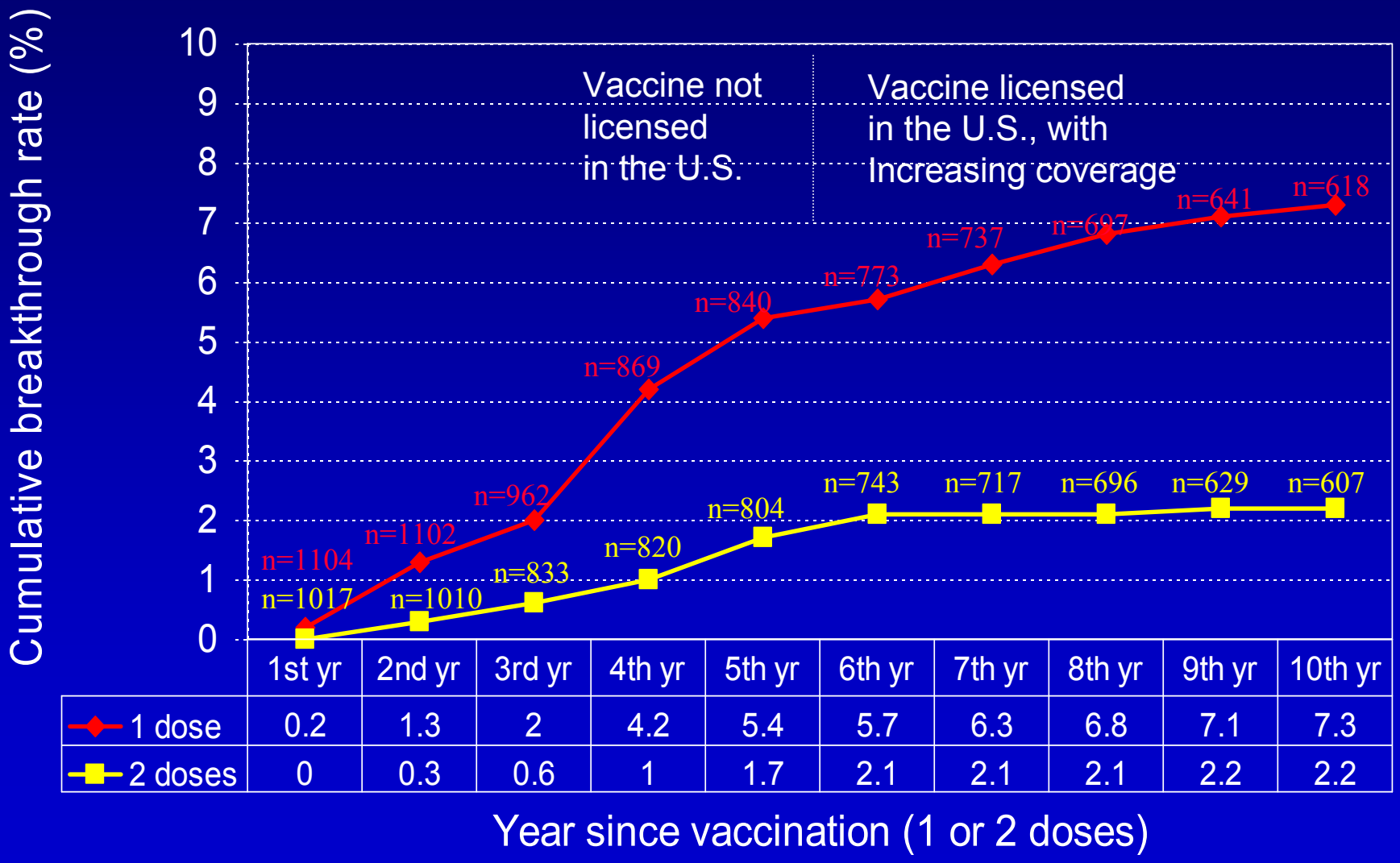


n=1,114	6 wk	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	9 yr
1 dose	85.7	86.9	90.9	93.2	92	95.5	93.7	94.3	94.5	95.3
2 doses	99.6	97.4	95	98.2	92.9	98.1	96.7	96.2	96	97
n=1,029										

Period of time since vaccination (1-2 doses)

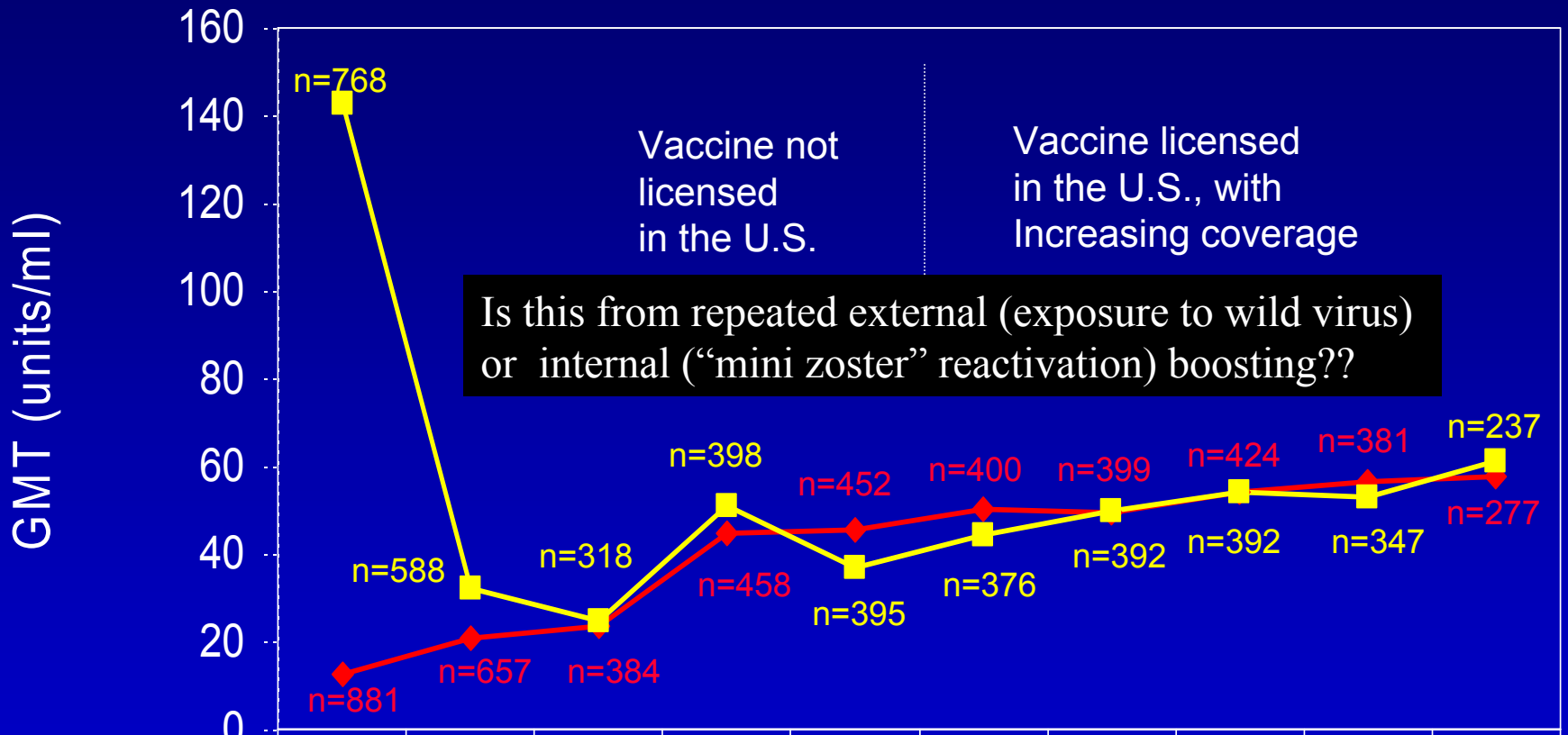
Var breakthrough, cumulative 1993-03 (10 yrs)

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



Varicella gpELISA GMT (10-yr Follow-Up)

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



n=1,114	6 wk	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	9 yr
1 dose	12.5	20.8	23.6	44.7	45.3	50.3	49.5	54.2	56.5	57.8
2 doses	142.6	32	24.6	50.9	36.8	44.3	49.7	54.2	52.8	61

n=1,029

Period of time since vaccination (1-2 doses)

Var 2nd dose incremental effectiveness, 2006

Nguyen et al. PIDJ Aug 2008;29(8):685-9

- ELEM SCH, PHILA (cont) – 2nd dose "Vaccine for Outbreak Control (VOC)" strategy.

- Var outbreak lasted from Oct 13 to Dec 16, 2006.
  - Students considered in 2-dose group if > 4 days after the 2nd dose.

- Total 57 Var cases occurred, with attack rates (AR) of:
  - 5/6 (83%) among the unvaccinated.
  - 43/99 (43%) in 1-dose gp.
  - 9/187 (5%) in 2-dose gp. (0/4 in 2-dose recip pre-outbreak).

Varicella modelling

- Being done in several countries to anticipate the changing epidemiology of varicella due to vaccine programs:
  - Canada & UK (Brisson, Edmunds et al. 2000-02 & 2010-11).
  - Australia (published by Gao et al.).
  - Finland (published by Karhunen et al.).

- In 2008-09 NACI requested Brisson model the impact of 1- vs 2-dose programs on varicella and zoster disease.
  - Used coverage assumptions from Quebec, paper published.
  - Cost-effectiveness paper not yet published.

Varicella 1- vs 2-dose model

Brisson et al. Vaccine Apr 2010;28(2010):3385-97

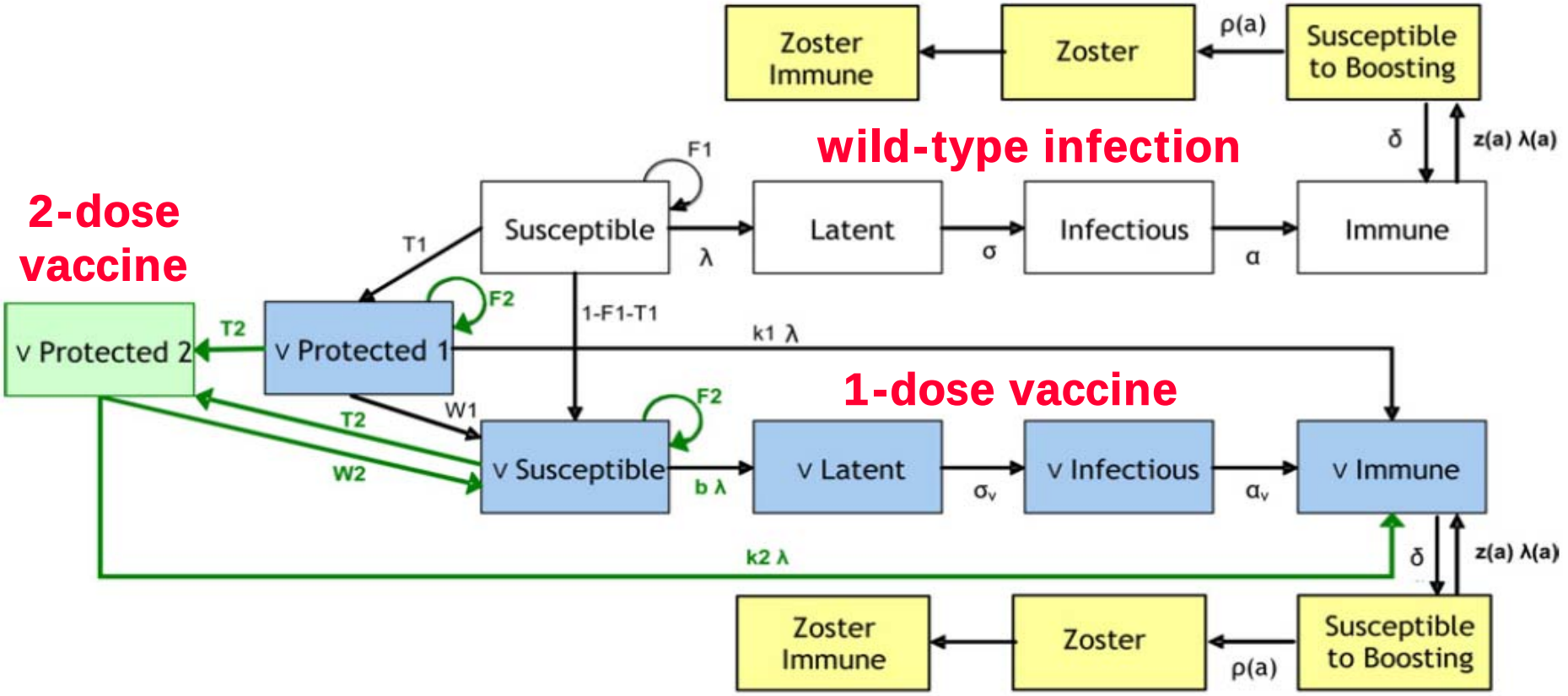
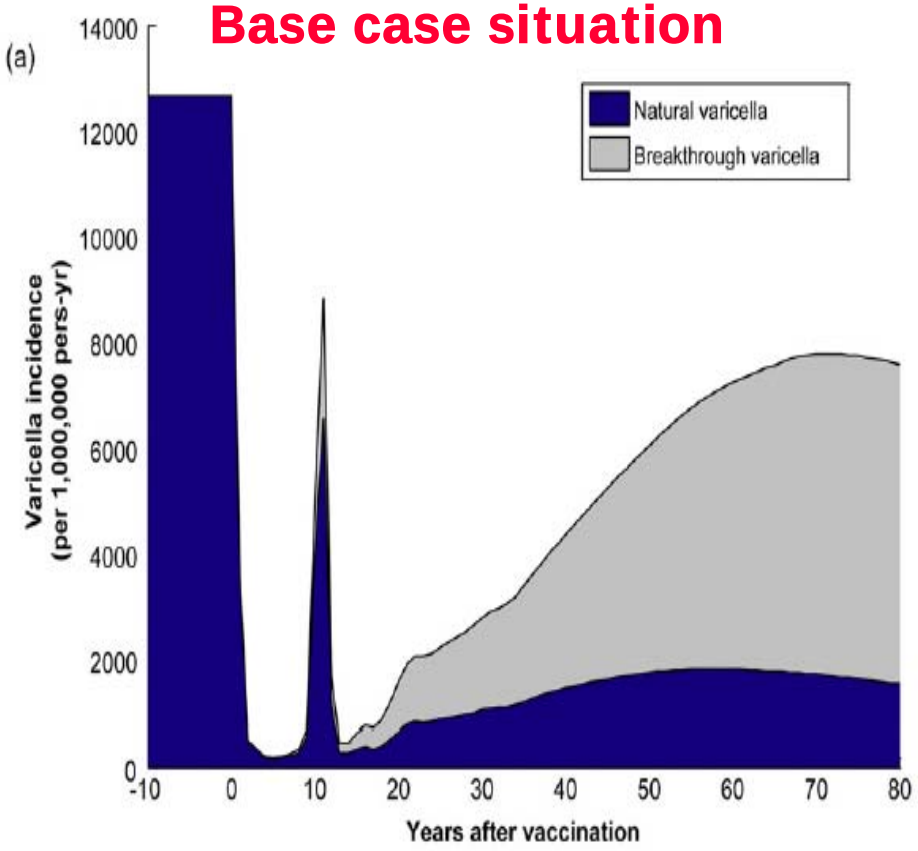


Fig. 1. Flow diagram of the natural history of varicella and zoster with and without vaccination. The mutually exclusive compartments represent the different VZV epidemiological states. Arrows represent the flow between these states. w = Waning rate from vaccine protected to vaccine susceptible; T = % who become temporarily protected after vaccination; F = % for which vaccine fails completely; 1-b = Degree of protection in vaccinated susceptibles; k = % vaccine protected who become immune due to contact with varicella; m = Rate of varicella infectiousness of vaccinees compared to non-vaccinees; λ = Force of infection; $1/\sigma$ = Duration of natural varicella latent period; $1/\alpha$ = Duration of natural varicella infectious period; $1/\sigma_v$ = Duration of breakthrough varicella latent period; $1/\alpha_v$ = Duration of breakthrough varicella infectious period; $1/\delta$ = Duration of immunity to zoster after exposure to varicella; z = % of effective varicella contacts that boost against zoster; $1/\rho$ = Rate of reactivation.

Varicella model – 1-dose impact

Brisson et al. Vaccine Apr 2010;28(2010):3385-97



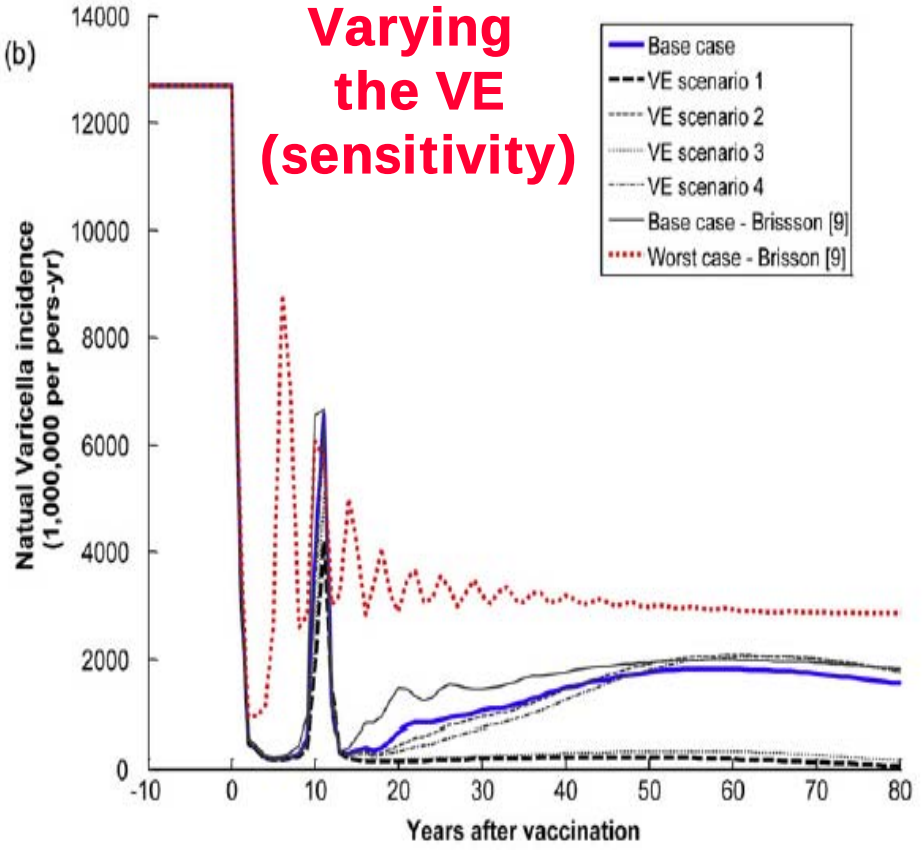
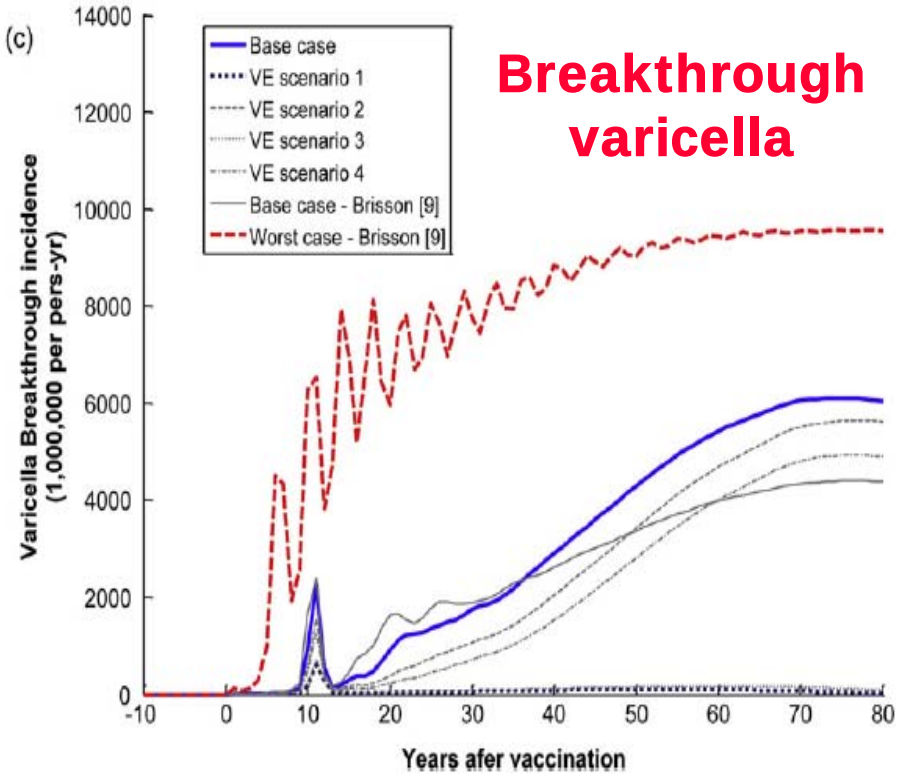


Fig. 3. Impact of 1-dose varicella vaccination on varicella. (a) Predicted incidence of natural and breakthrough varicella over time since vaccination (base case). (b) Impact of vaccine efficacy assumptions on the predicted incidence of natural varicella.

Varicella model – 1-dose impact

Brisson et al. Vaccine Apr 2010;28(2010):3385-97



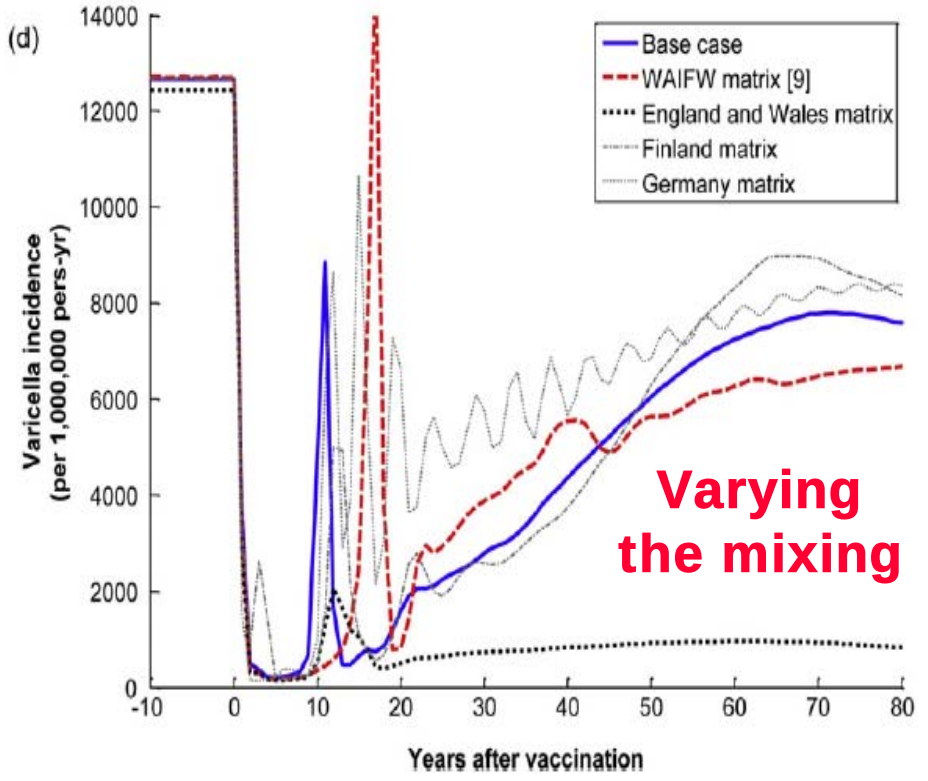


Fig. 3. Impact of 1-dose varicella vaccination on varicella. (c) Impact of vaccine efficacy assumptions on the predicted incidence of breakthrough varicella. (d) Impact of matrix assumptions on the predicted incidence of natural and breakthrough varicella. Natural varicella: full-blown cases that occur in unvaccinated individuals and primary failures. Breakthrough varicella: occur in seroconverted vaccinated individuals and is assumed to be significantly less severe than natural varicella.

Varicella model – 1-dose impact

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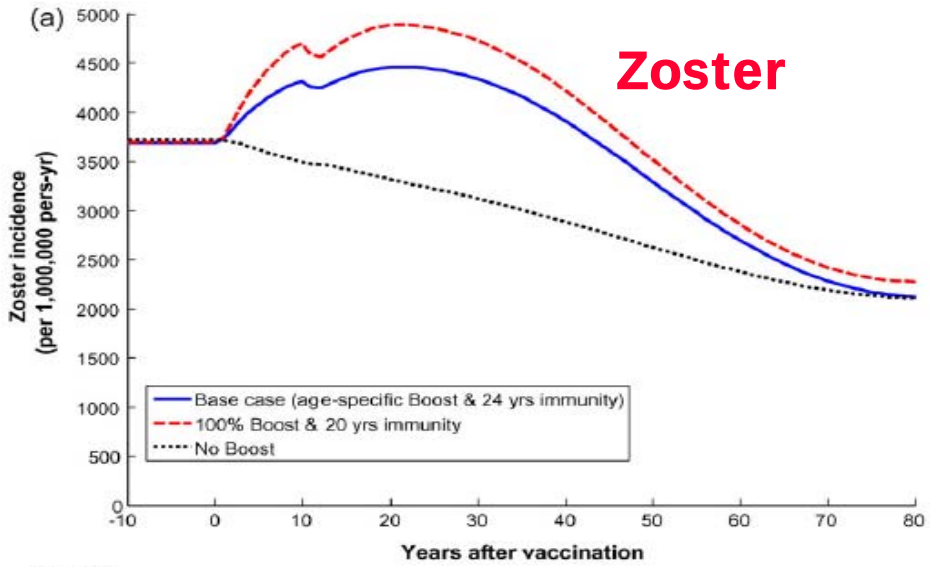

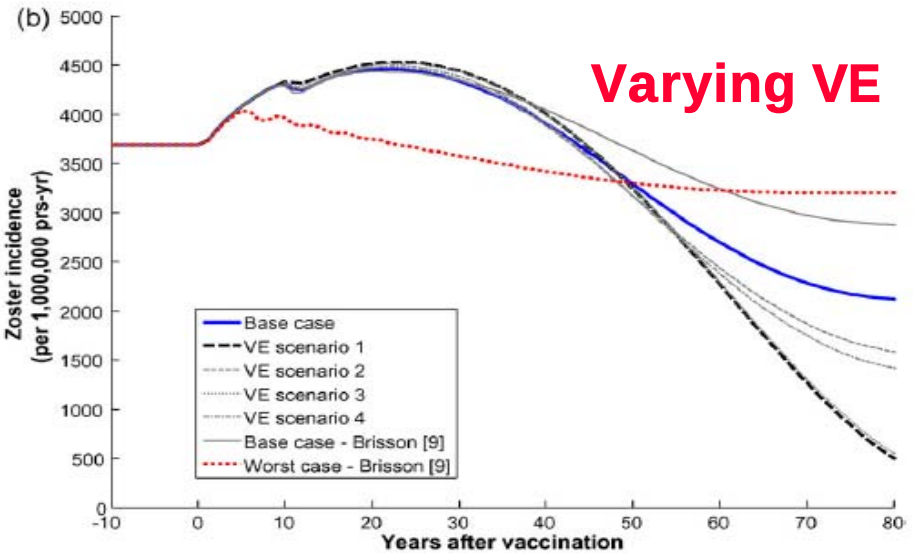

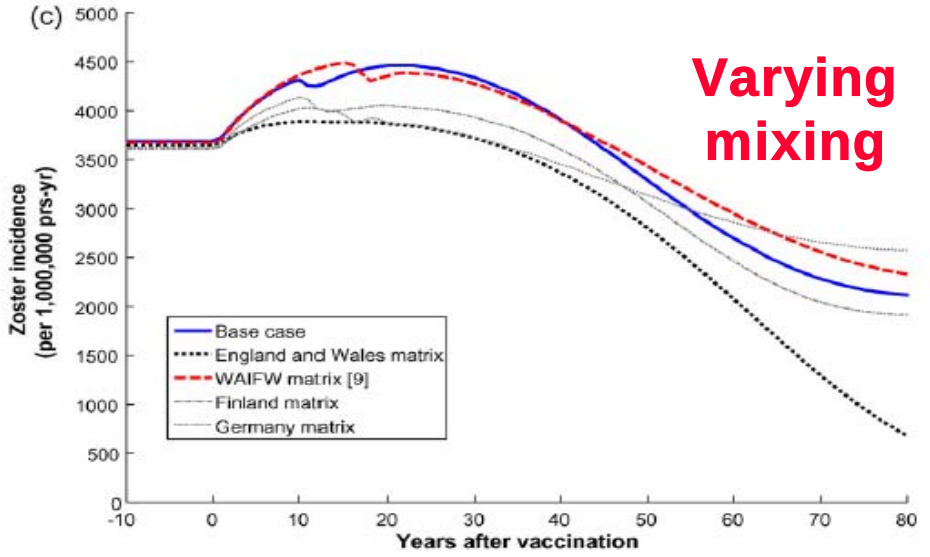

Fig. 4. Impact of 1-dose varicella vaccination on zoster. (a) Predicted incidence of zoster over time since vaccination. (b) Impact of vaccine efficacy assumptions on the predicted incidence of zoster. (c) Impact of force of infection and matrix assumptions on the predicted incidence of zoster.

Varicella model – 1- versus 2-doses

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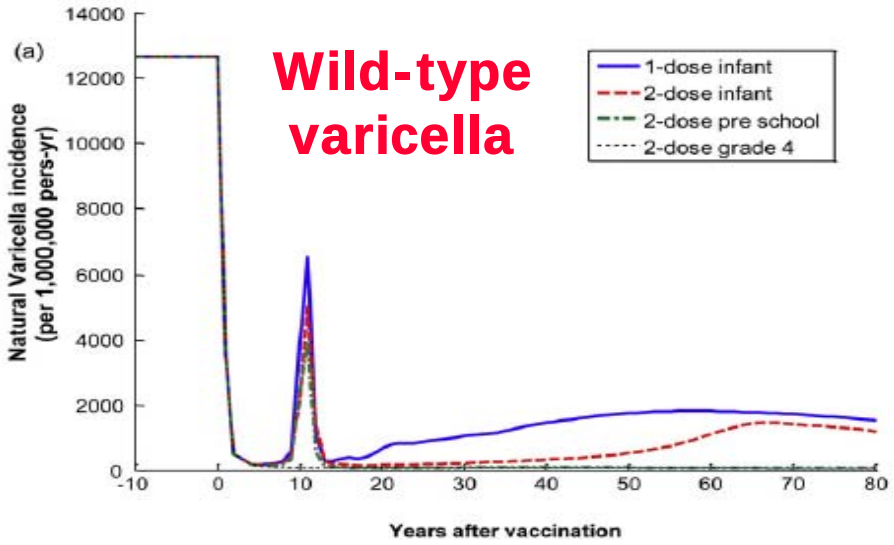

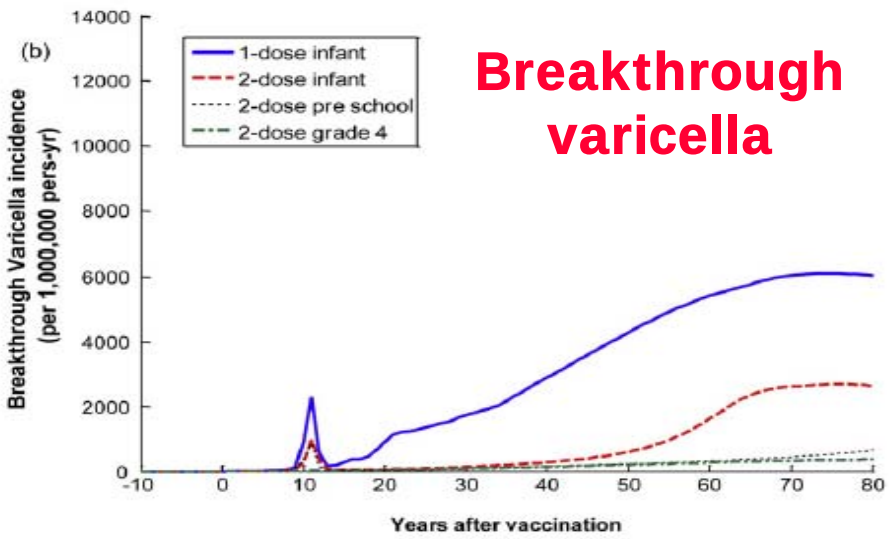

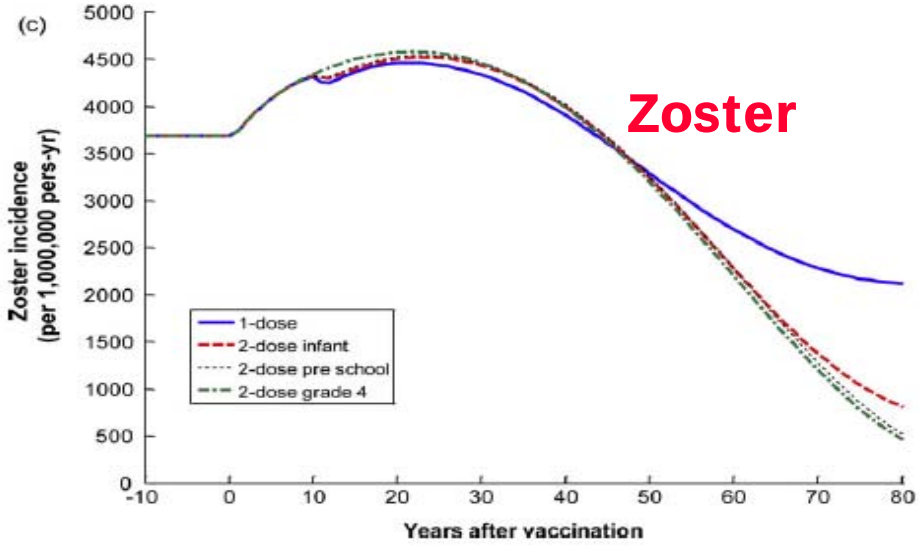

Fig. 5. Impact of a 2-dose varicella vaccination program. Predicted incidence of: (a) natural varicella, (b) breakthrough varicella and (c) zoster over time after 1- and 2-dose vaccination programs (base case assumptions, age-specific boost and 24 years immunity).

Conclusions

- Single-dose programs have been very successful → ↓disease incidence, hospitalizations and mortality (the minimum we want); the benefit appears to have plateau'd.

- However, breakthrough disease is common, probably impacting daycare and schools (no surveillance); model predicts a possible large increase in breakthrough cases at an older age (with unvaccinated cases, if coverage is too low).

- Two-dose programs can correct primary and secondary vaccine failures, hopefully prevent that large future wave.

Research challenges

- Best timing for the 2-doses – based on disease pattern, or cost-effectiveness?
  - Close together deals with 1° failure, reduces virus circulation?
  - Further apart better for 2° failure, longer lasting immunity?
- How do we catch-up the second dose? Who pays?
- Is breakthrough disease at advanced ages really more risky?
- What's happening in Canadian daycare/schools? To get at incidence, we need "VASP-North" (e.g. like Antelope Valley).

1- vs 2-dose varicella schedule, Canada

Features	1-dose	2-dose
↓ varicella disease incidence	Yes, by ~64% over an 80-year projection period	Yes, by ~86% over an 80-year projection period
↓ hospitalization	Yes	Anticipate further reduction
↓ mortality	Yes	Anticipate further reduction
↓ zoster in all ages	Yes, by ~5% over an 80-year projection period	Yes, by ~11% over 80-year projection period
↓ zoster in vaccinee	Yes	Anticipate further reduction
↓ invasive secondary Group A Streptococcus infection	Yes (study by Patel et al)	Anticipate further reduction

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1- vs 2-dose varicella schedule, Canada

Features	1-dose	2-dose
Breakthrough disease (severity)	Yes (in 7%–30%; the majority were mild cases)	Yes, further reduction (in ~2%; all cases were mild)
Breakthrough cases can transmit infection	Yes (if breakthrough disease is mod-severe)	Unknown (due to anticipated small # of cases)
↓ outbreaks	Yes, but outbreaks continue to occur in U.S. childcare centres/schools	Anticipate further reduction (still too early to ascertain)
Antibody levels	Lower seroconversion rates in post-licensure studies (after resetting the seroprotective titer to a higher level)	Significant boosting after the second dose whether administered 3 months later (2 doses of univalent vaccine) or 6 weeks to 4 years later (with 2 doses of MMRV)

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1- vs 2-dose varicella schedule, Canada

Features	1-dose	2-dose
Waning immunity	Yes (based on outbreak studies)	Anticipate less waning immunity (but rate of decline is unknown)
Shift of varicella disease to older ages	Shifted to mean of 22 years for wild type, and 41 years for breakthrough disease	Shifted to mean of 32 years for wild type, and 48 years for breakthrough disease
Cost-effectiveness	Cost-saving, for a single dose at 12 mos	Cost-effectiveness ratios per QALY gained of 2-dose versus 1-dose vaccination: $106,000 (2 doses in the second year of life), $41,000 (2 doses at 12 mos. & preschool), and $28,000 (2 doses at 12 mos. & Grade 4), respectively

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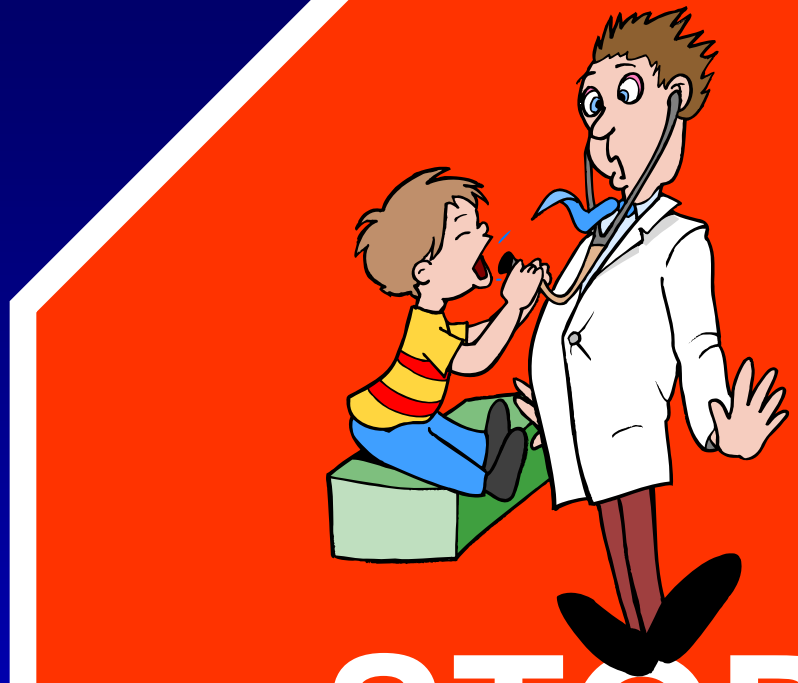

STOP!

Questions?