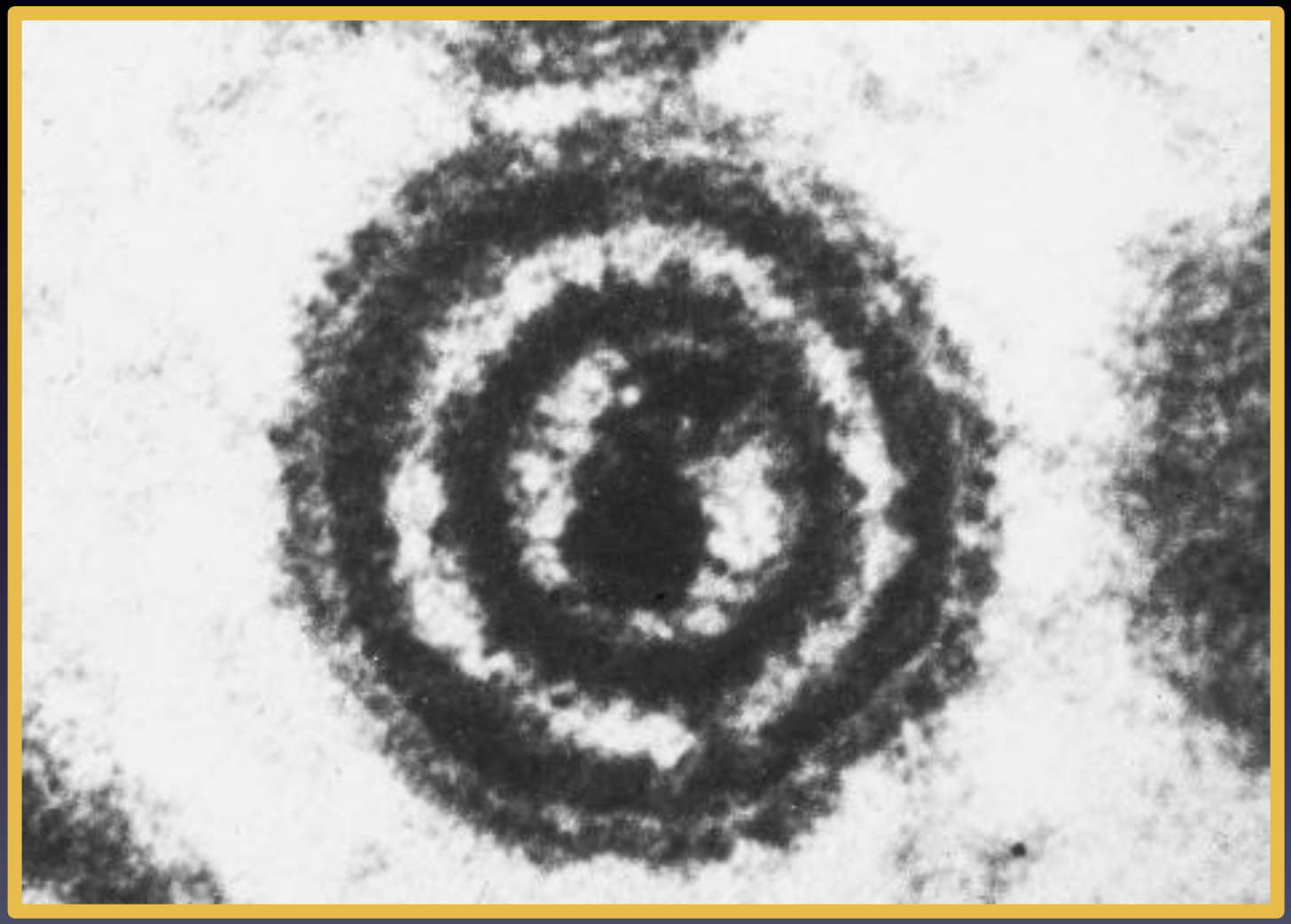
VARICELLA-ZOSTER VIRUS: DISEASE AND VACCINATION

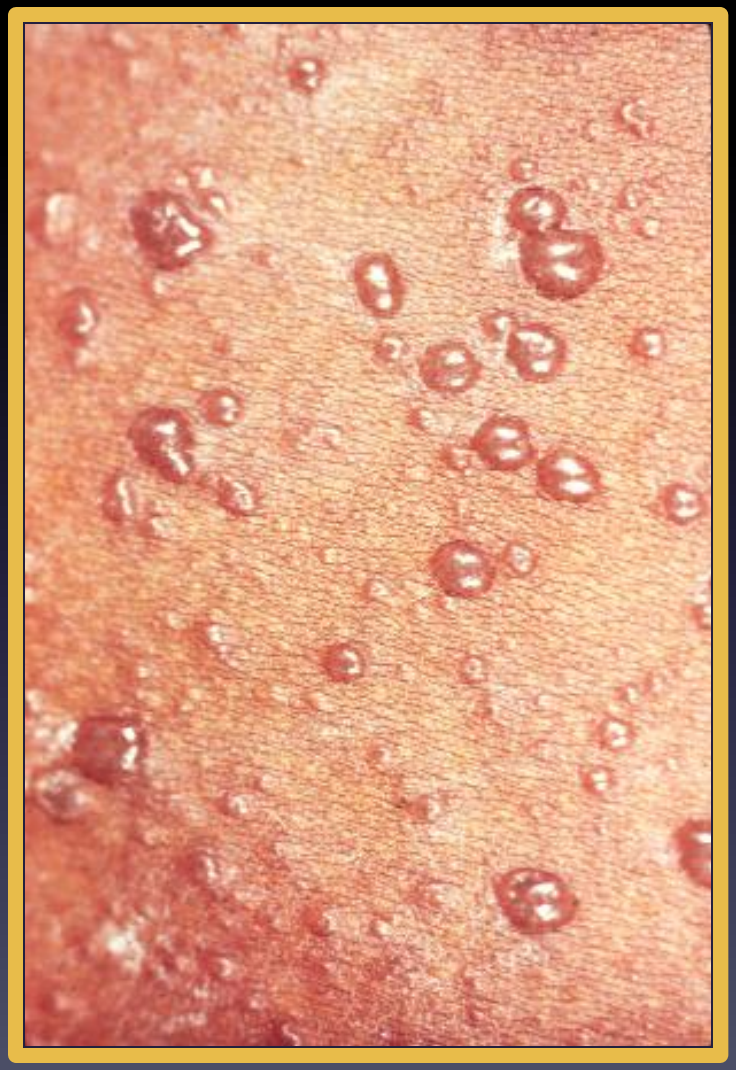
Anne A. Gershon, Jason Chen, Michael Gershon

Columbia University

Varicella Zoster Virus (VZV)



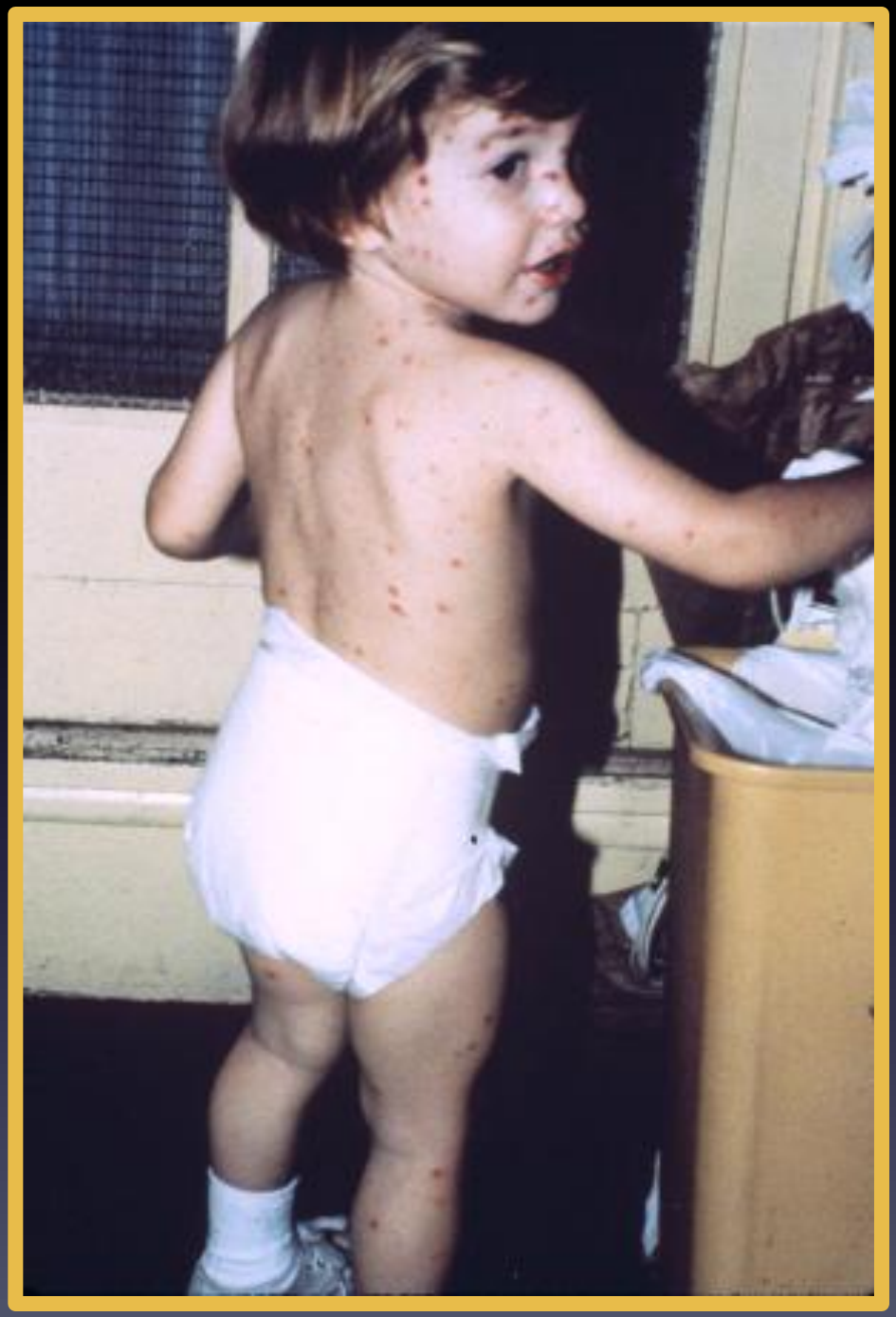
The rash of VZV is vesicular.



- Vesicular fluid is highly infectious.
  - Well-formed virions are suspended in it.

Natural History of VZV

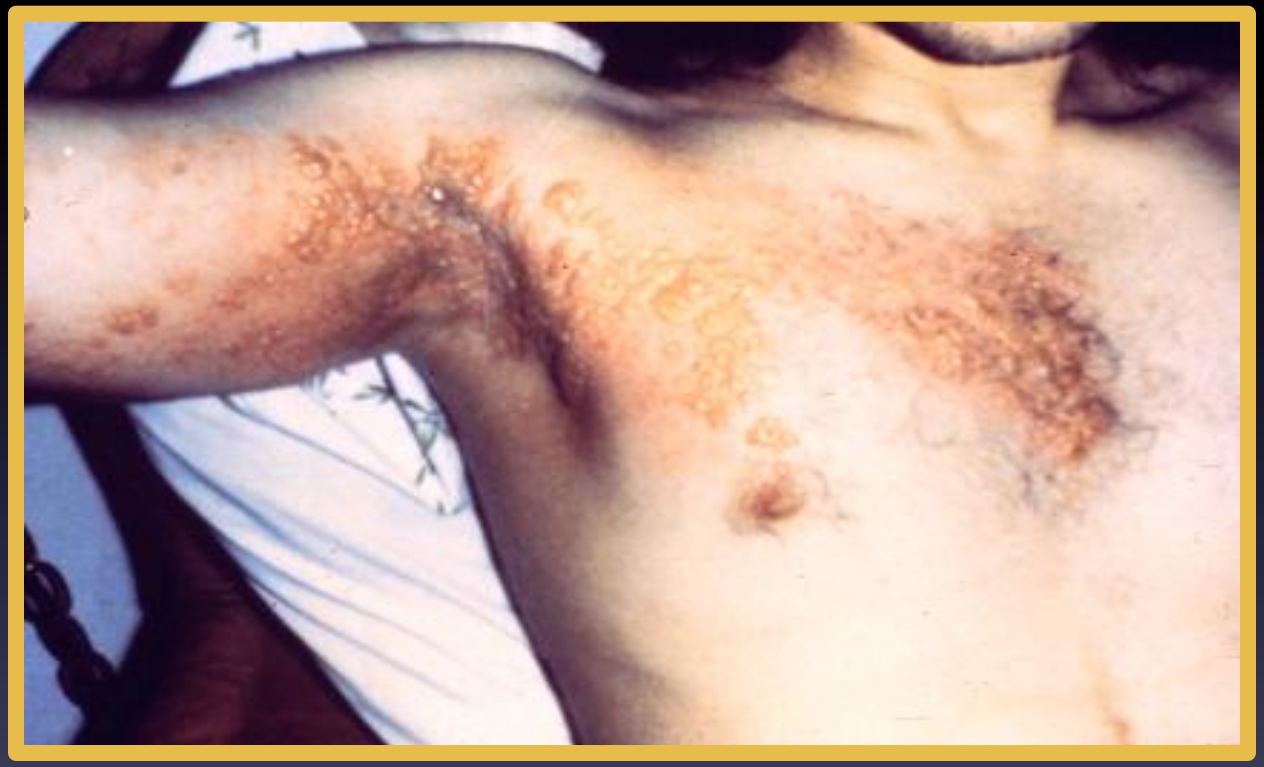
- Primary infection: varicella
  - Highly contagious (airborne)
  - Complications: bacterial superinfection, encephalitis, pneumonia, congenital syndrome
- Secondary infection: zoster
  - Due to reactivation of latent VZV
  - DNA, RNA, proteins in ganglia at autopsy
  - Zoster in vaccinees caused by Oka strain (1/3 due to wild type virus)
  - Due to low cell-mediated immunity (CMI) to VZV
- No asymptomatic shedding of infectious VZV as with HSV



Varicella is a generalized illness.

Infectious virions are produced in the skin vesicles.

Zoster is initially localized

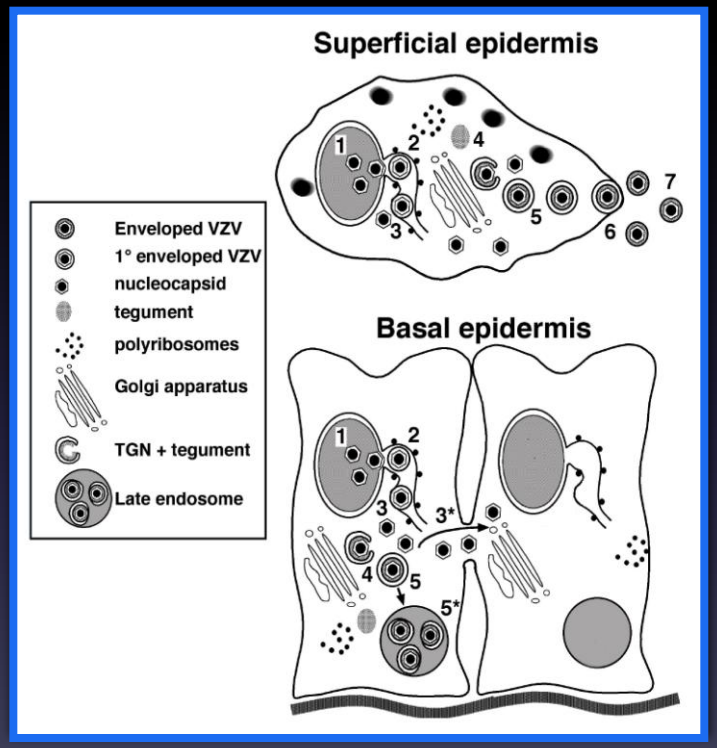


- Limited to 1-3 dermatomes.
- May disseminate in immunocompromised hosts.

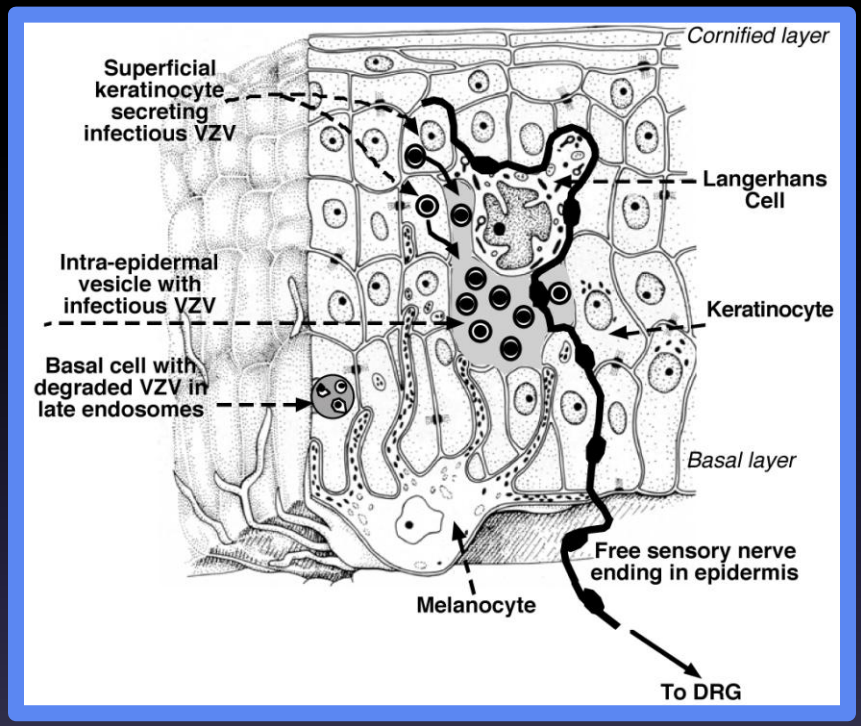
In the body VZV spreads from cell-to-cell

- In varicella, VZV is transported from the respiratory mucosa (tonsils) to the blood in T cells (viremia), where virus is not accessible to antibodies.
  - Because of cell-to-cell spread, and innate immune responses, early viral spread is slow, so the incubation period of varicella is long (~2 weeks).
  - Slow spread prevents host from being overwhelmed before the adaptive immune response develops
- T helper (TH1) and cytotoxic T cells are required for host control of virus by adaptive immunity

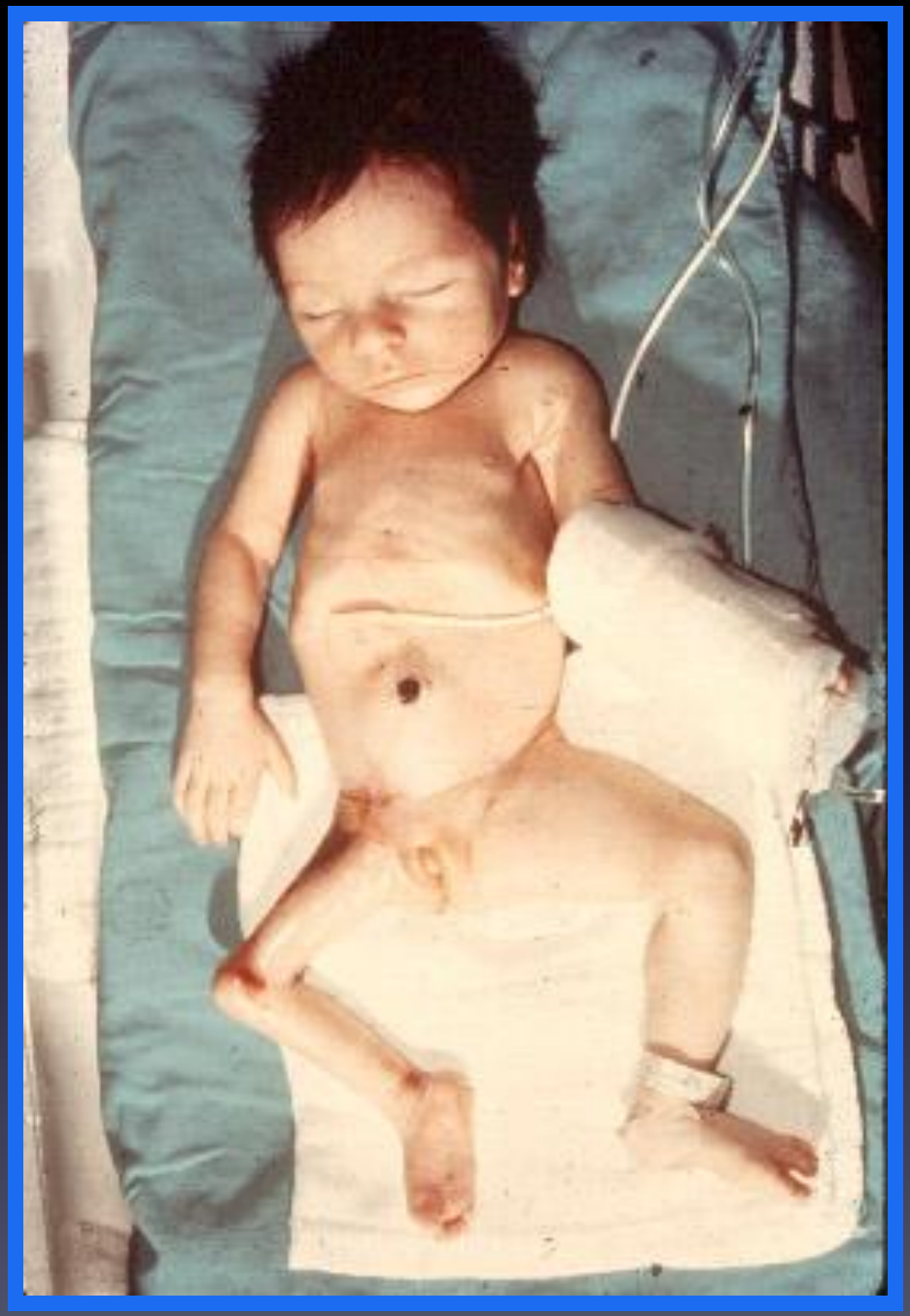
VZV spreads in two ways



VZV is highly cell-associated but spreads in two ways



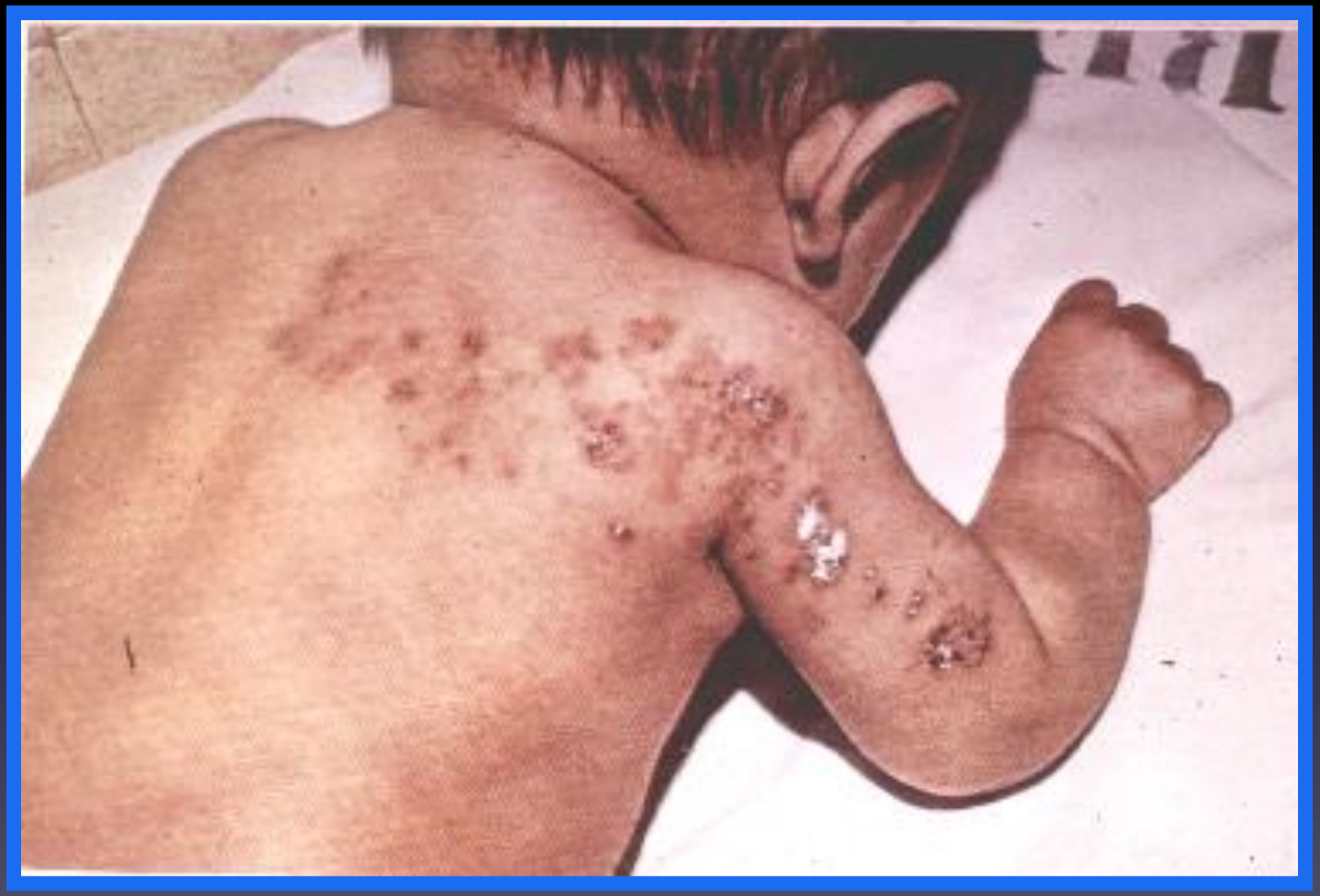
VZV latency is established by free virions that infect sensory nerve endings, and also by viremia



Congenital varicella syndrome

Fatal neonatal varicella

Zoster in a 3 month old



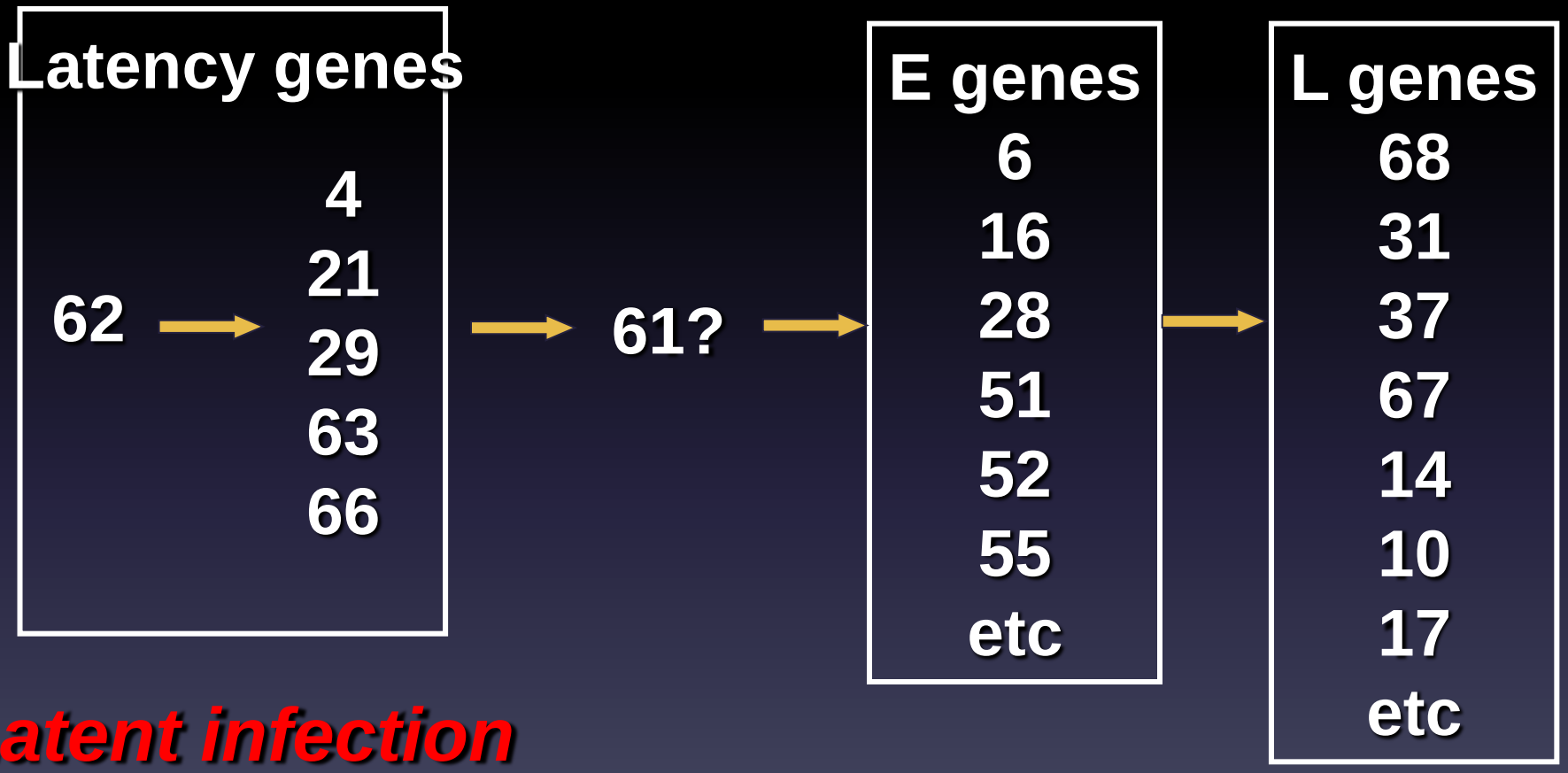
VZV In the Immunocompromised

- Varicella is likely to be severe
  - Prevent or modify with pre-formed antibodies just after exposure (VZIG)
  - Virus spreads from cell-cell in body
    - requires CMI (cellular immunity) for host defense
  - Treat most immunocompromised patients immediately with acyclovir
- The frequency of zoster is increased
  - Probably related to low CMI response
  - Likely to suffer post-herpetic neuralgia (PHN) (also elderly)

Latent Infection with VZV

- VZV becomes latent in DRG, CNG, enteric ganglia (ENS)
- 6 of 68 genes (also RNA and proteins) are expressed during latency
- Suggests regulatory proteins are blocked from normal action, leading to inhibition of cascade of gene expression preventing lytic infection from occurring (latency)
- Latency is established when cell-free VZV in skin vesicles invades neurons and also by viremia

Gene expression in latent & lytic VZV infection



Hay and Ruyechan, Semin Virol 1994

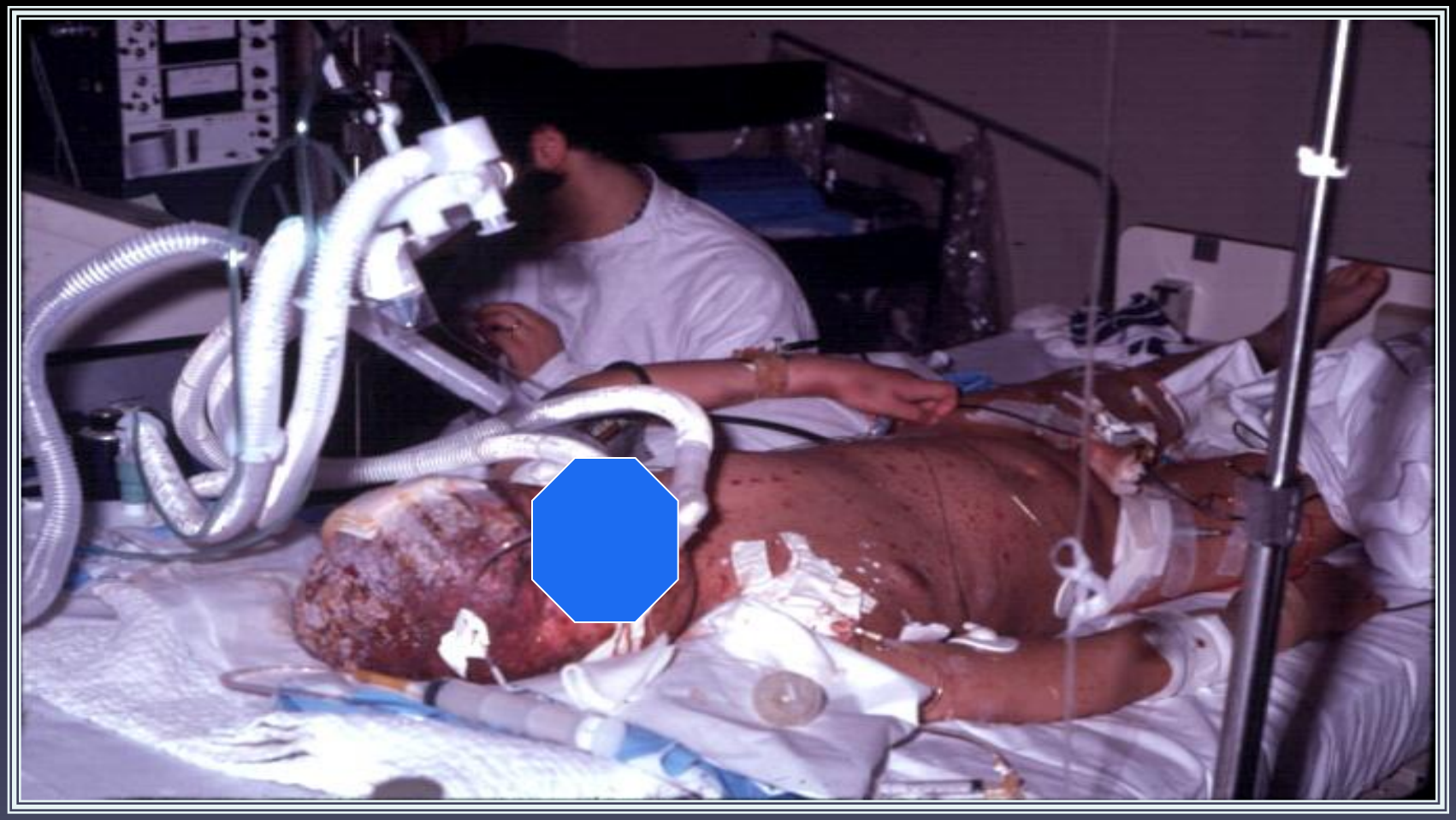
Varicella Vaccine and Zoster Vaccine

- Same vaccine (Oka strain) is used to prevent VZV primary infection (varicella) and reactivation (HZ)
  - Dose of VZV is 15 times greater in HZ vaccine than in varicella vaccine
  - HZ vaccine for those over age 50 years is a therapeutic vaccine
  - Mechanism of action for HZ vaccine: stimulate CMI to VZV
- VZV becomes latent in DRG, CNG, enteric ganglia (ENS) after varicella vaccine

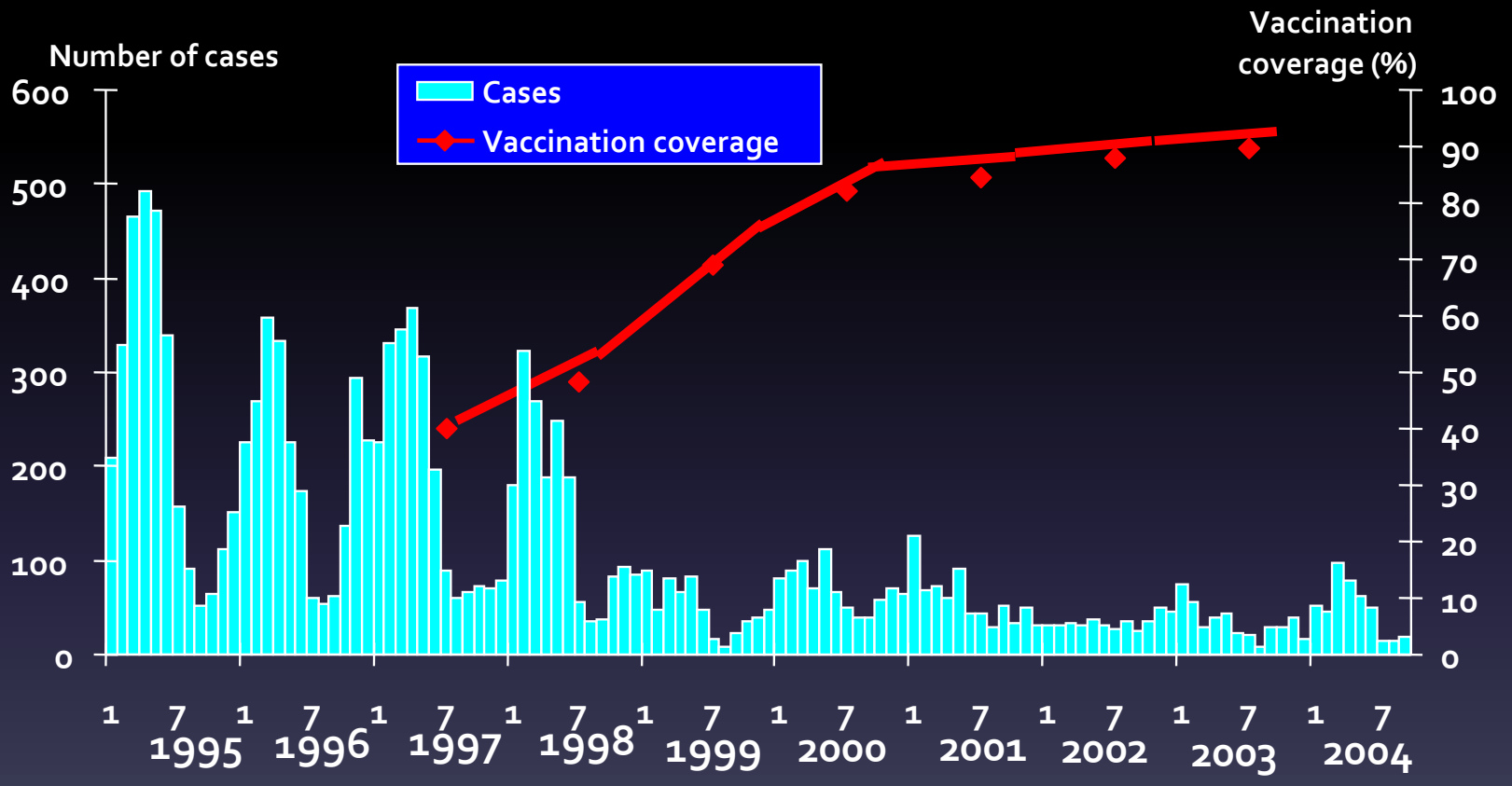
Varicella Vaccine (Oka)

- Live attenuated vaccine
- Most common complaint: mild rash in 5%
  - 1 month after vaccination; transmission rare
- Vaccine extremely safe; given as 2 doses
  - 1 dose: 85% completely protected; 15% partial immunity
  - 2 doses 98% effective in preventing varicella disease
- Little evidence for waning immunity
- Subsequent zoster is rare/unusual

Varicella in Immunocompromised Children May Be Fatal



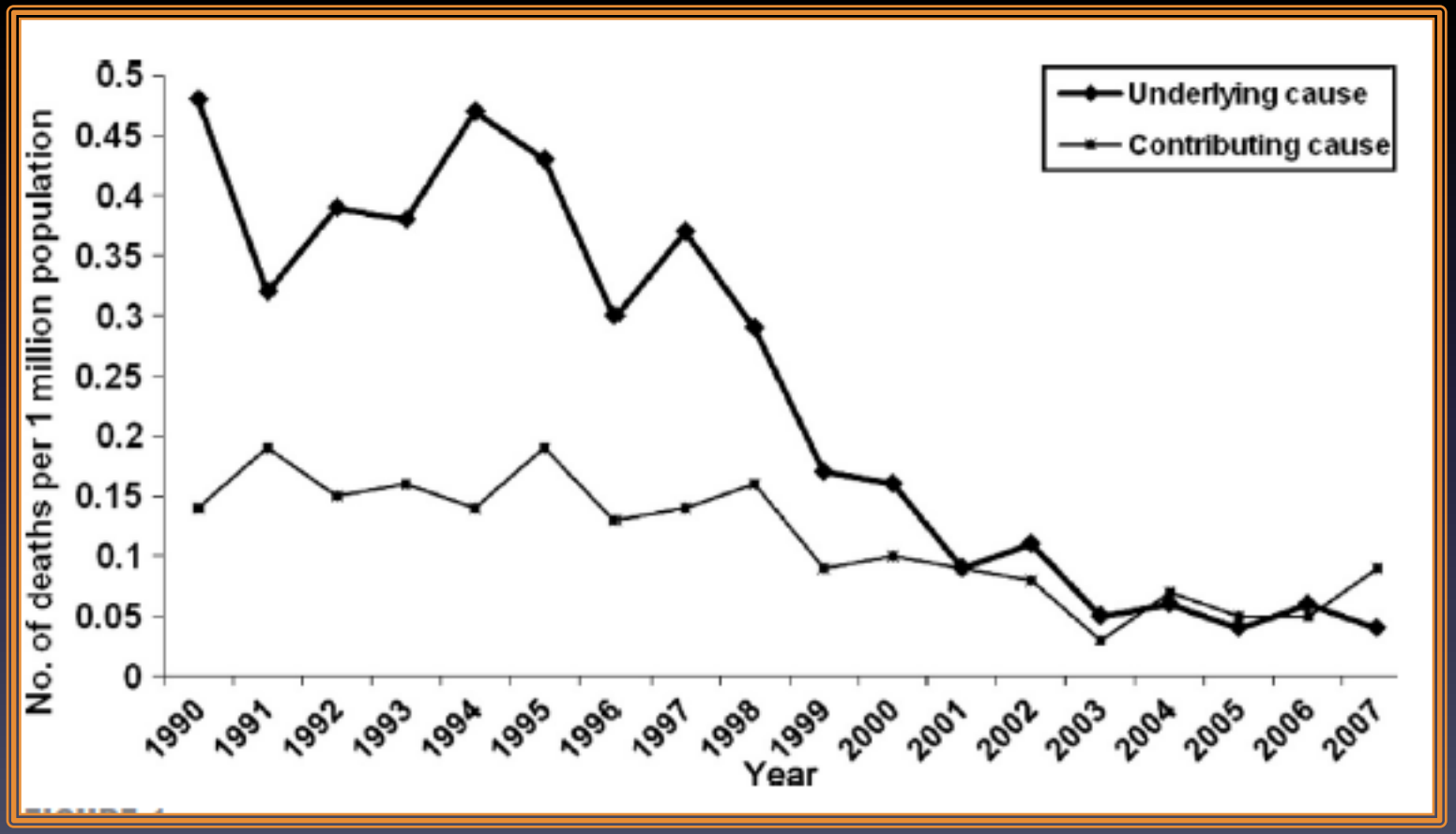
Reported Varicella and Annual Vaccine Coverage Antelope Valley* CA, U.S., 1995-2004



*Varicella Active Surveillance Project site

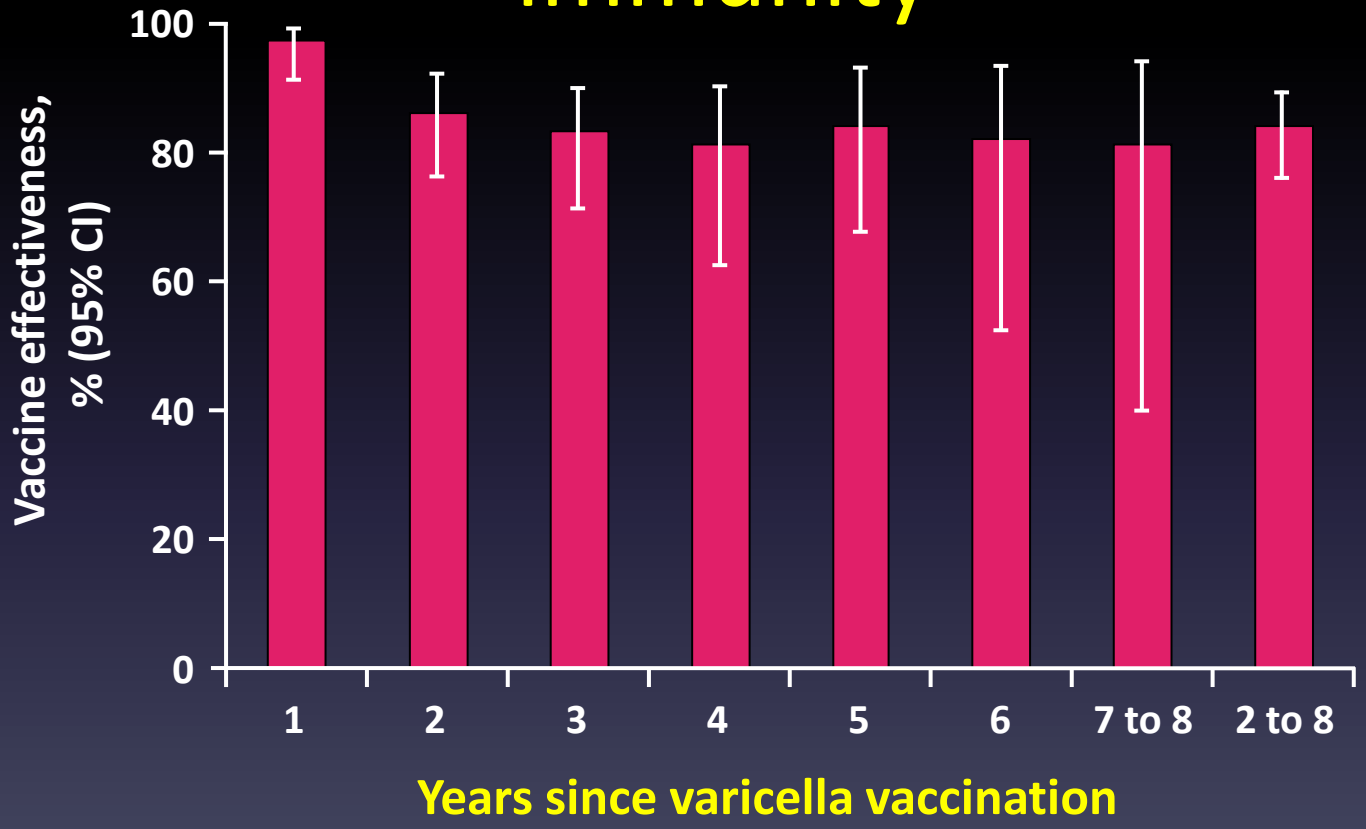
Seward J et al, JAMA 2002;287 (5):606-611 (data through 2000)

Varicella-related mortality rates in the United States, 1990 –2007



Marin et al, Pediatrics, 2011

Varicella vaccine effectiveness over time (case-control study): little or no waning of immunity



Adapted from Vásquez et al. *JAMA* 2004;291:851-855. Yale-Columbia study

Two Vaccine Doses Were Highly Effective in a Case Control Study

Number of doses received	Cases, N = 71 (%)	Controls, N = 140 (%)	p value
0 doses	**5** (7)	**1** (0.8)	
1 dose	66 (93)	117 (83.6)	
2 doses	**0 (0.0)**	22 (15.7)	**< 0.001**

The effectiveness of 2 doses of varicella vaccine vs 1 dose was 98.3%

Shapiro et al. JID 2011; Yale-Columbia Study

Numerous factors regarding VZV seem important for varicella vaccine's success

- Varicella has an incubation period of 2-3 weeks
- Early innate immune responses in skin (Arvin) and

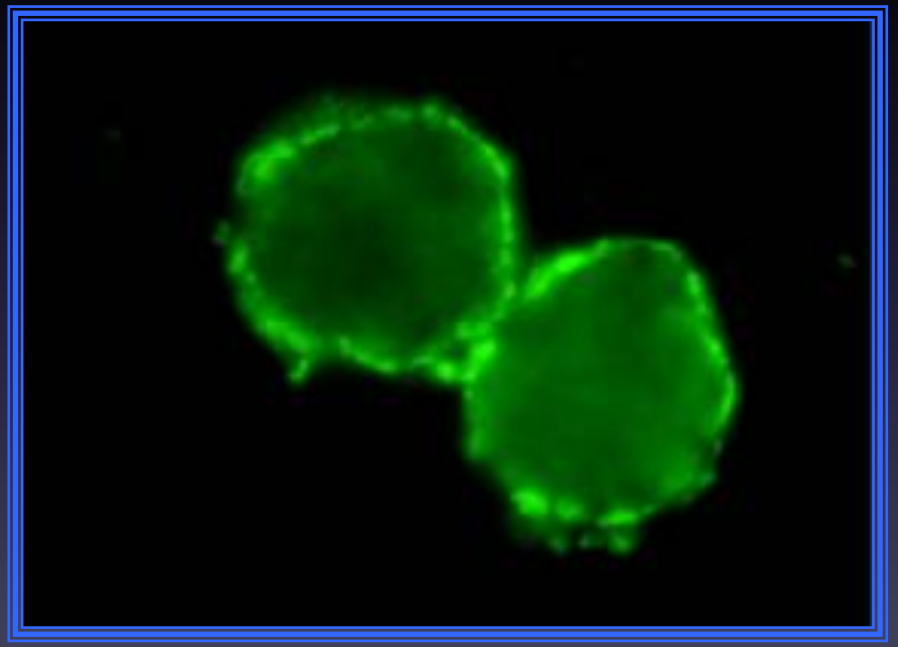
  cell-to –cell spread slow viral multiplication
- Viremia results in infection of organs
- VZV immune evasion occurs but is not well developed
- Can distinguish between vaccine and wild type VZVs
- Availability of an immune correlate for varicella (FAMA)
- Live attenuated vaccine

FAMA is the "gold standard" for assessment of varicella immunity (immune correlate)

In persons with a titer of ≥1:4,

fewer than 2% develop varicella after a household exposure (n=131)

Attack rate after household exposure in persons with a titer of <1:4 is 59% (n=68)



Michalik et al. *J Infect Dis*. 2008

VZV DNA can be identified as WT or vOka

Amplify ORFs 54, 38 look for Bgl1, Pst1

vOka is Bgl1+, Pst1-

US WT is Bgl1-/+, Pst1+

ORF 62, position 106262

- Oka has Sma1 site, WT does not
- sequencing of the segment 106035-106303 to determine whether T (WT) or C (Oka) is present at position 106262
- also positions 10811, 105705, and (107252) (Quinlivan JCM, 2012)

The incidence of zoster in vaccinees is low

Adult incidence extremely low (0.9/1000 person-years) (P-Y) (Hambleton JID 2008)

Lower rates in leukemic vaccinees than in leukemics after natural infection (4 studies in 1980s)

Healthy vaccinated children: 0.3/1000 P-Y; risk decreased ~4 times (Tseng 2008, Civen, 2009: PIDJ)

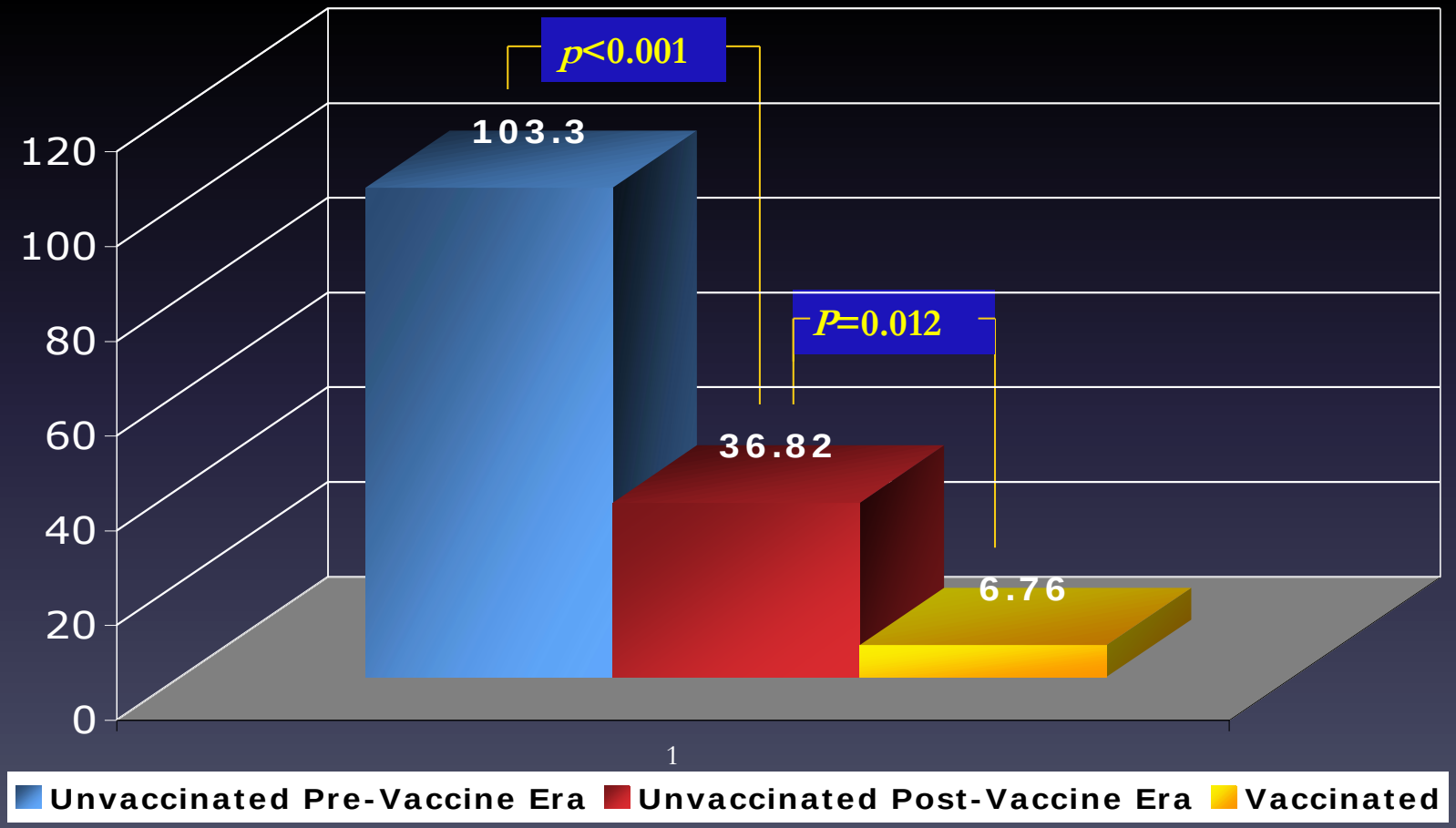
1/3 of cases are due to wild type virus

Rate of zoster in vaccinated HIV-infected children

no cases reported

Vaccination Prevents Varicella in HIV-infected children

Rate Per 1000 person years



Vaccination Prevents Zoster in HIV-infected Children

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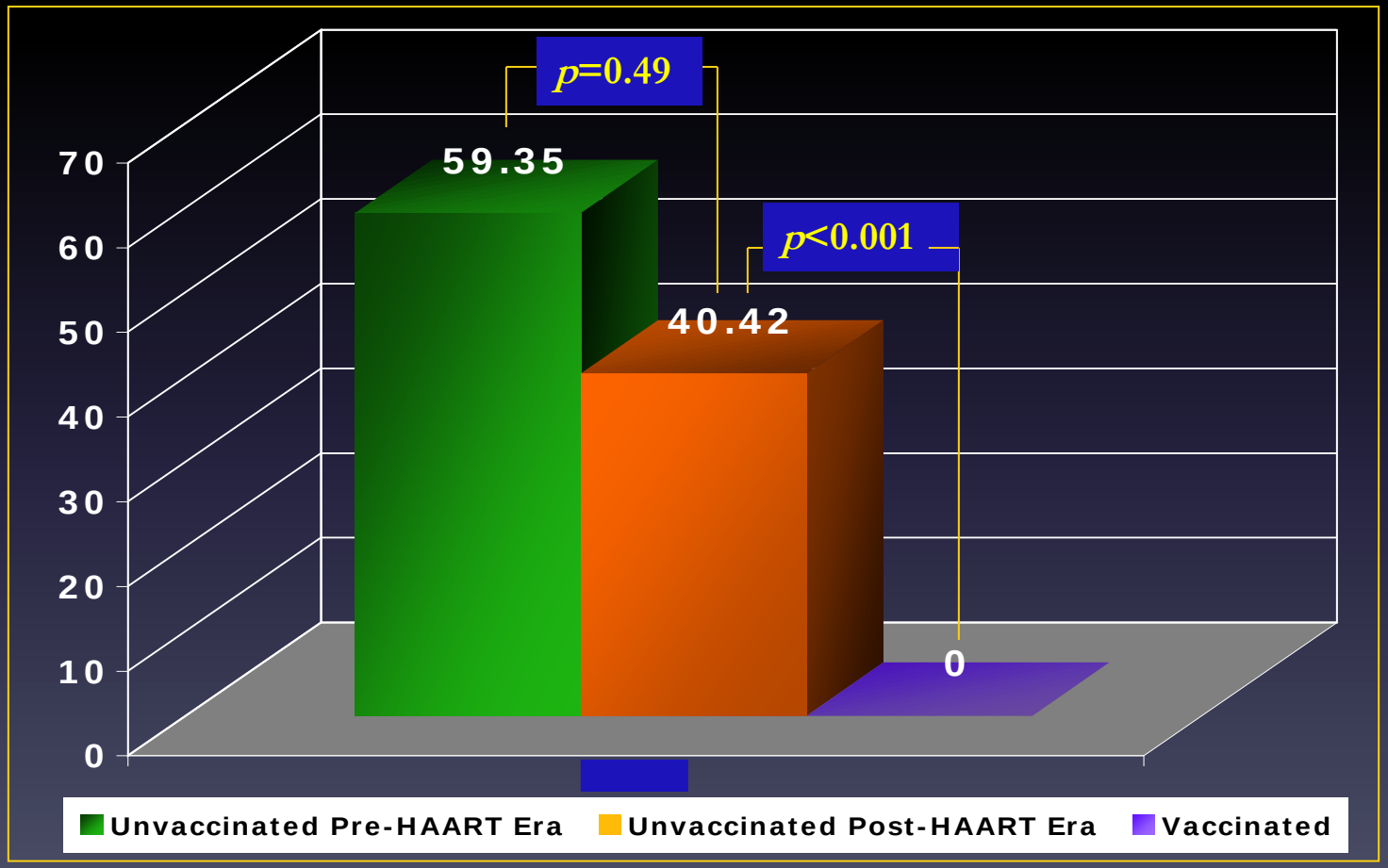


Sensory ganglia were obtained from autopsied children

- Autopsies were performed on 9 children soon after death (mean: 17.0 ± 1.5 hrs). 2/9 controls; 6/9 vaccinated

Age (yrs)	Vaccination	Cause of Death
1 (control)	no	seizure
1 (control)	no	MVA
1.75	yes	?
2	yes	?
2	yes	MVA
2	?	?
4	yes	MVA
8	yes	Gunshot
10	yes	Operative comp

Gershon et al, Transactions of the American Clinical and Climatological Association, 2012

No VZV DNA or RNA was found (PCR) in patients who were ≤ 1 year old and lacked history of varicella and VZV vaccination*

Patient	Trigeminal		Cervical		Thoracic		Lumbar	
Age	Right	Left	Right	Left	Right	Left	Right	Left
1	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0

DNA examined: ORF 4, 31, 63, 68; RNA examined: ORF 4, 29, 62, 63

* These patients were considered to be controls.

Latent VZV (DNA/RNA) was found (PCR) in ganglia at multiple levels

Distribution of VZV DNA/RNA in ganglia of vaccinated patients.

Patient		Trigeminal		Cervical		Thoracic		Lumbar		
Age	Vac	Right	Left	Right	Left	Right	Left	Right	Left	Type
1.75	Y	0	0	0	0	0	+	+	0	Oka
2	Y	0	0	0	0	+	0	+	0	WT
2	?	+	+	0	0	+	0	0	+	WT
2	Y	+	+	+	+	+	+	+	+	WT
4	Y	0	0	+	+	+	+	+	0	WT
8	Y	0	0	0	0	+	0	0	0	WT
10	Y	+	+	0	0	+	0	+	0	WT

DNA detected: ORF 4, 62. 63, 68; RNA detected: ORF 4, 29, 62, 63

Severe varicella vaccine reactions are rare *estimate 100 million doses distributed*

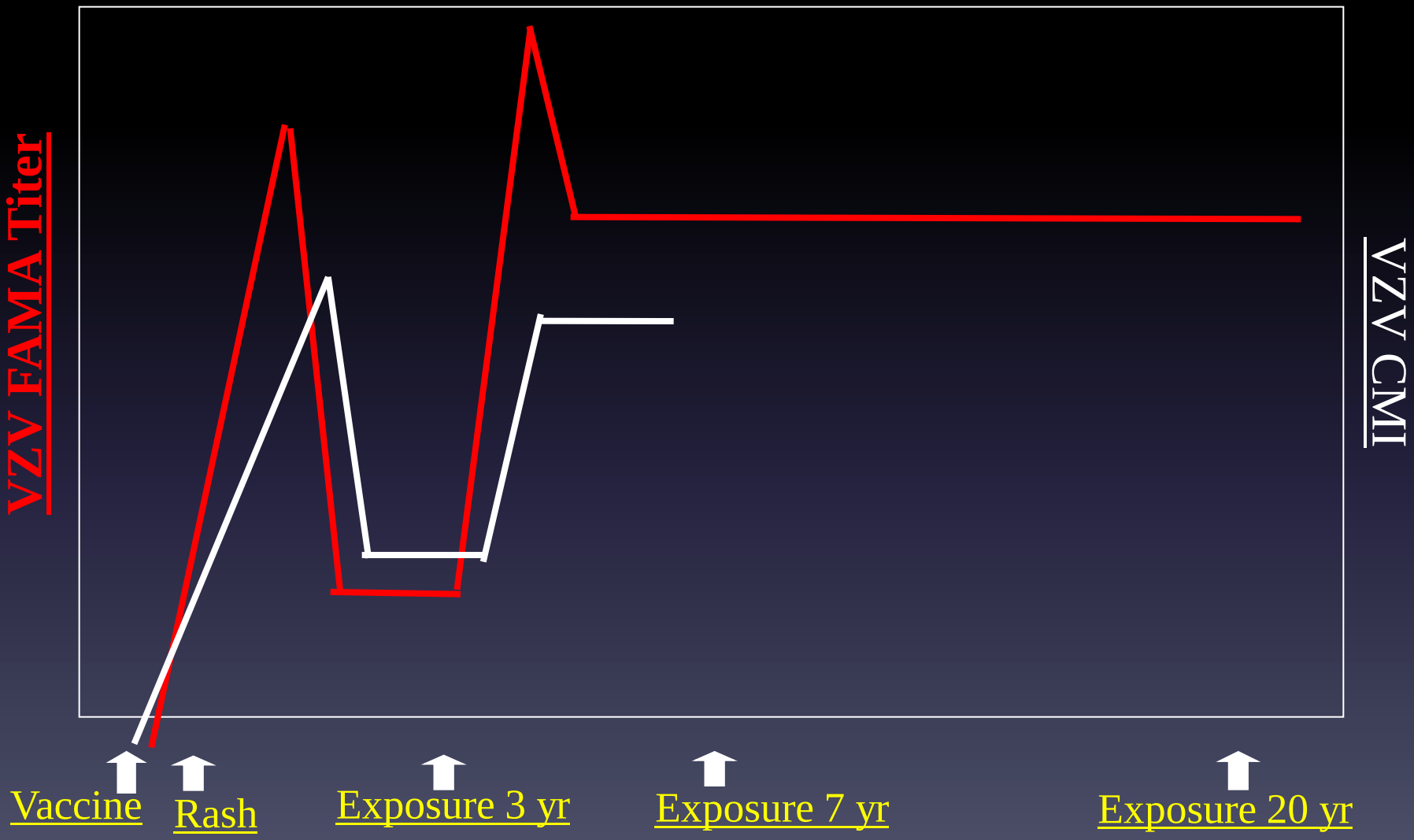
- 19 yo w cholangitis, lymphopenia
- 13 mo w undiagnosed ADA deficiency
- 16 mo w undiagnosed HIV and 8 CD_4 cells per mm3
- 5 yo w asthma, steroids
- 6 yo, 11 yo w undiagnosed NK cell deficiency (2 patients)
- 8 yo w Di George syndrome
- 24 yo hypopuitarism on steroids
- 3 yo w acute leukemia
- HZ with meningitis, ACV, and recovery with no sequelae (9)
  - Vaccination, cancer, severe zoster (2)
- 16 yo with VZV ulcer; VZV reactivation in ENS

VZV RNA is found in surgical specimens of gut from patients with a history of varicella or vaccination

ORF	4	29	31*	61*	62	63	66	68*	Total
varicella	4/6	0/6	0/6	0/6	0/6	5/6	1/6	0/6	6/6
%	67%	0	0	0	0	83%	17%	0	100%
vaccine	4/7	0/7	0/7	0/7	2/7	6/7	1/7	0/7	6/7
%	57%	0	0	0	29%	86%	14%	0	86%
No VZV	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
%	0	0	0	0	0	0	0	0	0%

- The transcripts that were detected were latency-associated
- Transcripts encoding proteins that were characteristic of lytic infection (31, 61,68) were absent

Immune Responses to VZV in an Adult Vaccinee



Will the incidence of zoster increase in the unvaccinated?

- Modeling predicted doubling of incidence of zoster for next 40 years, increased mortality: (2-4 to 4-8/1000 p-y)
- A number of studies show increase in zoster (since 1950s)
- Other recent studies show stable rates
- No diagnostic standardization
- Lack of good baseline data on incidence in pre-vaccine era
- Need to consider impact of other variables such as increasing age of population, immunocompromising illnesses, diabetes, stress
- Recent French study showed same incidence of HZ in isolated populations and general public (Gilliat et al, CID 2011)
- Asymptomatic reactivation may stimulate immunity to VZV

VZV DNA has been detected in saliva after space flight

Mehta et al (2004) detected VZV in saliva of astronauts after space flight despite absence of overt zoster.

VZV DNA Shedding In saliva (PCR)	Before	During	After	None
Astronauts (8)	1% +	30% +	30% +	
Controls (10) Sampled multiple times	0	0	0	0

Comments and Conclusions

- Varicella is a disease worth preventing
- Varicella vaccine is safe and effective in healthy hosts and as 2 doses
- When studies with varicella vaccine were initiated, its success in preventing disease was not really predicted (GAS); many said varicella was too mild a disease to be worth preventing
- In the early 1980s it was underappreciated that HZ could be prevented by vaccination
  - Recent information on HZ complications such as vasculopathy (Gilden) makes preventing HZ even more compelling
- Many investigators thought the vaccine would not work well because of viral latency; however lack of sterilizing immunity (reinfection and reactivation) have not presented a serious obstacle to success of VZV vaccines