

Excerpts from peer-reviewed abstracts concerning breakthrough varicella disease among vaccinees and the importance of exogenous re-exposures

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Abstract

When the varicella vaccine was licensed by the Food and Drug Administration (FDA) on March 17, 1995, cost-benefit analyses previously performed concerning the universal varicella vaccination program assumed there would be no deleterious effects on the closely related herpes zoster (shingles, HZ) epidemiology and that a single dose would confer life-long immunity. Physicians debated whether or not outside or exogenous exposures to varicella played a significant role in boosting cell-mediated immunity to help suppress the reactivation of HZ. As early as 1965, Dr. Hope-Simpson suggested that the curve of increasing HZ incidence with advancing age might have some correlation to the “frequency with which the different age groups encounter cases of varicella.” Several epidemiological studies in recent years have demonstrated such a correlation.
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Keywords: breakthrough varicella, herpes zoster, cell-mediated immunity (CMI)

1. Chickenpox outbreak in a highly vaccinated school population. (*Pediatrics*. 2004 Mar;113(3 Pt 1):455–9; Tugwell BD, Lee LE, Gillette H, Lorber EM, Hedberg K, Cieslak PR)

“... Students vaccinated >5 years before the outbreak were 6.7 times (95% confidence interval: 2.2–22.9) as likely to develop breakthrough disease as those vaccinated less than or equal to 5 years before the outbreak (15 of 65 [23%] vs 3 of 87 [3%]). ... Students vaccinated >5 years before the outbreak were at risk for breakthrough disease. Booster vaccination may deserve additional consideration.”

2. *What does epidemiology tell us about risk factors for herpes zoster?* (*Lancet Infect Dis*, 2004 Jan.; 4(1):26–33; Thomas SL, Hall AJ. Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK.)

“Reactivation of latent varicella zoster virus as herpes zoster is thought to result from waning of specific cell-mediated immunity... Risk factors identified in analytical studies that could explain this variation included age, sex, ethnicity, genetic susceptibility, **exogenous boosting of immunity from varicella contacts**, underlying cell-mediated immune disorders, mechanical trauma, psychological stress, and immunotoxin exposure. Our review highlights the lack of information about risk factors for zoster...”

3. *Varicella vaccination in England and Wales: cost-utility analysis*. (*Arch Dis Child*. 2003 Oct;88(10):862–9; Brisson M, Edmunds WJ. Immunisation Division, PHLS Communicable Disease Surveillance Centre, London NW9 5EQ, UK.)

“The model predicts that although the overall burden of varicella will significantly be reduced following mass infant vaccination, these benefits will be offset by a significant rise in zoster morbidity. ... **CONCLUSION:** Routine infant varicella vaccination is unlikely to be cost-effective and may produce an increase in overall morbidity. Adolescent vaccination is the

safest and most cost-effective strategy, but has the least overall impact on varicella.”

4. *Incidence of herpes zoster among children and adolescents in a community with moderate varicella vaccination coverage*. (*Vaccine*. 2003 Oct 1;21(27-30):4243–9; Goldman GS. P.O. Box 847, 93553, Pearblossom, CA, USA)

“... The true ascertainment-adjusted HZ incidence rate is 307 per 100,000 person-years among children <10. The unadjusted HZ rate among vaccinated children is 9.5 per 100,000 person-years and an estimated 22 per 100,000 vaccine doses. Unvaccinated children with a previous history of varicella may have greater sensitivity to exogenous exposures (boosting) and a poorer cell-mediated response following primary infection relative to older age groups.”

5. *Varicella vaccine—are two doses better than one?* (*N Engl J Med*, 2002 Dec 12; 347(24):1962–3; Gershon AA. Columbia University College of Physicians and Surgeons)

“... In this study, however, a longer interval between vaccination and exposure was associated with an increased risk. This association is particularly disquieting, because the phenomenon suggests that immunity may wane with time after immunization—the vaccinologist’s nightmare. ... The time for exploring the possibility of routinely administering two doses of varicella vaccine to children seems to have arrived.”

6. *Younger age at vaccination may increase risk of varicella vaccine failure*. (*J Infect Dis*. 2002 Jul 1;186(1):102–5. Epub 2002 Jun 05; Galil K, Fair E, Mountcastle N, Britz P, Seward J. Centers for Disease Control and Prevention, Atlanta, GA 30333, USA)

“... There were 41 cases of varicella among 131 attendees, with 14 cases (34%) among vaccinated children. VE was 79% against all varicella and 95% against moderate or severe varicella. Vaccination at <14 months was associated with an increased risk of breakthrough disease (relative risk, 3.0; 95%

confidence interval, 0.9-9.9). Despite varicella vaccination coverage of 80%, a sizeable outbreak occurred. Early age at vaccination may increase the risk of vaccine failure.”

7. *Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox.* (Vaccine. 2002 Jun 7;20(19-20):2500–7; Brisson M, Gay NJ, Edmunds WJ, Andrews NJ. Immunisation Division, PHLS Communicable Disease Surveillance Centre, London, UK.)

“We present data to confirm that exposure to varicella boosts immunity to herpes-zoster. We show that exposure to varicella is greater in adults living with children and that this exposure is highly protective against zoster (Incidence ratio=0.75, 95% CI, 0.63-0.89). ... Mass varicella vaccination is expected to cause a major epidemic of herpes-zoster, affecting more than 50% of those aged 10-44 years at the introduction of vaccination.”

8. *Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study.* (Lancet. 2002 Aug 31;360(9334):678–82. Thomas SL, Wheeler JG, Hall AJ. Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.)

“...Social contacts with many children outside the household and occupational contacts with ill children were associated with graded protection against zoster, with less than a fifth the risk in the most heavily exposed groups compared with the least exposed. ... INTERPRETATION: Re-exposure to varicella-zoster virus via contact with children seems to protect latently infected individuals against zoster. Reduction of childhood varicella by vaccination might lead to increased incidence of adult zoster. ...”

9. *Outbreak of varicella at a day-care center despite vaccination.* (N Engl J Med. 2002 Dec 12;347(24):1909–15. Galil K, Lee B, Strine T, Carraher C, Baughman AL, Eaton M, Montero J, Seward J. Centers for Disease Control and Prevention, Atlanta, USA.)

“In seven studies of the effectiveness of the varicella vaccine conducted since it was licensed, the effectiveness was 71 to 100 percent against disease of any severity and 95 to 100 percent against moderate and severe disease. We investigated an outbreak of varicella in a population of children with a high proportion of vaccinees who were attending a day-care center in a small community in New Hampshire.... The effectiveness of the vaccine was 44.0 percent (95 percent confidence interval, 6.9 to 66.3 percent) against disease of any severity and 86.0 percent (95 percent confidence interval, 38.7 to 96.8 percent) against moderate or severe disease. Children who had been vaccinated three years or more before the outbreak were at greater risk for vaccine failure than those who had been vaccinated more recently (relative risk, 2.6 [95 percent confidence interval, 1.3 to 5.3]). ...A longer interval since vaccination was associated with an increased risk of vaccine failure. Breakthrough infections in vaccinated, healthy persons can be as infectious as varicella in unvaccinated persons.”

10. *Evidence for frequent reactivation of the Oka varicella vaccine strain in healthy vaccinees.* (Arch Virol Suppl.

2001;(17):7–15; Krause PR. Laboratory of DNA Viruses, Division of Viral Products, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland 20892, USA)

“Pre-licensure clinical studies showed that mean serum anti-VZV levels among vaccinees continued to increase with time after vaccination. This was attributed to immunologic boosting caused by exposure to wild-type VZV in the community.”

11. *Lasting immunity to varicella in doctors study.* (L.I.V.I.D. study). (J Am Acad Dermatol. 1998 May;38(5 Pt 1):763–5; Solomon BA, Kaporis AG, Glass AT, Simon SI, Baldwin HE. Department of Dermatology, State University of New York Health Science Center at Brooklyn, USA.)

Physicians, pediatricians (who have a greater incidence of exposure to VZV) were reported to have lower rates of HZ than psychiatrists (who had the lowest VZV exposure rates).

12. *Universal vaccination against varicella* [Correspondence]. (N Engl J Med, 1998 Mar 5; 338(10):683; Spingarn RW, Benjamin JA, Meissner HC)

“It is unknown whether long-term immunity to varicella arises from an attack of the disease in childhood or from the virus's repeatedly (and naturally) boosting immunity because it is maintained in our communities. ... Yet policies of universal vaccination of children [against chickenpox] will serve, over time, to eradicate most, but not all, naturally occurring [chickenpox] and its immeasurable booster effect.”

13. *Varicella-zoster virus.* (Clin Microbiol Rev. 1996 Jul;9(3):361–81; Arvin AM. Department of Pediatrics, Stanford University School of Medicine, California 94305-5119, USA)

“These responses may persist because of periodic reexposures of immune individuals to VZV during the annual varicella epidemics. This mechanism of exogenous reexposure is supported by the observation that VZV is detected by PCR in oropharyngeal secretions of close contacts of patients with varicella.”

14. *The protective effect of immunologic boosting against zoster: an analysis in leukemic children who were vaccinated against chickenpox.* (J Infect Dis. 1996 Feb;173(2):450–3; Gershon AA, LaRussa P, Steinberg S, Mervish N, Lo SH, Meier P. Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, New York 10032, USA)

“... A Kaplan-Meier life-table analysis revealed that the incidence of zoster was lower in those given > 1 dose of vaccine (P < .05). A Cox proportional hazards analysis showed that both household exposure to varicella and receipt of > 1 dose of vaccine were highly protective (P < .01) against zoster. Thus, the risk of zoster is decreased by reexposure to varicella-zoster virus, either by vaccination or by close exposure to varicella.”

15. *Incidence of herpes zoster in pediatricians and history of reexposure to varicella-zoster virus in patients with herpes zoster.* (Kansenshogaku Zasshi. 1995 Aug;69(8):908–12 Article in Japanese. Terada K, Hiraga Y, Kawano S, Kataoka N. Department of Pediatrics, Kawasaki Medical School)

“We found that pediatricians have enhanced specific cellular immunity to varicella-zoster virus (VZV) compared with the general population, which may be due to reexposure to VZV from children with chickenpox...The incidence per 100,000 person-years of herpes zoster was 65.2 in those in their fifties and 158.2 in those in their sixties, which are 1/2 to 1/8 of other reports regarding the general population. ... We may think that the booster effect by reexposure to VZV plays an important role to prevent herpes zoster. Therefore, we can speculate that the varicella vaccine may protect against herpes zoster in the elderly by the enhanced specific cellular immunity due to the booster effect.”

16. *Cell-mediated immunity to varicella-zoster virus.* (J Infect Dis. 1992 Aug;166 Suppl 1:S35–41; Arvin AM. Department of Pediatrics, Stanford University School of Medicine, California)

“Exogenous reexposure to VZV results in enhanced T cell proliferation and may be an important mechanism for maintaining virus-specific cellular immunity. Providing exogenous reexposure by giving varicella vaccine to individuals who have preexisting natural immunity markedly increases the responder cell frequencies of T cells that proliferate in response to VZV antigen and the numbers of circulating CTL that recognize VZV proteins.”

17. *The epidemiology of varicella-zoster virus infections: the influence of varicella on the prevalence of herpes zoster.* (Epidemiol Infect, 1992 Jun; 108(3):513–28; Garnett GP, Grenfell BT. Department of Animal and Plant Sciences, Sheffield University)

“...However, new analysis of data collected by the Royal College of General Practitioners provides indirect evidence for the hypothesis that a high intensity of varicella transmission suppresses viral reactivation. ...Under some conditions, mass application of such vaccines may have the impact of increasing zoster incidence. The results presented here indicate that, before

starting any vaccination programme against varicella, its consequences need to be assessed in much more depth. “

18. *Epidemiology of chickenpox in England and Wales, 1967-85.* (Br Med J (Clin Res Ed). 1988 Mar 5;296(6623):673–6; Joseph CA, Noah ND. Public Health Service Communicable Disease Surveillance Centre, London)

“Using the Royal College of General Practitioners (RCGP) data set in England, a notable decrease in zoster incidence was reported in children following a varicella epidemic in the winter of 1980.”

19. *Immunologic evidence of reinfection with varicella-zoster virus.* (J Infect Dis. 1983 Aug;148(2):200–5; Arvin AM, Koropchak CM, Wittek AE)

“Resistance to reinfection with varicella-zoster virus (VZV) was evaluated in immune adults who had household exposure to varicella. Sixty-four percent of 25 adults exposed to varicella had a fourfold or greater rise in IgG antibody to VZV or had a high initial IgG antibody titer to VZV that declined by fourfold. IgM antibody was detected in only 12% of 25 VZV-immune subjects. Seventy percent of 23 subjects exposed to varicella had IgA antibody to VZV compared with 13% of 23 subjects with antibody to VZV who had no recent exposure (P less than 0.001, chi 2 test). ... The increase in immunity to VZV in many immune subjects exposed to VZV suggests the occurrence of subclinical reinfection.”

20. *The Nature of Herpes Zoster: a long-term study and a new hypothesis.* (Proc R Soc Med. 1965 Jan;58:9–20; Hope Simpson RE)

“The peculiar age distribution of zoster may in part reflect the frequency with which the different age groups encounter cases of varicella and, because of the ensuing boost to their antibody production have their attacks of zoster postponed.”