

Selected references:

WHO Position Paper on Varicella Vaccines, (WER March 1998)

Epidemiology and disease

Fairley CK, Miller E. Varicella-zoster virus epidemiology - a changing scene? J Infect Dis. 1996 Nov;174 Suppl 3:S314-9.

Chickenpox is a relatively mild disease in healthy children but may be life threatening in immuno-suppressed patients, neonates, and normal adults, especially smokers-for whom the risk of varicella pneumonia is high. The epidemiology of chickenpox appears to be changing: There has been an unexplained upward shift in the age distribution of cases over the last 20 years. This is reflected by increased consultations for chickenpox in general practices and more deaths in England and Wales. On the basis of hospital admissions for chickenpox in young adults, there is evidence of a similar trend in the United States. This epidemiologic change has important consequences for future mortality rates and for risk of infection in health care workers and pregnant women. The potential use of the varicella vaccine should be considered as a measure to reduce the risk of nosocomial transmission in view of the possible changing epidemiology of varicella.

Drwal-Klein LA, O'Donovan CA. Varicella in pediatric patients. Ann Pharmacother. 1993 Jul-Aug;27(7-8):938-49.

OBJECTIVE: To summarize the literature describing the epidemiology, transmission, clinical manifestations, diagnosis, treatment, and prevention of varicella in the pediatric population. **DATA SOURCES:** A literature search of English-language articles from 1982 to 1992 using MEDLINE and bibliographies of relevant articles. The search term used was varicella. **STUDY SELECTION:** All review articles and original studies addressing the epidemiology, transmission, clinical manifestations, complications, diagnosis, treatment, and prevention of varicella in pediatric patients were reviewed. Emphasis was placed on controlled studies done in the US. **DATA EXTRACTION:** Data from human studies were extracted by the authors and evaluated according to patient population, sample size, dosing regimen, efficacy, and safety. **DATA SYNTHESIS:** Varicella-zoster virus is a highly contagious virus that produces a common and costly disease in the pediatric population. The primary manifestation of varicella is the eruption of vesicular lesions. In most cases varicella is benign, but it can be associated with serious complications. Diagnosis is based primarily on clinical findings. Otherwise healthy children have traditionally received only symptomatic treatment for varicella, but recent literature suggests that antiviral therapy may be useful in these patients. Immunocompromised patients benefit from both symptomatic and antiviral therapy. Isolation and varicella-zoster immune globulin are used to prevent varicella. In the future, varicella vaccine will play an important role in preventing the disease. Varicella vaccine has been shown to be immunogenic and clinically effective in both

healthy and immunocompromised children. Adverse reactions associated with the vaccine include fever, injection-site reactions, and rash. Although zoster can follow vaccination, the incidence appears to be lower in vaccinated individuals. Preliminary studies have shown that the vaccine provides protection from varicella-zoster virus for an extended period of time. **CONCLUSIONS:** Varicella is a common, usually benign disease of childhood. All patients may benefit from symptomatic therapy. Current literature does not support the use of antiviral therapy in all pediatric patients with varicella. When commercially available, varicella vaccine will play an important role in prevention. Long-term studies are needed to fully assess the risk of developing varicella and zoster following vaccination.

Enders G, Miller E, Cradock-Watson J, Bolley I, Ridehalgh M. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. Lancet. 1994 Jun 18;343(8912):1548-51

In a joint prospective study in Germany and the United Kingdom between 1980 and 1993, 1373 women who had varicella and 366 who had herpes zoster during the first 36 weeks of gestation were followed up. 9 cases of congenital varicella syndrome were identified, all occurring after maternal varicella during the first 20 weeks of gestation. The highest risk (2.0%) was observed between 13-20 weeks gestation, with 7 affected infants identified among 351 pregnancies (95% CI of risk 0.8-4.1%). Only 2 cases of congenital varicella syndrome were identified among 472 pregnancies in which maternal varicella occurred before 13 weeks (observed risk 0.4%, 95% CI 0.05-1.5%). Herpes zoster in infancy was reported in 10 children whose mothers had had varicella in pregnancy. No infants with clinical evidence of intrauterine infection were born to the 366 women with herpes zoster in pregnancy (upper 95% confidence limit of estimated risk 1.0%). Varicella-zoster-specific IgM antibody was found at birth in 4 of 16 (25%) infants with clinical manifestations of intrauterine infection and persistent specific IgG antibody in 5 of 7 infants tested. The corresponding rates in asymptomatic infants whose mothers had varicella were 12% (76/615) and 7% (22/335) respectively. No serological evidence of intrauterine infection was found in infants whose mothers had herpes zoster in pregnancy. In 97 pregnant women, varicella occurred after post-exposure prophylaxis with anti-varicella-zoster immunoglobulin. No cases of congenital varicella syndrome or zoster in infancy occurred in this group. Our estimates provide a sound basis for counselling women with varicella in pregnancy. Although the risk of congenital varicella syndrome is small, the outcome for the affected infant is so serious that a reliable method of prenatal diagnosis would be valuable. In the long term, prevention of maternal varicella would be an option if a safe and effective vaccine were to become routinely available.

Preblud SR. Varicella: complications and costs. Pediatrics. 1986 Oct;78(4 Pt 2):728-35.

Varicella (chickenpox) has long been considered a benign, inevitable disease of childhood. Complications are generally mild and rarely severe, and virtually every individual is infected by adulthood. Infection is associated, however, with a high risk

of serious complications in certain high-risk groups, such as leukemic children. Concerns about the severity of varicella in this population have led to the development and testing of a live, attenuated vaccine. Because of the favorable results thus far available, the vaccine may soon be licensed for use in high-risk individuals. The fact that a vaccine may soon be available has led to an increased interest in the potential benefits of a childhood varicella vaccine program. The costs associated with varicella infection in normal persons without a varicella vaccination program have been estimated to be approximately \$400 million, 95% of which is the cost of caring for a child at home. Vaccination of normal 15-month-old children with a safe and effective vaccine with long-lasting immunity could reduce the cost by 66% and result in a savings of \$7 for every dollar spent on the vaccination program. This assumes that vaccine would be administered only once with measles, mumps, and rubella vaccine, that there would be no increase in the number of varicella cases in older persons who are at increased risk for complications, and that there would be no deleterious effect on the occurrence and severity of herpes zoster.(ABSTRACT TRUNCATED AT 250 WORDS)

The vaccine

Vaccine development

Takahashi M. The varicella vaccine. Vaccine development. Infect Dis Clin North Am. 1996 Sep;10(3):469-88

In this article, rationales and method of development of attenuated live varicella (Oka) vaccine are described, with biologic and biophysical characteristics of the vaccine virus. The results of early clinical trials in Japan are also described, along with the results of detection of viremia in vaccinees and a follow-up of incidence of zoster in acute leukemic children, which indicate possible immunopathogenesis of varicella and zoster.

Immunological aspects

Nader S, Bergen R, Sharp M, Arvin AM. Age-related differences in cell-mediated immunity to varicella-zoster virus among children and adults immunized with live attenuated varicella vaccine. J Infect Dis. 1995 Jan;171(1):13-7.

Live attenuated varicella vaccine elicits protection against varicella-zoster virus (VZV), but adults require two doses to achieve optimal seroconversion rates. To assess the potential role of cell-mediated immunity (CMI), T cell proliferation to VZV antigen was compared in children and adults. Mean stimulation indices (SI) in two cohorts of 39 children tested 6 weeks after vaccination were 28.6 +/- 6.21 and 22.1 +/- 3.84, whereas 20 adult vaccinees had a mean SI of 9.1 +/- 0.99 (P = .04). Vaccinees had significant increases in CMI after a second dose of vaccine. At 1 year, VZV CMI was significantly lower in adults after two doses (10.0 +/- 1.13 vs.

15.6 +/- 1.77; P = .02), even though 82% of children received one dose. Limitations in the adult helper T cell response to VZV antigens may explain the need for booster doses to elicit effective immunity and the more frequent occurrence of varicella when adult vaccines are exposed to wild type virus.

Bogger-Goren S, Baba K, Hurley P, Yabuuchi H, Takahashi M, Ogra PL. Antibody response to varicella-zoster virus after natural or vaccine-induced infection. J Infect Dis. 1982 Aug;146(2):260-5

The development of serum and nasopharyngeal antibody responses to varicella-zoster virus (VZV) was studied in groups of children after naturally acquired varicella or after immunization with the Oka strain of live attenuated VZV vaccine administered in varying doses via respiratory inhalation or subcutaneous injection. Natural infection, subcutaneous immunization, and respiratory inhalation of large doses of VZV vaccine consistently resulted in the development of VZV-specific IgG antibody responses in serum. Although the serum IgG antibody responses persisted for at least eight to 12 months (to date) after either form of infection, the antibody activity appeared to be four- to eight-fold higher after natural infection than after immunization. Transient IgG antibody responses were observed in serum after respiratory inhalation of smaller doses of VZV vaccine. Natural infection, but not VZV vaccine, was associated with the development of serum and nasopharyngeal IgA responses to VZV in most subjects.

Watson B, Gupta R, Randall T, Starr S. Persistence of cell-mediated and humoral immune responses in healthy children immunized with live attenuated varicella vaccine. J Infect Dis. 1994 Jan;169(1):197-9.

Two hundred fourteen healthy seronegative children immunized with various doses of Oka/Merck varicella vaccine were studied for persistence of varicella-zoster virus (VZV)-specific lymphocyte proliferation and antibodies to VZV as determined by a glycoprotein (gp) ELISA. Of the 140 vaccinees tested for VZV-specific lymphocyte proliferation, 94% had positive responses, with a mean stimulation index of 8.9 (range, 3.0-44.6). Of 214 tested by gpELISA, 95% were positive for up to 6 years after immunization; the geometric mean titer was 30.2 (range, 1.3-3510.0). Of 122 individuals tested both by ELISA and for VZV-specific lymphocyte proliferation, 91% had persistence of both responses. Persistence of cellular and humoral immune responses in a large percentage of vaccinees for up to 6 years after immunization with Oka/Merck varicella vaccine suggests that protection against severe varicella is likely to be similarly long-lasting.

Efficacy, safety, and duration of protection

André FE. Worldwide experience with the Oka-strain live varicella vaccine. Postgrad Med J. 1985;61 Suppl 4:113-20.

Sufficient safety and efficacy data have been obtained on a live varicella vaccine (Varilrix, Smith Kline-RIT) derived from the Oka-strain attenuated varicella-zoster virus to justify its recent licensure in several European countries for use in special indication groups. This review article summarizes the data obtained in Japan, Europe, and the United States. In addition, a survey of the published literature on clinical studies performed on as yet unlicensed Oka-strain varicella vaccines produced by the Biken Institute and Merck Sharp & Dohme is presented.

Asano Y. Varicella vaccine: the Japanese experience. J Infect Dis. 1996 Nov;174 Suppl 3:S310-3

Varicella vaccine developed by the Biken Institute (Osaka, Japan) was administered to 1.39 million subjects in Japan and 1.93 million in Korea between 1987 and 1993. Six years after licensure, it was assessed for safety and efficacy under the regulatory requirements of the Japanese government. Clinical symptoms were reported in 6.9% (580/8429) of vaccines (mostly healthy children) and seroconversion in 91.5% (2347/2565), and the mean antibody titer 1 month after immunization was 12.2. Despite 100 well-documented contacts with varicella patients, only 2 (2%) developed breakthrough varicella with very mild clinical features within 12 months of vaccination. Immunologic tests in 26 recipients showed presence of humoral and cellular immunities to varicella-zoster virus (VZV) for > or = 20 years. These data indicate that this live attenuated varicella vaccine provides long-term protective immunity against VZV infection.

Ramkissoon A, Coovadia HM, Jugnundan P, Haffejee IE, Meurice F, Vandevoorde D. Immunogenicity and safety of a live attenuated varicella vaccine in healthy Indian children aged 9-24 months. S Afr Med J. 1995 Dec;85(12):1295-8

OBJECTIVES. To investigate the safety of live attenuated varicella vaccine (Oka strain) and the optimal virus titre/dose required for immunogenicity in healthy South African children. **DESIGN.** Double-blind randomised clinical study using two different lots of varicella vaccine, each at two different titres. Subjects were randomly allocated to groups 1, 2, 3 and 4 to receive vaccine containing a mean virus titre of 10(4,5), 10(3,1), 10(3,9) and 10(2,7) PFUs per dose respectively. Clinical signs and symptoms were followed up for 42 days post-vaccination. Specific varicella antibodies were measured by an indirect immunofluorescence method in sera obtained on day 0 and day 42. **SETTING.** City Health Clinic, Chatsworth, Durban. **PARTICIPANTS.** A total of 200 healthy 9-24-month-old children were vaccinated, of whom 189 (44,5%) completed the study. **MAIN OUTCOME MEASURES.** Pre- and post-vaccination varicella antibody levels. Adverse events following varicella vaccination. **RESULTS.** The vaccine was safe and well tolerated. No local symptoms were reported. Skin reactions were specifically solicited in this study: 21 reactions were reported in 8.5% (17/200) of children. Vesicles were reported in 2 vaccines (< or = 10 vesicles in both cases). One serious adverse event was reported: hospitalisation for bronchopneumonia on day 16 post-vaccination which resolved without sequelae. Around day 42 post-vaccination

(range 35-63 days) all the 176 initially seronegative subjects had seroconverted for varicella antibodies. Post-vaccination geometric mean titres (GMTs) were 104.1, 66.2, 69.5 and 77.0 for groups 1-4 respectively. Six subjects who were initially seropositive maintained or increased their titres post-vaccination; 3 of the 6 showed a booster response (a > or = 4-fold increase from the pre-vaccination titre).

CONCLUSIONS. Varicella vaccine was found to be safe, immunogenic and well tolerated. No difference in seroconversion rates or GMTs, either between groups receiving the two vaccine lots or between groups receiving the different titres of each lot, was shown.

Naganuma Y, Osawa S, Takahashi R. Clinical application of a live varicella vaccine (Oka strain) in a hospital. Biken J. 1984 Sep;27(2-3):59-61

A total of 239 children, including 22 high-risk children and 55 non-high risk diseased children have been immunized with a live varicella vaccine (Oka strain) since June, 1978. No clinical reaction attributable to the vaccine has been observed. Of these children, 87 received emergency vaccination. Of 47 children receiving emergency vaccination because they had been in contact with varicella patients either in hospital, school or a playground, only 5 developed varicella and their symptoms were mild. Of 40 children receiving emergency vaccination because of exposure to varicella in their home, 10 developed mild varicella and 30 were protected. Clinical symptoms of varicella when seen seemed to be due to incomplete protection because the vaccine was given too late rather than to clinical reactions to the vaccine. During follow-up period of 6 to 66 months after vaccination, 8 children showed very mild rashes without fever as the result of exogenous varicella infection.

Ngai AL, Staehle BO, Kuter BJ, Cyanovich NM, Cho I, Matthews H, Keller P, Arvin AM, Watson B, White CJ. Safety and immunogenicity of one vs. two injections of Oka/Merck varicella vaccine in healthy children. Pediatr Infect Dis J. 1996 Jan;15(1):49-54

OBJECTIVE: To compare the safety and immunogenicity of a one- vs. two-dose regimen of Oka/Merck varicella vaccine in approximately 2000 healthy children 12 months to 12 years of age. **METHODOLOGY:** Subjects with a negative history of varicella were randomized to receive either one or two injections of the vaccine given 3 months apart and were followed for clinical reactions and serologic response (glycoprotein-based enzyme-linked immunosorbent assay). **RESULTS:** Both one- and two-dose vaccine regimens were generally well-tolerated. The incidences of varicelliform rash and fever were less frequent after the second injection. However, a slight increase in the incidence of injection site reactions was noted after the second injection; these were generally mild. Seroconversion rates by glycoprotein-based enzyme-linked immunosorbent assay were 98.2% (1700 of 1731) after one injection and 99.9% (717 of 718) after two injections. A significant ($P < 0.001$) boost in geometric mean titers was observed in children who received a second injection of vaccine 3 months after the first injection. Of the children who seroconverted at 6 weeks postregimen (one or two doses as assigned), 99.8% (528 of

529) of the one-dose group and 99.8% (473 of 474) of the two-dose group maintained antibody to varicella at 1 year with geometric mean titers of 19.5 and 31.2, respectively. **CONCLUSIONS:** Administration of a one- or two-dose regimen of the live Oka/Merck varicella vaccine (VARIVAX) is immunogenic and is generally well-tolerated in healthy children 1 to 12 years old. Antibody to varicella persists in > 99% of vaccinees 1 year after vaccination regardless of a one- or two-dose regimen. Long-term follow-up studies of this cohort of children may determine whether a two-dose regimen offers superior protection against chickenpox.

Varis T, Vesikari T. Efficacy of high-titer live attenuated varicella vaccine in healthy young children. J Infect Dis. 1996 Nov;174 Suppl 3:S330-4

The efficacy of a high-titer, reformulated varicella vaccine was studied in 513 10- to 30-month-old children. Vaccinees were randomly allocated to 5 groups to receive one of two lots of an original high-titer vaccine, one of two lots of a partially heat-inactivated vaccine, or placebo. Both vaccines were well tolerated. Seroconversion was detected in 100% and 99% of children immunized with the high- and low-titer vaccines, respectively. Sixty-five cases of serologically confirmed varicella-like disease were discovered during follow-up (mean, 29.3 months): 5 in the high-titer vaccine group, 19 in the low-titer vaccine group, and 41 in the placebo group ($P < .005$ for each difference). Thus, the protective efficacy of live attenuated varicella vaccine is dependent on vaccine titer. High-titer varicella vaccine induces excellent protection in healthy young children.

Watson BM, Laufer DS, Kuter BJ, Staehle B, White CJ, Starr SE. Safety and immunogenicity of a combined live attenuated measles, mumps, rubella, and varicella vaccine (MMR(II)V) in healthy children. J Infect Dis. 1996 Mar;173(3):731-4.

An investigational tetravalent combined measles, mumps, rubella, and varicella vaccine and measles-mumps-rubella and varicella vaccines at separate injection sites given at the same visit were evaluated with respect to safety and cell-mediated and humoral immune responses at 6 weeks and 1 year after vaccination. Varicella seroconversion rates and lymphocyte proliferation responses were 100% for both vaccine groups at 6 weeks and 1 year. However, the antibody titer to varicella was lower in the combined vaccine group at 6 weeks, but there was no statistical difference in cell-mediated immune responses. One-year geometric mean titers were not statistically different. Seroconversion rates for measles, mumps, and rubella were 100% for both vaccine at 6 weeks and 1 year. Long-term follow-up of these immune responses is planned.

Gershon AA, Steinberg S, Galasso G, Borkowsky W, Larussa P, Ferrara A, Gelb L. Live attenuated varicella vaccine in children with leukemia in remission. Biken J. 1984 Sep;27(2-3):77-81

One-hundred-ninety-one children with acute leukemia in remission for at least one year were immunized with 1 or more doses of live attenuated varicella vaccine. All were susceptible to varicella prior to vaccination. The only significant side effect was mild to moderate rash, seen especially in children with maintenance chemotherapy temporarily suspended for one week before and one week after vaccination. Children with rash were at some risk (10%) to transmit vaccine virus to varicella susceptibles with whom they had close contact.

Ferguson NM, Anderson RM, Garnett GP. Mass vaccination to control chickenpox: the influence of zoster. Proc Natl Acad Sci U S A. 1996 Jul 9;93(14):7231-5

The impact of transmission events from patients with shingles (zoster) on the epidemiology of varicella is examined before and after the introduction of mass immunization by using a stochastic mathematical model of transmission dynamics. Reactivation of the virus is shown to damp stochastic fluctuations and move the dynamics toward simple annual oscillations. The force of infection due to zoster cases is estimated by comparison of simulated and observed incidence time series. The presence of infectious zoster cases reduces the tendency for mass immunization to increase varicella incidence at older ages when disease severity is typically greater.

Prevention of varicella: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention. MMWR Recomm Rep. 1996 Jul 12;45(RR-11):1-36.

[No authors listed]

These recommendations represent the first statement by the Advisory Committee on Immunization Practices (ACIP) on the use of live, attenuated varicella virus vaccine--VARIVAX--manufactured by Merck and Company, Inc. and licensed in March 1995 for use in healthy persons \geq 12 months of age. In addition to presenting information regarding vaccine, this statement updates previous recommendations concerning the use of varicella zoster immune globulin (VZIG) as prophylaxis against varicella.

Cost-Effectiveness

Lieu TA, Cochi SL, Black SB, Halloran ME, Shinefield HR, Holmes SJ, Wharton M, Washington AE. Cost-effectiveness of a routine varicella vaccination program for US children. JAMA. 1994 Feb 2;271(5):375-81

OBJECTIVE--To evaluate the economic consequences of a routine varicella vaccination program that targets healthy children. METHODS--Decision analysis was used to compare the costs, outcomes, and cost-effectiveness of a routine vaccination program with no intervention. Clinical outcomes were based on a

mathematical model of vaccine efficacy that relied on published and unpublished data and on expert opinion. Medical utilization rates and costs were collected from multiple sources, including the Kaiser Permanente Medical Care Program and the California Hospital Discharge Database. RESULTS--A routine varicella vaccination program for healthy children would prevent 94% of all potential cases of chickenpox, provided the vaccination coverage rate is 97% at school entry. It would cost approximately \$162 million annually if one dose of vaccine per child were recommended at a cost of \$35 per dose. From the societal perspective, which includes work-loss costs as well as medical costs, the program would save more than \$5 for every dollar invested in vaccination. However, from the health care payer's perspective (medical costs only), the program would cost approximately \$2 per chickenpox case prevented, or \$2500 per life-year saved. The medical cost of disease prevention was sensitive to the vaccination coverage rate and vaccine price but was relatively insensitive to assumptions about vaccine efficacy within plausible ranges. An additional program for catch-up vaccination of 12-year-olds would have high incremental costs if the vaccination coverage rate of children of preschool age were 97%, but would result in net savings at a coverage rate of 50%. CONCLUSIONS--A routine varicella vaccination program for healthy children would result in net savings from the societal perspective, which includes work-loss costs as well as medical costs. Compared with other prevention programs, it would also be relatively cost-effective from the health care payer's perspective.