Varicella and Herpes Zoster Vaccination Position Paper – June 2014

References with abstracts cited in the position paper (alphabetical order)

Asano Y et al. Experience and reason: twenty-year follow-up of protective immunity of the Oka strain live varicella vaccine. Pediatrics. 1994;94(4 Pt 1):524-526.

Since the first report on the development of a live attenuated varicella vaccine in 1974, the vaccine has been studied extensively, with largely favorable results, in both healthy and leukemic children. It is now licensed in Japan, Korea, and some European countries, and is being considered for licensure in the United States. Although various clinical trials have established the safety, immunogenicity, and the efficacy of the vaccine, concern has been expressed that waning immunity in the vaccine recipients might allow the occurrence of more severe varicella later in life. We show data relevant to this concern on the approximately 20-year follow-up study of the vaccine recipients; this work further extends the experience of a long-term protective efficacy of the vaccine.

Asano Y et al. Long-term protective immunity of recipients of the OKA strain of live varicella vaccine. Pediatrics. 1985;75(4):667-671.

In spite of close contacts with patients who had varicella, 101 of 106 (95%) healthy and sick children (142 of 147 (97%) exposures of these children) who had received the OKA strain of live varicella vaccine 7 to 10 years earlier were protected against the disease completely. Among them, 37 of 38 (97%) vaccine recipients who received immunologic testing had varicella-zoster virus (VZV) antibodies tested by fluorescent antibody to membrane antigen method with a geometric mean titer of 1:9.3, and 37 of the 38 (97%) showed positive skin reaction to varicella-zoster virus antigen with erythema (mean diameter 13.4 mm). These findings were compared with those for 29 children who had contracted typical varicella 7 to 10 years earlier, whose seropositive rate was 100% with a geometric mean titer of 1:10.5, and 97% of whom (28/29) had positive skin reaction with mean diameter of 12.9 mm. These results indicate that the vaccine-induced protective immunity persists for approximately one decade and is almost equal to the long-term immunity following natural infection.

Background paper on herpes zoster vaccines- SAGE working group http://www.who.int/immunization/sage/meetings/2014/april/presentations_background_docs/en/accessed: 11.04.2014

Background paper on varicella vaccines- SAGE working group http://www.who.int/immunization/sage/meetings/2014/april/presentations_background_docs/en/ accessed: 11.04.2014

Baxter R et al. Long-term Effectiveness of Varicella Vaccine: A 14-Year, Prospective Cohort Study. Pediatrics.2013; Vol. 131 No. 5. pp. e1389 -e1396

BACKGROUND: Varicella vaccine was licensed in the United States in 1995 for individuals ≥12 months of age. A second dose was recommended in the United States in June 2006. Varicella incidence and vaccine effectiveness were assessed in a 14-year prospective study conducted at Kaiser Permanente Northern California. METHODS: A total of 7585 children vaccinated with varicella vaccine in their second year of life in 1995 were followed up prospectively for breakthrough varicella and herpes zoster (HZ) through 2009. A total of 2826 of these children received a second dose in 2006–2009. Incidences of varicella and HZ were estimated and compared with prevaccine era rates.

RESULTS: In this cohort of vaccinated children, the average incidence of varicella was 15.9 per 1000 person-years, nine- to tenfold lower than in the prevaccine era. Vaccine effectiveness at the end of the study period was 90%, with no indication of waning over time. Most cases of varicella were mild and occurred early after vaccination. No child developed varicella after a second dose. HZ cases were mild, and rates were lower in the cohort of vaccinated children than in unvaccinated children during the prevaccine era (relative risk: 0.61 [95% confidence interval: 0.43–0.89]). CONCLUSIONS: This study confirmed that varicella vaccine is effective at preventing chicken pox, with no waning noted over a 14-year period. One dose provided excellent protection against moderate to severe disease, and most cases occurred shortly after the cohort was vaccinated. The study data also suggest that varicella vaccination may reduce the risks of HZ in vaccinated children.

Bayer O et al. Metaanalysis of vaccine effectiveness in varicella outbreaks. Vaccine. 2007;25(37-38):6655-6660

There is a number of reports on varicella outbreaks in populations where a one dose varicella immunization program has been implemented. We performed a metaanalysis to provide a summary vaccine effectiveness (VE) estimate and to assess the possible impact of waning immunity by means of a subgroup analysis by time since immunization. We found a VE of 72.5% (95% CI 68.5–76.0) derived from 3157 children in 14 publications. Immunization coverage of the respective population was unrelated to VE. All studies (n = 4) that allowed the computation of VE over time since immunization showed a substantial decrease. In total, waning immunity was assessed by nine studies. Two reported no relation between VE and time since immunization without specifying how this had been assessed. Seven studies calculated relative risks for contracting varicella after prolonged as compared to a shorter period since immunization and reported an increased relative risk for prolonged periods. In conclusion, this metaanalysis confirms a limited effectiveness of one dose of varicella vaccine and points to waning immunity as an important causal factor. Waning might also be an issue with the newly recommended two dose vaccination schedule. Sustained surveillance for varicella outbreaks in populations with varicella immunization programs therefore is mandatory.

Brisson M et al. Modelling the impact of immunization on the epidemiology of varicella zoster virus. Epidemiol Infect 2000;125(December (3)):651–69.

The objective of this study was to develop and apply a dynamic mathematical model of VZV transmission to predict the effect of different vaccination strategies on the age-specific incidence and outcome of infection. To do so a deterministic realistic age-structured model (RAS) was used which takes account of the increased potential for transmission within school aged groups. Various vaccine efficacy scenarios, vaccine coverages and vaccination strategies were investigated and a sensitivity analysis of varicella incidence predictions to important parameters was performed. The model predicts that the overall (natural and breakthrough) incidence and morbidity of varicella would likely be reduced by mass vaccination of 12-month-old children. Furthermore, adding a catch-up campaign in the first year for 1-11 year olds seems to be the most effective strategy to reduce both varicella incidence and morbidity (in the short and long term), though with the possible detrimental effect of increasing the incidence of zoster.

Brisson M et al. The potential impact of varicella vaccination in low to middle income countries: A feasibility modeling study. Report to the SAGE working group on varicella and herpes zoster vaccines.

A dynamic transmission model was constructed to inform SAGE recommendations for varicella vaccination in low and middle income countries (LMIC). The model suggests that in most LMICs there is a high risk of shifts in the age at infection and increased mortality following 1-dose vaccination

when coverage is between 20% and 80%. Furthermore, vaccination coverage must be greater than about 60% to produce substantial reductions in morbidity. However, LMIC with very low seropositivity (less than 20-30% in 20 year olds) and the highest burden of disease are expected to have little to no shifts in the age at infection and important reductions in varicella-related mortality and morbidity, at intermediate levels of vaccination coverage. The Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC) found the model to be appropriate. Areas of future work to strengthen the model and thus conclusions include capturing uncertainties in seroprevalence data, case-fatality ratios and morbidity estimates. In terms of data needs, better information is required on varicella incidence and morbidity in LMICs. Future research will focus on extending the work to calculate cost-effectiveness of vaccination.

Brisson M. Economic Evaluation of Vaccination Programmes: A special reference to varicella vaccination. PhD thesis, Health Economics, City University, London, UK 2004.

Brunell PA et al. Zoster in infancy: failure to maintain virus latency following intrauterine infection. The Journal of pediatrics. 1981;98(1):71-73.

Chaves SS et al. Loss of vaccine-induced immunity to varicella over time. N Engl J Med. 2007; 356:1121-1129

BACKGROUND: The introduction of universal varicella vaccination in 1995 has substantially reduced varicella-related morbidity and mortality in the United States. However, it remains unclear whether vaccine-induced immunity wanes over time, a condition that may result in increased susceptibility later in life, when the risk of serious complications may be greater than in childhood. METHODS: We examined 10 years (1995 to 2004) of active surveillance data from a sentinel population of 350,000 subjects to determine whether the severity and incidence of breakthrough varicella (with an onset of rash >42 days after vaccination) increased with the time since vaccination. We used multivariate logistic regression to adjust for the year of disease onset (calendar year) and the subject's age at both disease onset and vaccination. RESULTS: A total of 11,356 subjects were reported to have varicella during the surveillance period, of whom 1080 (9.5%) had breakthrough disease. Children between the ages of 8 and 12 years who had been vaccinated at least 5 years previously were significantly more likely to have moderate or severe disease than were those who had been vaccinated less than 5 years previously (risk ratio, 2.6; 95% confidence interval [CI], 1.2 to 5.8). The annual rate of breakthrough varicella significantly increased with the time since vaccination, from 1.6 cases per 1000 person-years (95% CI, 1.2 to 2.0) within 1 year after vaccination to 9.0 per 1000 person-years (95% CI, 6.9 to 11.7) at 5 years and 58.2 per 1000 person-years (95% CI, 36.0 to 94.0) at 9 years. CONCLUSIONS: A second dose of varicella vaccine, now recommended for all children, could improve protection from both primary vaccine failure and waning vaccine-induced immunity.

Chaves SS et al. Safety of varicella vaccine after licensure in the United States: experience from reports to the vaccine adverse event reporting system, 1995-2005. The Journal of infectious diseases. 2008;197 Suppl 2:S170-177.

Widespread use of varicella vaccine in the United States could enable detection of rare adverse events not identified previously. We reviewed data from 1995 to 2005 from the Vaccine Adverse Event Reporting System, including data from laboratory analyses, to distinguish adverse events associated with wild-type varicella-zoster virus (VZV) versus those associated with vaccine strain. Almost 48 million doses of varicella vaccine were distributed between 1995 and 2005. There were 25,306 adverse events reported (52.7/100,000 doses distributed); 5.0% were classified as serious (2.6/100,000 doses distributed). Adverse events associated with evidence of vaccine-strain VZV included meningitis in patients with concurrent herpes zoster. Patients with genetic predispositions

may rarely have disease triggered by receipt of varicella vaccine. Overall, serious adverse events reported after varicella vaccination continue to be rare and must be considered relative to the substantial benefits of varicella vaccination. Ongoing safety surveillance and further studies may shed light on some of the hypothesized associations.

Derryck A et al. Varicella and zoster in children with human immunodeficiency virus infection. The Pediatric infectious disease journal. 1998;17(10):931-933.

Edmunds WJ et al. Effect of Vaccination on the Epidemiology of Varicella Zoster Virus. Journal of Infection (2002) 44:211-219

Varicella zoster virus (VZV) causes chickenpox (varicella) on primary exposure and can reactivate later in life to cause shingles (zoster). As primary infection is more serious in adults than children, and exposure to the virus might boost the immune response to both chickenpox and shingles, there are two main concerns regarding infant VZV vaccination: that it could lead to an increase in adult disease; and/or that it could lead to a temporary increase in the incidence of shingles. This paper reviews the evidence for such outcomes. The consensus view of mathematical modelling studies is that the overall varicella associated burden is likely to decrease in the long term, regardless of the level of vaccine coverage. On the other hand, recent evidence suggests that an increase in zoster incidence appears likely, and the more effective vaccination is at preventing varicella, the larger the increase in zoster incidence. Targeted vaccination of susceptible adolescents and/or the contacts of high-risk individuals can be effective at preventing disease in these individuals with minimal risk to the community. However, targeted strategies would not prevent most disease (including most severe disease), and will not lead to a long-term reduction in the incidence of zoster. Understanding the mechanisms for maintaining immunity against varicella and zoster is critical for predicting the long-term effects of vaccination. Meanwhile sensitive surveillance of both chickenpox and shingles is essential in countries that have implemented, or are about to implement, varicella vaccination.

EMA: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000674/WC500053462.pdf, accessed: 11.04.2014

Enders G et al. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. Lancet. 1994;343(8912):1548-1551.

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% Cl 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% Cl 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 who 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.

Feldman S et al. Varicella in children with cancer: impact of antiviral therapy and prophylaxis. Pediatrics. 1987;80(4):465-472.

To estimate the impact of antiviral therapy and prophylaxis on the natural course of the infection, 288 cases of varicella in children with cancer were reviewed. Among 127 patients with untreated infections, the overall mortality rate was 7%. Varicella-zoster virus pneumonitis developed in 28% of the untreated patients and was associated with a 25% mortality rate. Pneumonitis was much more likely to develop in patients with acute leukemia than in those with other malignancies (32% *v* 19%). Similarly, deaths due to pneumonitis were restricted to patients with acute leukemia. Lymphopenia (absolute lymphocyte count <500/μL) was significantly associated with varicella-zoster virus pneumonitis and a higher fatality rate among patients with this complication. Both acyclovir and adenine arabinoside, administered to 18 and 28 patients, respectively, stopped the progression of skin lesions; however, pneumonitis developed in none of the acyclovir recipients after two days of treatment, compared with 29% of the adenine arabinoside recipients (*P* = .03). Passive immunization in 45 children who subsequently had varicella was associated with an 11% incidence of varicella-zoster virus pneumonitis. Despite passive immunization of approximately 150 children, the attack rate of varicella at our institution remains unchanged. Results of this study demonstrate the efficacy of antiviral therapy and passive immunization in patients with childhood cancer and varicella, but prevention of the infection will require a universal vaccine.

Gershon A et al. Varicella vaccine. In: Plotkin S, Orenstein W, Offit P, editors. Vaccines. 6th ed: Saunders Elsevier; 2013. p. 836-869.

GlaxoSmithKline Inc. VARILRIX® [Product Monograph]. Ontario, CA: GlaxoSmithKline Inc.; 2013. http://www.gsk.ca/english/docs-pdf/product-monographs/Varilrix.pdf, accessed: 06.02.2014

Global Advisory Committee on Vaccine Safety, December 2012 http://www.who.int/wer/2013/wer8806.pdf?ua=1 accessed: 06.02.2014

Goh P et al. Safety and immunogenicity of early vaccination with two doses of tetravalent measles-mumps-rubella-varicella (MMRV) vaccine in healthy children from 9 months of age. Infection. 2007;35(5):32

BACKGROUND: This open, randomized, controlled study [208136/018] assessed the safety and immunogenicity of early vaccination with an experimental tetravalent measlesmumps-rubella-varicella (MMRV) vaccine (GlaxoSmithKline Biologicals) compared to concomitant administration of separate licensed MMR (Priorix™) and varicella (Varilrix™) vaccines (MMR+V). METHODS: Vaccines were administered as a two-dose course in healthy children at 9 and 12 months of age (N = 153 in the MMRV group and N = 146 in the MMR+V group). RESULTS: The incidence of fever of any intensity (axillary temperature ≥ 37.5 °C) during the 15 days of follow-up post-dose 1 was higher in the MMRV group than in the MMR+V group (48.3% vs 25.7%, respectively) but was low in both groups post-dose 2 (20.3% and 22.1%, respectively). The incidence of fever > 39.0 °C and the incidence of solicited local symptoms (pain, redness, swelling) were low (≤ 5.3% and ≤ 13.7%, respectively) in the two groups after each vaccine dose. Seroconversion rates were similar in the two groups for all vaccine antigens after each vaccine dose and were ≥ 99.2% for each antigen post-dose 2. Anti-measles GMT was higher in the MMRV group than in the MMR+V group after the first vaccine

dose. After the second dose, slight to moderate increases in measles, mumps and rubella antibody titers and a substantial increase in varicella antibody titer were seen in both groups, leading to higher GMTs in the MMRV group compared with the MMR+V group for measles, mumps and varicella. Anti-rubella antibody GMTs were similar in the two groups post-dose 2. CONCLUSION: Early vaccination with two doses of this experimental MMRV vaccine at 9 and 12 months of age was well-tolerated and at least as immunogenic as two doses of separate licensed MMR and varicella vaccines.

Goulleret N et al. Safety profile of live varicella virus vaccine (Oka/Merck): five-year results of the European Varicella Zoster Virus Identification Program (EU VZVIP). Vaccine. 2010;28(36):5878-5882.

BACKGROUND: VARIVAX® (Oka/Merck) is a live varicella vaccine, licensed in Europe since 2003. In addition to routine safety surveillance, the Varicella Zoster Virus Identification Program (VZVIP) analyzes clinical samples to establish whether adverse events (AEs) are associated with wild-type (wt) or vaccine varicella zoster virus (vVZV) strain. The European VZVIP provides data on VZV clade distribution. METHODS: Samples were collected from patients with selected AEs; the VZV strain was determined using polymerase chain reaction. RESULTS: From October 2003 to September 2008, 1006 spontaneous AE reports were analyzed (88% non-serious). Samples from 76/585 cases with selected AEs were collected. Of 55 VZV-positive/typable samples, wtVZV was detected in 40 and vVZV in 15 samples. Most rashes (32/44) ≤42 days postvaccination were associated with wtVZV. For breakthrough varicella, 6/9 cases were wtVZV-positive; none were vVZV-positive. For herpes zoster 9/17 cases were VZV-positive: eight vVZV, one wtVZV. One case of mild encephalitis was associated with vVZV. One of three cases of suspected secondary vVZV transmission was confirmed. Most wtVZV was clade 3 and clade 1. CONCLUSIONS: European experience confirms that Oka/Merck vaccine is generally well tolerated. wtVZV genotypes were consistent with the molecular epidemiology of VZV in Europe.

GRADE Table 1: Effectiveness of 1 dose against all varicella
http://www.who.int/entity/immunization/position_papers/varicella_grad_effectiveness_1_dose.pdf

GRADE Table 2: Effectiveness of 2 doses against all varicella
http://www.who.int/entity/immunization/position_papers/varicella_grad_effectiveness_2_doses.pdf

GRADE Table 3: Efficacy of herpes zoster vaccine
http://www.who.int/entity/immunization/position_papers/herpes_zoster_grad_efficacy.pdf

GRADE Table 4: Safety of varicella vaccine
http://www.who.int/entity/immunization/position_papers/varicella_grad_safety.pdf

GRADE Table 5: Safety of MMRV
http://www.who.int/entity/immunization/position_papers/mmrv_grad_safety.pdf

GRADE Table 6: Safety of herpes zoster vaccine
http://www.who.int/entity/immunization/position_papers/herpes_zoster_grad_safety.pdf

Guess HA et al. Population-based studies of varicella complications. Pediatrics. 1986;78(4 Pt 2):723-727.

Population-based data on varicella complications are presented using information both from national sample surveys of hospitalizations and physician office visits and from reviews of medical records for all cases occurring within one community (Olmsted County, Minnesota) during a specified period. Acute cerebellar ataxia is the most common neurologic complication of varicella and occurs about once in 4,000 varicella cases among children younger than 15 years of age. Among adults, varicella pneumonia is the most common complication and results in hospitalization about once in every 400 varicella cases. Overall, varicella accounts for approximately 4,000 hospitalizations and 364,000 physician office visits annually in the United States and represents an important continuing source of childhood and adult morbidity.

Guris D et al. Changing varicella epidemiology in active surveillance sites – United States, 1995–2005. J Infect Dis 2008;197(March (Suppl. 2)):S71–5.

Significant reductions in varicella incidence were reported from 1995 to 2000 in the varicella active surveillance sites of Antelope Valley (AV), California, and West Philadelphia (WP), Pennsylvania. We examined incidence rates, median age, and vaccination status of case patients for 1995–2005. Coverage data were from the National Immunization Survey. By 2005, coverage among children 19–35 months of age reached 92% (AV) and 94% (WP); 57% and 64% of case patients in AV and WP, respectively, were vaccinated; and varicella incidence declined by 89.8% in AV and 90.4% in WP. Incidence declined in all age groups, especially among children <10 years of age in both sites and among adolescents 10–14 years of age in WP. In AV, since 2000, the incidence among adolescents 10–14 and 15–19 years of age increased. Implementation of school requirements through 10th grade in WP may explain the differences in the decline in incidence among adolescents. Continued surveillance will be important to monitor the impact that the 2-dose vaccine policy in children has on varicella epidemiology.

Harger JH et al. Frequency of congenital varicella syndrome in a prospective cohort of 347 pregnant women. Obstetrics and gynecology. 2002;100(2):260-265.

OBJECTIVE: To estimate the rate of congenital varicella zoster virus syndrome in neonates born to women developing varicella zoster virus infections during pregnancy. METHODS: Pregnant women with clinical varicella zoster virus infection were enrolled at ten perinatal centers. Maternal and fetal immunoglobulin (Ig) G and IgM by fluorescent antibody confirmed 74.3% of cases. Specialists examined neonates at 0-6 months, 7-18 months, and 19-30 months after delivery to detect abnormalities of their eyes, hearing, and physical and developmental features. A hierarchical set of criteria was used to define congenital varicella syndrome. A jury of four investigators assigned the classification of all findings. RESULTS: In 362 women enrolled from 1993 to 1996, 15 had herpes zoster, and 347 had primary varicella zoster virus infection. Varicella zoster virus affected 140 women (38.7%) in the first trimester, 122 (33.7%) in the second trimester, and 100 (27.6%) in the third trimester. Five twin pairs were included. Only one case (0.4%) of definite congenital varicella syndrome was found, a 3360-g female infant having a left retinal macular lesion with typical skin scars after maternal varicella at 24 weeks. The maternal blood sample at birth was negative for IgG antibodies to toxoplasmosis and cytomegalovirus. Two cases involved fetal death at 20 weeks and fetal hydrops at 17 weeks after maternal varicella at 11 and 5 weeks, respectively. We found no cases of limb hypoplasia, microcephalus, or cataract. CONCLUSION: The frequency of congenital varicella syndrome is very low (0.4%) in a prospectively studied cohort. Eye examinations of exposed infants had a low yield.

Hastie I. Varicella-zoster virus affecting immigrant nurses. Lancet.Volume 316, Issue 8186, 19 July 1980, Pages 154–155

Huang YC, Lin TY, Chiu CH. Acyclovir prophylaxis of varicella after household exposure. Pediatr Infect Dis J 1995 February;14(2):152-4.

Jacobsen SJ et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine. 2009;27(34):4656-4661.

BACKGROUND: A combined measles, mumps, rubella, varicella live vaccine (MMRV, Merck and Co., Inc., US) was recently licensed in the US. Pre-licensure clinical trial data showed a significant increase in fever in days 5–12 following MMRV vaccination as compared to the vaccines given separately (MMR + V). This post-licensure retrospective cohort study was undertaken to assess the incidence of febrile convulsion following MMRV. METHODS: Children ages 12–60 months who received a first dose of MMRV in February 2006–June 2007 in a managed care organization were included in the study. Subjects were optimally matched on age, sex, and calendar date of vaccination to children who received MMR + V concomitantly in November 2003–January 2006, before MMRV licensure. Potential cases of febrile convulsion were identified through administrative data and adjudicated by expert panel, according to pre-specified criteria. RESULTS: During the 30 days post-vaccination, there were 128 and 94 potential convulsion cases among the 31,298 children in the MMRV and MMR + V cohorts, respectively. After review of available medical charts and adjudication, there were 84 cases of confirmed febrile convulsion, 44 (1.41/1000) and 40 (1.28/1000) in the MMRV and MMR + V cohorts, respectively (RR = 1.10, 95% CI = 0.72, 1.69). In days 5–12 following vaccination, a pre-specified period of interest, the respective numbers were 22 (0.70/1000) and 10 (0.32/1000) (RR = 2.20, 95% CI = 1.04, 4.65). CONCLUSION: These data suggest that the risk of febrile convulsion is increased in days 5–12 following vaccination with MMRV as compared to MMR + V given separately during the same visit, when post-vaccination fever and rash are also increased in clinical trials. While there was no evidence of an increase in the overall month following vaccination, the elevated risk during this time period should be communicated and needs to be balanced with the potential benefit of a combined vaccine.

Johnson CE et al. A long-term prospective study of varicella vaccine in healthy children. Pediatrics. 1997;100(5):761-766.

BACKGROUND: Studies in Japan and the United States have shown that varicella vaccine is both safe and efficacious. In 1984, we undertook a 10-year prospective study using a research lot of Oka/Merck varicella vaccine to assess antibody persistence and breakthrough chickenpox rates. In 1987, we began a similar prospective study with lots made in production facilities that ended after 6 years because many children were given a second dose. The purpose of this study is to report humoral antibody persistence and breakthrough chickenpox rates after 6 to 10 years of prospective follow-up. METHODS: One hundred forty-three seronegative children received a research lot (950 plaque-forming units/dose) with 97.9% seroconversion by an assay for fluorescent antibody to membrane antigen (FAMA). One hundred thirty-eight children received production lots (1145 to 3265 plaque-forming units/dose) with 93.5% seroconversion. Yearly chickenpox exposure surveys were completed by phone, and children were seen by a study nurse whenever chickenpox was suspected. A subset in each group had serum collected every 2 years and tested for FAMA antibody. RESULTS: In the research group there have been 25 cases of chickenpox in 137 seroconverters in a period of more than 10 years (yearly rate of 1.7%). In the production lot group there have been 22 cases of chickenpox in 129 seroconverters in a 6-year period (yearly rate of 2.8%). In the research group the median titer rose from 1:16 to 1:64 between 1 and 10 years. In the production group, the median titer did not change between 1, 2, and 4 years. Median antibody titers were compared between the research and production groups at 1, 2, and 4 years and did not differ. The rate of development of modified chickenpox has not increased with time since vaccination, and neither has the case severity. Children with FAMA titers ≤8 at 6-weeks' postvaccination were four times more

likely to develop chickenpox than those with titers ≥64. CONCLUSION: 1) Modified chickenpox has occurred in approximately 2% to 3% of vaccinees per year, regardless of the vaccine lot given. 2) FAMA titers have risen between 1 and 10 years in research lot recipients and remained the same in production lot recipients. 3) The likelihood of modified chickenpox developing is inversely related to the 6-week postvaccination FAMA titer.

Kerzner B et al. Safety and immunogenicity profile of the concomitant administration of ZOSTAVAX and inactivated influenza vaccine in adults aged 50 and older. J Am Geriatr Soc 2007;55(10):1499-1507.

OBJECTIVES: To evaluate the safety and immunogenicity of ZOSTAVAX administered concomitantly with inactivated influenza vaccine or sequentially in adults aged 50 and older. DESIGN: Randomized, blinded, placebo-controlled study. SETTING: Thirteen U.S. and seven European study sites. PARTICIPANTS: Three hundred eighty-two concomitantly, 380 sequentially vaccinated subjects. INTERVENTION: The concomitant vaccination group received influenza vaccine and ZOSTAVAX at separate injection sites on Day 1 and placebo at Week 4. The nonconcomitant vaccination group received influenza vaccine and placebo at separate injection sites on Day 1 and ZOSTAVAX at Week 4. MEASUREMENTS: Primary safety endpoints: vaccine-related serious adverse experiences (AEs) within 28 days postvaccination (PV); and diary card–prompted local and systemic AEs. Primary immunogenicity endpoints: geometric mean titer (GMT) and geometric mean fold rise (GMFR) from baseline of varicella-zoster virus (VZV) antibody (Ab) at 4 weeks PV according to glycoprotein enzyme-linked immunosorbent assay (gpELISA) and GMT of influenza Ab for the three vaccine strains (2005–2006 influenza season) at 4 weeks PV according to hemagglutination inhibition assay. Secondary immunogenicity endpoint: influenza seroconversion rates (SCRs). RESULTS: No serious AEs related to ZOSTAVAX were observed during the study. VZV Ab GMTs 4 weeks PV for the concomitant and sequential groups were 554 and 597 gpELISA U/mL, respectively. The estimated VZV Ab GMT ratio was 0.9 (95% confidence interval (CI)=0.8–1.0), indicating noninferior (*P*<.001 for the null hypothesis of GMT ratio <0.67) responses. Estimated VZV Ab GMFR from baseline in the concomitant group was 2.1 (95% CI=2.0–2.3), indicating acceptable fold rise. Estimated GMT ratios (concomitant/sequential) for influenza strains A(H1N1), A(H3N2), and B were 0.9 (95% CI=0.8–1.1), 1.1 (95% CI=0.9–1.3), and 0.9 (95% CI=0.8–1.1), respectively, and SCRs were comparable across both groups, with more than 85% achieving titers of 1:40 or greater, meeting regulatory criteria. CONCLUSION: ZOSTAVAX and influenza vaccine given concomitantly are generally well tolerated in adults aged 50 and older. Ab responses were similar whether ZOSTAVAX and influenza vaccine were given concomitantly or sequentially.

Klein NP et al. Measles-containing vaccines and febrile seizures in children age 4 to 6 years. Pediatrics. 2012;129(5):809-814.

BACKGROUND: In the United States, children receive 2 doses of measles-mumps-rubella vaccine (MMR) and varicella vaccine (V), the first between ages 1 to 2 years and the second between ages 4 to 6 years. Among 1- to 2-year-olds, the risk of febrile seizures 7 to 10 days after MMRV is double that after separate MMR + V. Whether MMRV or MMR + V affects risk for febrile seizure risk among 4- to 6-year-olds has not been reported. METHODS: Among 4- to 6-year-old Vaccine Safety Datalink members, we identified seizures in the emergency department and hospital from 2000 to 2008 and outpatient visits for fever from 2006 to 2008 during days 7 to 10 and 0 to 42 after MMRV and MMR + V. Incorporating medical record reviews, we assessed seizure risk after MMRV and MMR + V. RESULTS: From 2006 through 2008, 86 750 children received MMRV; from 2000 through 2008, 67 438 received same-day MMR + V. Seizures were rare throughout days 0 to 42 without peaking during days 7 to 10. There was 1 febrile seizure 7 to 10 days after MMRV and 0 after MMR + V. Febrile seizure risk was 1 per 86 750 MMRV doses (95% confidence interval, 1 per 3 426 441, 1 per

15 570) and 0 per 67 438 MMR + V doses (1 per 18 282). CONCLUSIONS: This study provides reassurance that MMRV and MMR + V were not associated with increased risk of febrile seizures among 4- to 6-year-olds. We can rule out with 95% confidence a risk greater than 1 febrile seizure per 15 500 MMRV doses and 1 per 18 000 MMR + V doses.

Klein NP. et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics. 2010;126(1):e1-8.

OBJECTIVE: In February 2008, we alerted the Advisory Committee on Immunization Practices to preliminary evidence of a twofold increased risk of febrile seizures after the combination measles-mumps-rubella-varicella (MMRV) vaccine when compared with separate measles-mumps-rubella (MMR) and varicella vaccines. Now with data on twice as many vaccine recipients, our goal was to reexamine seizure risk after MMRV vaccine. METHODS: Using 2000–2008 Vaccine Safety Datalink data, we assessed seizures and fever visits among children aged 12 to 23 months after MMRV and separate MMR + varicella vaccines. We compared seizure risk after MMRV vaccine to that after MMR + varicella vaccines by using Poisson regression as well as with supplementary regressions that incorporated chart-review results and self-controlled analyses. RESULTS: MMRV vaccine recipients (83 107) were compared with recipients of MMR + varicella vaccines (376 354). Seizure and fever significantly clustered 7 to 10 days after vaccination with all measles-containing vaccines but not after varicella vaccination alone. Seizure risk during days 7 to 10 was higher after MMRV than after MMR + varicella vaccination (relative risk: 1.98 [95% confidence interval: 1.43–2.73]). Supplementary analyses yielded similar results. The excess risk for febrile seizures 7 to 10 days after MMRV compared with separate MMR + varicella vaccination was 4.3 per 10 000 doses (95% confidence interval: 2.6–5.6). CONCLUSIONS: Among 12- to 23-month-olds who received their first dose of measles-containing vaccine, fever and seizure were elevated 7 to 10 days after vaccination. Vaccination with MMRV results in 1 additional febrile seizure for every 2300 doses given instead of separate MMR + varicella vaccines. Providers who recommend MMRV should communicate to parents that it increases the risk of fever and seizure over that already associated with measles-containing vaccines.

Krause PR et al. Efficacy, immunogenicity, safety, and use of live attenuated chickenpox vaccine. The Journal of pediatrics. 1995;127(4):518-525.

Kuter B et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. The Pediatric infectious disease journal. 2004;23(2):132-137.

BACKGROUND: The rate of varicella and persistence of varicella antibody after a one dose vs. a two dose regimen of varicella virus vaccine live Oka/Merck (VARIVAX; Merck & Co., Inc., West Point, PA) in approximately 2000 children were compared during a 9- to 10-year follow-up period. METHODS: Children 12 months to 12 years of age with a negative history of varicella were randomized in late 1991 to early 1993 to receive either one or two injections of varicella vaccine given 3 months apart. Subjects were actively followed for varicella, any varicella-like illness or zoster and any exposures to varicella or zoster on a yearly basis for 10 years after vaccination. Persistence of varicella antibody was measured yearly for 9 years. RESULTS: Most cases of varicella reported in recipients of one or two injections of vaccine were mild. The risk of developing varicella >42 days postvaccination during the 10-year observation period was 3.3-fold lower ($P < 0.001$) in children who received two injections than in those who received one injection (2.2% vs. 7.3%, respectively). The estimated vaccine efficacy for the 10-year observation period was 94.4% for one injection and 98.3% for two injections ($P < 0.001$). Measurable serum antibody persisted for 9 years in all subjects. CONCLUSIONS: Administration of either one or two injections of varicella vaccine to healthy children results in long

term protection against most varicella disease. The two dose regimen was significantly more effective than a single injection.

Kuter BJ et al. Oka/Merck varicella vaccine in healthy children: final report of a 2-year efficacy study and 7-year follow-up studies. Vaccine. 1991;9(9):643-647.

A large double-blind, randomized, placebo-controlled trial of live attenuated Oka/Merck varicella vaccine was conducted among healthy children, 1–14 years of age. During the first varicella season, the efficacy of the vaccine among susceptible children was 100%[1]. During the second varicella season, 22 children were diagnosed with varicella: 21 cases in placebo recipients and one in a vaccine recipient. The overall efficacy of the vaccine through two varicella seaons was 98%. After the code for the study was broken, the original group of vaccine recipients continued to be followed for development of varicella. The estimated proportion of vaccine recipients who remained varicella-free at the end of 7 years was 95%. The 23 cases of varicella that occurred in vaccine recipients over the 7-year period were considerably milder than natural varicella. The average number of lesions was 53, 50% of the children had non-vesicular rashes, and 14% of the children had a temperature ⩾ 38.9°*C* (102°*F*), oral. The persistence of antibody in a subset of vaccine recipients followed for 6 years was 100%.

Kuter BJ et al. Oka/Merck varicella vaccine in healthy children: final report of a 2-year efficacy study and 7-year follow-up studies. Vaccine. 1991;9(9):643-647.

Langan S et al. Herpes Zoster Vaccine Effectiveness against Incident Herpes Zoster and Post-herpetic Neuralgia in an Older US Population: A Cohort Study. PlosMed 2013; 10(4): e1001420

BACKGROUND: Herpes zoster is common and has serious consequences, notably post-herpetic neuralgia (PHN). Vaccine efficacy against incident zoster and PHN has been demonstrated in clinical trials, but effectiveness has not been studied in unselected general populations unrestricted by region, full health insurance coverage, or immune status. Our objective was to assess zoster vaccine effectiveness (VE) against incident zoster and PHN in a general population-based setting. METHODS AND FINDINGS: A cohort study of 766,330 fully eligible individuals aged ≥65 years was undertaken in a 5% random sample of Medicare who received and did not receive zoster vaccination between 1st January 2007 and 31st December 2009. Incidence rates and hazard ratios for zoster and PHN were determined in vaccinated and unvaccinated individuals. Analyses were adjusted for age, gender, race, low income, immunosuppression, and important comorbidities associated with zoster, and then stratified by immunosuppression status. Adjusted hazard ratios were estimated using time-updated Cox proportional hazards models. Vaccine uptake was low (3.9%) particularly among black people (0.3%) and those with evidence of low income (0.6%). 13,112 US Medicare beneficiaries developed incident zoster; the overall zoster incidence rate was 10.0 (9.8–10.2) per 1,000 person-years in the unvaccinated group and 5.4 (95% CI 4.6–6.4) per 1,000 person-years in vaccinees, giving an adjusted VE against incident zoster of 0.48 (95% CI 0.39–0.56). In immunosuppressed individuals, VE against zoster was 0.37 (95% CI 0.06–0.58). VE against PHN was 0.59 (95% CI 0.21–0.79). CONCLUSIONS: Vaccine uptake was low with variation in specific patient groups. In a general population cohort of older individuals, zoster vaccination was associated with reduction in incident zoster, including among those with immunosuppression. Importantly, this study demonstrates that zoster vaccination is associated with a reduction in PHN.

Leibovitz E et al. Varicella-zoster virus infection in Romanian children infected with the human immunodeficiency virus. Pediatrics. 1993;92(6):838-842.

OBJECTIVES: Varicella-zoster virus (VZV) infections can cause severe disease in immunocompromised individuals. To evaluate the spectrum of VZV infections in human immunodefidency virus (HIV)-infected children, we retrospectively analyzed all the cases of VZV infection in a cohort of children cared for at a hospital for infectious diseases in Bucharest, Romania. METHODS: The records of 391 HIV-infected children admitted to the acquired immunodeficiency syndrome pavilion of Colentina Hospital during the period January 1, 1991, through March 31, 1992, were reviewed for evidence of VZV infection. The diagnosis of varicella or zoster was made clinically and information was collected concerning course of the illness, number of skin lesions, and clinical evidence of complications. Lymphocyte subpopulation typing, as an estimate of immune function, was performed by either a standard fluorescent activated flow cytometric method or by immunofluorescent technique. RESULTS: Thirty-eight cases of varicella (9.7%) and seven cases of zoster (1.8%) were adequately documented among the 391 records reviewed. The duration of varicella was prolonged; in 57% of the children it was greater than 10 days. Forty percent of children with varicella developed a complication, including superinfection of the skin, pneumonia, or thrombocytopenia. None of the children developed clinical hepatitis or encephalitis. Two children (5%) died during varicella, both of respiratory failure. None of the 7 children with zoster had chronic, recurrent, or disseminated lesions. Lymphocyte subset analysis was available for 22 of 38 children with varicella and 3 of 7 children with zoster. Fifteen of the 22 children had normal, age-adjusted, absolute CD4 counts within 3 months of the diagnosis of varicella. All 3 children with zoster who had lymphocyte subset analysis had low CD4 counts and absolute numbers. None of the 45 children received antiretroviral therapy and only 1 child with varicella and 1 with zoster received acyclovir. CONCLUSIONS: The spectrum of VZV infection in this hospitalized group of HIV-infected children was broad. The majority (57%) experienced a prolonged course of disease and a higher rate of complications than normal children hospitalized with varicella.

Levin M. Zoster vaccine. In: Plotkin S, Orenstein W, Offit P, editors. Vaccines. 6th ed: Saunders Elsevier; 2013. p. 969-980.

Lolekha S et al. Effect of climatic factors and population density on varicella zoster virus epidemiology within a tropical country. The American journal of tropical medicine and hygiene. 2001;64(3-4):131-136

Blood samples were collected from healthy subjects, aged 9 months-29 years in urban and rural communities from 4 distinct regions in Thailand, to determine the seroprevalence rate of varicella-zoster virus (VZV) antibody and its relationship with demographic, climatic, and socioeconomic factors. The overall seroprevalence rate was 52.8% and increased from 15.5% in the 9-month to 4-year-old group to 75.9% in the 20-29 year-olds. The age-adjusted seroprevalence was significantly higher in the cooler than in the warmer regions. In the warmer regions only, the age-specific seroprevalence was significantly higher in the urban population than in the rural population. In Thailand, climate is the main determinant of VZV seroprevalence. The delayed onset of natural immunity is more marked in warmer climate areas. Population density is a secondary determinant; in the warmer areas, the pattern of adolescent and adult susceptibility was greater in rural than in urban areas.

Lozano R et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2095–128

BACKGROUND: Reliable and timely information on the leading causes of death in populations, and how these are changing, is a crucial input into health policy debates. In the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010), we aimed to estimate annual deaths for

the world and 21 regions between 1980 and 2010 for 235 causes, with uncertainty intervals (UIs), separately by age and sex. METHODS: We attempted to identify all available data on causes of death for 187 countries from 1980 to 2010 from vital registration, verbal autopsy, mortality surveillance, censuses, surveys, hospitals, police records, and mortuaries. We assessed data quality for completeness, diagnostic accuracy, missing data, stochastic variations, and probable causes of death. We applied six different modelling strategies to estimate cause-specific mortality trends depending on the strength of the data. For 133 causes and three special aggregates we used the Cause of Death Ensemble model (CODEm) approach, which uses four families of statistical models testing a large set of different models using different permutations of covariates. Model ensembles were developed from these component models. We assessed model performance with rigorous out-of-sample testing of prediction error and the validity of 95% UIs. For 13 causes with low observed numbers of deaths, we developed negative binomial models with plausible covariates. For 27 causes for which death is rare, we modelled the higher level cause in the cause hierarchy of the GBD 2010 and then allocated deaths across component causes proportionately, estimated from all available data in the database. For selected causes (African trypanosomiasis, congenital syphilis, whooping cough, measles, typhoid and parathyroid, leishmaniasis, acute hepatitis E, and HIV/AIDS), we used natural history models based on information on incidence, prevalence, and case-fatality. We separately estimated cause fractions by aetiology for diarrhoea, lower respiratory infections, and meningitis, as well as disaggregations by subcause for chronic kidney disease, maternal disorders, cirrhosis, and liver cancer. For deaths due to collective violence and natural disasters, we used mortality shock regressions. For every cause, we estimated 95% UIs that captured both parameter estimation uncertainty and uncertainty due to model specification where CODEm was used. We constrained cause-specific fractions within every age-sex group to sum to total mortality based on draws from the uncertainty distributions. FINDINGS: In 2010, there were 52·8 million deaths globally. At the most aggregate level, communicable, maternal, neonatal, and nutritional causes were 24·9% of deaths worldwide in 2010, down from 15·9 million (34·1%) of 46·5 million in 1990. This decrease was largely due to decreases in mortality from diarrhoeal disease (from 2·5 to 1·4 million), lower respiratory infections (from 3·4 to 2·8 million), neonatal disorders (from 3·1 to 2·2 million), measles (from 0·63 to 0·13 million), and tetanus (from 0·27 to 0·06 million). Deaths from HIV/AIDS increased from 0·30 million in 1990 to 1·5 million in 2010, reaching a peak of 1·7 million in 2006. Malaria mortality also rose by an estimated 19·9% since 1990 to 1·17 million deaths in 2010. Tuberculosis killed 1·2 million people in 2010. Deaths from non-communicable diseases rose by just under 8 million between 1990 and 2010, accounting for two of every three deaths (34·5 million) worldwide by 2010. 8 million people died from cancer in 2010, 38% more than two decades ago; of these, 1·5 million (19%) were from trachea, bronchus, and lung cancer. Ischaemic heart disease and stroke collectively killed 12·9 million people in 2010, or one in four deaths worldwide, compared with one in five in 1990; 1·3 million deaths were due to diabetes, twice as many as in 1990. The fraction of global deaths due to injuries (5·1 million deaths) was marginally higher in 2010 (9·6%) compared with two decades earlier (8·8%). This was driven by a 46% rise in deaths worldwide due to road traffic accidents (1·3 million in 2010) and a rise in deaths from falls. Ischaemic heart disease, stroke, chronic obstructive pulmonary disease (COPD), lower respiratory infections, lung cancer, and HIV/AIDS were the leading causes of death in 2010. Ischaemic heart disease, lower respiratory infections, stroke, diarrhoeal disease, malaria, and HIV/AIDS were the leading causes of years of life lost due to premature mortality (YLLs) in 2010, similar to what was estimated for 1990, except for HIV/AIDS and preterm birth complications. YLLs from lower respiratory infections and diarrhoea decreased by 45-54% since 1990; ischaemic heart disease and stroke YLLs increased by 17-28%. Regional variations in leading causes of death were substantial. Communicable, maternal, neonatal, and nutritional causes still accounted for 76% of premature mortality in sub-Saharan Africa in 2010. Age standardised death rates from some key disorders rose (HIV/AIDS, Alzheimer's disease, diabetes mellitus, and chronic kidney disease in particular), but for most diseases, death rates fell in the past two decades; including major vascular diseases, COPD, most forms of cancer, liver cirrhosis, and

maternal disorders. For other conditions, notably malaria, prostate cancer, and injuries, little change was noted. INTERPRETATION: Population growth, increased average age of the world's population, and largely decreasing age-specific, sex-specific, and cause-specific death rates combine to drive a broad shift from communicable, maternal, neonatal, and nutritional causes towards non-communicable diseases. Nevertheless, communicable, maternal, neonatal, and nutritional causes remain the dominant causes of YLLs in sub-Saharan Africa. Overlaid on this general pattern of the epidemiological transition, marked regional variation exists in many causes, such as interpersonal violence, suicide, liver cancer, diabetes, cirrhosis, Chagas disease, African trypanosomiasis, melanoma, and others. Regional heterogeneity highlights the importance of sound epidemiological assessments of the causes of death on a regular basis.

MacIntyre CR et al. Concomitant administration of zoster and pneumococcal vaccines in adults≥60 years old 1. Hum Vaccin 2010;6(11):894-902.

This study evaluated safety & immunogenicity of ZOSTAVAX® (zoster vaccine: ZV) administered concomitantly versus nonconcomitantly with PNEUMOVAX® 23 (pneumococcal vaccine: PPV23). This randomized, double-blind, placebo-controlled study enrolled 473 subjects ≥60 years old in 1:1 ratio to receive ZV & PPV23 concomitantly (Day 1) or nonconcomitantly (PPV23 Day 1, ZV Week 4). Blood samples obtained for pneumococcal polysaccharide (PnPs) antibody (Ab) testing by enzyme-linked immunosorbent assay (ELISA) and varicella-zoster virus (VZV) Ab testing by glycoprotein ELISA. Subjects followed for adverse experiences (AEs) for 28 days postvaccination. Mean baseline VZV geometric mean titers (GMT) in nonconcomitant group were lower than concomitant group. Four weeks postvaccination with ZV, VZV Ab response in concomitant group was not similar to nonconcomitant group; estimated VZV GMT ratio [concomitant/nonconcomitant] was 0.70 (95% CI, 0.61-0.80). VZV Ab response was acceptable in concomitant group; estimated geometric mean foldrise (GMFR) from baseline was 1.9 (95% CI, 1.7-2.1). PnPs serotype-specific Ab responses were similar in both groups. All 6 reported serious AEs were deemed not related to study vaccine. Postvaccination of ZV, incidence of injection-site AEs was similar in both groups; clinical AEs were numerically but not significantly higher in nonconcomitant group. In summary, VZV GMT Ab response induced by ZV administered concomitantly with PPV23 was inferior to that induced nonconcomitantly. These results indicate that, to avoid a potential decrease in ZV immunogenicity, ZV & PPV23 should not be given concomitantly. Concomitant administration did not affect response to PPV23 serotypes tested. When administered concomitantly, ZV & PPV23 vaccines were generally well tolerated.

Maretic Z et al. Comparisons between chickenpox in a tropical and a European country. The Journal of tropical medicine and hygiene. 1963;66:311-315.

Marin M et al. Varicella prevention in the United States: a review of successes and challenges. Pediatrics 2008;122(September(3)):e744–51.

OBJECTIVE: In 1995, the United States was the first country to introduce a universal 1-dose childhood varicella vaccination program. In 2006, the US varicella vaccine policy was changed to a routine 2-dose childhood program, with catchup vaccination for older children. The objective of this review was to summarize the US experience with the 1-dose varicella vaccination program, present the evidence considered for the policy change, and outline future challenges of the program. METHODS: We conducted a review of publications identified by searching PubMed for the terms “varicella,” “varicella vaccine,” and “herpes zoster.” The search was limited to US publications except for herpes zoster; we reviewed all published literature on herpes zoster incidence. RESULTS: A single dose of varicella vaccine was 80% to 85% effective in preventing disease of any severity and >95% effective in preventing severe varicella and had an excellent safety profile. The vaccination

program reduced disease incidence by 57% to 90%, hospitalizations by 75% to 88%, deaths by >74%, and direct inpatient and outpatient medical expenditures by 74%. The decline of cases plateaued between 2003 and 2006, and outbreaks continued to occur, even among highly vaccinated school populations. Compared with children who received 1 dose, in 1 clinical trial, 2-dose vaccine recipients developed in a larger proportion antibody titers that were more likely to protect against breakthrough disease and had a 3.3-fold lower risk for breakthrough disease and higher vaccine efficacy. Two studies showed no increase in overall herpes zoster incidence, whereas 2 others showed an increase. CONCLUSIONS: A decade of varicella prevention in the United States has resulted in a dramatic decline in disease; however, even with high vaccination coverage, the effectiveness of 1 dose of vaccine did not generate sufficient population immunity to prevent community transmission. A 2-dose varicella vaccine schedule, therefore, was recommended for children in 2006. Data are inconclusive regarding an effect of the varicella vaccination program on herpes zoster epidemiology.

Merck & Co., Inc. VARIVAX® [Package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2013. http://www.merck.com/product/usa/pi_circulars/v/varivax/varivax_pi.pdf, accessed: 06.02.2014

Merck & Co., Inc. ZOSTAVAX® (Zoster Vaccine Live) [HIGHLIGHTS OF PRESCRIBING INFORMATION] http://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi2.pdf, accessed: 06.02.2014

Merck/CDC Pregnancy Registry for Varicella-Zoster Virus-Containing Vaccines. The 16th Annual Report, 2011. http://www.merckpregnancyregistries.com/varivax.html, accessed: 06.02.2014
Meyer PA et al. Varicella mortality: trends before vaccine licensure in the United States, 1970-1994. The Journal of infectious diseases. 2000;182(2):383-390

We examined varicella deaths in the United States during the 25 years before vaccine licensure and identified 2262 people who died with varicella as the underlying cause of death. From 1970 to 1994, varicella mortality declined, followed by an increase. Mortality rates were highest among children; however, adult varicella deaths more than doubled in number, proportion, and rate per million population. Despite declining fatality rates, in 1990–1994, adults had a risk 25 times greater and infants had a risk 4 times greater of dying from varicella than did children 1–4 years old, and most people who died of varicella were previously healthy. Varicella deaths are now preventable by vaccine. Investigation and reporting of all varicella deaths in the United States is needed to accurately document deaths due to varicella, to improve prevention efforts, and to evaluate the vaccine's impact on mortality.

Mofenson LM et al. Centers for Disease Control and Prevention; National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America; Pediatric Infectious Diseases Society American Academy of Pediatrics. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep. 2009;58(RR-11):1-166.

This report updates and combines into one document earlier versions of guidelines for preventing and treating opportunistic infections (OIs) among HIV-exposed and HIV-infected children, last published in 2002 and 2004, respectively. These guidelines are intended for use by clinicians and other health-care workers providing medical care for HIV-exposed and HIV-infected children in the United States. The guidelines discuss opportunistic pathogens that occur in the United States and one that might be acquired during international travel (i.e., malaria). Topic areas covered for each OI

include a brief description of the epidemiology, clinical presentation, and diagnosis of the OI in children; prevention of exposure; prevention of disease by chemoprophylaxis and/or vaccination; discontinuation of primary prophylaxis after immune reconstitution; treatment of disease; monitoring for adverse effects during treatment; management of treatment failure; prevention of disease recurrence; and discontinuation of secondary prophylaxis after immune reconstitution. A separate document about preventing and treating of OIs among HIV-infected adults and postpubertal adolescents (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents) was prepared by a working group of adult HIV and infectious disease specialists.

The guidelines were developed by a panel of specialists in pediatric HIV infection and infectious diseases (the Pediatric Opportunistic Infections Working Group) from the U.S. government and academic institutions. For each OI, a pediatric specialist with content-matter expertise reviewed the literature for new information since the last guidelines were published; they then proposed revised recommendations at a meeting at the National Institutes of Health (NIH) in June 2007. After these presentations and discussions, the guidelines underwent further revision, with review and approval by the Working Group, and final endorsement by NIH, CDC, the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Disease Society (PIDS), and the American Academy of Pediatrics (AAP). The recommendations are rated by a letter that indicates the strength of the recommendation and a Roman numeral that indicates the quality of the evidence supporting the recommendation so readers can ascertain how best to apply the recommendations in their practice environments.

An important mode of acquisition of OIs, as well as HIV infection among children, is from their infected mother; HIV-infected women coinfected with opportunistic pathogens might be more likely than women without HIV infection to transmit these infections to their infants. In addition, HIV-infected women or HIV-infected family members coinfected with certain opportunistic pathogens might be more likely to transmit these infections horizontally to their children, resulting in increased likelihood of primary acquisition of such infections in the young child. Therefore, infections with opportunistic pathogens might affect not just HIV-infected infants but also HIV-exposed but uninfected infants who become infected by the pathogen because of transmission from HIV-infected mothers or family members with coinfections. These guidelines for treating OIs in children therefore consider treatment of infections among all children, both HIV-infected and uninfected, born to HIV-infected women.

Additionally, HIV infection is increasingly seen among adolescents with perinatal infection now surviving into their teens and among youth with behaviorally acquired HIV infection. Although guidelines for postpubertal adolescents can be found in the adult OI guidelines, drug pharmacokinetics and response to treatment may differ for younger prepubertal or pubertal adolescents. Therefore, these guidelines also apply to treatment of HIV-infected youth who have not yet completed pubertal development.

Major changes in the guidelines include 1) greater emphasis on the importance of antiretroviral therapy for preventing and treating OIs, especially those OIs for which no specific therapy exists; 2) information about the diagnosis and management of immune reconstitution inflammatory syndromes; 3) information about managing antiretroviral therapy in children with OIs, including potential drug--drug interactions; 4) new guidance on diagnosing of HIV infection and presumptively excluding HIV infection in infants that affect the need for initiation of prophylaxis to prevent Pneumocystis jirovecii pneumonia (PCP) in neonates; 5) updated immunization recommendations for HIV-exposed and HIV-infected children, including hepatitis A, human papillomavirus, meningococcal, and rotavirus vaccines; 6) addition of sections on aspergillosis; bartonella; human herpes virus-6, -7, and -8; malaria; and progressive multifocal leukodystrophy (PML); and 7) new recommendations on discontinuation of OI prophylaxis after immune reconstitution in children. The report includes six tables pertinent to preventing and treating OIs in children and two figures describing immunization recommendations for children aged 0--6 years and 7--18 years.

Because treatment of OIs is an evolving science, and availability of new agents or clinical data on existing agents might change therapeutic options and preferences, these recommendations will be periodically updated and will be available at http://AIDSInfo.nih.gov.

Ngai AL et al. Safety and immunogenicity of one vs. two injections of Oka/Merck varicella vaccine in healthy children. The Pediatric infectious disease journal. 1996;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.

Ogunjimi B, van Damme P, Beutels P. Herpes Zoster Risk Reduction through Exposure to Chickenpox Patients: A Systematic Multidisciplinary Review. June 21, 2013. PLoS ONE. DOI: 10.1371/journal.pone.0066485

Varicella-zoster virus (VZV) causes chickenpox and may subsequently reactivate to cause herpes zoster later in life. The exogenous boosting hypothesis states that re-exposure to circulating VZV can inhibit VZV reactivation and consequently also herpes zoster in VZV-immune individuals. Using this hypothesis, mathematical models predicted widespread chickenpox vaccination to increase herpes zoster incidence over more than 30 years. Some countries have postponed universal chickenpox vaccination, at least partially based on this prediction. After a systematic search and selection procedure, we analyzed different types of exogenous boosting studies. We graded 13 observational studies on herpes zoster incidence after widespread chickenpox vaccination, 4 longitudinal studies on VZV immunity after re-exposure, 9 epidemiological risk factor studies, 7 mathematical modeling studies as well as 7 other studies. We conclude that exogenous boosting exists, although not for all persons, nor in all situations. Its magnitude is yet to be determined adequately in any study field.

Oxman MN. et aline A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352(22):2271-2284.

BACKGROUND: The incidence and severity of herpes zoster and postherpetic neuralgia increase with age in association with a progressive decline in cell-mediated immunity to varicella–zoster virus (VZV). We tested the hypothesis that vaccination against VZV would decrease the incidence, severity, or both of herpes zoster and postherpetic neuralgia among older adults. METHODS: We enrolled 38,546 adults 60 years of age or older in a randomized, double-blind, placebo-controlled trial of an

investigational live attenuated Oka/Merck VZV vaccine ("zoster vaccine"). Herpes zoster was diagnosed according to clinical and laboratory criteria. The pain and discomfort associated with herpes zoster were measured repeatedly for six months. The primary end point was the burden of illness due to herpes zoster, a measure affected by the incidence, severity, and duration of the associated pain and discomfort. The secondary end point was the incidence of postherpetic neuralgia. RESULTS: More than 95 percent of the subjects continued in the study to its completion, with a median of 3.12 years of surveillance for herpes zoster. A total of 957 confirmed cases of herpes zoster (315 among vaccine recipients and 642 among placebo recipients) and 107 cases of postherpetic neuralgia (27 among vaccine recipients and 80 among placebo recipients) were included in the efficacy analysis. The use of the zoster vaccine reduced the burden of illness due to herpes zoster by 61.1 percent (P<0.001), reduced the incidence of postherpetic neuralgia by 66.5 percent (P<0.001), and reduced the incidence of herpes zoster by 51.3 percent (P<0.001). Reactions at the injection site were more frequent among vaccine recipients but were generally mild. CONCLUSIONS: The zoster vaccine markedly reduced morbidity from herpes zoster and postherpetic neuralgia among older adults.

Pinchinat S et al. Similar herpes zoster incidence across Europe: results from a systematic literature review. BMC Infect Dis 2013;13:170.

BACKGROUND: Herpes zoster (HZ) is caused by reactivation of the varicella-zoster virus (VZV) and mainly affects individuals aged ≥50 years. The forthcoming European launch of a vaccine against HZ (Zostavax®) prompts the need for a better understanding of the epidemiology of HZ in Europe. Therefore the aim of this systematic review was to summarize the available data on HZ incidence in Europe and to describe age-specific incidence. METHODS: The Medline database of the National Library of Medicine was used to conduct a comprehensive literature search of population-based studies of HZ incidence published between 1960 and 2010 carried out in the 27 member countries of the European Union, Iceland, Norway and Switzerland. The identified articles were reviewed and scored according to a reading grid including various quality criteria, and HZ incidence data were extracted and presented by country. RESULTS: The search identified 21 studies, and revealed a similar annual HZ incidence throughout Europe, varying by country from 2.0 to 4.6/1 000 person-years with no clearly observed geographic trend. Despite the fact that age groups differed from one study to another, age-specific HZ incidence rates seemed to hold steady during the review period, at around 1/1 000 children <10 years, around 2/1 000 adults aged <40 years, and around 1–4/1 000 adults aged 40–50 years. They then increased rapidly after age 50 years to around 7–8/1 000, up to 10/1 000 after 80 years of age. Our review confirms that in Europe HZ incidence increases with age, and quite drastically after 50 years of age. In all of the 21 studies included in the present review, incidence rates were higher among women than men, and this difference increased with age. This review also highlights the need to identify standardized surveillance methods to improve the comparability of data within European Union Member States and to monitor the impact of VZV immunization on the epidemiology of HZ. CONCLUSIONS: Available data in Europe have shortcomings which make an accurate assessment of HZ incidence and change over time impossible. However, data are indicative that HZ incidence is comparable, and increases with age in the same proportion across Europe.

Prymula R et al. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine versus one dose of monovalent varicella vaccine: a multicentre, observer-blind, randomised, controlled trial. The Lancet. 2014; Volume 383, Issue 9925, Pages 1313–1324

BACKGROUND: Rates of varicella have decreased substantially in countries implementing routine varicella vaccination. Immunisation is possible with monovalent varicella vaccine or a combined measles-mumps-rubella-varicella vaccine (MMRV). We assessed protection against varicella in naive

children administered one dose of varicella vaccine or two doses of MMRV. METHODS: This study was done in ten European countries with endemic varicella. Healthy children aged 12–22 months were randomised (3:3:1 ratio, by computer-generated randomisation list, with block size seven) to receive 42 days apart (1) two doses of MMRV (MMRV group), or (2) MMR at dose one and monovalent varicella vaccine at dose two (MMR+V group), or (3) two doses of MMR (MMR group; control). Participants and their parents or guardians, individuals involved in assessment of any outcome, and sponsor staff involved in review or analysis of data were masked to treatment assignment. The primary efficacy endpoint was occurrence of confirmed varicella (by detection of varicella zoster virus DNA or epidemiological link) from 42 days after the second vaccine dose to the end of the first phase of the trial. Cases were graded for severity. Efficacy analyses were per protocol. Safety analyses included all participants who received at least one vaccine dose. This trial is registered with ClinicalTrials.gov, number NCT00226499. FINDINGS: Between Sept 1, 2005, and May 10, 2006, 5803 children (mean age 14·2 months, SD 2·5) were vaccinated. In the efficacy cohort of 5285 children, the mean duration of follow-up in the MMRV group was 36 months (SD 8·8), in the MMR+V group was 36 months (8·5) and in the MMR group was 35 months (8·9). Varicella cases were confirmed for 37 participants in the MMRV group (two moderate to severe), 243 in the MMR+V group, and 201 in the MMR group. Second cases occurred for three participants (all in the MMR+V group). Varicella cases were moderate to severe for two participants in the MMRV group, 37 in the MMR+V group (one being a second case that followed a mild first case); and 117 in the MMR group. Efficacy of two-dose MMRV against all varicella was 94·9% (97·5% CI 92·4–96·6), and against moderate to severe varicella was 99·5% (97·5–99·9). Efficacy of one-dose varicella vaccine against all varicella was 65·4% (57·2–72·1), and against moderate to severe varicella (post hoc) was 90·7% (85·9–93·9). The most common adverse event in all groups was injection-site redness (up to 25% of participants). Within 15 days after dose one, 57·4% (95% CI 53·9–60·9) of participants in the MMRV group reported fever of 38°C or more, by contrast with 44·5% (41·0–48·1) with MMR+V, and 39·8% (33·8–46·1) with MMR. Eight serious adverse events were deemed related to vaccination (three MMRV, four MMR+V, one MMR). All resolved within the study period. INTERPRETATION: These results support the implementation of two-dose varicella vaccination on a short course, to ensure optimum protection from all forms of varicella disease.

Public Health Agency of Canada, Varicella-zoster virus, Pathogen safety data sheet- infectious substances. http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/var-zo-eng.php, accessed: 06.02.2014

Reisinger KS et al. A combination measles, mumps, rubella, and varicella vaccine (ProQuad) given to 4- to 6-year-old healthy children vaccinated previously with M-M-RII and Varivax. Pediatrics. 2006;117(2):265-272

BACKGROUND: In the United States, children receive primary doses of M-M-RII (Merck & Co, Inc, West Point, PA) and Varivax (Merck & Co, Inc) beginning at 12 months, often at the same health care visit. Currently a second dose of M-M-RII is given to 4- to 6-year-old children, to increase vaccination rates and to reduce the number of individuals without detectable antibodies. A second dose of a varicella-containing vaccine may result in similar benefits. OBJECTIVES: To demonstrate that ProQuad (measles, mumps, rubella, and varicella virus vaccine live; Merck & Co, Inc) may be given in place of a second dose of M-M-RII or second doses of M-M-RII and Varivax for 4- to 6-year-old children. METHODS: Four- to 6-year-old children who had been immunized previously with M-M-RII and Varivax were assigned randomly to receive either ProQuad and placebo (*N* = 399), M-M-RII and placebo (*N* = 195), or M-M-RII and Varivax (*N* = 205) and were then monitored for safety and immunogenicity. RESULTS: ProQuad was generally well tolerated. Similarity (noninferiority) was demonstrated in postvaccination antibody responses to measles, mumps, and rubella between recipients of ProQuad and all recipients of M-M-RII and in responses to varicella between recipients

of ProQuad and recipients of Varivax. Postvaccination seropositivity rates for antibodies against all 4 viruses were nearly 100% in all 3 groups. Small fold increases were observed for measles, mumps, and rubella antibody titers. In contrast, substantial boosts in varicella antibody titers were observed among recipients of a second dose of varicella vaccine, administered as ProQuad or Varivax. CONCLUSIONS: ProQuad may be used in place of a second dose of M-M-RII or second doses of M-M-RII and Varivax for 4- to 6-year-old children.

Requirements for varicella vaccine (live), WHO Technical Report Series, No. 848, 1994, http://www.who.int/biologicals/publications/trs/areas/vaccines/varicella/WHO_TRS_848_A1.pdf
Richard et al. Should health care workers in the tropics be immunized against varicella? Journal of Hospital Infection (2001) 47: 243–245

In tropical regions, chickenpox affects both adults and children. Therefore, healthcare workers in the tropics are vulnerable to hospital-acquired varicella infection and they may transmit infection to susceptible hospitalized individuals. Although the varicella vaccine is safe and effective, its cost is a deterrent to its use in routine immunization programmes. In order to assess whether vaccination of susceptible healthcare workers to prevent hospital-acquired transmission may be justified, we have documented the frequency of varicella among healthcare workers in our hospital. There were 96 admissions for varicella during the 1993–1997 period; staff and student nurses accounted for 76%. The peak season of admission was from February to April. The attack rate in staff and student nurses was 0.78 and 1.54 per 100 person-years, respectively. While community outbreaks of varicella occur in this region once in 4–5 years, hospital outbreaks of varicella occurred every year. This poses the risk of transmission to hospitalized patients, with serious consequences among immunocompromized individuals. Therefore, we recommend systematic selective vaccination of susceptible healthcare workers to break this cycle of annual varicella outbreaks among hospital personnel.

Rozenbaum MH et al. Cost-effectiveness of varicella vaccination programs: an update of the literature. Expert review of vaccines. 2008;7(6):753-782.

Varicella is one of the most common infectious diseases in childhood, caused by the varicella zoster virus. Although vaccines are available, there are only a few countries with an early-childhood vaccination program. Most countries mainly focus on vaccination of high-risk groups, such as susceptible healthcare workers. One of the main concerns with a routine early-childhood vaccination program is a potential (temporal) increase of the incidence of herpes zoster among elderly adults. In this review, we focus on the cost–effectiveness of varicella vaccination and on the methodology used in the health–economic studies. In particular, we focus on the perspective adopted, type of model used, the modeled effect on herpes zoster, the vaccine efficacy and price, and on the value of time lost by infection. The vast majority of studies show vaccination of high-risk groups – including susceptible adolescents – to be cost saving. Routine early-childhood vaccination programs are always cost saving if indirect costs of production losses are included, or cost effective, as long as the potential negative effects on zoster are not taken into account. We note that most studies included in the review used old vaccine prices and a single dose of the varicella vaccine, whereas multiple doses are now becoming the standard. Despite that, those aspects limit the timeliness of our review and we believe that the current work does provide useful insights in the cost–effectiveness of varicella vaccination.

Safety of varicella and MMRV vaccines: A systematic review
http://www.who.int/immunization/sage/meetings/2014/april/presentations_background_docs/en/ accessed: 11.04.2014

The World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) established the Working Group on Varicella and Herpes Zoster Vaccines to review the evidence and formulate recommendations on use of varicella and herpes zoster vaccines. This systematic review utilized the PubMed database to extract publications on the safety of varicella and MMRV vaccines in immunocompetent and immunocompromised individuals. 244 articles, published before October 2013, were extracted and ultimately 84 were included in the review. RCTs, observational studies and postlicensure safety data were included. No increased incidence of serious adverse events following immunization was identified. MMRV, compared to MMR only or MMR+V, demonstrated a higher risk of adverse events and serious adverse events, including a higher risk of febrile seizures.

Schmader KE et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years.Clin Infect Dis 2012;54(7):922-928.

BACKGROUND: Herpes zoster (HZ) adversely affects individuals aged 50–59, but vaccine efficacy has not been assessed in this population. This study was designed to determine the efficacy, safety, and tolerability of zoster vaccine for preventing HZ in persons aged 50–59 years. METHODS: This was a randomized, double-blind, placebo-controlled study of 22 439 subjects aged 50–59 years conducted in North America and Europe. Subjects were given 1 dose of licensed zoster vaccine (ZV) (Zostavax; Merck) and followed for occurrence of HZ for ≥1 year (mean, 1.3 years) postvaccination until accrual of ≥96 confirmed HZ cases (as determined by testing lesions swabs for varicella zoster virus DNA by polymerase chain reaction). Subjects were followed for all adverse events (AEs) from day 1 to day 42 postvaccination and for serious AEs (SAEs) through day 182 postvaccination. RESULTS: The ZV reduced the incidence of HZ (30 cases in vaccine group, 1.99/1000 person-years vs 99 cases in placebo group, 6.57/1000 person-years). Vaccine efficacy for preventing HZ was 69.8% (95% confidence interval, 54.1–80.6). AEs were reported by 72.8% of subjects in the ZV group and 41.5% in the placebo group, with the difference primarily due to higher rates of injection-site AEs and headache. The proportion of subjects reporting SAEs occurring within 42 days postvaccination (ZV, 0.6%; placebo, 0.5%) and 182 days postvaccination (ZV, 2.1%; placebo, 1.9%) was similar between groups. CONCLUSIONS: In subjects aged 50–59 years, the ZV significantly reduced the incidence of HZ and was well tolerated.

Schmader KE et al. Persistence of the Efficacy of Zoster Vaccine in the Shingles Prevention Study and the Short-Term Persistence Substudy. Clinical Infectious Diseases 2012;55(10):1320–8

BACKGROUND: The Shingles Prevention Study (SPS; Department of Veterans Affairs Cooperative Study 403) demonstrated that zoster vaccine was efficacious through 4 years after vaccination. The Short-Term Persistence Substudy (STPS) was initiated after the SPS to further assess the persistence of vaccine efficacy. METHODS: The STPS re-enrolled 7320 vaccine and 6950 placebo recipients from the 38 546–subject SPS population. Methods of surveillance, case determination, and follow-up were analogous to those in the SPS. Vaccine efficacy for herpes zoster (HZ) burden of illness, incidence of postherpetic neuralgia (PHN), and incidence of HZ were assessed for the STPS population, for the combined SPS and STPS populations, and for each year through year 7 after vaccination. RESULTS: In the STPS as compared to the SPS, vaccine efficacy for HZ burden of illness decreased from 61.1% to 50.1%, vaccine efficacy for the incidence of PHN decreased from 66.5% to 60.1%, and vaccine efficacy for the incidence of HZ decreased from 51.3% to 39.6%, although the differences were not statistically significant. Analysis of vaccine efficacy in each year after vaccination for all 3 outcomes showed a decrease in vaccine efficacy after year 1, with a further decline thereafter. Vaccine efficacy was statistically significant for the incidence of HZ and the HZ burden of illness through year 5. CONCLUSIONS: Vaccine efficacy for each study outcome was lower in the STPS than in the SPS. There is evidence of the persistence of vaccine efficacy through year 5 after vaccination but, vaccine efficacy is uncertain beyond that point.

Schmid DS, Jumaan AO. Impact of Varicella Vaccine on Varicella-Zoster Virus Dynamics. Clin Microbiol Rev. 2010 Jan;23(1):202-17.

Summary: The licensure and recommendation of varicella vaccine in the mid-1990s in the United States have led to dramatic declines in varicella incidence and varicella-related deaths and hospitalizations. Varicella outbreaks remain common and occur increasingly in highly vaccinated populations. Breakthrough varicella in vaccinated individuals is characteristically mild, typically with fewer lesions that frequently do not progress to a vesicular stage. As such, the laboratory diagnosis of varicella has grown increasingly important, particularly in outbreak settings. In this review the impact of varicella vaccine on varicella-zoster virus (VZV) disease, arising complications in the effective diagnosis and monitoring of VZV transmission, and the relative strengths and limitations of currently available laboratory diagnostic techniques are all addressed. Since disease symptoms often resolve in outbreak settings before suitable test specimens can be obtained, the need to develop new diagnostic approaches that rely on alternative patient samples is also discussed.

Seward JF et al. Varicella disease after introduction of varicella vaccine in the United States, 1995-2000. JAMA : the journal of the American Medical Association. 2002;287(5):606-611.

CONTEXT: Before licensure of varicella vaccine in 1995, varicella was a universal childhood disease in the United States, causing 4 million cases, 11 000 hospitalizations, and 100 deaths every year. OBJECTIVE: To examine population-based disease surveillance data in 3 communities to document the impact of the varicella vaccination program. DESIGN, SETTING, AND SUBJECTS: Active surveillance for varicella conducted among the populations of Antelope Valley, Calif; Travis County, Tex; and West Philadelphia, Pa; from January 1, 1995, to December 31, 2000. Reporting sites included child care centers, schools, universities, physicians, public health clinics, hospitals, emergency departments, and households. MAIN OUTCOME MEASURES: Trends in number and rate of varicella cases and hospitalizations; varicella vaccine coverage. RESULTS: From 1995 through 1998, in each surveillance area, the number of verified varicella cases varied from year to year with marked springtime seasonality. In 1999, the number and rates of varicella cases and hospitalizations declined markedly. From 1995 through 2000, in Antelope Valley, Travis County, and West Philadelphia, varicella cases declined 71%, 84%, and 79%, respectively. Cases declined to the greatest extent among children aged 1 to 4 years, but cases declined in all age groups, including infants and adults. In the combined 3 surveillance areas, hospitalizations due to varicella declined from a range of 2.7 to 4.2 per 100 000 population in 1995 through 1998 to 0.6 and 1.5 per 100 000 population in 1999 and 2000, respectively (P = .15). By 2000, vaccine coverage among children aged 19 to 35 months was 82.1%, 73.6%, and 83.8% in Los Angeles County, Texas, and Philadelphia County, respectively. CONCLUSIONS: Varicella disease has declined dramatically in surveillance areas with moderate vaccine coverage. Continued implementation of existing vaccine policies should lead to further reductions of varicella disease in these communities and throughout the United States.

Shinjoh M, Takahashi T. Varicella zoster exposure on paediatric wards between 2000 and 2007: safe and effective post-exposure prophylaxis with oral aciclovir. J Hosp Infect 2009 June;72(2):163-8.

Varicella zoster virus is highly contagious and can cause serious complications in immunocompromised patients. To prevent people exposed to the virus from developing secondary varicella we have used oral aciclovir as post-exposure prophylaxis (PEP) since 2000. Between 2000 and 2007, there were 11 unexpected occurrences of varicella and 11 unexpected occurrences of zoster in our paediatric wards. There were 174 contacts, 131 exposed to varicella and 43 exposed to zoster. A total of 163 (94%) received PEP and 11 (6%) did not. The rates of secondary infection

among contacts given prophylaxis with aciclovir only were 2.1% (3/141) for all contacts and 1.3% (1/76) for immunocompetent contacts. The rate of secondary infection among contacts not given PEP was significantly higher (18%, 2/11) ($P < 0.05$). No adverse events due to PEP were reported. We conclude that oral aciclovir PEP following exposure to VZV on paediatric wards is both safe and effective.

Simberkoff MS et al. Safety of herpes zoster vaccine in the shingles prevention study: a randomized trial. Ann Intern Med 2010;152(9):545-554.

BACKGROUND: The herpes zoster vaccine is effective in preventing herpes zoster and postherpetic neuralgia in immunocompetent older adults. However, its safety has not been described in depth. OBJECTIVE: To describe local adverse effects and short- and long-term safety profiles of herpes zoster vaccine in immunocompetent older adults. DESIGN: Randomized, placebo-controlled trial with enrollment from November 1998 to September 2001 and follow-up through April 2004 (mean, 3.4 years). A Veterans Affairs Coordinating Center generated the permutated block randomization scheme, which was stratified by site and age. Participants and follow-up study personnel were blinded to treatment assignments. (ClinicalTrials.gov registration number: NCT00007501) SETTING: 22 U.S. academic centers. PARTICIPANTS: 38 546 immunocompetent adults 60 years or older, including 6616 who participated in an adverse events substudy. INTERVENTION: Single dose of herpes zoster vaccine or placebo. MEASUREMENTS: Serious adverse events and rashes in all participants and inoculation-site events in substudy participants during the first 42 days after inoculation. Thereafter, vaccination-related serious adverse events and deaths were monitored in all participants, and hospitalizations were monitored in substudy participants. RESULTS: After inoculation, 255 (1.4%) vaccine recipients and 254 (1.4%) placebo recipients reported serious adverse events. Local inoculation-site side effects were reported by 1604 (48%) vaccine recipients and 539 (16%) placebo recipients in the substudy. A total of 977 (56.6%) of the vaccine recipients reporting local side effects were aged 60 to 69 years, and 627 (39.2%) were older than 70 years. After inoculation, herpes zoster occurred in 7 vaccine recipients versus 24 placebo recipients. Long-term follow-up (mean, 3.39 years) showed that rates of hospitalization or death did not differ between vaccine and placebo recipients. LIMITATIONS: Participants in the substudy were not randomly selected. Confirmation of reported serious adverse events with medical record data was not always obtained. CONCLUSION: Herpes zoster vaccine is well tolerated in older, immunocompetent adults.

Stratton K et al. eds. Adverse events of vaccines: evidence and causality. Washington, DC, Institute of Medicine of the National Academies. August 2011.

In 1900, for every 1,000 babies born in the United States, 100 would die before their first birthday, often due to infectious diseases. Today, vaccines exist for many viral and bacterial diseases. The National Childhood Vaccine Injury Act, passed in 1986, was intended to bolster vaccine research and development through the federal coordination of vaccine initiatives and to provide relief to vaccine manufacturers facing financial burdens. The legislation also intended to address concerns about the safety of vaccines by instituting a compensation program, setting up a passive surveillance system for vaccine adverse events, and by providing information to consumers. A key component of the legislation required the U.S. Department of Health and Human Services to collaborate with the Institute of Medicine to assess concerns about the safety of vaccines and potential adverse events, especially in children.

Adverse Effects of Vaccines reviews the epidemiological, clinical, and biological evidence regarding adverse health events associated with specific vaccines covered by the National Vaccine Injury Compensation Program (VICP), including the varicella zoster vaccine, influenza vaccines, the

hepatitis B vaccine, and the human papillomavirus vaccine, among others. For each possible adverse event, the report reviews peer-reviewed primary studies, summarizes their findings, and evaluates the epidemiological, clinical, and biological evidence. It finds that while no vaccine is 100 percent safe, very few adverse events are shown to be caused by vaccines. In addition, the evidence shows that vaccines do not cause several conditions. For example, the MMR vaccine is not associated with autism or childhood diabetes. Also, the DTaP vaccine is not associated with diabetes and the influenza vaccine given as a shot does not exacerbate asthma.

Adverse Effects of Vaccines will be of special interest to the National Vaccine Program Office, the VICP, the Centers for Disease Control and Prevention, vaccine safety researchers and manufacturers, parents, caregivers, and health professionals in the private and public sectors.

Systematic review of available evidence on effectiveness and duration of protection of varicella vaccines
http://www.who.int/immunization/sage/meetings/2014/april/presentations_background_docs/en/ accessed:11.04.2013

Szucs TD et al. A systematic review of the cost effectiveness of herpes zoster vaccination. Pharmacoeconomics 2013;31(2):125-136.

BACKGROUND: The varicella zoster virus (VZV) can cause two infections: chickenpox or herpes zoster (HZ). Whereas chickenpox infections are normally mild but common among children, HZ infections are common among elderly people and can give rise to post-herpetic neuralgia (PHN), a severe and painful complication. OBJECTIVES: This review aimed to summarize the literature available on the cost effectiveness of HZ vaccination and to summarize key issues for decision makers to consider when deciding on the reimbursement of HZ vaccination. METHODS: We conducted a literature search of the databases PubMed and EMBASE using EndNote X4 from Thomson Reuters. The following combinations of keywords were used: 'herpes zoster vaccine' AND 'cost(-)effectiveness' or AND 'economic evaluation', 'herpes zoster vaccination' AND 'cost(-)effectiveness' or AND 'economic evaluation', 'varicella zoster vaccine' AND 'cost(-)effectiveness' or AND 'economic evaluation', and 'varicella zoster vaccination' AND 'cost(-)effectiveness' or AND 'economic evaluation'. RESULTS: A total of 11 studies were identified and included. Cost-effectiveness analyses of varicella zoster vaccination were excluded. The quality of the included studies ranged from 'moderate' to 'moderate to good' according to the *British Medical Journal* guidelines of Drummond and Jefferson and the Quality of Health Economic Studies (QHES) score of Ofman et al. Most studies evaluated the cost effectiveness of universal HZ vaccination in adults aged 50 years or 60 years and older. Data sources and model assumptions regarding epidemiology, utility estimates and costs varied between studies. All studies calculated costs per QALY, which allows comparing costs of interventions in different diseases. The costs per QALY gained and the incremental cost-effectiveness ratio (ICER) differed between studies depending on the age at vaccination, duration of vaccine efficacy, cost of vaccine course and economic perspective. All but one of the studies concluded that most vaccination scenarios are cost effective and the vaccination of specific subgroups such as the older age group is most cost effective. CONCLUSIONS: Model input parameters such as age at vaccination, vaccine costs, HZ incidence, PHN length and duration of vaccine efficacy had a great impact on the estimated cost effectiveness of HZ vaccination. To compare the results of different cost-effectiveness studies of HZ vaccination, uniform methods should be used and the most important input parameters used for the different models should be critically assessed.

Tanuseputro P et al. Population-based incidence of herpes-zoster after introduction of a publicly funded varicella vaccination program. Vaccine 2011;29(November (47)):8580–4.

BACKGROUND: Past varicella infection (chicken pox) may reactivate into herpes zoster (shingles). Varicella vaccination leads to a reduction in cases of varicella that may in turn increase herpes zoster rates due to reduction in the immune boosting effect of exposure to varicella zoster virus against varicella reactivation. We assessed the impact of childhood varicella vaccination in Ontario, Canada on zoster incidence and healthcare visits, and established baseline zoster rates prior to zoster vaccine introduction. METHODS: We used population-based, administrative databases to identify zoster incidence and healthcare use from April 1992 to March 2010. RESULTS: After routine varicella vaccination, zoster incidence rates decreased 29% for children aged 0–9 and changed minimally for other ages. Age-standardized rates of hospitalizations during the study period declined by 53%, while outpatient rates declined by 9%. The annual zoster incidence for those 60 or older was 740 per 100,000. CONCLUSIONS: In the early post-varicella vaccination period, incidence rates of medically attended herpes zoster did not increase for the overall population and decreased moderately for children 9 years and younger, the age group targeted for varicella vaccination.

Thiry N et al. Economic evaluations of varicella vaccination programmes: a review of the literature. PharmacoEconomics. 2003;21(1):13-38.

Chickenpox infections are generally mild but due to their very high incidence among healthy children they give rise to considerable morbidity and occasional mortality. With the development of a varicella vaccine in the early 1970s and its progressive licensing in many countries, interest in the efficiency of varicella immunisation programmes grew. The objective of this review was to discuss the methodological aspects and results of published economic evaluations of varicella vaccination. From this, we attempted to make recommendations. A computerised search was carried out; 17 full economic evaluations of varicella vaccination were retrieved. The review identified the methodological divergences and similarities between the articles in four areas: study design, epidemiological data, economic data and model characteristics. We assessed to what extent the applied methods conform to general guidelines for the economic evaluation of healthcare interventions and compared the studies' results. The desirability of a universal vaccination programme depends on whose perspective is taken. Despite variability in data and model assumptions, the studies suggest that universal vaccination of infants is attractive to society because large savings occur from averted unproductive days for parents. For the healthcare payer, universal vaccination of infants does not generate savings. Vaccination of susceptible adolescents has been proposed by some authors as a viable alternative; the attractiveness of this is highly dependent on the negative predictive value of anamnestic screening. Targeted vaccination of healthcare workers and immunocompromised individuals appears relatively cost effective. Findings for other target groups are either contradictory or provide insufficient evidence for any unequivocal recommendations to be made. High sensitivity to vaccine price was reported in most studies. This review highlights that some aspects of these studies need to be further improved before final recommendations can be made. First, more transparency, completeness and compliance to general methodological guidelines are required. Second, because of the increasing severity of varicella with age, it is preferable and in some cases essential to use dynamic models for the assessment of universal vaccination strategies. Third, most studies focused on the strategy of vaccinating children only while their results depended heavily on disputable assumptions (regarding vaccine effectiveness and impact on herpes zoster). Since violation of these assumptions could have important adverse public health effects, we suggest pre-adolescent vaccination as a more secure alternative. This option deserves more attention in future analyses.

Thomas SL et al. Contacts with varicella or with children and protection against herpes-zoster in adults: a case–control study. Lancet 2002;360(August (9334)):678–82.

BACKGROUND: Whether exogenous exposure to varicella zoster-virus protects individuals with latent varicella-zoster virus infection against herpes zoster by boosting immunity is not known. To test the hypothesis that contacts with children increase exposure to varicella-zoster virus and protect latently infected adults against zoster, we did a case-control study in south London, UK. METHODS: From 22 general practices, we identified patients with recently diagnosed zoster, and control individuals with no history of zoster, matched to patients by age, sex, and practice. Participants were asked about contacts with people with varicella or zoster in the past 10 years, and social and occupational contacts with children as proxies for varicella contacts. Odds ratios were estimated with conditional logistic regression. FINDINGS: Data from 244 patients and 485 controls were analysed. On multivariable analysis, protection associated with contacts with a few children in the household or via childcare seemed to be largely mediated by increased access to children outside the household. 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. The strength of protection diminished after controlling for known varicella contacts; the latter remained significantly protective (odds ratio 0·29 [95% CI 0·10–0·84] for those with five contacts or more). 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. Vaccination of the elderly (if effective) should be considered in countries with childhood varicella vaccination programmes.

Tseng HF et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. JAMA 2011;305(2):160-166.

CONTEXT: Approximately 1 million episodes of herpes zoster occur annually in the United States. Although prelicensure data provided evidence that herpes zoster vaccine works in a select study population under idealized circumstances, the vaccine needs to be evaluated in field conditions. OBJECTIVE: To evaluate risk of herpes zoster after receipt of herpes zoster vaccine among individuals in general practice settings. DESIGN, SETTING, AND PARTICIPANTS: A retrospective cohort study from January 1, 2007, through December 31, 2009, of individuals enrolled in the Kaiser Permanente Southern California health plan. Participants were immunocompetent community-dwelling adults aged 60 years or older. The 75 761 members in the vaccinated cohort were age matched (1:3) to 227 283 unvaccinated members. MAIN OUTCOME MEASURE: Incidence of herpes zoster. RESULTS: Herpes zoster vaccine recipients were more likely to be white, women, with more outpatient visits, and fewer chronic diseases. The number of herpes zoster cases among vaccinated individuals was 828 in 130 415 person-years (6.4 per 1000 person-years; 95% confidence interval [CI], 5.9-6.8), and for unvaccinated individuals it was 4606 in 355 659 person-years (13.0 per 1000 person-years; 95% CI, 12.6-13.3). In adjusted analysis, vaccination was associated with a reduced risk of herpes zoster (hazard ratio [HR], 0.45; 95% CI, 0.42-0.48); this reduction occurred in all age strata and among individuals with chronic diseases. Risk of herpes zoster differed by vaccination status to a greater magnitude than the risk of unrelated acute medical conditions, suggesting results for herpes zoster were not due to bias. Ophthalmic herpes zoster (HR, 0.37; 95% CI, 0.23-0.61) and hospitalizations coded as herpes zoster (HR, 0.35; 95% CI, 0.24-0.51) were less likely among vaccine recipients. CONCLUSIONS: Among immunocompetent community-dwelling adults aged 60 years or older, receipt of the herpes zoster vaccine was associated with a lower incidence of herpes zoster. The risk was reduced among all age strata and among individuals with chronic diseases.

Tsolia M et al. Live attenuated varicella vaccine: evidence that the virus is attenuated and the importance of skin lesions in transmission of varicella-zoster virus. National Institute of Allergy and Infectious Diseases Varicella Vaccine Collaborative Study Group. J Pediatr. 1990 Feb;116(2):184-9.

To examine whether the live varicella vaccine virus is attenuated, we analyzed varicella vaccine-induced contact cases of clinical chickenpox in healthy siblings of immunized children with leukemia. A rash developed approximately 1 month later in 156 children with leukemia who had been vaccinated. Vaccine-type virus was isolated from 25 of these children. Of 88 known susceptible healthy siblings who were exposed to a vaccine with a rash and from whom follow-up information was available, there was evidence of infection in 15 (17%). Of 15 siblings with seroconversion, 11 (73%) also acquired a mild rash with an average of 38 lesions and no accompanying systemic symptoms. Vaccine-type virus was isolated from four of the contact siblings. Tertiary transmission was documented once. Contact siblings with seroconversion were protected during future household exposure to chickenpox, which occurred in four instances. There was a direct relationship between transmission from vaccinees to varicella-susceptible close contacts and the presence and number of skin lesions in children with leukemia after vaccination. We conclude that in the transmission of varicella, the virus probably originates from skin lesions of infected persons and reaches the respiratory tract of those with secondary cases by the airborne route. On the basis of the mildness of the contact illness, the higher-than-normal rate of subclinical primary infection with varicella-zoster virus in contacts, and the lower-than-normal rate of spread of the vaccine virus to susceptible children in the household, we further conclude that the vaccine virus is attenuated. There was no evidence of reversion of the vaccine virus to virulence.

Varicella disease burden and varicella vaccine: http://www.who.int/immunization/sage/meetings/2014/april/2_SAGE_April_VZV_Seward_Varicella.pdf?ua=1, accessed 08.05.2014

Varis T et al. Efficacy of high-titer live attenuated varicella vaccine in healthy young children. The Journal of infectious diseases. 1996;174 Suppl 3:S330-334.

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 < or = .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.

Vesikari T et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. Lancet. 2013;381(9869):825-835.

BACKGROUND: Meningococcal serogroup B disease disproportionately affects infants. We assessed lot-to-lot consistency, safety and immunogenicity, and the effect of concomitant vaccination on responses to routine vaccines of an investigational multicomponent vaccine (4CMenB) in this population. METHODS: We did primary and booster phase 3 studies between March 31, 2008, and Aug 16, 2010, in 70 sites in Europe. We used two series of sponsor-supplied, computer-generated randomisation envelopes to allocate healthy 2 month-old infants to receive routine vaccinations (diphtheria-tetanus-acellular pertussis, inactivated poliovirus, hepatitis B plus Haemophilus influenzae type b, and seven-valent pneumococcal vaccine) at 2, 4, and 6 months of age alone, or concomitantly with 4CMenB or serogroup C conjugate vaccine (MenC) in: 1) an open-label, lot-to-lot immunogenicity and safety substudy of three 4CMenB lots compared with routine vaccines alone

(1:1:1:1, block size eight); or 2) an observer-blind, lot-to-lot safety substudy of three 4CMenB lots compared with MenC (1:1:1:3, block size six). At 12 months, 4CMenB-primed children from either substudy were randomised (1:1, block size two) to receive 4CMenB booster, with or without measles-mumps-rubella-varicella (MMRV) vaccine. Immunogenicity was assessed by serum bactericidal assay with human complement (hSBA) against serogroup B test strains, and on randomly selected subsets of serum samples for routine vaccines; laboratory personnel were masked to assignment. The first coprimary outcome was lot-to-lot consistency (hSBA geometric mean ratio of all lots between 0·5 and 2·0), and the second was an immune response (hSBA titre ≥5) for each of the three strains. The primary outcome for the booster study was immune response to booster dose. Immunogenicity data for 4CMenB were for the modified intention-to-treat population, including all infants from the open-label substudy who provided serum samples. The safety population included all participants who contributed safety data after at least one dose of study vaccine. These trials are registered with ClinicalTrials.gov, numbers NCT00657709 and NCT00847145. FINDINGS: We enrolled 2627 infants in the open-label phase, 1003 in the observer-blind phase, and 1555 in the booster study. Lot-to-lot consistency was shown for the three 4CMenB lots, with the lowest 95% lower confidence limit being 0·74 and the highest upper limit being 1·33. Of 1181–1184 infants tested 1 month after three 4CMenB doses (all lots pooled), 100% (95% CI 99–100) had hSBA titres of 5 or more against strains selective for factor H binding protein and neisserial adhesin A, and 84% (82–86) for New Zealand outer-membrane vesicle. In a subset (n=100), 84% (75–91) of infants had hSBA titres of 5 or more against neisseria heparin binding antigen. At 12 months of age, waning titres were boosted by a fourth dose, such that 95–100% of children had hSBA titres of 5 or more for all antigens, with or without concomitant MMRV. Immune responses to routine vaccines were much the same with or without concomitant 4CMenB, but concomitant vaccination was associated with increased reactogenicity. 77% (1912 of 2478) of infants had fever of 38·5°C or higher after any 4CMenB dose, compared with 45% (295 of 659) after routine vaccines alone and 47% (228 of 490) with MenC, but only two febrile seizures were deemed probably related to 4CMenB. INTERPRETATION: 4CMenB is immunogenic in infants and children aged 12 months with no clinically relevant interference with routine vaccines, but increases reactogenicity when administered concomitantly with routine vaccines. This breakthrough vaccine offers an innovative solution to the major remaining cause of bacterial meningitis in infant and toddlers. FUNDING: Novartis Vaccines and Diagnostics.

Weibel RE et al. Live attenuated varicella virus vaccine. Efficacy trial in healthy children. The New England journal of medicine. 1984;310(22):1409-1415.

We conducted a double-blind, placebo-controlled efficacy trial of the live attenuated Oka/Merck varicella vaccine among 956 children between the ages of 1 and 14 years, with a negative clinical history of varicella. Of the 914 children who were serologically confirmed to be susceptible to varicella, 468 received vaccine and 446 received placebo. The vaccine produced few clinical reactions and was well tolerated. There was no clinical evidence of viral spread from vaccinated children to sibling controls. Approximately eight weeks after vaccination, 94 per cent of the initially seronegative children who received vaccine had detectable antibody to varicella. During the nine-month surveillance period, 39 clinically diagnosed cases of varicella, 38 of which were confirmed by laboratory tests, occurred among study participants. All 39 cases occurred in placebo recipients; no child who received vaccine contracted varicella. The vaccine was 100 per cent efficacious in preventing varicella in this population of healthy children ($P<10^{-9}$).

WHO Global Advisory Committee on Vaccine Safety, 12–13 June 2013. http://www.who.int/vaccine_safety/committee/reports/wer8829.pdf, accessed: 06.02.2014

WHO The Immunological Basis for Immunization Series Module 10: Varicella-zoster virus2008. http://whqlibdoc.who.int/publications/2008/9789241596770_eng.pdf, accessed: 06.02.2014

Wiegering V et al. Varicella-zoster virus infections in immunocompromised patients - a single centre 6-years analysis. BMC pediatrics. 2011;11:31.

BACKGROUND: Infection with varicella-zoster virus (VZV) contemporaneously with malignant disease or immunosuppression represents a particular challenge and requires individualized decisions and treatment. Although the increasing use of varicella-vaccines in the general population and rapid initiation of VZV-immunoglobulins and acyclovir in case of exposure has been beneficial for some patients, immunocompromised individuals are still at risk for unfavourable courses. METHODS: In this single center, 6-year analysis we review incidence, hospitalization and complication rates of VZV-infections in our center and compare them to published data. Furthermore, we report three instructive cases. RESULTS: Hospitalization rate of referred children with VZV-infections was 45%, among these 17% with malignancies and 9% under immunosuppressive therapy. Rate of complications was not elevated in these two high-risk cohorts, but one ALL-patient died due to VZV-related complications. We report one 4-year old boy with initial diagnosis of acute lymphoblastic leukemia who showed a rapidly fatal outcome of his simultaneous varicella-infection, one 1.8-year old boy with an identical situation but a mild course of his disease, and an 8.5-year old boy with a steroid-dependent nephrotic syndrome. This boy developed severe hepatic involvement during his varicella-infection but responded to immediate withdrawl of steroids and administration of acyclovir plus single-dose cidofovir after nonresponse to acyclovir after 48 h. CONCLUSION: Our data show that patients with malignant diseases or immunosuppressive therapy should be hospitalized and treated immediately with antiviral agents. Despite these measures the course of VZV-infections can be highly variable in these patients. We discuss aids to individual decision-making for these difficult situations.