

Live attenuated vaccine for the prevention of varicella-zoster virus infection: does it work, is it safe and do we really need it in the UK?

In 1996 the USA introduced a programme of mass varicella vaccination for children aged 12–18 months. This measure has resulted in a fall in the annual incidence of varicella in the USA by over 70 % and a reduction in associated hospital admission rates (Seward *et al.* 2002). Clinical studies in Japan, the USA and Europe have shown the vaccine to be effective. Ninety five per cent of healthy children seroconvert after one dose of the vaccine (White *et al.*, 1991; Kuter *et al.*, 1991; Weibel *et al.*, 1984), while leukaemic children immunized during maintenance therapy, and healthy adults, require two doses to achieve 90 % seroconversion (LaRussa *et al.*, 1996; Hardy *et al.*, 1991). Clinical protection against subsequent (breakthrough) varicella appears to be good, although estimates of protection within the first 10 years vary between 65 and 97 % depending on the potency of the vaccine preparation used (Varis & Veskari, 1996; Weibel *et al.*, 1984). In a study of 4042 healthy children and adolescents, protection appeared to correlate with the titre of varicella-zoster virus (VZV)-specific antibody at 6 weeks post-vaccination (White *et al.*, 1991).

Current vaccines are live attenuated, derived from the Oka strain of VZV. Doses of 2500 p.f.u., representative of current vaccines, produce near to 85–90 % protection and overall only 2 and 3 % of healthy childhood vaccinees continue to develop breakthrough varicella each year (Asano *et al.*, 1994; Johnson *et al.*, 1997). The figure for breakthrough infection is higher in adults (30–40 %) (Ampofo *et al.*, 2002) and leukaemic children (13 %) (Hardy *et al.*, 1991). However, breakthrough varicella is considerably less severe than primary varicella in unvaccinated individuals, with most cases having fewer than 60 lesions and less than one third of cases having fever (Ampofo *et al.*, 2002). The picture is confirmed by case controlled studies which show the vaccine to be 85 % protective against varicella and 97 % protective against severe disease (Vazquez *et al.*, 2001) and by post-licensing

studies of vaccinated and unvaccinated children exposed to varicella in day-care settings (Clements *et al.*, 1999).

The vaccine thus appears to be effective, but how safe is it? The main adverse effect following immunization is a minor skin rash. The frequency of rash related to immunization in healthy children (i.e. occurring within 1–6 weeks), is about 5 % and there are very few skin lesions (generally fewer than 10) (Weibel *et al.*, 1984; Gershon, 1995). Recent studies on the Merck vaccine have demonstrated that rashes within the first 2 weeks of immunization are exclusively wild-type in origin, while those occurring after 2 weeks are vaccine-related (Sharrar *et al.*, 2000). No data are available for the GlaxoSmithKline vaccine. Other common adverse events include fever (15 %), temporary discomfort at the injection site (19–24 %) and rash at the injection site (3–4 %) (Weibel *et al.*, 1984; Gershon, 1995). Similar mild adverse events are seen in healthy adolescents and adults. However, the rate of vaccine-associated rash in adults is 10 %, twice that seen in healthy children (Ampofo *et al.*, 2002). Follow-up of 90 000 healthy children and adults who were vaccinated with the Oka vaccine following its licensing in the USA in 1995 supports its safety profile, with no serious adverse events seen (Black *et al.*, 1999). In vaccinated leukaemic children, the incidence of adverse events in the first 6 weeks after immunization is higher than in healthy children, and this, coupled with a reluctance to interrupt chemotherapy for immunization, has led to other approaches to preventing serious varicella in immunosuppressed children, in particular immunization of seronegative household contacts of children suffering from leukaemia and cancer (Kappagoda *et al.*, 1999). One study showed no transmission of Oka vaccine by family members to the patient with cancer, suggesting this may be a safe measure to reduce the risk of varicella in these patients (Kappagoda *et al.*, 1999).

Indeed, transmission of the vaccine virus from immunocompetent contacts is rare,

having been documented in only three cases out of 15 million doses of varicella vaccine distributed (ACIP, 1999). One of these cases involved a pregnant woman who underwent elective termination of her pregnancy. No evidence of vaccine virus infection of the fetus was found in this case or in any of the other cases in which vaccine has been inadvertently given to pregnant women.

What about persistence of immunity? Apart from the data on the incidence of breakthrough cases, which now span up to 10 years, there is good evidence that vaccine-induced antibody persists for many years. In a 20-year follow-up after immunization, 25–26 young adults who had been immunized as children remained seropositive (Asano *et al.*, 1984). Similarly, of over 500 healthy children who were followed for up to 6 years, 95 % remained seropositive (Arvin & Gershon, 1996). The immune response, however, is less persistent in adults or leukaemic children who are immunized, than in healthy children (LaRussa *et al.*, 1996). Nonetheless, more than 80 % of healthy adults have persistence of antibodies to VZV for 7–13 years after immunization (Gershon, 1995). Cell-mediated immunity has also been shown to persist. Maintenance of immune responses and lower rates of breakthrough infections are associated with household exposure to varicella (Gershon *et al.*, 1996). This raises the question as to how well immunity will persist once circulating wild-type VZV is eliminated by vaccine (Garnett & Grenfell, 1992)

Similar fears have been raised about rates of zoster once wild-type VZV is eliminated. There is now good evidence that lifetime contact with children (a surrogate marker for contact with VZV) is highly protective against zoster (Brisson *et al.*, 2002). Eradication of varicella would be estimated to increase the risk of zoster until such time as there were no more people infected with wild-type VZV. The Oka vaccine strain has been shown to cause zoster significantly less frequently than wild-type VZV in leukaemic and healthy children as well as in healthy

adults (LaRussa *et al.*, 1996). It has also been estimated that, unless concerted catch-up programmes to vaccinate older children and seronegative adults are included in a vaccination programme, outbreaks of VZV may occur within 20–40 years (Edmunds & Brisson, 2002). If the mean age of those infected is shifted upwards, concomitantly greater burden of disease may occur.

A recent estimate of the cost benefit of different vaccination strategies in Canada, taking into account the effect of vaccine on both varicella and zoster, concluded that the most beneficial strategy would involve vaccination of seronegative 12-year-olds (Brisson & Edmunds, 2002). This would allow continued circulation of wild-type VZV in younger age groups and boosting of immunity. This strategy would only reduce by half hospitalizations and mortality due to varicella, as the main burden of disease is in children. However, it would avoid the problems of increased zoster which might follow mass childhood vaccination.

The link between waning cellular immunity and the development of herpes zoster has prompted investigators to explore the possibility that Oka strain vaccine might be used to boost immunity in elderly patients and reduce the incidence of zoster. Prevention of zoster using the current vaccine would be cost-effective in terms of the cost of drugs, pain clinic follow up and GP consultations (Brisson *et al.*, 2000). To test how effective Oka vaccination would be in reducing zoster in the elderly, a large-scale placebo-controlled trial is currently under way in the USA (Oxman, 1995). Zoster is not uncommon in younger people, with two-thirds of cases occurring in those aged under 65 years. A study in the UK is currently evaluating the burden of disease due to zoster to determine whether prevention would be cost effective.

So should vaccination against varicella be introduced into the UK? In the USA, universal varicella vaccination has been shown to reduce epidemics of varicella with concomitant reductions in related morbidity and hospitalization among children and adults (Seward *et al.*, 2002). Some question marks remain as to the long-term effects of vaccine used in a population-wide programme. Eradication of circulating wild-type VZV may reduce boosting of immunity in latently infected individuals, leading to an increase in cases of zoster (Garnett & Grenfell, 1992). Prevention of zoster by vaccinating those latently infected

with wild-type VZV might in itself be cost-effective and is being evaluated in the USA. More data are needed in the UK before universal immunization against varicella and/or zoster is considered.

In the meantime, there is good evidence that targeted vaccination of healthcare workers is economically beneficial (Gray *et al.*, 1997) and licensing of vaccine for this group and for contacts of immunocompromised patients has already been approved in the UK. Targeted vaccination of healthcare workers will obviate the need for time consuming and costly follow up of VZV exposures and removal of staff from work. However, there are still some concerns that healthcare workers who remain susceptible may, as a result, be at higher risk of infection and must therefore be identified and counselled accordingly. Similarly, as the number of doses of VZIG dispensed for susceptible pregnant women who come into contact with varicella increases, there is mounting interest in evaluating whether immunization of seronegative women of childbearing age might be feasible and cost effective.

Judith Breuer

Skin Virus Laboratory, Department of Cutaneous Research, 25–29 Ashfield St, London E1 1BB, UK

Correspondence: Judith Breuer (j.breuer@qmul.ac.uk)

Ampofo, K., Saiman, L., LaRussa, P., Steinberg, S., Annunziato, P. & Gershon, A. (2002). Persistence of immunity to live attenuated varicella vaccine in healthy adults. *Clin Infect Dis* **34**, 774–779.

Arvin, A. M. & Gershon, A. A. (1996). Live attenuated varicella vaccine. *Annu Rev Microbiol* **50**, 59–100.

Asano, Y., Suga, S., Yoshikawa, T., Kobayashi, I., Yazaki, T., Shibata, M., Tsuzuki, K. & Ito, S. (1994). Experience and reason: twenty year follow up of protective immunity of the Oka live varicella vaccine. *Pediatrics* **94**, 524–526.

Black, S., Shinefield, H., Ray, P., Lewis, E., Hansen, J., Schwalbe, J., Coplan, P., Sharrar, R. & Guess, H. (1999). Postmarketing evaluation of the safety and effectiveness of varicella vaccine. *Pediatr Infect Dis J* **18**, 1041–1046.

Brisson, M. & Edmunds, W. J. (2002). The cost-effectiveness of varicella vaccination in Canada. *Vaccine* **20**, 1113–1125.

Brisson, M., Edmunds, W. J., Gay, N. J., Law, B. & De Serres, G. (2000). Analysis of varicella

vaccine breakthrough rates: implications for the effectiveness of immunisation programmes. *Vaccine* **18**, 2775–2778.

Brisson, M., Gay, N. J., Edmunds, W. J. & Andrews, N. J. (2002). Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. *Vaccine* **20**, 2500–2507.

Clements, D. A., Moreira, S. P., Coplan, P. M., Bland, C. L. & Walter, E. B. (1999). Postlicensure study of varicella vaccine effectiveness in a day-care setting. *Pediatr Infect Dis J* **18**, 1047–1050.

Edmunds, W. J. & Brisson, M. (2002). The effect of vaccination on the epidemiology of varicella zoster virus. *J Infect* **44**, 211–219.

Garnett, G. P. & Grenfell, B. T. (1992). The epidemiology of varicella-zoster virus infections: a mathematical model. *Epidemiol Infect* **108**, 495–511.

Gershon, A. A. (1995). Varicella-Zoster virus: prospects for control. *Adv Pediatr Infect Dis* **10**, 93–123.

Gershon, A. A., LaRussa, P., Steinberg, S., Mervish, N., Lo, S. H. & Meier, P. (1996). The protective effect of immunologic boosting against zoster: an analysis in leukemic children who were vaccinated against chickenpox. *J Infect Dis* **173**, 450–453.

Gray, A. M., Fenn, P., Weinberg, J., Miller, E. & McGuire, A. (1997). An economic analysis of varicella vaccination for health care workers. *Epidemiol Infect* **119**, 209–220.

Hardy, I., Gershon, A. A., Steinberg, S. P. & LaRussa, P. (1991). The incidence of zoster after immunization with live attenuated varicella vaccine. A study in children with leukemia. *N Engl J Med* **325**, 1545–1550.

Johnson, C. E., Stancin, T., Fattlar, D., Rome, L. P. & Kumar, M. L. (1997). A long-term prospective study of varicella vaccine in healthy children. *Pediatrics* **100**, 761–766.

Kappagoda, C., Shaw, P., Burgess, M. & Cramer, L. (1999). Varicella vaccine in non-immune household contacts of children with cancer or leukaemia. *J Paediatr Child Health* **35**, 341–345.

Kuter, B. J., Weibel, R. E., Guess, H. A. & 7 other authors (1991). Oka/Merck varicella vaccine in healthy children: final report of a 2-year efficacy study and 7-year follow-up studies. *Vaccine* **9**, 643–647.

LaRussa, P., Steinberg, S. & Gershon, A. A. (1996). Varicella vaccine for immunocompromised children: results of collaborative studies in the United States and Canada. *J Infect Dis* **174** (Suppl.), S320–S323.

Oxman, M. N. (1995). Immunization to reduce the frequency and severity of herpes zoster and its complications. *Neurology* **45** (Suppl.), S41–S46.

ACIP (1999). Prevention of varicella. Update recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* **48** (RR-6), 1–5.

Seward, J., Watson, B. M., Peterson, C. L. & 9 other authors (2002). Varicella disease after introduction of varicella vaccine the United States 1995–2000. *JAMA* **287**, 606–611.

Sharrar, R. G., LaRussa, P., Galea, S. A., Steinberg, S. P., Sweet, A. R., Keatley, R. M., Wells, M. E., Stephenson, W. P. & Gershon, A. A. (2000). The postmarketing safety profile of varicella vaccine. *Vaccine* **19**, 916–923.

Varis, T. & Vesikari, T. (1996). Efficacy of high-titer live attenuated varicella vaccine in healthy young children. *J Infect Dis* **174**, S330–S334.

Vazquez, M., LaRussa, P. S., Gershon, A. A., Steinberg, S. P., Freudigman, K. & Shapiro, E. D. (2001). The effectiveness of the varicella vaccine in clinical practice. *N Engl J Med* **344**, 955–960.

Weibel, R. E., Neff, B. J., Kuter B. J. & 7 other authors (1984). Live attenuated varicella virus vaccine: efficacy trial in healthy children. *N Engl J Med* **310**, 1409–1411.

White, C. J., Kuter, B. J., Hildebrand, C. S. & 7 other authors (1991). Varicella vaccine (VARIVAX) in healthy children and adolescents results from clinical trials, 1987 to 1989. *Pediatrics* **87**, 604–610.