

# Vaccination to prevent varicella and shingles

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## Abstract

**Vaccination of healthy children against varicella using the live attenuated Oka vaccine has been available in Japan and south Korea for several years. In 1996, a programme of universal vaccination of children to prevent varicella was introduced in the USA and other countries, including Canada, Germany, and Sweden, have licensed the vaccine for use in healthy children. This article reviews the origin of the Oka vaccine and the evidence for vaccine safety and efficacy in children and adults. Universal vaccination of children and targeted vaccination of groups at risk of severe varicella are discussed. The possible use of the Oka vaccine to prevent zoster is reviewed, and initiatives to develop new varicella zoster virus vaccines are outlined.**

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In the UK, chickenpox (varicella) is generally a mild, self limiting disease that occurs, for the most part, in young children. The most common complication occurring in healthy children is staphylococcal or streptococcal bacterial superinfection. More rarely, 1/200 000 healthy children will develop a pneumonitis or encephalitis. However, in immunocompromised patients, pregnant women, and healthy adults, varicella can be severe and in some cases life threatening.<sup>1-3</sup> Furthermore, fetal varicella syndrome, which occurs in 1-2% of babies born to mothers infected in the first 20 weeks of pregnancy, is now an important cause of congenital abnormalities in the UK.

Since its development in the mid 1970s, the live attenuated Oka vaccine has been used extensively to prevent primary infection in vulnerable groups.<sup>4</sup> In 1996, the vaccine was licensed in the USA for the universal vaccination of children<sup>5</sup> and is also available for general vaccination in Japan and south Korea.<sup>6</sup> In the UK, where some of the early trials of vaccine safety and efficacy were first carried out in the early 1980s, the vaccine is not licensed for use but can be obtained on a named patient basis. The possibility that the vaccine could be given to prevent or reduce reactivation of varicella zoster virus (VZV)—that is, shingles and its sequelae—is also now under examination.<sup>7</sup> New approaches to vaccination, including the incorporation of peptides into virus-like particles<sup>8</sup> and vaccination of naked VZV DNA,<sup>9 10</sup> are also being explored.

## Development and production of Oka

The live attenuated Oka vaccine was developed in 1974.<sup>4 11</sup> Virus from a child with varicella was serially passaged at low temperature (34°C) in human fibroblasts, followed by passage in guinea pig embryo fibroblasts and production of a standardised seed lot in human diploid cells. Production of the vaccine is now standardised according to the World Health Organisation's "good manufacturing process".<sup>11</sup>

## Differences between Oka and wild-type varicella virus

It is important for studies of efficacy and attenuation that Oka can be differentiated from wild-type virus.

### BIOLOGICAL DIFFERENCES

Oka can be distinguished by reduced plaque size in human embryo lung cells at 39°C compared with wild-type varicella but better growth at 34°C. Oka also replicates better than wild-type virus in guinea pig embryo fibroblasts.<sup>4</sup> The Oka vaccine strain replicates less well than the parental Oka strain in implants of epithelial cells that had been grafted on to a severe combined immunodeficient (SCID) human/mouse model,<sup>12</sup> and this might be related to expression of glycoprotein C. More recently, in an in vitro model the Oka vaccine strain replicated in T cells as well as clinical isolates but spread less well to epithelial cell lines.<sup>13</sup> Although the exact basis for this biological difference is unknown, the behaviour of Oka could be mimicked by deletion of open reading frame 47 (ORF47) from wild-type viruses.

### GENETIC VARIATION

Genetic differences between Oka and wild-type viruses originating in the USA and UK have been found by restriction enzyme analysis and the polymerase chain reaction.<sup>14-17</sup> These appear to reflect geographical differences, with strains originating from the USA and UK distinguishable from Oka by the presence of a PstI restriction site in gene 38.<sup>15 16</sup> In Japan, up to 30% of strains are indistinguishable from Oka at this marker and 3% are identical to Oka at all known polymorphic markers.<sup>17</sup> More recent data, in which 34 kb at the 3' end of the Oka vaccine and parental strain genomes were sequenced has revealed several nucleotide differences between the two. The functional importance of these is not known.<sup>18</sup> Moreover, polymorphisms in ORF62 appear to distinguish Oka from all Japanese and US strains tested.

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### Clinical studies with Oka

#### MEASURES OF VACCINE EFFICACY

Clinical studies indicate that vaccination offers good protection against varicella. However, there has been only one placebo controlled study of varicella vaccine. In that study, 468 children were immunised with a dose of 17 000 plaque forming units (pfu) and 446 were given placebo.<sup>19</sup> Over the following nine months, there were 39 cases of chickenpox, which all occurred in the placebo recipients, giving a vaccine efficacy of 100%. During the second year of the study, one vaccinated child developed chickenpox, giving an efficacy rate of 98%. The children who originally received placebo were then vaccinated. During seven years of follow up, it was estimated that 95% of the vaccinees remained free of varicella. This high degree of protection may be accounted for by the titre of the vaccine (17 000 pfu) used. This titre is the highest dose ever used but is impractical to produce on a commercial scale.<sup>20</sup> However, even at this high titre, the vaccine was found to be well tolerated.<sup>19</sup>

#### BREAKTHROUGH VARICELLA

In unimmunised, susceptible adults, the attack rate is approximately 90% after household exposure to chickenpox. Vaccinated adults have a lower degree of protection than children; their attack rate after household exposure to varicella is 30–40%,<sup>21</sup> compared with children with leukaemia, who have an attack rate of about 13%,<sup>22</sup> and healthy children who have an attack rate of about 10%.<sup>23 24</sup> In all these groups, breakthrough infections are milder than natural infections. The incidence of fever and the numbers of lesions are lower in both vaccinated children with leukaemia and healthy children.<sup>19 25</sup> Risk factors for breakthrough varicella include age < 14 months at immunisation and low titre of vaccine dose.<sup>26</sup>

#### SAFETY OF OKA STRAIN VARICELLA VACCINE

Several clinical studies have documented that the Oka strain varicella vaccine is safe and provides effective long term immunity. The main adverse effect after immunisation is a minor skin rash. The frequency of rash reported after immunisation in healthy children is about 5% and there are very few skin lesions (in general, < 10%).<sup>2 27</sup> Other common adverse events include fever (15%), temporary discomfort at the injection site (19–24%), and rash at the injection site (3–4%).<sup>2 27</sup> 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.<sup>20</sup> Follow up of 90 000 healthy children and adults who were vaccinated with Oka after its licensing in the USA in 1995 supports its safety profile, with no serious adverse events seen.<sup>28 29</sup> However, in vaccinated children with leukaemia, the incidence of adverse events in the first six weeks after immunisation is significantly higher than in healthy children. A vaccine associated rash was the most

common adverse event reported after immunisation. Fifty per cent of children with leukaemia receiving chemotherapy developed a rash, compared with 5% of children no longer receiving chemotherapy in a study of 548 children with leukaemia. Other adverse events were reported less frequently—in about 5% of these children.<sup>20</sup> Another strategy has been to vaccinate the seronegative household contacts of children suffering with leukaemia and cancer. One study showed no transmission of Oka by family members to the patient with cancer, suggesting that this might be a safe measure to reduce the risk of varicella in these patients.<sup>30</sup>

Transmission of the vaccine strain is rare and has been documented in healthy immunocompetent contacts in three cases out of 15 million doses of varicella vaccine distributed.<sup>31</sup>

### Immune responses to varicella vaccine

#### SEROCONVERSION

In general, the rate of seroconversion after vaccination is high, with 95% of healthy children seroconverting after one dose of the vaccine.<sup>19 27 32 33</sup> In contrast, only 80–85% of children with leukaemia seroconvert after one dose and this rises to 90% after two doses. Seronegative healthy adults have been vaccinated successfully in several studies but, as with children with leukaemia, most investigators found that two doses of vaccine are required to achieve a seroconversion rate of more than 90%.<sup>20</sup>

#### PERSISTENCE OF ANTIBODY RESPONSE AFTER SEROCONVERSION

In a 20 year follow up after immunisation, 25 of 26 young adults who had been immunised as children remained seropositive.<sup>6</sup> Similarly, of over 500 healthy children who were followed for up to six years, 95% remained seropositive.<sup>20</sup> However, the immune response is less persistent in adults or children with leukaemia who are immunised than in healthy children.<sup>2</sup> Nonetheless, more than 80% of healthy adults have persistence of antibodies to varicella from seven to 13 years after immunisation.<sup>2</sup>

#### CELL MEDIATED IMMUNITY

In children, a good cell mediated immune response is produced after one dose of vaccine. In contrast, for adults two doses are required to produce the same degree of cellular immune response.<sup>20 34 35</sup> This difference may be explained by the changes in the immune system that accompany aging, including a decreased ability of T cells to recognise VZV antigens, which appears to begin at about 40 years of age.<sup>24</sup>

#### CORRELATES OF PROTECTION

It is uncertain which responses to vaccination correlate with protection. There is good evidence that cell mediated immunity correlates with protection but less consensus that the presence of antibody is protective.<sup>23</sup> The severity or incidence of varicella did not increase with time for children with leukaemia who had originally seroconverted after vaccination but

who subsequently became seronegative over a period of up to 11 years.<sup>36</sup> In contrast, the attack rate of breakthrough varicella after household exposure in 83 children was 8% in seropositive children and 29% in seronegative children.<sup>37</sup> Furthermore, protection correlated with the titre of VZV specific antibody at six weeks after vaccination in a study of 4042 healthy children and adolescents.<sup>32</sup>

#### BOOSTER DOSES

Natural boosting can occur because of periodic re-exposure during varicella epidemics and this could be a reason why immune responses persist.<sup>38-40</sup> Immunity to VZV can also be maintained by subclinical reactivations of latent virus resulting in endogenous re-exposure to viral antigens.<sup>41</sup> Recently, it has been proposed that the maintenance of antibody values in vaccinees can only be explained if endogenous reactivation of Oka is occurring.<sup>42</sup>

Vaccination has also been shown to give prolonged immune responses. However, the persistence of immunity has been questioned, and there are concerns about the risk of varicella outbreaks in non-responders and in those who were vaccinated some time previously if the vaccine is used widely. Therefore, studies have evaluated the responses to booster doses of vaccine given several years after initial immunisation. Booster doses are associated with increases in humoral<sup>43-44</sup> and cellular immunity<sup>44</sup> in immunocompetent adults and are well tolerated.<sup>43-44</sup> However, although it seems likely that booster doses will increase protection, this remains to be proved formally in field trials.

#### Vaccine formulation

##### DOSAGE

The titre of vaccine, as assessed by the number of pfu of virus, is correlated with the intensity of the immune response and protective efficacy. Higher titres of infectious virus result in higher rates of seroconversion, and higher amounts of antibody.<sup>43-45-46</sup> Although greater T cell proliferation also appears to be related to higher titres of virus in the vaccine,<sup>27-46</sup> this might in fact reflect the effect of increased antigen content.<sup>20-45</sup> Recipients of Oka or partially heat inactivated aliquots from the same batch showed no difference in cell mediated immune responses.<sup>45</sup> The titre of virus rather than antigen content also correlates with the degree of protection offered by the vaccine. Among 5131 children aged 0-30 months, the efficacy of a high titre vaccine (10 000-15 850 pfu) in preventing breakthrough varicella was 88%, as opposed to 55% efficacy of a low titre vaccine (630-1260 pfu) ( $p = 0.05$ ). This result has implications for storage and handling of the vaccine because the vaccine is labile and sensitive to light.

##### OKA STRAIN VARICELLA VACCINE IN COMBINATION WITH MMR VACCINE

The recent licensing of the Oka strain varicella vaccine in the USA has led to the suggestion that the addition of the varicella vaccine to the measles-mumps-rubella (MMR) combination

vaccine would make universal vaccination more feasible and acceptable.<sup>47-48</sup> A preparation containing both the MMR vaccine and the varicella vaccine (MMRV) has been compared with the MMR vaccine and varicella vaccine (MMR+V) injected at separate sites either at the same visit or six weeks apart.<sup>47-48</sup> In all groups seroconversion was 100% for all viruses. Although the antibody titre to varicella was lower in the MMRV group at six weeks there was no difference between the groups at one year. There was no significant difference in lymphocyte proliferation responses between the groups<sup>47</sup> and no differences in the frequency of local and systemic reactions.

##### ZOSTER AFTER OKA

Studies in children with leukaemia suggest that the rate of zoster is lower in those who have been vaccinated (2%) as compared with matched children with leukaemia who had experienced natural varicella (15%).<sup>37-49</sup> In 268 healthy adults who had received two doses of vaccine, three months apart, the calculated incidence of herpes zoster was 12.8 cases/100 000 person years, compared with an expected rate of 77 cases/100 000 person years.<sup>50</sup> There are several hypotheses as to why herpes zoster is less common after vaccination than natural infection. It may be simply because the vaccine virus has been attenuated. Alternatively, because vaccination seldom causes skin lesions, the virus is less likely to infect the sensory nerves and associated ganglia. Support for the importance of a skin rash comes from studies of vaccinated children with leukaemia in whom the risk of developing zoster was nearly six times higher if the vaccinee had a history of VZV related rash than if no rash had occurred.<sup>37</sup> The apparent importance of a skin rash for the development of herpes zoster has led to the prediction that the incidence of herpes zoster will be lower in healthy vaccinees than those who have had natural infection. This is because a vaccine associated rash and breakthrough varicella are unusual in healthy vaccinated adults or children.<sup>2-49</sup>

##### VACCINATION TO REDUCE THE INCIDENCE OF HERPES ZOSTER

The link between waning cellular immunity and the development of herpes zoster has prompted investigators to explore the possibility that the Oka strain vaccine might be used to boost immunity in elderly patients and reduce the incidence of zoster. In one study the vaccine was administered to 200 elderly individuals (mean age, 67 years). The responder cell frequency increased from 1/70 000 peripheral blood mononuclear cells (PBMCs) to 1/40 000 PBMCs. This response is comparable to that seen after natural infection and to that observed in 40 year old individuals.<sup>51-52</sup> The increase in VZV specific, cell mediated immunity was long lasting, with a half life of 54 weeks.<sup>52</sup> In the four years of observation, only one case of herpes zoster was virologically confirmed and two cases were immunologically confirmed. None of the cases

was associated with prolonged zoster associated pain or extensive rash.<sup>52</sup> However, 10–15% of subjects failed to respond to the vaccine. More recently, similar increases in cell mediated immunity and antibody responses to VZV have been seen in a randomised controlled study in which patients aged over 55 years were vaccinated with Oka, whereas the controls received pneumococcal vaccination.<sup>53</sup> This study concluded that the Oka vaccine titre affected neither the humoral nor the cell mediated immune response, a result that conflicted with previous studies and remains to be verified.

To test how effective Oka vaccination would be in reducing zoster in the elderly a large scale, placebo controlled trial is under way.<sup>7</sup>

### Other vaccines

#### KILLED VACCINE

Experiments with heat inactivated Oka vaccine suggest that although the nature of the cell mediated response is not altered, the magnitude of class 1 restricted killing is decreased.<sup>54</sup> This suggests that the inactivated vaccine is less well presented and probably less immunogenic.

#### ALTERNATIVE VACCINES

The development of alternative vaccines to Oka is still in its infancy. Fragments of VZV glycoprotein E and assembly proteins presented on yeast Ty virus-like particles induced VZV specific proliferative cell responses using primed lymphocytes from Oka vaccinated individuals. gE and IE 62 synthetic peptides presented on monocytes also induce cellular proliferation of primed lymphocytes. However, the same peptides presented by dendritic cells induce proliferation of naïve PBMCs. Therefore, this system could be used to predict the potential immunogenicity of protein epitopes. Injection of mice with a recombinant glycoprotein B peptide, an immunodominant epitope in vivo, induced strong neutralising antibodies, whereas recombinant glycoprotein E peptides, which are also immunodominant in human infection, did not. DNA vaccination of mice with genes encoding gE<sup>14</sup> and IE62<sup>14</sup> has also been shown to induce good antibody and T cell responses.

### Vaccination strategies

Two approaches to preventing varicella and its complications are possible: targeted and universal vaccination.

#### UNIVERSAL VACCINATION

Studies in the USA, Germany, and France show that universal vaccination of young children (15–18 months) is cost effective if both medical and non-medical costs (parental days off work) are taken into account.<sup>55–59</sup> Direct medical cost savings can be made if vaccination of susceptible adolescents (12 year olds) only is carried out, but this approach is less likely to succeed in reducing the incidence of varicella.<sup>58–59</sup> However, in all cases the analyses used resource data where the costs of treatment of varicella are high. For example, in the

German model if aciclovir use in adults (> 14 years) is less than 40%, no cost benefit is seen even when indirect costs are included.<sup>59</sup> Since 1996, universal vaccination of all children aged 12–18 months has been recommended by the Advisory Committee on Immunisation Practices (ACIP) in the USA. In addition, vaccination of healthy seronegative persons over 13 years, including healthcare workers, is recommended in addition to post exposure vaccination to contain outbreaks. Immunisation of patients with deficiencies of cell mediated immunity other than certain children with acute lymphoblastic leukaemia was previously discouraged. However, a recent update now advocates the immunisation of asymptomatic human immunodeficiency virus positive children.<sup>31</sup>

Over nine million doses of vaccine have now been administered in the USA and 6580 adverse events recorded. Although 4% of these were serious adverse events, the rate is lower than for natural disease. Of 14 deaths reported, eight had other explanations, three had other probable explanations, and in three not enough information was available to determine the cause.

#### TARGETED VACCINATION

The cost benefits of targeted vaccination have been demonstrated for several groups at risk of severe varicella. In a study of 472 children with leukaemia, it was 11–13 times cheaper to vaccinate children than to treat them.<sup>58</sup> Vaccinating susceptible women of childbearing age would reduce both maternal and fetal complications associated with varicella in pregnancy.<sup>60–61</sup> Vaccination of susceptible women of childbearing age may be particularly cost beneficial in populations where the seronegativity rates are high (10–20%)—for example, among immigrant populations in east London (J Breuer, 2001, unpublished). Targeted vaccination of susceptible healthcare workers has also been proposed as a means of reducing risk to immunosuppressed patients, simplifying infection control procedures, and reducing the costs of controlling outbreaks and days lost from work.<sup>62</sup>

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