A review of the varicella vaccine in immunocompromised individuals

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Summary
Background: Individuals with underlying cell-mediated immunodeficiency disorders are at high risk of developing severe, life-threatening illness associated with varicella-zoster virus infection. A live-attenuated varicella vaccine is recommended for routine childhood immunisation in some countries. In healthy children, the vaccine is efficacious and safe but because immunocompromised individuals may be unable to limit replication of live-attenuated vaccine viruses, the varicella vaccine is not recommended for them and there are few exceptions.

Objectives: The purpose of this paper is to review the published studies addressing the use of the varicella vaccine in people with cell-mediated immunodeficiency disorders.

Methods: A computerised search on the PubMed database was used to collect the relevant papers published up to March 2003.

Results: The varicella vaccine has been extensively studied in susceptible children with acute lymphoblastic leukaemia in remission, but studies involving individuals with other immunodeficiency disorders are scarce. Some of the current recommendations are based on very few and small studies with short follow-up. Immunocompromised individuals should be given the varicella vaccine only with complete knowledge of their clinical and immunological conditions and after considering the risks of natural infection and vaccination.

Introduction

The varicella-zoster virus (VZV) causes two clinical diseases: primary VZV infection is manifested by varicella (chickenpox) after which the virus establishes latency in dorsal root ganglia. As a result of waning cell-mediated immunity, VZV may reactivate years or decades later causing herpes zoster (shingles).

Varicella is predominantly a disease of childhood. In most temperate countries, more than 90%
of cases of varicella occur in persons under 15 years of age.1 Serologic studies have shown that more than 90% of adults are immune to VZV.1 There are suggestions of higher rates of susceptibility to VZV amongst adults in tropical areas.1 In Brazil, a seroprevalence study showed that 57% of children aged under 5 years, 86% of those from six to ten years and 95% of adolescents and adults were seropositive to VZV.2

Varicella is highly contagious. Secondary attack rates greater than 85% amongst susceptible children after household or close exposure have been reported.3,4 Secondary familial cases of varicella are usually more severe than primary cases.5 The great majority of primary VZV infection involves uncomplicated chickenpox in otherwise healthy children. However, severe illness with visceral involvement, mainly pneumonia, hepatitis and encephalitis, and fatal outcome may occur. Children less than one year of age, adults and immunocompromised individuals, particularly those with impairment of cell-mediated immunity, are at high risk for developing complications.5—12

Approximately 15—20% of the general population will experience reactivation of VZV during their lifetime.1,3,4 The elderly and patients with underlying immunodeficiency disorders are at increased risk of reactivation of latent viruses. Immunocompromised individuals are also at higher risk of developing complications, such as multidermatomal and visceral involvement, and recurrences of herpes zoster.1,5

Immunosuppressive chemotherapy is being increasingly used, more intense immunosuppression is given to patients and immunocompromised individuals are living longer. Paralleling this rise in the number of latently immunosuppressed patients, there is an increasing number of persons infected with HIV, leading to an increase in the number of individuals at risk of developing severe illness if they contract VZV infection. VZV illnesses in patients with immunodeficiency disorders require admission to hospital and the use of antiviral drugs. Moreover, exposure to varicella often results in suspension or delay of scheduled chemotherapy in susceptible persons with malignant disorders and transplant recipients, increasing the risk of progression of underlying disease or graft rejection.1,12 The socioeconomic consequences of VZV disease in immunocompromised patients are catastrophic. Administering the varicella vaccine to the healthy susceptible siblings of immunodepressed children has been shown to be a safe and effective strategy to indirectly protect high-risk children by decreasing their household exposure to VZV.12,14 Nevertheless, community-acquired varicella remains a source of infection for immunocompromised individuals. Passive immunisation with varicella zoster-immunoglobulin (VZIG), administered within three days of exposure, is effective in preventing disease or in reducing severity of illness in susceptible immunocompromised persons.1,8 However, this approach requires recognition of the exposure and needs to be repeated after each exposure. About half of the cases of varicella amongst immunodepressed children occur without a recognised exposure to VZV, and both severe and fatal varicella has been documented despite appropriate immunoprophylaxis with VZIG.8,15 Furthermore, VZIG is expensive and in increasingly short supply. These limitations make passive immunisation a less than optimum strategy for preventing chickenpox. Permanent protection provided by administering the vaccine to the high-risk susceptible persons themselves would be preferable.

The varicella vaccine

A live-attenuated varicella vaccine (Oka strain) was developed in Japan in 197416 and was first licensed for use in high-risk children in some European countries (1984), in Japan (1987) and in Korea (1988).1 It was licensed for use in healthy children in Japan and Korea in 1989, in the USA, Sweden and Germany in 1995, and in Canada, in 1998.1,6 It was licensed for use in high-risk children in some European countries (1984), in Japan (1987) and in Korea (1988).1 It was licensed for use in healthy children in Japan and Korea in 1989, in the USA, Sweden and Germany in 1995, and in Canada, in 1998.1,6

A single dose of the vaccine (≥1000 plaque forming units—PFU/0.5 mL) results in seroconversion in 95% of healthy children.1,6 The efficacy of the vaccine is about 70—90% in preventing chickenpox and 95—100% in protecting against severe illness.5,6,17,18 The vaccine is less immunogenic in healthy adolescents and adults, hence the recommendation of administering two doses, four to eight weeks apart, to persons aged over 12 years.1 The varicella vaccine induces both humoral and cell-mediated immune responses.15—19 Mean antibody titers are usually lower after vaccination than after natural VZV infection.1 Antibody titers have been observed to increase over time after immunisation, presumably due to sub-clinical re-exposure to the wild-type virus or endogenous reactivation.1,10 Japanese studies have shown that immunity to varicella following vaccination lasts for at least ten to 20 years.16,19,21 However, in Japan, vaccination against varicella is optional and the vaccine coverage is low (<20%) allowing circulation of the wild-type virus.16,19,21 There are concerns about the duration of immunity induced by the vaccine without being boosted by re-exposure to the wild-type virus.16,19
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The vaccine is safe and well tolerated in healthy individuals. The most common adverse effects are reactions at the injection site (pain, swelling, redness and rash) observed in 7–30% of vaccinees.1,5,17 The frequency of fever varies from 0–36%.17 A generalised mild varicella-like rash was reported in approximately 5% of vaccinees.4,17,18 Post-licensure studies found that most adverse effects were mild.22,23 Serious adverse events were rare and the role of the vaccine-strain virus was not confirmed for the great majority of them.72,23

The World Health Organization recommends considering routine childhood immunisation against varicella in countries where the disease is an important public health and socioeconomic issue, where the vaccine is affordable and where high (from 85–95%) and sustained vaccine coverage can be achieved.5 In Brazil, routine childhood immunisation against varicella is not currently feasible, considering its high costs and other public health priorities.24 In the USA and Canada, the vaccine is recommended for all children aged 12 to 18 months and for susceptible older children, adolescents and adults.1,6 In the USA, the introduction of the varicella vaccine to the routine childhood immunisation program has already been followed by a reduction in the incidence of varicella in both vaccinated and unvaccinated children in areas with moderate vaccine coverage, suggesting a herd protection effect.25,26

Although the vaccine is highly protective and safe, and routine childhood immunisation against VZV seems to be cost-effective,17–19 there are obstacles to universal immunisation. There is a perception that varicella is a mild disease in healthy children and concerns that the efficacy of the vaccine could wane, in case of no re-exposure to VZV, leading to a shift in the epidemiology of the disease with an increase in the number of cases of chickenpox in adolescents and adults.27

Varicella vaccine coverage rates vary greatly over the USA and the persistence of areas with low vaccine coverage creates the potential for circulation of the wild-type virus.25,26 Furthermore, how the varicella vaccination will affect the incidence of herpes zoster is not yet clear. Exposure to varicella can boost specific VZV immunity, reducing the risks of reactivation.28 Mathematical models predict that the incidence of varicella would rapidly decline following the implementation of routine immunisation,28,29 but ‘the loss of exogenous boosting resulting from the decline in varicella incidence could cause an increase in the incidence of shingles in short to medium term. This increase in incidence of zoster is likely to continue for a number of decades. The more effective the programme is at reducing the incidence of varicella, then the larger the increase in the incidence of zoster’.29

In places where universal childhood immunisation against varicella has been adopted, administering the vaccine to the majority of the susceptible population, including immunocompromised persons, is critical to decrease the circulation of the wild-type virus. In resource-poor countries, where the incidence of varicella is high and routine administration of the varicella vaccine for all children is not viable, targeted vaccination may be a strategy to protect high-risk individuals from severe disease, even though no impact on the epidemiology of the infection is expected.4,29

Immunocompromised persons may be unable to limit replication of live-attenuated vaccine viruses resulting in life-threatening vaccine-induced illness.29 Severe varicella with visceral involvement caused by the vaccine-strain virus has been occasionally reported in intensely immunodepressed subjects who were inadvertently vaccinated.30,31 The ability of the varicella vaccine-strain virus to establish latency and reactivate32 complicates even more its use in individuals with immunodeficiency disorders. Currently, the varicella vaccine may be given to persons with impaired humoral immunity.27,32 However, because of the risks of administering a live-attenuated vaccine to individuals with underlying cell-mediated immunodeficiency disorders, the vaccine is not recommended for them, with few exceptions.1,24,27,32–35

Objectives

The aim of this review is to discuss the methodological aspects and results of published studies referring to the use of the varicella vaccine in persons with underlying cell-mediated immunodeficiency disorders. Based on that, the recommendations that may already be made for these individuals and which studies are required to develop better knowledge in this area will be evaluated.

Methods

The relevant papers published up to March 2003 were collected through a computerised search on the PubMed database using the keywords ‘varicella vaccine’. There was no language restriction. The search was carried out on 21 January 2003, and repeated on 8 April 2003. Of the 866 items found, only 91 papers referring to the use of the vaccine in...
Table 1  Current recommendations for administering varicella vaccine to individuals with underlying immunodeficiency disorders.

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with impaired humoral immunity.</td>
<td>27,32</td>
</tr>
<tr>
<td>Patients with acute lymphoblastic leukemia (ALL) who:</td>
<td>1,24,27,33</td>
</tr>
<tr>
<td>are 12 months to 17 years of age</td>
<td></td>
</tr>
<tr>
<td>have a negative history of varicella</td>
<td></td>
</tr>
<tr>
<td>have leukemia in remission for at least 12 months</td>
<td></td>
</tr>
<tr>
<td>have a peripheral blood lymphocyte count $\geq 700 \text{cells/mm}^3$</td>
<td></td>
</tr>
<tr>
<td>have a platelet count of $\geq 100,000 \text{mm}^3$ within 24 hours of vaccination are not being submitted to radiotherapy; chemotherapy should be withheld for seven days before and after immunisation.</td>
<td></td>
</tr>
<tr>
<td>Bone marrow transplant recipients who:</td>
<td>33</td>
</tr>
<tr>
<td>are immunocompetent</td>
<td></td>
</tr>
<tr>
<td>are not receiving immunosuppressant drugs;</td>
<td></td>
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<tr>
<td>do not have graft versus host disease two years or more after the transplant.</td>
<td></td>
</tr>
<tr>
<td>Children and susceptible adolescents and adults in chronic dialysis.</td>
<td>34</td>
</tr>
<tr>
<td>Candidates for solid organ transplantation who are susceptible to VZV at least three weeks before grafting.</td>
<td>24</td>
</tr>
<tr>
<td>Children who have conditions that require systemic steroid therapy:</td>
<td>1</td>
</tr>
<tr>
<td>if they are receiving $&lt;2 \text{mg/kg of body weight or a total of} 20 \text{mg/day of prednisone}$ or its equivalent</td>
<td></td>
</tr>
<tr>
<td>those who are receiving high doses of systemic steroids ($\geq 2 \text{mg/kg prednisone}$) for $\geq$ two weeks may be vaccinated after steroid therapy has been discontinued for at least three months.</td>
<td></td>
</tr>
<tr>
<td>Susceptible subjects that will be submitted for chemotherapy (in clinical trials).</td>
<td>24</td>
</tr>
<tr>
<td>HIV-infected children:</td>
<td>24,27,32,35</td>
</tr>
<tr>
<td>in CDC class N1 or A1*</td>
<td></td>
</tr>
<tr>
<td>with age-specific CD4 T lymphocyte count $\geq 25%$ or $\geq 20%$.</td>
<td></td>
</tr>
<tr>
<td>HIV-infected susceptible adults and adolescents:</td>
<td>24,35</td>
</tr>
<tr>
<td>without clinical signs of immunodeficiency</td>
<td></td>
</tr>
<tr>
<td>with CD4 T lymphocyte count of $\geq 20%$.</td>
<td></td>
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</tbody>
</table>

*In CDC’s paediatric HIV classification system, Class 1 is an immunologic category defined as ‘no evidence of immunodeficiency’. Two clinical categories under Class 1 are considered: N1 is defined as ‘no signs or symptoms’, and A1 is defined as ‘mild signs or symptoms’. 

Individuals with underlying cell-mediated immunodeficiency disorders (leukaemias, solid tumours, chronic liver disease, end-stage renal failure, bone marrow or solid organ transplantation, HIV infection, and use of corticosteroids) were retained. Randomised controlled trials, open-label trials, cohort studies, reviews, and case reports of adverse effects were selected. Letters (four) were excluded. Additionally, post-licensure adverse events reports (two) and guidelines and recommendations for immunisation against varicella from the World Health Organization, the Centers for Disease Control and Prevention, the American Academy of Pediatrics, Health Canada (National Advisory Committee on Immunization), and the Ministry of Health of Brazil were included.

Clinical trials involving individuals with underlying immunodeficiency disorders

The live-attenuated varicella vaccine has been extensively studied in susceptible children with acute lymphoblastic leukaemia (ALL), but studies involving individuals with other immunodeficiency disorders such as solid tumours, bone marrow and solid organ transplantation, end-stage renal failure, chronic liver disease, conditions requiring chronic steroid therapy and HIV infection are limited. Very few randomised controlled trials were conducted in these individuals. Considering prior evidence of the vaccine efficacy in healthy children, placebo-controlled randomised trials involving immunodepressed individuals would not be eth-
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Low titers of anti-VZV IgG antibodies. Tests of susceptibility to VZV reactivation are related to declining T-cell immunity against VZV but not to cell-mediated immunity after vaccination. The frequency of adverse effects, particularly of varicella-like illness, has been somewhat higher than that observed in healthy children. In Japanese trials, the frequency of rash was greater in children with leukaemia in remission who had received a placebo. In this case, only seroconversion was used as a measure of vaccine efficacy.

Children with acute lymphoblastic leukemia (ALL) and other malignancies

Children with acute lymphoblastic leukemia (ALL) have been the most extensively studied immunocompromised group. By the end of 1983, Japanese trials had involved 326 children with ALL. A multi-centre trial conducted between 1980 and 1992 in the USA and Canada, by the National Institute of Allergy and Infectious Diseases (NIAID) Varicella Vaccine Collaborative Study Group, involving 575 children provided the best evidence that supports the recommendations of administering the varicella vaccine to these individuals. Serological methods have been used as a surrogate measure of the efficacy of the vaccine, as well as to detect waning immunity over time after vaccination. In healthy children, antibody titers measured by an ELISA assay that detects antibodies to VZV glycoprotein (gp-ELISA) has been strongly correlated with protection against varicella. Those who had post-vaccination gp-ELISA titers ≥5U subsequently had lower incidence of varicella than those who had post-vaccination gp-ELISA titers <5U. When varicella developed in children with post-vaccination gp-ELISA ≥5U, it was milder than illness in children with post-vaccination gp-ELISA <5U. However, different serological tests (ELISA, IFA (indirect fluorescent antibody) and FAMA (fluorescence antibody to membrane antigen)) with different sensitivity and specificity were used to measure post-vaccination anti-VZV antibodies in clinical trials. Not all these tests have been evaluated as predictors of protection against varicella. Furthermore, amongst children with malignancies, serological evidence of immunity may be falsely reassuring. There are reports of varicella in seropositive children who underwent organ transplantation. On the other hand, failure to detect antibodies against VZV does not necessarily imply susceptibility, since cell-mediated immunity may be intact. Finally, susceptibility to VZV reactivation is related to declining T-cell immunity against VZV but not to low titers of anti-VZV IgG antibodies. Tests of cell-mediated immunity are not readily available in clinical practice and were applied in very few trials of the varicella vaccine. To evaluate the vaccine efficacy by the rates of breakthrough varicella, studies with large sample size and long follow-up are required. However, most trials involving immunocompromised individuals were small and had short follow-up. In this case, only seroconversion was used as a measure of vaccine efficacy.
rash related to the vaccine was more frequent and extensive in children for whom maintenance immunosuppressant drugs had been suspended for immunisation (50%) than in those who had completed chemotherapy before vaccination (5%). Steroid therapy in the week before or in the week following vaccination was associated with extensive vaccine-induced rashes. Rashes were less frequent after the second dose of the vaccine. Restriction enzyme analysis of DNA from virus isolates showed that rashes appearing one to six weeks after vaccination were due to the vaccine-strain virus, whereas late rashes (more than six weeks after vaccination) were related to the wild-type virus.53,65

In the NIAID study, 13% of vaccinees who had initiated maintenance chemotherapy before vaccination (5%) had greater frequency or severity of adverse effects.55,60 Cell-mediated immunity against VZV was detected in three of four children developed rash with fever after the second dose of the vaccine.61 The long-term duration of immunity after two-dose regimens still needs to be determined. In the NIAID study, 13% of vaccinees who had initially seroconverted became seronegative over a follow-up of up to 11 years, even though the incidence and severity of breakthrough varicella did not increase over time.55,60 Cell-mediated immunity against VZV was detected in three of four children with malignancies who had initially seroconverted after vaccination and lost detectable anti-VZV antibodies.55,60

Prospective cohort studies showed that children with leukaemia who had been given the varicella vaccine were less likely to develop herpes zoster than those who had had natural VZV infection. In Japanese trials, herpes zoster occurred earlier in leukaemic children who had been naturally infected with VZV than in those who had been vaccinated. Moreover, the rates of zoster seemed to be lower in those children with leukemia in remission for whom maintenance chemotherapy was suspended before and after vaccination (3.8%) than in those vaccinated without suspension of immunosuppressant drugs (7.4%).

In the NIAID study, the relative risk of herpes zoster was greater in vaccinees who had developed a VZV rash after vaccination (either caused by the vaccine-strain virus or by the wild-type virus) in comparison to those who had never had a rash (RR = 5.75, 95% CI, 1.3 to 25.7). A Kaplan-Meier life-table analysis showed that the rate of herpes zoster in leukemic children who had been given more than one dose of the vaccine was lower than in children who received just one dose.59 Household exposure to VZV after vaccination was also protective against herpes zoster.59 Finally, from 548 children with ALL who had been given the varicella vaccine in the NIAID trial, 21 eventually received a bone marrow transplant; herpes zoster was observed in 14% (3/21) of transplanted children and in 1.9% (10/527) of those who had not been transplanted.58 Both wild-type VZV53 and vaccine-strain virus53,82 have been isolated from herpes zoster lesions in children with leukaemia who had been vaccinated.

Very few children with malignancies other than ALL were included in trials.66—70,73,77,78,83,84 In a Japanese study, a child with lymphosarcoma developed a varicella-like illness after vaccination.85 Moreover, eight of 20 children with lymphoma who were given the vaccine developed rashes and in four of them the rash was severe. After that, children with lymphoma and lymphosarcoma were not included in clinical trials.61 Children with other solid tumours who were given the vaccine have not had greater frequency or severity of adverse effects.55,60 Further studies involving patients with solid tumours are necessary.

The great majority of studies included only children with leukaemia and other malignant conditions in remission. This approach has been safe and efficient in protecting children who might later suffer a relapse of their underlying illness, even though susceptible children are not protected against varicella during the most intense induction phase of immunosuppressive therapy, when the morbidity of VZV infection is expected to be greater. One attempt to vaccinate leukemic children during the induction phase of chemotherapy was catastrophic: three of four children developed rash with fever and one of them had visceral involvement (hepatitis and encephalopathy).49 However, in another small study, the vaccine was administered to children with cancer on the first day of chemotherapy with promising results.78 Seroconversion or an increase in the titers of VZV antibodies occurred in
most of the vaccinees and only four of 13 seronegative children had mild adverse reactions to the vaccine (fever and/or rash). This strategy may lead to early immunity protecting these high-risk children soon after the diagnosis of cancer and deserves further studies.

Most studies involving patients with malignant disorders were conducted during the late 1970s and early 1980s. Because current chemotherapy is likely to be more intensely immunosuppressive than the one used in those days, it is prudent to withhold chemotherapy at least one week before and one week after vaccination. There are small studies evaluating the use of the vaccine in susceptible high-risk children after nosocomial exposure to varicella that showed prevention or attenuation of the disease when the vaccine was administered one to five days after exposure. Although passive prophylaxis with VZIG is more appropriate in the case of an immunocompromised person with known exposure to VZV, the vaccine may be useful when VZIG is not available.

**Bone marrow transplant (BMT) recipients**

The live-attenuated varicella vaccine is contraindicated for bone marrow transplant (BMT) recipients within 24 months after grafting. The use of the vaccine is restricted to research protocols for patients ≥24 months after BMT who are presumed immunocompetent.

There is just one small study examining the use of the live-attenuated varicella vaccine in recipients of BMT who were no longer receiving immunosuppressive therapy. Fifteen children were given one dose of the vaccine (2000 PFU) 12 to 23 months after BMT. No adverse reaction was observed. Eight of nine seronegative children seroconverted and a rise in antibody titers was observed in three of six children with low antibody titers prior to immunisation. Antibodies persisted for at least 24 months in six of the eight who had seroconverted. None of the vaccinees developed varicella or herpes zoster during the 24-month follow-up period, whereas 24.1% (32/133) of retrospectively reviewed BMT recipients who had not been immunised developed herpes zoster within a period of 32 months after grafting. There were three cases of disseminated zoster and three recurrences among the historical controls. Further research is needed to determine the safety, immunogenicity, and efficacy of the live-attenuated varicella vaccine in BMT recipients.

Protecting BMT recipients from VZV disease is a particular challenge, since illness is usually due to reactivation of latent viruses rather than to new exposure and most diseases occur within the first year post-transplantation when patients are severely immunosuppressed. Reconstitution of VZV immunity is delayed for months and often does not occur until after the patient experiences a reactivation of latent viruses. An investigational heat-inactivated whole-virus varicella vaccine (Oka-strain live-attenuated varicella vaccine killed by heat) was evaluated in recipients of BMT who were seropositive to VZV in two small randomised controlled trials (vaccine or no intervention). When given to BMT adults one month after grafting, a single dose of the inactivated vaccine induced VZV-specific cell-mediated immunity, even though no clinical effects were seen. In a three-dose regimen (one, two and three months post-transplantation), the vaccine reduced the severity of herpes zoster in vaccinees as compared to subjects who did not receive the intervention. In adults with lymphoma who received BMT, a four-dose regimen, in which the first dose was given 30 days before transplantation and three doses were given after grafting (at 30, 60 and 90 days), the inactivated vaccine significantly reduced the risk of herpes zoster that was observed in 13% (7/53) of vaccinees and in 33% (19/58) of unvaccinated patients. The vaccine was well tolerated. The inactivated varicella vaccine may be useful for early reconstitution of specific VZV immunity after hematopoietic transplantation, but further studies are needed.

**Patients with chronic kidney and liver disease, and solid organ transplantation**

Experience with the varicella vaccine is largely limited to susceptible children and adolescents with chronic renal failure and chronic liver disease prior to organ transplantation. For these patients the live-attenuated vaccine administered in both single and two-dose regimens (from 1000 to 2000 PFU/dose) seems to be effective and safe. Serocconversion rates ranged from 50% to 95% after one dose of the vaccine, and from 73.5% to 100% after two-dose regimens. Adverse events were no more frequent or serious than those observed in healthy children. In centres where the vaccine was administered before solid organ transplantation, a decrease in the incidence of both varicella and herpes zoster post-transplant was observed; this is in comparison to incidents in historical controls. Declining titers of anti-VZV antibodies over time after grafting has been observed in children with chronic liver or kidney disease who had been
immunised before transplantation.90,97 Individuals who had been transplanted after immunisation tended to have lower antibody titers in the first two years after grafting than those who had not undergone transplantation.94 However, no differences between the two groups were observed 30 months after grafting, suggesting that the decrease in VZV antibody levels post-transplant is transient.94 In another study, seven liver transplant recipients, who had been vaccinated prior to transplantation and presented waning immunity after grafting, were given a second dose of the vaccine one year post-transplantation.97 No adverse effects were observed and 57% presented an increase in antibody titers after re-vaccination.97 However, the incidence of breakthrough varicella over time after vaccination was not evaluated in these studies. Further studies are necessary to evaluate whether booster doses of the vaccine are needed to keep protection against VZV illnesses after solid organ transplantation.

Just one study evaluated the vaccine in susceptible children who had already received kidney transplantation.91 in an open-label trial, one dose of the vaccine was given to 17 transplant recipients who were seronegative to VZV, without modification of the immunosuppressive therapy.93 No differences in seroconversion rates and in frequency of adverse reactions to the vaccine were observed between transplant recipients and patients with end-stage renal disease on chronic haemodialysis.91 Further trials are required before varicella vaccine is routinely administered to recipients of solid organ transplantation.

Considering that varicella in organ transplant recipients may be life-threatening and concerns about decreased immunogenicity and increased risks of live vaccines in the post-transplantation period, most experts recommend vaccinating susceptible patients prior to grafting wherever possible.35,95—101 The targeted immunisation of children before kidney or liver transplantation seems to be a cost-effective strategy.15,102 A survey of paediatric nephrologists published in 1997, soon after the vaccine was licensed, showed that over 70% of them recommend varicella vaccination for patients on dialysis or with renal failure.103

Children with steroid-sensitive nephrotic syndrome

The experience is limited to open-label clinical trials involving children with steroid-sensitive nephrotic syndrome in remission, who were taking low-dose steroid therapy (≤2mg/kg/day, maximum 40mg of prednisone) or for whom corticosteroids were suspended one or two weeks before vaccination.16,104—106 In this very controlled situation, the vaccine seems to be immunogenic and well tolerated. Seroconversion rates after two doses of vaccine (from 85—100%) were similar to those observed in healthy children. Adverse reactions were no more frequent than in healthy children.16,104—106 Relapse of nephrotic syndrome following vaccination was observed,105,106 but because the studies were uncontrolled and involved a small sample size, it is not clear whether these relapses were related to immunisation or occurred by chance.106

Neither the long-term duration of immunity, nor the rate of herpes zoster in vaccinees was evaluated in these studies, since all of them had short follow-up (up to two years).

HIV infection

There is evidence that natural varicella in HIV-seropositive children does not affect progression of HIV infection107,108 suggesting that immunisation of HIV-infected children against varicella is unlikely to worsen their HIV infection.108

Just one small open-label clinical trial has been published suggesting that the vaccine may be safe in asymptomatic or mildly symptomatic HIV-infected children, even though it seems to be less immunogenic than it is in healthy children.109 Two doses of the vaccine (≥1350PFU) were administered to 41 susceptible HIV-infected children in CDC class N1 or A1 at the time of immunisation. In CDC’s paediatric HIV classification system, Class 1 is an immunologic category defined as ‘no evidence of immunodeficiency’. Two clinical categories under Class 1 are considered: N1 is defined as ‘no signs or symptoms’, and A1 is defined as ‘mild signs or symptoms’. Seroconversion occurred in 53% and 60% of vaccinees after one and two doses, respectively.109 Local reactions (observed in 20% of vaccinees after the first dose) and systemic reactions to the vaccine (in 37%) were mild. Rash related to the vaccine occurred only twice after the first dose and once after the second dose. A marginally significant fall in CD4 T lymphocytes and a significant increase in HIV viral load were observed at four weeks after the first dose of vaccine, but no significant effect was seen at eight weeks.109

The duration of immunity following vaccination, as well as the rates of breakthrough varicella and herpes zoster has not yet been evaluated.

On the other hand, there is a report of severe illness with rash, pneumonia and polyradiculopathy caused by the vaccine-strain varicella virus in a
previously undiagnosed HIV-infected child who presented clinical category B3 and absolute CD4 T cell count of 8 cells/mm³ at the time of diagnosis, suggesting a potential risk of vaccinating HIV-infected children with more advanced T-cell dysfunction.

Even considering the limited data on the use of the vaccine in this population, the American Academy of Pediatrics and CDC recommend considering the varicella vaccine for HIV-infected children in CDC class N1 or A1, with age-specific CD4 T lymphocyte count ≥25%, after weighting potential risks and benefits, since HIV-infected children are at high risk of developing severe illness related to VZV infection.

Conclusions and future studies

Immunocompromised individuals should be vaccinated with the live-attenuated varicella vaccine only with a complete knowledge of their clinical and immunological condition as well as their therapeutic regimen, and after considering the relative risks of the VZV natural infection and vaccination. Some of the current recommendations are based on a few small studies with short follow-up. It is necessary to extend the knowledge of the safety and efficacy of the vaccine in patients with solid tumours, pre- and post-organ transplantation, with HIV infection and conditions that require chronic use of corticosteroids. The long-term safety and efficacy of varicella vaccine in high-risk individuals still need to be determined and require continued monitoring of breakthrough varicella and herpes zoster in immunocompromised vaccinees.

Administering the varicella vaccine to immunocompromised persons with latent VZV infection represents a potential strategy for preventing or at least reducing the severity of herpes zoster in these high-risk individuals. Immunisation with high doses of the live-attenuated vaccine (≥3000 PFU) was shown to be safe and to boost cell-mediated immunity against VZV in healthy persons aged ≥55 with a previous history of varicella. Among healthy elderly subjects who were followed up for six years, it appears that the incidence of herpes zoster was not reduced by vaccination but the reported episodes of zoster were atypically mild.

An investigational heat-inactivated vaccine seems to be equally effective in boosting cell-mediated immunity in elderly persons. The role of the vaccine in preventing or attenuating VZV reactivation in immunocompromised individuals remains an unexplored field.

If routine childhood immunisation against varicella results in a decreased incidence of chickpox, re-evaluation of vaccination programs for immunocompromised patients will be necessary. There may be less need to protect VZV seronegative immunocompromised individuals against varicella, since the risks of exposure to the wild-type virus will be reduced. However, booster doses of the varicella vaccine may be needed to protect immunocompromised persons who are seropositive to VZV (either after vaccination or natural infection) from developing herpes zoster.

It is desirable to provide protection to susceptible immunocompromised individuals as early as it is safe. The investigational heat-inactivated varicella vaccine might be useful for early immunisation of severely immunodepressed subjects without the risks of administering a live-attenuated virus vaccine to these individuals, but further studies are necessary.

Conflict of Interest: No conflicting interest declared.

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