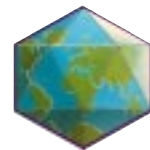


Recommendations from the  
IHMF Management Strategies Workshop and  
3rd Annual Meeting

Editors: Dr S Kroon  
Dr MJ Wood

# MANAGEMENT OF VARICELLA

Jointly sponsored by the University of Alabama School of Medicine,  
University of Alabama at Birmingham, USA and the  
*International Herpes Management Forum* (IHMF)



**IHMF**  
International  
Herpes Management  
— Forum —

# Participants

## CO-CHAIRS:

- Dr S Kroon** Specialist in Dermatology and Venereology,  
Odense University Hospital, Pederstrup Vej 40, DK 5210 Odense NV, Denmark
- Dr MJ Wood** Consultant Physician,  
Department of Infection and Tropical Medicine, Birmingham Heartlands Hospital,  
Bordesley Green East, Birmingham B9 5ST, UK

## SPEAKERS:

- Dr Y Asano** Professor of Pediatrics,  
Department of Pediatrics, Fujita Health University, Toyoake, Aichi 470-11, Japan
- Dr M Levin** Professor of Pediatrics and Medicine,  
Pediatric Infectious Diseases Section,  
University of Colorado Health Sciences Center,  
Campus Box C227, 4200 East 9th Avenue, Denver CO 80262, USA
- Dr D Nathwani** Consultant Physician,  
Infection and Immunodeficiency Service, Kings Cross Hospital,  
Clipington Road, Dundee DD3 8EA, UK
- Dr TF Schwarz** Senior Consultant, Lecturer (Assistant Professor),  
Department of Virology, Max von Pettenkofer Institute for  
Hygiene and Medical Microbiology, University of Munich,  
Pettenkofer Street 9a, D-80336 Munich, Germany
- Dr G Koren** Professor of Pediatrics,  
Department of Pediatrics, University of Toronto, 555 University Avenue,  
Toronto Ontario M5S 1X8, Canada
- Dr M Myers** Professor and Chairman,  
Department of Pediatrics, Northwestern University, 2300 Childrens Plaza #86,  
Chicago IL 60614, USA
- Dr MN Oxman** Professor of Medicine and Pathology,  
Section of Infectious Diseases, University of California SD-VA Medical Center,  
3350 La Jolla Village Drive,  
San Diego CA 92161, USA
- Professor RJ Whitley** Professor of Pediatrics, Microbiology and Medicine,  
The University of Alabama at Birmingham, Suite 616 Children's Hospital,  
1600 7th Avenue South, Birmingham AL 35233-0011, USA

## DISCUSSANTS:

- Professor A Sivayathorn** Associate Professor of Dermatology,  
Department of Dermatology, Faculty of Medicine, Siriraj Hospital,  
Mahidol University, Prannok Street, Bangkok 10700, Thailand
- Dr E Sandström** Associate Professor, Chief of the STD and HIV Services,  
Department Dermato-venereology, Södersjukhuset,  
S-118 83 Stockholm, Sweden
- Dr K Elliott** Assistant Attending Neurologist,  
Pain Service Department of Neurology, Memorial Sloan Kettering Cancer Center,  
1275 York Avenue, New York NY 10021, USA
- Dr J White** Consultant Dermatologist,  
Royal South Hants Hospital, Brintons Terrace, Southampton,  
Hampshire SO9 4PE, UK

The above were participants in the *Management Strategies* Workshop.

The contribution of the participants at the 3rd Annual Meeting of the IHMF is also acknowledged.

The *International Herpes Management Forum* (IHMF) was established to improve the awareness, understanding, counselling and management of infections caused by herpesviruses. Steered by the IHMF Board of Professor Richard Whitley, Dr Susanne Kroon, Dr Martin Wood, Dr Lawrence Corey, Dr Antonio Volpi, Dr Koichi Yaminishi and Professor Paul Griffiths, the IHMF involves international Opinion Leaders in all aspects of medical management of herpesvirus infections including herpes simplex virus (HSV), varicella zoster virus (VZV) and cytomegalovirus (CMV) infections.

The sixth IHMF workshop was held on 10–12 February 1995 to discuss the management of varicella in immunocompetent and immunocompromised individuals. This workshop reviewed the epidemiology of varicella worldwide and evaluated different approaches to the prevention and treatment of varicella, including vaccination strategies and the use of antivirals. Particular attention was focused on the care of the immunocompromised and also those at risk of more severe disease, such as otherwise healthy adults, pregnant women and neonates. The aim of the workshop was to improve the management of varicella and quality of life across all patient populations and to develop recommendations for the best practice of preventing and treating varicella.

The draft recommendations were discussed at the 3rd Annual Meeting of the IHMF that took place on 17–20 November 1995. This publication, *Management of Varicella*, is part of the series, *Management Strategies in Herpes*. It contains the amendments made to the guidelines following extensive discussion at the 3rd Annual Meeting.

The editors would like to thank all the participants at the 3rd Annual Meeting for their contribution and especially the Co-Chairs of the working groups.

This series of monographs is jointly sponsored by the University of Alabama School of Medicine, Division of Continuing Medical Education and the IHMF. This publication is CME accredited for American and Canadian physicians (see page 40 for details).

The information contained in this publication should enable the physician to:

- ◆ Understand the epidemiology of varicella and the geographical variations in its prevalence
- ◆ Describe the characteristics of varicella in immunocompetent and immunocompromised individuals and the neonate
- ◆ Understand the different approaches to pre- and post-exposure prophylaxis and treatment of varicella in immunocompetent individuals
- ◆ Review the different approaches to pre- and post-exposure prophylaxis and treatment of varicella in immunocompromised individuals
- ◆ Define approaches to the management of varicella infections in immunocompetent and immunocompromised individuals and the neonate
- ◆ Understand the cost-effectiveness of treatment of varicella

## Target Audience

The information contained in *Management of Varicella* is aimed at physicians, healthcare workers and other individuals involved in the management of varicella.

## Chapter 1 Epidemiology of Varicella

- ◆ The Immunocompetent Host 5
- ◆ Immune-Altered Individuals at Risk of More Severe Disease 7
- ◆ The Immunocompromised Host 10

## Chapter 2 Management of Immunocompetent Patients with Varicella

- ◆ Pre-Exposure Prophylaxis 13
- ◆ Post-Exposure Prophylaxis 15
- ◆ Treatment 18
- ◆ Cost-Effectiveness of Treatment 20

## Chapter 3 Management of Immunocompromised Patients with Varicella

- ◆ Pre-Exposure Prophylaxis 25
- ◆ Post-Exposure Prophylaxis 26
- ◆ Treatment 27

## Chapter 4 Summary and Recommendations

- ◆ Epidemiology 29
- ◆ Management of Immunocompetent Patients 30
- ◆ Management of Immunocompromised Patients 32
- ◆ Future Directions 34

## Appendix

- ◆ Aciclovir in Pregnancy Registry 35

## References 36

## Acknowledgements 38

## Glossary 39

## Epidemiology of Varicella

Measures of the epidemiology of varicella zoster virus (VZV) infection derive from seroprevalence studies and from reported cases in general practice. VZV antibodies are detected in sera collected from various populations. The results are extrapolated to provide an overall estimate of VZV prevalence. However, because of the small sample size and the different techniques used to store and analyse collected sera, comparison between data sets may be difficult.

In the UK, information on the incidence of varicella is available through cases reported to the Royal College of General Practitioners (RCGP) by sentinel practices in England and Wales since 1967, and in Scotland through statutory notifications since 1989.

### The Immunocompetent Host

#### *Geographical variations*

Studies in immunocompetent populations show that the epidemiology of VZV infection differs between tropical and temperate countries. In temperate countries, the majority of primary infections usually occur before 10 years of age. This is reflected in the seroprevalence of VZV, which in the USA and Germany increases sharply in young children, reaching a maximum of about 90–95% in the adolescent population; only about 5% of individuals remain susceptible to varicella after the age of 15 years.<sup>1–3</sup>

In tropical countries, primary VZV infection tends to occur much later in life with peak seroprevalence only being reached in adults over 40 years of age. Comparison of VZV seroprevalence in St Lucia (tropical) with overall data from Germany, Spain, the USA and Japan (temperate) shows that peak seroprevalence occurs at a later age. Between the ages of 20 and 40 years VZV seroprevalence is only 20–60%, a figure very much lower than the 95% seroprevalence observed in temperate climates over the same age range.<sup>4</sup> Therefore, in St Lucia, VZV is acquired later in life, towards adulthood (Figure 1).<sup>4</sup>

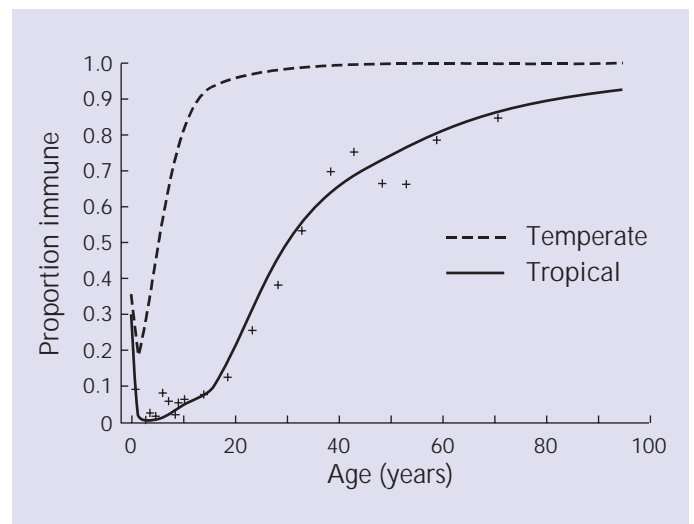


Figure 1: VZV seroprevalence in St Lucia (tropical) compared with combined data from Germany, Spain, the USA and Japan (temperate)<sup>4</sup>

Retrospective analyses of seroprevalence studies from the mid-1970s and early-1980s show that the mean age of infection in most tropical countries is over 20 years of age, and that the overall seroprevalence of VZV in those over 15 years of age appears to be low (41–72%) compared to that found in temperate climates.<sup>4</sup> Similar patterns are found in tropical countries such as Nigeria, where seroprevalence in adults is as low as 30%,<sup>5</sup> in French Guyana,<sup>6</sup> where it is only 63% in the 21–40 years age group and in the Cap Verde Islands where it is 55%.<sup>7</sup>

# Chapter 1

In countries with intermediate climates, the seroprevalence of VZV appears to fall between the two extremes. In Nepal, VZV seroconversion rates are highest among the age groups 10–14 years and  $\geq 15$  years and show an overall seroprevalence in adults

of about 80%, a figure between that found in St Lucia (60%) and the USA, Japan or Europe (95%).<sup>8</sup>

In a comparison of the mean monthly case reports of varicella in India, Nigeria and Sri Lanka, no relationship could be established between reported incidence and climatic or seasonal changes.<sup>4</sup> In India, the highest incidence of varicella occurs during seasons of low temperature and high humidity, whereas in Nigeria the highest incidence is encountered during cool dry months of low temperature and low humidity. In Sri Lanka the incidence is highest when the temperature is high and humidity is low. Therefore, although the distribution of varicella cases differs between countries, the variations do not appear to be *predictable* from climate or seasonal changes (Figure 2).<sup>4</sup>

## Changes in the age of infection

The mean annual rate of varicella in the UK is estimated to be about 600 cases per 100 000 people, which is approximately the same as the birth rate. The same is true in the USA, but some recent studies in the UK and USA suggest that the mean age of acquiring varicella may be rising, with an increasing number of cases occurring in adults.<sup>9–11</sup>

A study by Miller & Marshall found that before 1975, fewer than 10% of varicella cases reported to the RCGP were in 15–44 year-olds.<sup>11</sup> A recent report suggests that this figure had increased to 20% by 1992 (Figure 3).<sup>11</sup> This represents an incidence of about three cases per 1000 in adults aged 15–44 years.

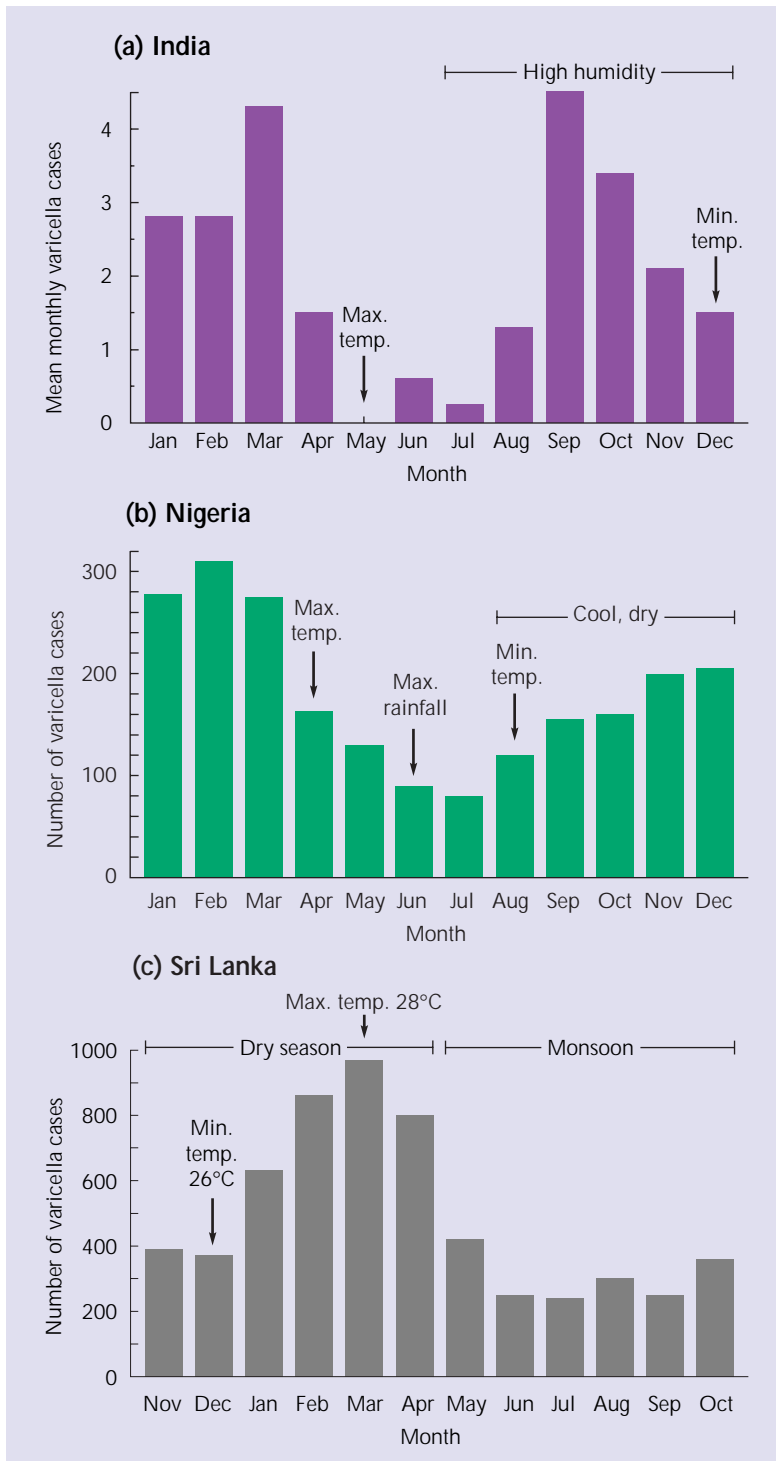


Figure 2: Incidence of reported cases of varicella throughout the year in India, Nigeria and Sri Lanka.<sup>4</sup>

Similar trends have emerged from a study in the USA which reported an increase in hospitalizations due to adult varicella among army and navy recruits.<sup>10</sup> Hospital records for 10 687 adult varicella admissions were reviewed and showed an 18-fold increase in the number of admissions during 1975–1988 among navy recruits and a four-fold increase between 1980–1988 among army personnel, suggesting an increase in the varicella susceptibility of the young adult population.<sup>10</sup>

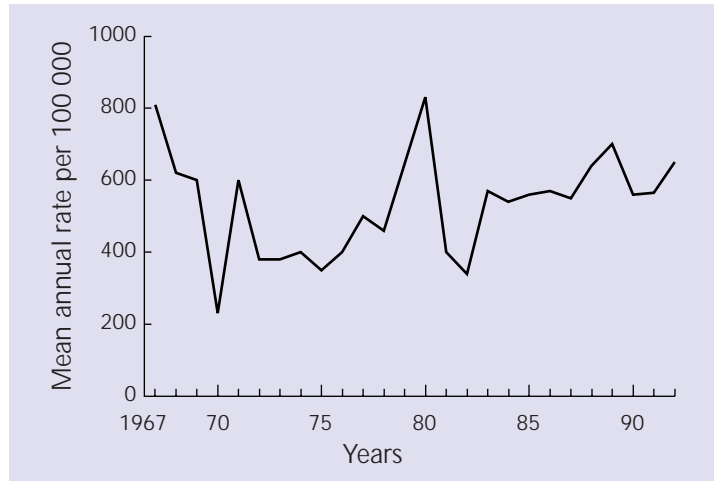


Figure 3: Mean annual rate of reported varicella cases in England and Wales since 1967<sup>11</sup>

This apparent change in age distribution may be the result of different susceptibilities to varicella infection. Emigrants, refugees and students from low-VZV endemicity countries (low seroprevalence of VZV) may be considered high-risk groups for acquisition of varicella when they emigrate to countries of high-VZV endemicity and are then particularly susceptible to infection as adults.

A study of Puerto Rican army recruits (17–34 years of age) found a low seroprevalence of VZV antibody (42%),<sup>12</sup> suggesting that this population would be highly susceptible to VZV infection and, in another study of USA Navy and Marine Corps recruits, Hispanics were found to have a lower seroprevalence of VZV antibody than other ethnic/racial groups.<sup>13</sup> The higher varicella susceptibility of recruits from Hispanic backgrounds may also explain the results from the study in Gray *et al.*<sup>10</sup> Similar susceptibility was noted in a European study of Tamil refugees; a high proportion (44%) of refugees entering Denmark developed VZV infection within the first few months after arrival and of these 38% were adults.<sup>14</sup>

The study by Miller & Marshall also noted an increase in mortality from varicella in the UK, with deaths in adults accounting for 74% (89 deaths, mortality rate 0.043 per 100 000) of all reported varicella-related deaths between 1986 and 1990 compared with 57% (40 deaths, mortality rate 0.021 per 100 000) between 1971 and 1975.<sup>9</sup> A similar study by Preblud & D'Angelo from the USA, between 1972 and 1977, found a rate of only 24% of varicella-related deaths in adults over 20 years of age; the reason for the differences between these studies in the 1970s is unclear.<sup>15</sup> The higher rates of mortality in adults may be biased by a decreased mortality from varicella in immunocompromised children; the advent of antiviral therapy and its widespread use in this population has considerably decreased mortality.

## Immune-Altered Individuals at Risk of More Severe Disease

### *Immune-altered adults*

Seronegative or susceptible adults are known to be at risk of varicella pneumonitis if they develop varicella.<sup>15,19,20</sup> The risk is increased in men and among smokers; an Australian study showed the risk to be 15 times that of non-smokers.<sup>21</sup>

## Pregnant women and the neonate

There is growing recognition that *immune-altered* individuals such as pregnant women and neonates are at greater risk from severe or life-threatening disease. Compared with otherwise healthy children and adults, these individuals are less able to mount a vigorous T-cell response to infection and are therefore more likely to suffer severe or progressive disease.

According to seroepidemiological studies in Germany for example, only 5.2% of women of child-bearing age (15–40 years) lack antibodies to VZV.<sup>22</sup> In North America, an estimated 6% of varicella cases occur during child-bearing age,<sup>23</sup> but only 0.05–0.07% of pregnancies are complicated by VZV infection.<sup>24</sup> In the UK, it has been estimated that 0.3% of gestations are associated with varicella infection.<sup>11</sup>

The pregnant woman may be at greater risk for developing severe varicella and its complications than non-pregnant women of the same age.<sup>10,25</sup> In a study of 43 pregnant women with varicella, nine women (20%) had varicella-associated morbidity (pneumonia, premature labour, premature delivery) and one woman died.<sup>25</sup> The altered immune status of the mother during pregnancy may contribute to the severity of the disease.

Because of the risk to the mother, varicella zoster immune globulin (VZIG) is recommended as prophylaxis for a seronegative pregnant woman following exposure to varicella (see Chapter 2).

## Fetal infection (early pregnancy)

Maternal infection with varicella during early pregnancy can result in fetal embryopathy (Table 1). Although embryopathy is a potentially serious consequence of maternal varicella infection, recent studies have shown the actual risk of the fetus developing embryopathy following maternal varicella to be very low (2%), with the greatest risk when maternal infection occurs during Weeks 8–20 of gestation.<sup>26,27</sup>

### Embryopathy associated with varicella infection

● Skin	scarring
● Limb	hypoplasia of bone and muscle
● CNS	microcephaly, mental retardation, sphincter dysfunction
● Eye	cataract, chorioretinitis, microphthalmia

Table 1: Clinical characteristics of embryopathy

In a controlled study by Pastuzak *et al.*,<sup>26</sup> the pregnancy outcomes of 106 pregnant women with clinically diagnosed varicella infection in the first 20 weeks of pregnancy were compared with 106 unexposed, age-matched controls. The risk of varicella embryopathy after infection in the first 20 weeks was found to be only one in 86 live births (1.2%) from this study (Table 2).<sup>26</sup> When these results were pooled with those of four previous studies the mean risk was estimated to be 2.2%.

From this percentage the incidence of congenital varicella syndrome in the UK is estimated to be

1.6 per 100 000 births or 10 births per year.<sup>27</sup>

These findings were supported by a larger, uncontrolled study of 1373 pregnant women exposed to varicella in the first 36 weeks of pregnancy. In this study, embryopathy occurred in seven out of 351 (2%) infants whose mothers developed varicella infection between Weeks 13–20 of gestation, in two out of 472 (0.4%) whose mothers were infected during Weeks 8–13 and in none of 477 pregnancies where maternal infection was acquired after Week 20 (Table 2).<sup>27</sup>

Study	Fetal risk*		
	Number of infected/Number of live born (%)		
	First trimester	Second trimester	Third trimester
Siegel (1973) <sup>28</sup>	2/27 (7.4)	0/32	2/76 (2.6)
Enders (1984) <sup>22</sup>	0/23	0/8	0/2
Paryani & Arvin (1986) <sup>25</sup>	1/11 (9.0)	0/11	0/16
Balducci <i>et al</i> (1992) <sup>29</sup>	0/35	NG	NG
Enders <i>et al</i> (1994) <sup>27</sup>	2/472 (0.4)	7/351 (2.0)	0/477
Pastuzak <i>et al</i> (1994) <sup>26</sup>	–	1/86 (1.2) <sup>†</sup>	0/14

\* Ratio of the number of infants with congenital varicella syndrome compared with the total number of live-born infants  
 NG = Not given  
<sup>†</sup> Estimated risk for mothers infected in the first 20 weeks of pregnancy

Table 2: Pooled results from prospective studies measuring fetal risk after maternal varicella infection during pregnancy<sup>27</sup>

### Neonatal infection (late pregnancy)

The most important factor that predisposes to severe disease in the *neonate* is the time of onset of maternal illness in relation to delivery. The usual interval between onset of rash in the mother and onset in the neonate is 9–15 days. When maternal varicella has an onset between 4 days before and 2 days after delivery, with the appearance of symptoms in the neonate 5–10 days after birth, there will have been no transplacental transfer of maternal antibody and this frequently leads to severe disease in the newborn. Untreated, such neonatal varicella has an associated mortality rate as high as 30%.<sup>22,30</sup>

### Immune-altered children

Dowell & Bresee<sup>31</sup> suggested that systemic steroid therapy alone increases the risk of developing varicella,<sup>31</sup> although the design of this study has been criticized.<sup>32</sup> Crissalli & Terragna<sup>33</sup> noted that 11 out of 26 children who were recovering from varicella infection suffered relapse following cortisone administration.<sup>33</sup> More recently, there have been case reports of severe or progressive varicella in children receiving systemic or inhaled corticosteroids for asthma or other diseases.<sup>34–36</sup> As the number of children who suffer *urban* asthma appears to be increasing, it is possible that this will have a significant impact on the evolving epidemiology of severe varicella.<sup>37</sup>

The minimum duration or dose of steroid therapy which can increase the risk of developing progressive varicella is at present not known. Children receiving systemic corticosteroids (more than 1 mg/kg/day) or continuous inhaled steroids during the 1–2 weeks prior to varicella exposure should be considered immune-altered and may have an increased risk of developing progressive varicella compared with untreated children. Current guidelines in the UK suggest that all susceptible children who have received doses of corticosteroids for any reason other than for replacement, regardless of the duration of treatment, within 3 months prior to exposure should be considered at risk of more severe disease. However, in a study of 101 children receiving corticosteroid therapy (prednisolone, 2 mg/kg/day) for asthma and other allergic disorders, only one child developed progressive varicella.<sup>38</sup>

## The Immunocompromised Host

The immunocompromised population is growing rapidly; increased use of chemotherapy for cancer treatment, transplantations requiring immunosuppression and the expanding population of HIV-infected individuals in recent years mean that prevention and treatment of infections in this population (at risk of more severe disease), is becoming recognized as an increasingly important issue (Table 3).

Immunocompromised	Immune-Altered/Others
<ul style="list-style-type: none"> <li>◆ HIV-infected individuals</li> <li>◆ Leukaemic children</li> <li>◆ Transplant recipients</li> <li>◆ Patients receiving chemotherapy (e.g. for cancer)</li> </ul>	<ul style="list-style-type: none"> <li>◆ Adults</li> <li>◆ Pregnant women</li> <li>◆ Neonates</li> <li>◆ Patients receiving steroids</li> </ul>

Table 3: Patients at risk of severe varicella

### Progressive varicella

Immunologically incompetent individuals have a 20–40% risk of suffering a severe, progressive form of varicella which can often be fatal (Table 4). Although the mortality rate of varicella among otherwise healthy children is estimated at about two per 100 000 cases (<0.002%),<sup>16,17</sup> in immunocompromised individuals the mortality from varicella may reach 7–10%.<sup>18</sup> Newly emerging syndromes associated with progressive varicella are being identified which may carry additional morbidity and mortality for the profoundly immunocompromised (Table 4). Chronic hyperkeratotic lesions in individuals with AIDS have not been reported to represent an additional risk for the transmission of VZV.

### Immunocompromised children

Since varicella is primarily a childhood disease, most available data regarding the epidemiology of varicella in immunocompromised individuals are derived from studies in children.

Children with acute lymphoblastic leukaemia appear to be particularly vulnerable to developing severe varicella and have a high mortality from complications of the disease. In one study of 127 untreated immunocompromised children who developed varicella, pneumonitis occurred in 29/91 (32%) of leukaemic children and was associated with a mortality rate of 31%. This was higher than the incidence of pneumonitis seen in children with other malignancies (e.g. non-Hodgkin's lymphoma, acute myelocytic leukaemia, Hodgkin's disease) of whom only 7/36 (19%) developed pneumonitis and none died.<sup>18</sup>

Studies in HIV-infected children suggest that fatal varicella is uncommon. The severity of the disease may depend upon the degree of immunosuppression caused by HIV.<sup>39,40</sup> In a recent retrospective study in children with HIV infection, a 10% attack rate for varicella was reported which was associated with a 40% risk of developing severe disease, but mortality was low (Table 5).<sup>41</sup>

### Characteristics of progressive varicella

- Clinical involvement of organ systems other than the skin and mucous membranes
- Clinically significant haemorrhage
- Persistence of active infection for more than 8 days

### Clinical syndromes associated with progressive varicella

- Bacterial septicaemia
- Pneumonitis, encephalitis and hepatitis
- Haemorrhagic varicella
- \*Chronic varicella (hyperkeratotic disease, especially in individuals with AIDS and bone marrow transplant [BMT] recipients)
- \*Recurrent syndromes (repeated episodes of varicella with progressively shorter intervals between attacks, especially in children with HIV)
- \*Re-infection syndrome (patients previously seropositive for VZV re-acquire exogenous infection)
- \*Acute retinal necrosis syndrome
- \*Multifocal leukoencephalitis

\*Newly recognized syndromes associated with varicella in the immunocompromised

Table 4: Characteristics and complications of progressive varicella

	Number of children (%) (n=391)
• Varicella (% of total population)	38 (9.7)*
• Duration >10 days	22 (57.9) <sup>†</sup>
• Complication <sup>††</sup>	15 (39.5) <sup>†</sup>
• Death	2 (5.3) <sup>†</sup>

\*There were an additional 9 mild cases by history  
<sup>†</sup>Percentage of children with varicella  
<sup>††</sup>Pneumonia, skin superinfection, thrombocytopenia

Table 5: Incidence and outcome of varicella among HIV-infected children<sup>41</sup>

There is a lack of data regarding the severity of varicella in HIV-positive adults.

Individuals receiving chemotherapy for an underlying disorder are immunocompromised and are therefore at greater risk from developing severe, progressive varicella. In this situation (e.g. following bone marrow transplantation, solid-organ transplantation, or treatment for cancer), VZV may disseminate widely and is frequently

associated with complications resulting in high morbidity and mortality.<sup>42-44</sup>

### Nosocomial transmission

For both immunocompromised individuals and immunocompetent adults, the hospital represents a high-risk setting for transmission and acquisition of virus from infectious patients with severe, progressive disease and from visitors or healthcare workers who may be unknowingly incubating the infection.<sup>45-47</sup>

The risk of nosocomial transmission may be underestimated because many of the contacts are not identified (e.g. visitors to patients). Healthcare workers are not only at particular risk of acquiring nosocomial varicella (in some countries there may be a high proportion of emigrants from low-endemicity countries), but they may also pose a risk of transmitting virus to patients. In one study of 595 exposed healthcare workers, 32 were found to be serologically susceptible and two developed varicella.<sup>45</sup> In a recent report, one doctor incubating varicella in a hospital setting infected 50 patients, including some undergoing chemotherapy or bone marrow transplantation, and a second doctor exposed 38 patients to the disease.<sup>47</sup>

### Other sources of exposure

Although there is a risk of VZV acquisition in hospitals and clinics, family and playmates appear to be primary sources of exposure for the acquisition of varicella by both the immunocompromised (and immunocompetent) child. Unfortunately, the source of exposure may often be unknown. Analysis of previously vaccinated children who experienced breakthrough varicella following exposure provides an estimate of the proportion of exposures from different sources (Table 6).<sup>48-52</sup> These types of analyses suggest that family members of immunocompromised children would be an appropriate target population for immunization with a varicella vaccine.

Source of exposure	Immunocompromised children	Otherwise healthy children
Family	13	5
School/playmates	11	13
Other source of exposure*	7	5
<b>Total</b>	<b>31</b>	<b>23</b>

\* Including exposure to herpes zoster, neighbourhood exposure etc.

Table 6: Cases of breakthrough varicella following vaccination – sources of exposure<sup>48-52</sup>

## Management of Immunocompetent Patients with Varicella

### Pre-Exposure Prophylaxis

For immunocompetent individuals, vaccination with live-attenuated varicella vaccine (Oka strain), is currently the only available option for pre-exposure varicella prophylaxis. This vaccine was developed in 1974 and licensed for human immunization in Japan in 1987, although since then only an estimated 18% of the total Japanese population of susceptible individuals have been vaccinated. In addition, this vaccine is now licensed in the USA and Korea; it is also available on a compassionate basis in the UK and some European countries.

#### Pre-exposure prophylaxis of varicella in children

Pre-exposure prophylaxis with live-attenuated varicella vaccine in children has been well documented and shown to provide effective long-term immunity.<sup>1-6</sup> Data collected from 8429 children (aged 2–6 years) vaccinated between 1986 and 1992, showed that nearly all children seroconverted (83–92%) following vaccination and only a small proportion (4–7%) experienced adverse clinical reactions (fever, rash or local reaction [Table 1]).<sup>6</sup> Although breakthrough varicella developed in 13% of the vaccine recipients, the clinical features were very mild – 65% experienced no or very low-grade fever, 75% had mild skin rashes – and the clinical course tended to be short.

#### Methods of preventing/modifying varicella infection

Pre-exposure	Oka varicella vaccine
Post-exposure	Varicella zoster immune globulin (VZIG)
	Oka varicella vaccine (<3 days after exposure)
	Aciclovir (7–14 days after exposure)

	Healthy children	High-risk group <sup>*</sup>	Non-high-risk group <sup>†</sup>
Clinical reaction	544/7923(6.9%) (fever, rash, local reaction)	2/46 (4.3%)	34/460 (7.4%)
Seroconversion	2150/2330 (92.2%)	22/26 (84.6%)	175/209 (83.7%)

<sup>\*</sup> Immunocompromised children;  
<sup>†</sup> Children with underlying diseases but not immunocompromised

Source: Official report to the Japanese government for post-marketing data collected 6 weeks after vaccination between September 1986 and September 1992<sup>6</sup>

Table 1: Follow-up of children vaccinated with Oka varicella vaccine<sup>6</sup>

Five- and 10-year follow-up studies show that long-term protective immunity (assessed by humoral immunity and skin test reactions) is maintained in nearly 97% of vaccinated children.<sup>3,4</sup> Similar results have recently been published from a 20-year follow-up study of Oka vaccine recipients.<sup>5</sup> Only 2% of the 96 recipients who replied to questionnaires developed breakthrough varicella and all 26 recipients who underwent immunological testing were still seropositive (judged by the fluorescent antibody to membrane antigen [FAMA] technique and skin testing). Importantly, none of the 20 vaccinated subjects exposed to natural varicella from family members developed varicella.

## Properties of the live-attenuated varicella vaccine (Oka)

- ◆ Causes little or no clinical reaction\*
- ◆ Induces antibody
- ◆ Induces cell-mediated immunity (delayed type hypersensitivity as measured by skin tests)
- ◆ Lack of contact infection in most cases
- ◆ Induces long-term protective immunity
- ◆ Prevents disease when administered up to 3 days after exposure (post-exposure prophylaxis)
- ◆ Incidence of herpes zoster in vaccinated leukaemic children lower than in comparable children infected naturally with wild-type virus

\* Mild clinical reactions in 15–75% of leukaemic children

### Pre-exposure prophylaxis of varicella in adults

Varicella is much more severe in adults than in children; although less than 10% of varicella cases in the USA occur in adults, they account for nearly a quarter of all varicella-related deaths.<sup>7–9</sup> Susceptible adults therefore represent a potentially important target group for varicella vaccination.





### Vaccination against primary varicella infection

Successful immunization of adults with live-attenuated Oka varicella vaccine has been well documented and provides a degree of protective immunity.<sup>10–12</sup> Two doses of vaccine are needed for optimum protection, producing a seroconversion rate of >90%.<sup>11</sup> Healthy adults do not respond as well to vaccination as do healthy or even leukaemic children and retain their immune response for a shorter time (Table 2).<sup>10,11,13,14</sup> Approximately 25% of vaccinees who seroconvert lose detectable antibodies to varicella zoster virus (VZV) after 6 years, although they appear to retain partial protection.<sup>12</sup> They also have a lower degree of protection than children; vaccinated healthy adults with household exposures to varicella have an attack rate of 30–40%,<sup>13</sup> compared with leukaemic children with an attack rate of about 13%<sup>15</sup> and healthy children with an attack rate of about 10%.<sup>16</sup>

The poorer immunogenic response in adults may be explained by an age-related decline in cell-mediated immune (CMI) responses. Results from a recent study found a significant difference in CMI responses of adults and children.<sup>17</sup> VZV CMI measured by responder cell frequency and stimulation index, was significantly lower in adults after two doses of vaccine than in children after a single dose. However, it should be noted that the responder cell frequency in adults does increase following vaccination.

### Responder cell frequency

- ◆ Responder cell frequency is a measure of the proportion of peripheral blood lymphocytes (e.g. one in 14 000) that respond to VZV antigen

	Healthy children	Leukaemic children	Healthy adults
 Seroconversion rate (%)			
1 dose	95	82	88
2 doses	NG	98	94
 Vaccine rash (%)	5	50	10
 Protection after household exposure (%)	90	85	70
 Antibody persistence (% [10 years])	>90	90	75*

NG = Not given;  
\* After 6 years

Table 2: Responses to varicella vaccination in different patient populations<sup>14</sup>

### Vaccination to prevent reactivation of VZV

It is not yet known what impact the widespread vaccination of adults will have on the incidence of herpes zoster. Studies in leukaemic children, who are at much higher risk of developing herpes zoster (incidence rate of 10–20%) than healthy children (incidence rate of 0.05–0.074%), show that the incidence of herpes zoster is actually lower in vaccine recipients than among those who acquire varicella naturally.<sup>15,18</sup>

There is evidence to suggest that CMI to VZV declines with age and that this is closely correlated with the increase in incidence and severity of herpes zoster observed in the elderly. Varicella immunization of elderly individuals boosts VZV-specific CMI and may, therefore, decrease the incidence and severity of herpes zoster.<sup>19,20</sup> In a pilot study of 202 elderly individuals (55 to >87 years of age), immunization antibody levels to VZV were boosted over a 12-month period, and CMI responses (measured by responder cell frequency) were increased for at least 48 months.<sup>19</sup> Currently, no data are available to confirm whether immunization attenuates or prevents herpes zoster, but a large study is planned in the USA, involving 27 000 seropositive adults over 60 years of age to assess the protective effects of vaccination.

## Post-Exposure Prophylaxis

### Post-exposure prophylaxis of varicella in children

#### Vaccination

Live-attenuated varicella vaccine may be effective for post-exposure prophylaxis (prevention of disease after suspected contact, but in the absence of clinical signs or symptoms) in children provided it is given sufficiently soon after exposure. A small, controlled study of 26 immunocompetent children showed that Oka vaccine given within 3 days of initial exposure to VZV prevented the development of varicella symptoms; all of the unvaccinated controls went on to develop the disease.<sup>21</sup> Post-exposure prophylaxis is recommended by the American Academy of Pediatrics for unimmunized children at increased risk of infection.<sup>22</sup> There are no data regarding post-exposure vaccination in the immunocompromised individual.

Although VZIG given shortly after exposure can prevent or modify the course of infection, VZIG is not effective once disease is established. Administration of VZIG is recommended as post-exposure prophylaxis for susceptible children at high risk of developing severe varicella, by the American Academy of Pediatrics in their 1994 Red Book publication.<sup>22</sup>

For maximum protection, VZIG must be given intramuscularly within 2 days of and not more than 4 days after exposure to varicella. It may be worthwhile to administer VZIG later after exposure although there are no data to support this approach: despite this lack of data, the UK authorities still recommend the administration of VZIG up to 10 days after exposure. Table 3 gives a summary of the types of individuals considered to be appropriate candidates for VZIG administration.<sup>22</sup>

### Individuals considered appropriate for VZIG administration following varicella exposure

- ◆ Immunocompromised children without a history of varicella
- ◆ Susceptible pregnant women
- ◆ Newborn infants whose mothers have varicella within 5 days before or 48 hours after delivery
- ◆ Hospitalized premature infants (>28 weeks gestation) whose mothers have no history of varicella
- ◆ Hospitalized premature infants (<28 weeks gestation or <1000 g) regardless of maternal history

Table 3: Red Book recommendations for candidates for VZIG administration following varicella exposure<sup>22</sup>

### Antiviral agents

Clinical studies have shown that post-exposure administration of antiviral therapy with aciclovir may be effective in reducing the severity of clinical disease, if it is administered relatively late in the incubation period (starting within 7–9 days of exposure) but before rash onset. In 50 exposed infants and children, oral aciclovir (40–80 mg/kg/day started 7–9 days after exposure to VZV and given for 7 days) prevented the development of clinical varicella in 21 out of 25 treated children; all of the 25 untreated children in the control group developed varicella.<sup>23</sup> Timing is important in antiviral post-exposure prophylaxis. In another study, 10 out of 13 children given aciclovir 1–3 days after exposure developed varicella, suggesting that antiviral prophylaxis with aciclovir is less successful if used too early in incubation, namely before the second viraemic stage (Figure 1).<sup>24</sup>

One of the concerns about such administration of aciclovir is whether it might lead to reduced immune responses and therefore increased susceptibility to varicella in adult life. Studies to date have shown that aciclovir initiated *after* the onset of rash has no detectable effect on the ability to raise an immune response to VZV in otherwise healthy children and adolescents.<sup>25</sup> In a study in healthy children by Asano *et al*,<sup>23</sup> aciclovir was given as post-exposure prophylaxis following contact with

an infected household member. Seroconversion occurred in 21/25 (84%) of the aciclovir-treated group. Four children did not seroconvert to VZV 1–2 months after aciclovir treatment. It is unknown whether they were not infected with VZV or whether aciclovir completely inhibited VZV replication. Further data are needed to clarify the immune responses.

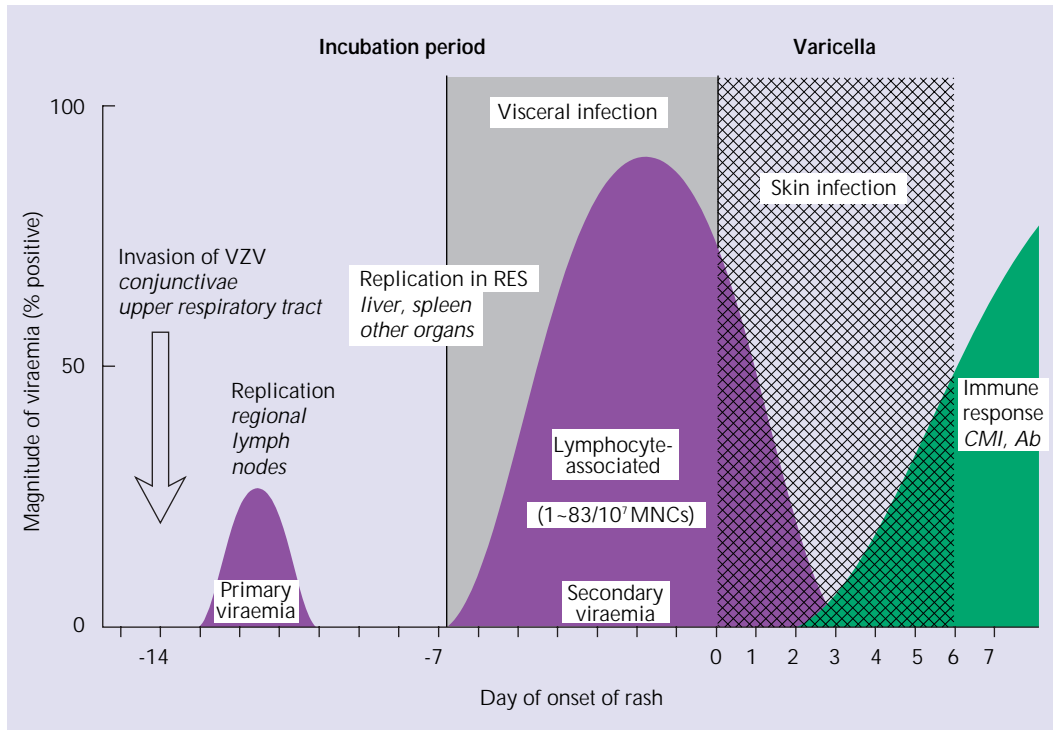


Figure 1: Time course of varicella infection<sup>24</sup>

#### Properties of post-exposure antiviral therapy with oral aciclovir

- Effective when given during secondary viraemia (Days 7–14 post exposure)
- Permits subclinical infection (VZV DNA in blood, FAMA [late antigen], skin reaction to antigen)
- Mild suppression of specific immune response (delayed FAMA response); antibody should be measured 2–3 months after treatment
- Persistence of FAMA and skin reaction 1 year after infection (95% of recipients still have antibody and skin reaction)

#### Post-exposure prophylaxis in pregnancy and the neonate

Susceptible, pregnant women exposed to varicella have a risk of more severe disease and, if infected during Weeks 8–20 of gestation, have about a 2% chance of their infant developing congenital varicella (see Chapter 1, page 8). Neonatal varicella contracted from the mother is often severe.

VZIG administration to the mother is recommended following exposure and administration to the infant is advised if the mother develops varicella 5 days before to 2 days after delivery.<sup>22</sup> A consensus at the 3rd Annual Meeting of the IHMF suggested

that VZIG could reasonably be given as post-exposure prophylaxis to neonates born to mothers who have varicella within 7 days before or after delivery. Despite VZIG prophylaxis, approximately two-thirds of infants exposed to maternal varicella around the time of delivery will become infected.<sup>26</sup> Although in most cases the infection is mild, fatal outcomes in VZIG treated infants have been reported in infants whose mothers developed varicella rash in the period 4 days before to 2 days after delivery.<sup>27-29</sup> It is not known whether vaccination will be able to prevent the manifestations of congenital varicella.<sup>11</sup>

## Treatment

Early antiviral therapy with oral aciclovir (within 24 hours of rash onset) has been shown to be effective in reducing the symptoms of varicella in children,<sup>25,30</sup> adolescents<sup>31</sup> and adults,<sup>7</sup> but whether antiviral treatment should be widely used in otherwise healthy children remains controversial.

### Children

Dunkle *et al*<sup>25</sup> compared oral aciclovir (20 mg/kg four times daily for 5 days) with placebo given within 24 hours of rash onset in 815 children with varicella (2–12 years old) and showed that aciclovir was well tolerated and significantly reduced all cutaneous events (Table 4)<sup>25</sup> and systemic symptoms (fever and mean constitutional illness scores) compared to placebo.

	Aciclovir (n=367)	Placebo (n=357)	P
Mean number of lesions (median)	294 (277)	347 (386)	<0.001
Patients with >500 lesions (%)	78 (21.3)	137 (38.4)	<0.001

Table 4: Cutaneous events in children receiving either aciclovir or placebo<sup>25</sup>

Approximately 20% of immunocompetent children with varicella are destined to have a prolonged course of the disease (lesions still forming at 6 days compared with about 3 days normally), but there is, at the moment, no way of predicting which children will suffer the longer course.<sup>25</sup> Certain subpopulations can be identified as having a greater need for antiviral therapy (see Table 6). These include otherwise healthy individuals over the age of 18 years, pregnant women and secondary or tertiary household exposures (who have been shown to suffer more severe disease than the index case).

### Adolescents

Early treatment with oral aciclovir (within 24 hours of rash onset) showed similar benefits in adolescents.<sup>25,31</sup> In a study of adolescents 13–18 years of age, Balfour *et al*,<sup>31</sup> showed that oral aciclovir (800 mg four times daily for 5 days) significantly reduced the time to cessation of new lesion formation, days to maximum number of lesions and the maximum number of lesions by about 1 day compared with placebo.<sup>31</sup> As with children and adults, evidence regarding the effect of aciclovir in otherwise healthy adolescents on the incidence of complications is inconclusive.<sup>7,25,31</sup>

## Adults

Intravenous aciclovir has been shown to shorten the course of uncomplicated varicella in normal adults,<sup>32</sup> but parenteral therapy is expensive and is neither practical nor desirable.

If treatment is started sufficiently early after the onset of rash, oral aciclovir can be beneficial in the treatment of adult varicella. In a study of 148 naval recruits with uncomplicated varicella, oral aciclovir (800 mg five times daily for 7 days) started within 24 hours of rash onset, reduced the duration of varicella and the severity of symptoms compared with placebo (Table 5).<sup>7</sup>

	Early group (<24 hours)			Late group (25–72 hours)		
	Aciclovir (n=38)	Placebo (n=38)	P	Aciclovir (n=36)	Placebo (n=36)	P
Time to maximum number of skin lesions (days)	1.5	2.1	0.002	1.3	1.2	0.86
Days of new lesion formation	2.7	3.3	0.03	3.0	2.3	0.03
Time to onset of cutaneous healing (days)	2.6	3.3	<0.001	2.4	2.3	0.79
Time to 100% crusting (days)	5.6	7.4	0.001	7.0	6.8	0.96
Maximum number of lesions	268	500	0.04	233	158	0.03

Table 5: Efficacy of oral aciclovir in adult varicella<sup>7</sup>

## Immune-altered individuals

### Immune-altered children

Otherwise healthy children with underlying disorders which could be worsened by varicella should also be considered as candidates for antiviral treatment (Table 6).<sup>33</sup> Children with cardiopulmonary disease (cystic fibrosis, congenital heart disease) who have a febrile illness can often have exacerbation of their underlying disorder. Similarly, anorexia and fever associated with varicella could have a serious impact in the diabetic child. Patients with skin disorders (such as atopic dermatitis, pustular psoriasis, severe burns) are at increased risk from serious bacterial superinfection, and children receiving corticosteroids as treatment for asthma may be at increased risk following varicella exposure and should be considered candidates for treatment.<sup>33</sup>

### Pregnant women and the neonate

If a woman is pregnant, the potential benefits of treatment should be balanced against potential fetal adverse outcomes. In the first trimester, approximately 500 women have received aciclovir with no excess of fatal malformations. Whilst the data are not strong enough to exclude a teratogenic effect of aciclovir, this drug should not be withheld in early pregnancy if clinically indicated. Furthermore, no reason is apparent to withhold aciclovir in the second or third trimester; the complications of varicella are more common in adults and pregnant women. Varicella zoster pneumonitis has been shown to have a high mortality so it is recommended that all patients are treated. It is

also recommended that for the management of varicella, pregnant women should be treated with oral aciclovir (800 mg five times daily for 7 days). If a woman has complicated disease, intravenous aciclovir should be given (10 mg/kg every 8 hours).

All patients should be advised that aciclovir is not licensed for use in pregnancy. Therefore, whenever aciclovir is prescribed during any stage of pregnancy, the fetal outcome should be reported to the Aciclovir in Pregnancy Registry (see page 35 for details).

Seronegative pregnant women exposed to VZV should be given VZIG prophylaxis, if available, within 4 days of exposure.

Neonates developing varicella should be observed closely and treated with intravenous aciclovir. Treatment of individuals who have previously received VZIG is controversial and treatment should be individualized. Neonates with varicella embryopathy do not need isolation from other children, but the neonate of a mother with active varicella should be isolated while in hospital from birth to Day 21 (or Day 28 if the infant has been given VZIG).

Target groups	Specific high-risk underlying diseases
Individuals over 18 years of age	Congenital/neonatal infections
Pregnant women	Cardiopulmonary disease (cystic fibrosis, congenital heart disease)
Secondary or tertiary household exposures	Diabetes
Children receiving steroid therapy (asthma)	Chronic or severe skin disorders (atopic dermatitis, pustular psoriasis, burns)
All immunocompromised individuals	Any significant chronic illness

Table 6: Target populations to consider for treatment of varicella<sup>33</sup>

## Cost-Effectiveness of Treatment

Cost-effectiveness analysis is a form of economic evaluation in which the cost of alternative treatments is compared with outcome, measured in units such as cost per symptom-free day. Economic analyses of medical interventions in varicella have largely been performed in North America and are, therefore, heavily dependent on North American resource utilization data and may not be applicable to other countries. They employ *assumptions* regarding complications and indirect costs as there are limited scientific data available.

The interpretation of economic value of an intervention is complicated by the need to consider various perspectives, e.g. the patient, society and the healthcare provider. The healthcare provider may be concerned about direct medical costs (e.g. those relating to drug acquisition, medical care and management of infections), whereas society and the individual may focus on indirect costs (e.g. health-related productivity losses) and intangible costs (e.g. symptom impact on the individual and on caregivers [Table 7]). However, cost-consequence models allow an economic analysis of total costs and a broad range of outcomes. The models can be adapted to different perspectives and can take into account new therapies, more definitive data and other modifications.

Direct (medical)		Indirect (non-medical)	Intangible
• Drug costs	• Nurse advice	• Travel costs	• Effect on quality of life of family unit
• Other consumables	• Clinic/home visit	• Loss of earnings to parents or carers	• Symptom impact
• Transmission of infection to other susceptible contacts	• Emergency department visit	• Loss of earnings to patients (adults)/ productivity loss	
• Cost of treating severe complication	• Hospitalization	• Loss to society	

Table 7: The costs of varicella<sup>34</sup>

### Antiviral therapy

Cost-consequence models have examined the difference in severity and impact of varicella in children and adults for treatment with aciclovir compared with no treatment.<sup>35</sup> In children, treatment with aciclovir is cost-effective compared with no treatment. The combination of indirect and direct costs in the model estimates an overall cost saving of approximately 9.6% (US\$413 versus US\$457) with aciclovir versus no treatment, despite the initial cost associated with the drug. The indirect costs considered in the analysis related only to the potential work loss for the caregiver, the value to the child of lost school days was not included.<sup>35</sup> Symptom impact, measured by the effect on the caregiver (not the impact on the child) was reduced by 20%.<sup>35</sup>

The cost-consequence analysis of treatment with aciclovir compared with no treatment for adults have been examined in a non-military setting and a military setting in North America.<sup>35</sup> This subdivision of the adult population was made because a clinical trial of aciclovir in the military was a good source of information on the effects of treatment and because hospitalization for varicella (required for quarantine in the military) has implications for direct medical costs as well as indirect costs.

Aciclovir was assumed to lower the risk of severe complications and, thereby, the costs of treatment. The results associated in the afore-mentioned military trial showed that return to work was, on average, 1.8 days earlier with aciclovir therapy. This allowed derivation of the productivity losses for treatment and no treatment. The total direct and indirect costs for the non-military population were estimated to be US\$584 for the no-treatment group and US\$445 for the aciclovir group. The estimated total cost difference for the military population is substantially higher: US\$3584 for no treatment compared with US\$2445 for aciclovir. The higher cost is due to the requirement for hospitalization in this particular patient group.<sup>35</sup>

For both of the adult groups considered (military and non-military), the cost-consequence analysis showed that combined direct and indirect costs are lower with aciclovir treatment. The analyses illustrate that costs associated with the management of VZV should include much more than just drug acquisition costs. The findings which suggest that aciclovir is a cost-effective intervention are heavily influenced by indirect costs.

## Chapter 2

Nathwani *et al* have estimated the implied value of achieving one day of symptom relief or preventing one hospital admission in the UK after an episode of varicella treated with aciclovir (implied value is cost of treatment divided by days of symptom relief or number of admissions avoided). They have estimated that the cost per day of symptom relief in acute varicella is US\$70 (£44) to US\$170 (£107) (Table 8)<sup>36</sup> if one day of symptom relief is achieved. These estimates demonstrate that the cost per day of symptom relief falls as the number of days of symptom relief achieved increases. Based on their current admission rates,<sup>36</sup> the estimated cost per admission avoided to their own unit in Scotland, assuming that treating all varicella cases with aciclovir would reduce hospitalization rates by half, is US\$35 262 (£22 177). This calculation was based on the number of admissions avoided and did not take into account savings in other direct or indirect costs. From these data, the routine treatment of all children and adults with varicella would not appear to be a cost-effective use of resources, even if it is highly effective at reducing hospital admission rates. It would still seem reasonable to offer aciclovir treatment to high-risk subpopulations outlined previously, but the cost-effectiveness of treatment in these groups requires confirmation.

Number of days of symptoms relief	Comment	Paediatric dosing (US\$70/£44 per course)	Adult dosing (US\$170/£107 per course)
1	Mean result for adults and children with varicella	US\$70 (£44)	US\$170 (£107)
2		US\$35 (£22)	US\$85 (£54)
4	Maximum result for adults and children with varicella	US\$18 (£12)	US\$43 (£27)
10	Mean result for adults with herpes zoster	NA	US\$18 (£11)

NA = Not applicable

Table 8: Cost-effectiveness of symptom relief by aciclovir<sup>36</sup>

Several studies have assessed the economic burden of varicella in otherwise healthy children in terms of medical and non-medical costs (Table 9).<sup>37–39</sup> For example, Lieu *et al*<sup>39</sup> showed that the mean value of work lost in a US study of 179 families was US\$293 per family or US\$183 per varicella case. More recently, a study by McKenna & Hunt developed and evaluated a questionnaire to measure the impact of varicella on quality of life, which they termed *family disruption*.<sup>40</sup> The three key parameters of this were parental distress, changes in the behaviour of the ill child and general disruption of family arrangements, all of which were significantly affected over the first few days of the child's illness. This measure of family disruption could be useful in the future to evaluate the impact of antiviral therapy on health outcomes.

A potential cause of reduced productivity is associated with caregivers having to stay off work to care for infected children. In the USA, the mean value of work lost because of varicella is estimated to be US\$203/family.<sup>39</sup> However, children were sick

enough to need to stay at home for only one-third as many days as they actually stayed away because of school exclusion policies.<sup>39</sup> Some of the indirect costs of varicella could be reduced by a reappraisal of present school/day care exclusion policies that prevent children returning to school sooner than 5 days after rash onset, despite clear evidence that the child is most infectious before the rash appears and much less so after the appearance of rash.<sup>41</sup>




	Medical (direct)	Non-Medical (indirect)
 Guess <i>et al</i> (1986) <sup>37</sup>	Healthcare costs (drugs, hospitalizations, doctor visits) = US\$17 million (£11 million)	Loss of wages = US\$383 million (£240 million)
 Brunell (1993) <sup>38</sup>	Drug costs (all children with aciclovir) = US\$220 million (£138 million)	Not performed
 Lieu <i>et al</i> (1994) <sup>39</sup>	Medical costs = US\$90 million (£57 million)	Work loss costs = US\$439 million (£276 million)

Table 9: Summary of studies assessing the economic impact of varicella<sup>37-39</sup>

## Vaccination

The cost-effectiveness of universal routine vaccination of pre-school (<6 years), healthy children has recently been addressed using a mathematical model of vaccine efficacy.<sup>42</sup> This study concluded that at a vaccine price of US\$35, from a healthcare perspective that considers medical costs only, routine vaccination would not save money; the programme would cost approximately US\$2 per varicella case prevented. However, from a societal perspective that includes the work-loss costs as well as medical costs, vaccination would save US\$5 for every dollar invested. An earlier cost-benefit study, also found that a varicella vaccine that provided lifelong immunity would save US\$7 for every dollar invested in vaccination, but if only medical costs were considered then varicella vaccination would cost money.<sup>42</sup>

This analysis<sup>42</sup> can be compared with studies of other vaccination and preventive health programmes. At an estimated cost per life saved of US\$2500, varicella vaccine appears to be relatively cost-effective from the healthcare provider's perspective when compared with other vaccination and prevention programmes. However, since varicella causes very few deaths, this mortality-based measure may under represent the programme's cost-effectiveness. Furthermore, herpes zoster may be milder in vaccinated healthy individuals than unvaccinated individuals, but as there are few data on the long-term incidence of herpes zoster in the vaccinated population, the analysis did not model the incidence and costs of herpes zoster. There are other possibilities that are not modelled and include potential costs arising from decline of immunity as adults, which may result in treatment of more serious disease and the requirement for re-vaccination later in life.

Universal vaccination of pre-school children in the USA has been recommended by the American Academy of Pediatrics Committee on Infectious Diseases<sup>22</sup> and appears to be cost-effective. However, for older children and adolescents with a negative or

uncertain history the cost-effectiveness of vaccinating is less clear. An alternative to presumptive vaccination is serotesting with follow-up vaccination. The cost-effectiveness analysis of these two approaches demonstrates that presumptively vaccinating all patients with a negative or uncertain history of varicella is projected to be a relatively cost-effective policy for school-age children but not for adolescents. The policies that used serotesting were most cost-effective for adolescents.<sup>43</sup>

The vaccination of susceptible leukaemic children (<10 years old) is cost-effective compared with no vaccination. In a population of 472 patients, 54% of whom were varicella susceptible, the ratio of vaccination cost to exposure cost and episode cost was 1:12.5. It is, therefore, 11–13 times cheaper to vaccinate this group than to treat them.<sup>43</sup> For other immunocompromised groups, there is relatively little information on the cost-effectiveness of vaccination.

### *Summary*

The economic analyses of medical interventions in varicella have largely been performed in North America and are, therefore, heavily dependent on North American resource utilization data. The results of these analyses indicate that cost-effectiveness is very reliant on indirect costs. Therefore, the findings that the use of aciclovir and pre-school vaccination are a relatively cost-effective use of resources cannot easily be applied to other countries. Cost-consequence studies should be performed in other countries to establish the cost-effectiveness of antiviral therapy and vaccination.

## Management of Immunocompromised Patients with Varicella

### Pre-Exposure Prophylaxis

#### *Pre-exposure prophylaxis in children*

Live-attenuated varicella vaccine (Oka strain) can be used prophylactically in leukaemic children who have been in remission for 9 months or more.<sup>1,2</sup> Immunization with two doses of vaccine, 3 months apart, results in 95% seroconversion and confers about 85% protective immunity, with 75% of recipients maintaining positive antibody titres for up to 10 years.<sup>2</sup> About 50% of vaccine recipients develop a vaccine-associated rash which may require no therapy but which can be treated effectively with oral aciclovir.<sup>2</sup>

Although 15–20% of vaccinated children lose antibody with time, protective immunity does not appear to decrease significantly and any breakthrough varicella is usually mild, with only around 5% of cases requiring antiviral therapy.<sup>3</sup>

Importantly, vaccination with Oka vaccine appears to provide good protection against developing varicella from household or family exposure, one of the commonest sources of varicella exposure for the immunocompromised child. In one study, only 13% of 102 vaccinated leukaemic children exposed to varicella in the home developed breakthrough varicella.<sup>3</sup>

The timing of vaccination of leukaemic children can be difficult as chemotherapy normally has to be withheld for at least 1 week before and 1 week after vaccine administration. However, several small studies in leukaemic children have shown that continuing chemotherapy with 6-mercaptopurine during vaccination does not appear to interfere with the ability to generate an antibody response.<sup>4</sup>

A few small studies have shown that the live-attenuated varicella vaccine may also be effective and well tolerated in renal transplant recipients.<sup>5,6</sup> In the most recent study, 34 children on chronic dialysis for end-stage renal disease or who had undergone renal transplantation were given a single dose of live-attenuated varicella vaccine; renal transplant recipients received triple immunosuppressive therapy (prednisone, cyclosporine and azathioprine) throughout their vaccination. Most of the children (85%) developed antibodies within 6 months and, of those followed for longer than 2 years, 76% maintained positive antibody titres.<sup>6</sup>

Other potential target populations for vaccination include children receiving corticosteroids for asthma, HIV-infected individuals, non-exposed women of child-bearing age and non-exposed young adults. A number of clinical trials have been planned to investigate the efficacy and safety of the vaccine in different immunocompromised populations; these trials are beginning in the USA and Japan now that the vaccine is licensed and available in large quantities.

## Post-Exposure Prophylaxis

### *Antiviral therapy*

While post-exposure prophylaxis with aciclovir can be successful in immunocompetent patients, there are no data available on antiviral post-exposure prophylaxis in immunocompromised patients.

In otherwise healthy children, post-exposure antiviral prophylaxis against varicella is effective because it reduces viral replication while the immune response develops; patients develop protective immunity without developing severe clinical symptoms. In the immunocompromised individual, immunity may not develop during administration of the antiviral, and residual virus infection may still cause severe disease after prophylaxis is stopped. This seems to be the case in healthy children who receive antiviral prophylaxis too early after exposure; they develop varicella more often than when post-exposure prophylaxis is given later.<sup>7,8</sup>

### *Varicella zoster immune-globulin*

Varicella zoster immune-globulin (VZIG) has been used successfully as post-exposure prophylaxis in a variety of different immunocompromised populations (mostly children), including renal and liver transplant recipients and those with leukaemia or solid tumours.<sup>9-11</sup>

Given within 96 hours of exposure, VZIG reduces the incidence of complications, lessens the severity of the disease and increases the proportion of immunocompromised patients who experience subclinical varicella.<sup>11</sup> In some instances VZIG appears to prolong the incubation period of varicella with the result that a proportion of treated children develop varicella up to 28 days after VZIG administration; for this reason immunocompromised children who need to remain in hospital should be isolated for 4 weeks after VZIG administration.

There are no placebo-controlled studies in immunocompromised patients using VZIG for post-exposure prophylaxis, but comparison with historical controls and clinical experience shows that VZIG is effective in this population.<sup>11</sup> In one large uncontrolled study, VZIG was administered to 2412 immunocompromised children (<16 years of age) with a range of underlying illnesses (including leukaemia, non-Hodgkin's lymphoma and Hodgkin's disease) within 4 days of exposure to VZV.<sup>11</sup> Breakthrough varicella subsequently occurred in 561 children (454 clinical varicella, 107 subclinical). However, VZIG reduced by 10-fold the incidence of pneumonia, encephalitis and death from varicella in these immunocompromised children and was associated with milder disease and a greater incidence of subclinical varicella (Table 1).<sup>11-13</sup> Between 25% and 50% of all immunocompromised VZIG recipients may remain susceptible to varicella after VZIG administration.<sup>11</sup>

Moderately-to-severely immunocompromised individuals should receive post-exposure prophylaxis with VZIG, if available, within 4 days of exposure. If varicella develops it needs to be treated with intravenous or oral antivirals based on assessment of the patient's clinical condition. In settings where VZIG is not available, more data are needed on alternative post-exposure prophylaxis modalities for immunocompromised individuals.

Disease category	VZIG	Historical control (no VZIG)
	Number (% of evaluable) <sup>*</sup>	Expected number (%) <sup>††</sup>
Clinical varicella		
1–10 pox	56 (13)	0 (0)
11–50 pox	132 (31)	23 (5)
51–100 pox	59 (13)	41 (9)
>100 pox	178 (42)	390 (86)
Unknown	29 (1.2)	
Subclinical varicella		
	107 (4.4)	14 (~3)
<hr/>		
Total	561 (23)	
<hr/>		
Pneumonitis	13 (2.9) <sup>†</sup>	113 (25) <sup>†</sup>
Encephalitis	2 (0.4) <sup>†</sup>	15 (3.3) <sup>†</sup>
Death	3 (0.6) <sup>†</sup>	32 (7) <sup>†</sup>

<sup>\*</sup>Adapted from Levin *et al.*<sup>11</sup> total receiving VZIG = 2412  
<sup>†</sup>Per cent of varicella  
<sup>††</sup>Data from Feldman *et al.*<sup>12</sup> for pox number and subclinical varicella, and from Ross<sup>13</sup> for complications (pneumonitis, encephalitis, etc.)

Table 1: Varicella following VZIG administration to exposed immunocompromised children versus historical control<sup>11–13</sup>

## Treatment

Pneumonitis is the major complication of varicella among immunocompromised hosts and is associated with a high mortality. Early treatment (within 24 hours of rash onset) with intravenous aciclovir (500 mg/m<sup>2</sup>/dose every 8 hours for 5–7 days) significantly lowers the probability of pneumonitis and death in immunocompromised children with varicella.<sup>14,15</sup> The risk of developing pneumonitis is inversely related to lymphocyte count, and children with leukaemia appear to be particularly susceptible to this disease.<sup>15</sup> Among these patients, varicella pneumonitis has an incidence of 32% and a mortality rate of 31% (Table 2).<sup>15</sup>

Although there have not been any controlled trials of oral aciclovir in immunocompromised children with varicella, there are anecdotal reports of successful therapy in some children with HIV. Oral therapy is discouraged for significantly immunocompromised individuals.

Intravenous therapy should be administered to all individuals with severe varicella whether or not it is within 24 hours of rash onset. Moderately-to-severely immunocompromised individuals – including transplant recipients and HIV-positive individuals with low CD4 cell counts – should be treated with intravenous aciclovir (10 mg/kg every 8 hours for adults, 500 mg/m<sup>2</sup> every 8 hours for children) as it is the only antiviral licensed for the intravenous treatment of immunocompromised patients. The efficacy of alternative oral agents with equivalent activity (e.g. valaciclovir) has not yet been confirmed in this group. Once the patient is afebrile and there are no new lesions, oral therapy with aciclovir or valaciclovir should be given to complete a 7–10 day course.

Individuals who are immunocompromised to a lesser degree (those with HIV infection and normal CD4 cell counts or patients on steroids) may be treated with a clinically proven oral antiviral.

Acute leukaemia (91 children)	10% mortality 32% varicella zoster virus (VZV) pneumonitis 31% mortality from pneumonitis
Others (solid tumour: 36 children)	0% mortality 19% VZV pneumonitis

Table 2: Outcome of untreated varicella in paediatric cancer patients<sup>15</sup>

Early treatment is important; patients with evidence of visceral dissemination before starting aciclovir therapy tend to have a poorer prognosis than do those in whom aciclovir is initiated early.<sup>16</sup>

## Summary and Recommendations

### Epidemiology

#### *Immunocompetent host*

Evidence for an upwards shift in the age distribution in the incidence of varicella amongst immunocompetent populations in temperate countries is inconclusive. Data are largely from the UK and the USA and further work is needed to clarify the situation in these and other countries. Several hypotheses were proposed for the observed differences in varicella incidence between tropical and temperate climates. These include methods of data collection and different analytical techniques, but the underlying causes of this finding remain unclear. Emigration of individuals from low-endemicity countries to high-endemicity countries may have an impact on the epidemiology of varicella, but this must be investigated with rigorous surveys.

#### *Pregnancy and the neonate*

The pregnant woman is believed to be at special risk for severe varicella because of immune modification associated with pregnancy. The fetus is at increased risk from the impact of maternal varicella between Weeks 8 and 20 of term; during this time the risk of embryopathy is greatest (up to 2%). The consequences for the neonate are severe, with deformity and possible brain damage occurring as a result of intra-uterine varicella. At present there are very few data concerning the impact of VZIG or aciclovir on this risk.

There is some evidence for high-risk factors (i.e. nutrition, smoking or no history of varicella) but further information is needed. Hospital admissions of anyone over the age of 21 years with varicella should be analysed to see if pregnant women are more or less at risk of severe varicella infection than age-matched, non-pregnant women, and to determine the outcome of varicella infection and identify possible risk factors for severe disease. The issue of whether to test women for varicella zoster virus (VZV) remains unresolved.

#### *Immunocompromised host*

The incidence of varicella in different immunocompromised populations revealed that family, school and playmates are major sources of exposure for the immunocompromised child and that the hospital setting is a high-risk environment for seronegative adults who may be exposed to patients with varicella. All immunocompromised patients are more likely to suffer severe progressive disease and this appears to be related to the degree of immune dysfunction. There is limited information on the epidemiology of varicella in individuals with HIV and AIDS and more data are required on the incidence and severity of varicella in children with HIV. It may be appropriate to conduct studies in countries with a high prevalence of this particular group.

Children receiving systemic corticosteroids (more than 1 mg/kg/day) or continuous inhaled steroids during the 1–2 weeks prior to varicella exposure should be

considered immunocompromised and may have an increased risk of developing progressive varicella compared to untreated children. Underlying disease is more likely to be an important factor in predisposing the individual to progressive varicella than is the dose or duration of steroid therapy.

## Management of Immunocompetent Patients

### *Pre-exposure prophylaxis*

#### *Vaccination*

Vaccination has been used successfully in Japan to prevent disease in children and appears to be well tolerated and effective, although as yet only a small proportion of the population has been vaccinated. Vaccination in immunocompetent children has the advantage of preventing the complications of varicella such as pneumonia and bacterial superinfection. It will also immunize individuals who may enter high-risk groups later in life. Adult vaccination with live-attenuated vaccine produces a poorer immune response than in children.

It is recommended that evaluation of the consequences of universal childhood immunization is performed using data from the USA. The surveillance and reporting of data regarding vaccination in the USA must be improved. To facilitate the evaluation of both varicella and herpes zoster, these should be made reportable diseases.

Universal routine vaccination will be most effective if the whole population is vaccinated: if a small proportion of the population were not immunized there is a danger that those individuals would be susceptible to more severe disease as adults. Vaccination of groups of high-risk susceptible adults (including healthcare workers, teachers, persons with chronic diseases and women of childbearing age before pregnancy) is appropriate. Immunization of siblings of immunocompromised young adults and pre-pubescent females, may also be appropriate.

There are concerns about the possibility of increasing the incidence of adult varicella and herpes zoster if widespread vaccination of younger children is adopted. Another concern is the duration of immunity from vaccination should the vaccination be successful enough to eliminate the circulation of wild-type varicella. It may be necessary to re-vaccinate a proportion of the population and the cost implications of this are not known.

### *Post-exposure prophylaxis*

#### *Varicella zoster immune-globulin*

Post-exposure prophylaxis with varicella zoster immune-globulin (VZIG) may be appropriate for certain susceptible populations. There is a general consensus that VZIG is most effective if administered within 4 days of exposure.

Following an outbreak of varicella in hospital, patients who are susceptible and need to stay in hospital should be considered for VZIG and isolated from Day 8–21 (8–28 if VZIG is given) after the rash onset in the index case. The index case should be isolated until the rash is no longer vesicular.

The interpretation of data on the effect of VZIG is hampered by the lack of standardization of the antibody content. It is important to develop a standardized

assay for the antibody content and to standardize the antibody in VZIG to allow consistency between lots of VZIG within a country and between countries.

### Vaccination and post-exposure antiviral therapy

There is evidence that post-exposure prophylaxis of varicella in otherwise healthy children with live-attenuated vaccine is effective if given up to 3 days post-exposure and that, similarly, post-exposure therapy with aciclovir is effective if started 7–9 days after exposure and continued for 7 days. There are still concerns regarding the impact that such antiviral therapy might have on the immune response. More information is required on the timing of administration of antiviral therapy and on the relationship between efficacy and the amount of infectious virus in the vaccine.

The impact of vaccination on the incidence of herpes zoster and the cost of treating herpes zoster (and varicella) later in life should be addressed in cost-effectiveness studies. Furthermore, the impact of vaccination should be addressed in tropical countries where the incidence of varicella is higher in adults.

## Treatment

### Antiviral therapy

Varicella in immunocompetent individuals of all ages can be effectively treated with oral aciclovir (800 mg five times daily for 7 days in those over 12 years, 20 mg/kg four times daily for 5 days in children), if treatment is started within 24 hours of rash onset. The clinical benefits are statistically significant but modest. The complications of varicella are more common in adults and it is recommended that all patients aged more than 18 years are treated with a clinically proven antiviral. There is insufficient data to justify universal treatment of all children and teenagers with antivirals, although more information is needed on age-related risks, particularly at what stage of puberty adult risk occurs. An alternative strategy to universal treatment is to consider susceptible children, who are more likely to suffer complications or more severe varicella, for treatment with a clinically proven antiviral within 24 hours of rash onset. Targeting such children and teenagers can be difficult but high-risk groups include secondary or tertiary cases in a household, individuals with chronic or severe skin disorders and individuals with chronic diseases (including severe asthma). It remains to be determined whether all children with chronic diseases are at increased risk.

#### Risk groups for antiviral therapy

- Secondary or tertiary cases in a household
- Individuals with chronic or severe skin disorders
- Individuals with chronic disease (including severe asthma)

The cost-effectiveness of antiviral therapy for varicella is largely based on experience with aciclovir. The cost-effectiveness findings for aciclovir treatment of adults and children are very dependent on indirect costs. The studies have largely been performed in North America and, as a consequence, they are heavily dependent on North American resource utilization data. Thus, although there is some evidence that the use of aciclovir in adults and children is a cost-effective use of resources in North America, this finding cannot be easily applied to other countries, especially resource-poor countries. Cost-consequence studies should be performed in other countries to establish the cost-effectiveness of antiviral treatment.

In the USA, an estimated half of all parents seek treatment for their child with varicella, whereas less than a third of parents in the UK do so. Parents of children with varicella need to be aware of the treatment options available to them and the likely benefits and outcomes of giving treatment. Parental wishes should be considered in deciding whether to treat varicella in the otherwise healthy child; in a high-risk immunocompetent child with asthma, parent education is particularly important.

In some countries, school exclusion policies do not allow children to return to school until 5 days (or longer) after rash onset. As children are most infective just before rash onset, these policies are questionable and contribute to high indirect costs (parent loss of earnings); school exclusion policies need to be reconsidered.

## Management of Immunocompromised Patients

### Prophylaxis

A number of different approaches may be adopted for preventing disease in immunocompromised individuals. Possibilities include:

- ◆ Education of the at-risk population
- ◆ Antiviral post-exposure prophylaxis
- ◆ Vaccination of target populations (e.g. leukaemics, organ-transplant recipients)
- ◆ VZIG post-exposure passive immunization

### Education

Education is considered an unlikely route for prevention as most patients do not recognize their exposure and vaccination of the entire population may not be practical.

### Antiviral post-exposure prophylaxis

Antiviral prophylaxis carries the risk of encouraging a longer incubation period of the disease in immunocompromised individuals. Very early treatment with aciclovir, amounting to post-exposure prophylaxis may not be advisable in certain immunocompromised individuals such as children with leukaemia, because their immune suppression may not allow them to develop a suitable immune response following antiviral therapy. Additional data are required on the dosage and timing of aciclovir and other antivirals for post-exposure prophylaxis in immunocompromised individuals.

### Vaccination of target populations

Targeting subpopulations for vaccination would be the preferred option for preventing varicella infection in susceptible immunocompromised individuals; specific target groups include immunocompromised adults and children (leukaemia, solid tumours, pre-transplant and patients on steroids). Vaccinating leukaemic children has been shown to be 11–13 times cheaper than treating varicella in this population. There is, however, a paucity of information on the cost-effectiveness of vaccinating high-risk groups such as children with HIV infection or those receiving steroids. The varicella vaccine is licensed for use in the USA and Japan but only in the immunocompetent individual and is available on a compassionate basis in many other countries (including the UK). Where immunocompromised children are not vaccinated they must be treated with aciclovir at the first sign of infection unless the child is known to have responded to vaccination.

### VZIG post-exposure passive immunization

Moderately-to-severely immunocompromised individuals should receive post-exposure prophylaxis with VZIG, if available, within 4 days of exposure. Should the patient develop varicella, treatment with intravenous or oral antivirals based on an assessment of the patient's clinical condition is indicated. In settings where VZIG is not available, more data are needed on alternative post-exposure prophylaxis modalities for immunocompromised individuals.

### Treatment

Intravenous antiviral therapy should be administered to all individuals with severe varicella; moderately-to-severely immunocompromised individuals, including transplant recipients and HIV-positive individuals with low CD4 cell counts, should be treated with intravenous aciclovir (10 mg/kg every 8 hours for adults, 500 mg/m<sup>2</sup> every 8 hours for children) or alternative oral agents with equivalent activity should be considered if they are available. If the patient is afebrile and there are no new lesions, oral therapy should be given as a 7–10 day course. Individuals who are immunocompromised to a lesser degree, such as those with HIV infection and normal CD4 cell counts or asthmatics on low-dose steroids, may be treated with a clinically proven oral antiviral.

### Pregnancy and the neonate

#### Pregnant woman

If a woman is pregnant, the potential benefits of treatment should be balanced against potential fetal adverse outcomes. In the first trimester, approximately 300 women have received aciclovir with no excess of malformations. Whilst the data are not strong enough to exclude a teratogenic effect of aciclovir, this drug should not be withheld in early pregnancy if clinically indicated. Furthermore, there is no apparent reason to withhold aciclovir in the second or third trimester. The complications of varicella are more common in adults and pregnant women. Varicella pneumonitis has been shown to have a high mortality, so it is recommended that all patients are treated. Pregnant women should be treated with oral aciclovir (800 mg five times daily for 7 days). If a woman has complicated disease, intravenous aciclovir should be given (10 mg/kg every 8 hours).

All patients should be advised that aciclovir is not licensed for use in pregnancy. Therefore, whenever aciclovir is prescribed during any stage of pregnancy, the fetal outcome should be reported to the Aciclovir in Pregnancy Registry (see page 35).

Seronegative pregnant women exposed to VZV should be given VZIG prophylaxis, if available, within 4 days of exposure.

#### Neonates and children

Neonates born to mothers who have varicella 5 days before to 2 days after delivery should be given VZIG to help to modify the disease course that may develop in the infant. A consensus at the *3rd Annual Meeting of the IHMF* suggested that VZIG could reasonably be given as post-exposure prophylaxis to neonates born to mothers who have varicella within 7 days before or after delivery. Neonates less than 4 weeks old at exposure do not require VZIG if they are delivered at term and the mother has had

varicella in the past. Premature neonates whose mother is varicella-susceptible need VZIG if they are less than 2 weeks old at exposure. Hospitalized, exposed premature infants (<28 weeks old or <1000 g birth weight) should receive VZIG regardless of maternal varicella history.

Neonates developing varicella should be observed closely and treated with intravenous aciclovir. Treatment of individuals who have previously received VZIG is controversial and treatment should be individualized. Neonates with varicella embryopathy do not need isolation from other children, but the neonate of a mother with active varicella should be isolated while in hospital from birth to Day 21 (or Day 28 if the infant has been given VZIG).

## Future directions

The apparent shift in age of infection needs to be monitored and the reason for the different seroprevalence rates in different countries explored.

More data are needed from prospective, controlled trials concerning the incidence and severity of varicella in HIV-infected individuals and the risk of severe disease in other subgroups such as asthmatic children, patients with varicella complications and secondary or tertiary cases.

Little is known about the influence of antiviral treatment or post-exposure VZIG on pregnancy outcome for the mother or neonate. A pregnancy registry would be of value to evaluate the effect of antiviral treatment or post-exposure VZIG in early pregnancy.

While the current varicella vaccine is effective, active research into vaccines that do not rely upon live or attenuated viruses for their efficacy, is encouraged. Vaccination strategies with vaccines that are not neurotropic and which do not establish latency, would be a significant improvement on currently available vaccines and may encourage more widespread use.

Further studies should be performed with currently available vaccines to provide more information on the duration of long-term immunity. In immunocompromised children with cancer more work is needed to assess the value of vaccination in preventing or modifying the disease.

More cost-consequence studies are needed to assess the outcomes for vaccination and antiviral therapy in healthcare systems outside the USA.

More data are needed on the use of antivirals for post-exposure prophylaxis on outcome and effect on immune response.

## Aciclovir in Pregnancy Registry

The Aciclovir in Pregnancy Registry continues to register pregnancy exposures to aciclovir; healthcare providers are encouraged to report such exposures to the registrar ([800] 722-9292, extension 58465 [from the USA] or +1 919 315-8465 [from other countries]). Copies of the updated Registry report are available from the same telephone numbers. Written reports and requests should be addressed to: Aciclovir in Pregnancy Registry, Glaxo Wellcome Inc, 3030 Cornwallis Road, Research Triangle Park, NC 27709, USA.

## CHAPTER 1

- Muench R, Nassim C, Niku S *et al*. Seroepidemiology of varicella. *J Infect Dis* 1986;**153**:153–155.
- Schneweis KE, Krentler Ch, Wolff MH. Durchseuchung mit dem varicella-zoster virus und serologische Feststellung der Erstinfektionsimmunität. *Dtsch Med Wschr* 1985;**110**:453–457.
- Finger R, Hughes JP, Meade BJ *et al*. Age-specific incidence of varicella. *Pub Health Rep* 1994;**109**(6):750–755.
- Garnett GP, Cox MJ, Bundy DAP *et al*. The age of infection with varicella-zoster virus in St Lucia, West Indies. *Epidemiol Infect* 1993;**110**:361–372.
- Sixl W, Schneeweiss WD, Withalm H *et al*. Serologic testing of human blood samples for infectious diseases in the Abeokuta and the Minna Hospitals/Nigeria. *J Hyg Epidemiol Microbiol Immunol* 1987;**31** (suppl 4):490–492.
- Poveda JD, Babin M, Bonnici JF *et al*. Etude sérologique de la prévalence des herpesviridae en Guyane Française. *Bull Soc Path Exot* 1986;**79**:207–212.
- Sixl W, Sixl-Voigt B. Serological screenings of various infectious diseases on the Cap Verde Islands (west Africa). *J Hyg Epidemiol Microbiol Immunol* 1987;**31**(suppl 4):469–471.
- Kubo T, Rai SK, Nakanishi M *et al*. Seroepidemiological study of herpes viruses in Nepal. *South East Asian J Trop Med Pub Health* 1991;**22**:323–325.
- Miller E, Vurdian J, Farrington P. Shift in age in chickenpox. *Lancet* 1993a;**341**:308–309.
- Gray LCCR GC, Palinkas LA, Kelley MAJ PW. Increasing incidence of varicella hospitalizations in United States Army and Navy Personnel: Are today's teenagers more susceptible? Should recruits be vaccinated? *Pediatrics* 1990;**86**(6):867–873.
- Miller E, Marshall R. Epidemiology, outcome and control of varicella-zoster infection. *Rev Med Microbiol* 1993b;**4**:222–230.
- Longfield JN, Winn RE, Gibson RL *et al*. Varicella susceptibility in a population from the tropics. *Arch Intern Med* 1990;**150**:970–973.
- Struewing JP, Hyams KC, Tueller JE *et al*. The risk of measles, mumps, and varicella among young adults: A serosurvey of US Navy and Marine Corps Recruits. *Am J Pub Health* 1993;**83**(12):1717–1720.
- Kjersem H and Jepsen S. Varicella among immigrants from the tropics, a health problem. *Scand J Soc Med* 1990;**18**:171–174.
- Preblud SR, D'Angelo LJ. Chickenpox in the United States, 1972–1977. *J Infect Dis* 1979;**140**:257–260.
- Bullowa JGM, Wishik SM. Complications of varicella. I. Their occurrence among 2,534 patients. *Am J Dis Child* 1935;**49**:923–926.
- Preblud SR, Orenstein WA, Bart KJ. Varicella: clinical manifestations, epidemiology and health impact in children. *Pediatr Infect Dis* 1984;**3**:505–509.
- Feldman S, Lott L. Varicella in children with cancer: impact of antiviral therapy and prophylaxis. *Pediatrics* 1987;**80**(4):465–472.
- Weber DM, Pellicchia JA. Varicella pneumonia. Study of prevalence in adult men. *JAMA* 1965;**192**:288–289.
- Ellis ME, Neal KR, Webb AK. Is smoking a risk factor for pneumonia in adults with chickenpox? *BMJ* 1987;**294**:1002.
- Grayson ML, Newton-John H. Smoking and varicella pneumonia. *J Infect* 1988;**16**:312.
- Enders G. Varicella-zoster virus infection in pregnancy. *Prog Med Virol* 1984;**29**:166–196.
- Naeye RL, Talarid (Eds). *Risk factors in pregnancy and diseases of the fetus and newborn*. Baltimore: William & Wilkins, 1983.
- Sever J, White LR. Intrauterine infections. *Annu Rev Med* 1968;**19**:471–486.
- Paryani SG, Arvin AM. Intrauterine infection with varicella-zoster virus after maternal varicella. *N Engl J Med* 1986;**314**:1542–1546.
- Pastuzak AL, Levy M, Schick B *et al*. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. *N Engl J Med* 1994;**330**:901–905.
- Enders G, Miller E, Cradock-Watson J *et al*. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. *Lancet* 1994;**343**:1548–1551.
- Siegel M. Congenital malformations following chickenpox, measles, mumps and hepatitis: results of a cohort study. *JAMA* 1973;**226**:1521–1524.
- Balducci J, Rodis JF, Rosengren S *et al*. Pregnancy outcome following first trimester varicella infection. *Obstet Gynecol* 1992;**79**:506.
- American Academy of Pediatrics: *Committee on infectious diseases*, 23rd edn. 1994; pp 510–517.
- Dowell SF, Bresee JS. Severe varicella associated with steroid use. *Pediatrics* 1993;**92**:223–228.
- Reiches NA, Jones JF. Steroids and varicella. *Pediatr* 1993;**92**:288–289.
- Crissalli M, Terragna A. Modificazioni indotte dal cortisone sull'esantema varicelloso. *Gazz Sanit* 1956;**27**:297–300.
- Starr SE. Varicella in children receiving steroids for asthma: risk and management. *Pediatr Infect Dis J* 1992;**11**:419–420.
- Abzug MJ, Cotton MF. Severe chickenpox after intranasal use of corticosteroids. *J Pediatr* 1993;**123**:577–579.
- Schell DH, Paducah KY. Risks of chickenpox in asthmatic children receiving inhalation steroids and therapeutic recommendations. *Pediatr Infect Dis J* 1993;**12**:174–175.
- Gergen PJ, Mullally DI, Evans R. National survey of prevalence of asthma among children in the United States, 1976 to 1980. *Pediatrics* 1988;**81**:1–7.
- Girsh LS, Yu M, Jones J *et al*. A study of the risk of mortality of varicella in patients with bronchial asthma or other allergic diseases receiving corticosteroid therapy. *Ann All* 1966;**24**:690–693.
- Kelley R, Mancao M, Lee F *et al*. Varicella in children with perinatally acquired human immunodeficiency virus infection. *J Pediatr* 1994;**124**:271–273.
- Srugo I, Israele V, Wittek AE. Clinical manifestations of varicella-zoster virus infections in human immunodeficiency virus-infected children. *AJDC* 1993;**147**:742–745.
- Leibovitz E, Cooper D, Giurgiutin D *et al*. Varicella-zoster virus infection in Romanian children infected with the human immunodeficiency virus. *Paediatrics* 1993;**92**:838–842.
- Myers MG. Viremia caused by varicella-zoster virus: association with malignant progressive varicella. *J Infect Dis* 1979;**140**:229–233.
- Lynfield R, Herrin JT, Rubin RH. Varicella in pediatric renal transplant patients. *Pediatrics* 1992;**90**(2):216–220.
- Budu K, Tubergen DG, Levin MJ. The frequency and consequences of varicella exposure and varicella infection in children receiving maintenance therapy for acute lymphoblastic leukaemia. 1995; in press.
- Alter SJ, Hammond JA, McVey CJ *et al*. Susceptibility to varicella-zoster virus among adults at high risk for exposure. *Infection Control* 1986;**7**:448–451.
- Weber DJ, Rutala WA, Parkham C. Impact and costs of varicella prevention in a university hospital. *AJPH* 1988;**78**:19–23.
- Lewis DA, Jenks PA, Gent AEM *et al*. Varicella-zoster vaccination for healthcare workers. *Lancet* 1994;**343**:1362–1363.
- Takahashi M, Kamiya H, Babak *et al*. Clinical experience with Oka live varicella vaccine in Japan. *Postgr Med J* 1985;**61**:S61–S67.
- Gershon AA, Steinberg S, Gelb L *et al*. A multicentre trial of live attenuated varicella vaccine in children with leukaemia in remission. *Postgr Med J* 1985;**61**:S73–S78.
- Broyer M, Boudailliez B. Varicella vaccine in children with chronic renal insufficiency. *Postgr Med J* 1985;**61**:S103–S106.
- Asano Y, Nagai T, Miyata T *et al*. long-term protective immunity of recipients of Oka strain of live varicella vaccine. *Pediatrics* 1985;**75**:667–671.
- Arbeter AM, Starr S, Plotkin S. Varicella vaccine studies in healthy children. *Pediatrics* 1986;**78**:S748–S756.

## CHAPTER 2

- Weibel RE, Neff BJ, Kuter BJ *et al*. Live attenuated varicella virus vaccine. Efficacy trial in healthy children. *N Engl J Med* 1984;**310**(22):1409–1415.
- Weibel RE, Kuter BJ, Neff BJ *et al*. Live Oka/Merck varicella vaccine in healthy children. Further clinical and laboratory assessment. *JAMA* 1985;**254**(17):2435–2439.
- Asano Y, Albrecht P, Vujcic LK *et al*. Five-year follow-up study of recipients of live varicella vaccine using enhanced neutralization and fluorescent antibody membrane antigen assays. *Pediatrics* 1983;**72**(3):291–294.
- Asano Y, Itakura N, Hiroishi Y *et al*. Viral replication and immunologic responses in children naturally infected with varicella-zoster virus and in varicella vaccine recipients. *J Infect Dis* 1985;**152**(5):863–868.
- Asano Y, Suga S, Yoshikawa T *et al*. Twenty-year follow-up of protective immunity of the Oka strain live varicella vaccine. *Pediatrics* 1994;**94**(4):524–526.

6. Asano personal communication.
7. Wallace MR, Bowler WA, Murray NB *et al.* Treatment of adult varicella with oral acyclovir. A randomized, placebo-controlled trial. *Ann Intern Med* 1992;**117**:358–363.
8. Wallace MR, Hooper DG. Inconclusive hepatitis C virus antibody results in African Sera. *J Infect Dis* 1993;**167**:254.
9. Preblud SR, D'Angelo LJ. Chickenpox in the United States, 1972–1977. *J Infect Dis* 1979;**140**:257–260.
10. Arbeter AM, Starr SE, Plotkin SA. Varicella vaccine studies in healthy children and adults. *Pediatrics* 1986;**78**(4 pt 2):748–756.
11. Gershon AA, Steinberg SP, LaRussa P *et al.* Immunization of healthy adults with live attenuated varicella vaccine. *J Infect Dis* 1988;**158**(1):132–137.
12. Hardy I, Gershon AA. Prospects for use of a varicella vaccine in adults. *Infect Dis Clin N Am* 1990;**4**:160–173.
13. Gershon AA, LaRussa P, Steinberg S. Live attenuated varicella vaccine: current status and future uses. *Semin Pediatr Infect Dis* 1991;**2**:171–178.
14. Gershon AA, LaRussa P, Hardy I *et al.* Varicella vaccine: The American experience. *J Infect Dis* 1992;**166**(suppl 1):S63–S68.
15. Hardy I, Gershon AA, Steinberg SP *et al.* The incidence of zoster after immunization with live attenuated varicella vaccine. A study in children with leukemia. *N Engl J Med* 1991;**325**(22):1545–1550.
16. White CJ, Kuter BJ, Hildebrand CS *et al.* Varicella vaccine (VARIVAX) in healthy children and adolescents: results from clinical trials 1987 to 1989. *Pediatrics* 1991;**87**:604–610.
17. Nader S, Bergen R, Sharp M *et al.* Age-related differences in cell-mediated immunity to varicella-zoster virus among children and adults immunized with live attenuated varicella vaccine. *J Infect Dis* 1995;**171**:13–17.
18. Lawrence R, Gershon AA, Holzman R *et al.* The risk of zoster after varicella vaccination in children with leukemia. *N Engl J Med* 1988;**318**(9):543–548.
19. Levin MJ, Murray M, Rotbart HA *et al.* Immune response of elderly individuals to a live attenuated varicella vaccine. *J Infect Dis* 1992;**166**:253–259.
20. Levin MJ, Murray M, Zerbe GO *et al.* Immune responses of elderly persons 4 years after receiving a live attenuated varicella vaccine. *J Infect Dis* 1994;**170**:522–526.
21. Asano Y, Nakayama H, Yazaki T *et al.* Protection against varicella in family contacts by immediate inoculation with live varicella vaccine. *Pediatrics* 1977;**59**(1):3–7.
22. American Academy of Pediatrics: *Committee on Infectious diseases*, 23rd edn. 1994; pp 510–517.
23. Asano Y, Yoshikawa T, Suga S *et al.* Post-exposure prophylaxis of varicella in family contact by oral acyclovir. *Pediatrics* 1993;**92**(2):219–222.
24. Suga S, Yoshikawa T, Ozaki T *et al.* Effect of oral acyclovir against primary and secondary viraemia in incubation period of varicella. *Arch Dis Child* 1993;**69**:639–643.
25. Dunkle LM, Arvin AM, Whitley RJ *et al.* A controlled trial of acyclovir for chickenpox in normal children. *N Engl J Med* 1991;**325**(22):1539–1544.
26. Miller E, Marshall R, Vurdien J. Epidemiology, outcome and control of varicella-zoster infection. *Rev Med Microbiol* 1993;**4**:222–230.
27. Bakshi SS, Miller TC, Kaplan M *et al.* Failure of varicella-zoster immunoglobulin in modification of severe congenital varicella. *Pediatr Infect Dis* 1986;**5**:699–702.
28. King SM, Gorensen M, Ford-Jones EL *et al.* Fatal varicella-zoster infection in a newborn treated with varicella-zoster immunoglobulin. *Pediatr Infect Dis* 1986;**5**:588–589.
29. Holland P, Isaacs D, Moxon ER. Fatal neonatal varicella infection. *Lancet* 1986;ii:1156.
30. Balfour HH Jr, Kelly JM, Suarez CS *et al.* Acyclovir treatment of varicella in otherwise healthy children. *J Pediatr* 1990;**116**(4):633–639.
31. Balfour HH Jr, Rotbart HA, Feldman S *et al.* Acyclovir treatment of varicella in otherwise healthy adolescents. *J Pediatr* 1992;**120**(4):627–633.
32. Al-Nakib W, Al-Kandari S, El-Khalik DMA *et al.* A randomized controlled study of intravenous acyclovir (Zovirax) against placebo in adults with chickenpox. *J Infect* 1983;**6**(suppl 1):49–56.
33. Feldman S. Acyclovir therapy for varicella in otherwise healthy children and adolescents. *J Med Virol Suppl* 1993;**1**:85–89.
34. Nathwani D, MacDonald T, Davey PG. Economic issues in the prevention and treatment of varicella zoster virus infections. *Herpes* 1995;**2**(1):21–22.
35. Paul JE, Mausekopf JA, Bell L. Cost-consequence models for varicella-zoster virus infections. *Pharmacotherapy* 1995;**15**(suppl 5): 49S–58S.
36. Nathwani D, MacDonald T, Davey P. Cost-effectiveness of acyclovir for varicella infections in immunocompetent patients: a British perspective. *Infect Dis Clin Prac* 1995;**4**(2):1–8.
37. Guess HA, Broughton DD, Melton III LJ *et al.* Population-based studies of varicella complications. *Pediatrics* 1986;**78**(suppl):723–727.
38. Brunell PA. Managing childhood chickenpox. Cost implications. *PharmacoEconomics* 1993;**3**(2):91–93.
39. Lieu TA, Black SB, Rieser N *et al.* The cost of childhood chickenpox: parents' perspective. *Pediatr Infect Dis J* 1994;**13**:173–177.
40. McKenna SP and Hunt SM. A measure of family disruption for use in chickenpox and other childhood illnesses. *Soc Sci Med* 1994;**38**(5):725–731.
41. Moore DA, Hopkins RS. Assessment of a school exclusion policy during chickenpox outbreak. *Am J Epidemiol* 1991;**133**:1161–1167.
42. Preblud SR, Orenstein WA, Koplan JP *et al.* A benefit cost-analysis of a childhood varicella vaccination programme. *Postgrad Med* 1985;**61**:17–22.
43. Lieu TA, Finkeler LJ, Soerl ME *et al.* Cost-effectiveness of varicella serotesting versus presumptive vaccination of school-age children and adolescents. *Pediatrics* 1995;**95**(5):632–638.

## CHAPTER 3

1. Gershon AA, Steinberg SP, Gelb L *et al.* Live attenuated varicella vaccine use in immunocompromised children and adults. *Pediatrics* 1986;**78**:757–762.
2. Gershon AA, LaRussa P, Steinberg S. Live attenuated varicella vaccine: current status and future uses. *Semin Pediatr Infect Dis* 1991;**2**:171–178.
3. Gershon AA, Steinberg SP and the National Institute of Allergy and Infectious Diseases Varicella Vaccine Collaborative Study Group. Live attenuated varicella vaccine: Protection in healthy adults compared with leukemic children. *J Infect Dis* 1990;**161**:661–666.
4. Arbeter AM, Granowetter L, Starr SE *et al.* Immunization of children with acute lymphoblastic leukemia with live attenuated varicella vaccine without complete suspension of chemotherapy. *Pediatrics* 1990;**85**(3):338–344.
5. Broyer M, Boudailliez B. Varicella vaccine in children with chronic renal insufficiency. *Postgrad Med J* 1985;(suppl 4):103–106.
6. Zamora I, Simon JM, Da Silva ME *et al.* Original article: Attenuated varicella virus vaccine in children with renal transplants. *Pediatr Nephrol* 1994;**8**:190–192.
7. Suga S, Yoshikawa T, Ozaki T *et al.* Effect of oral acyclovir against primary and secondary viraemia in incubation period of varicella. *Arch Dis Child* 1993;**69**:639–643.
8. Asano Y, Yoshikawa T, Suga S *et al.* Post-exposure prophylaxis of varicella in family contact by oral acyclovir. *Pediatrics* 1993;**92**(2):219–222.
9. Lynfield R, Herrin JT, Rubin RH. Varicella in pediatric renal transplant patients. *Pediatrics* 1992;**90**(2):216–220.
10. McGregor RS, Zitelli BJ, Urbach AH *et al.* Varicella in pediatric orthotopic liver transplant recipients. *Pediatrics* 1989;**83**(2):256–261.
11. Levin MJ, Nelson WL, Preblud SR *et al.* Clinical trials with varicella-zoster virus immunoglobulins. In: *Clinical Use of Intravenous Immunoglobulins*. London: Academic Press, 1986;pp255–267.
12. Feldman S, Hughes T, Daniel CB. Varicella in children with cancer: seventy-seven cases. *Pediatrics* 1975;**56**:388–397.
13. Ross AH. Modification of chickenpox in family contacts by administration of gamma globulin. *N Engl J Med* 1962;**267**:369–376.
14. Feldman S and Lott L. Varicella in children with cancer: impact of antiviral therapy and prophylaxis. *Pediatrics* 1987;**80**(4):465–472.
15. Prober CG, Kirk LE, Keeney RE. Acyclovir therapy of chickenpox in immunosuppressed children – a collaborative study. *J Pediatr* 1982;**101**(4):622–625.
16. Balfour HH. Intravenous acyclovir therapy for varicella in immunocompromised children. *J Pediatr* 1984;**104**:134–136.

# Acknowledgements

We wish to thank the following publishers and individuals for permission to reproduce tables and figures in this publication:

## CHAPTER 1

**Figures 1 and 2** from *Epidemiology and Infection* 1993;**110**:361–372. Copyright Cambridge University Press.

**Figure 3** from Miller E *et al. Reviews in Medical Virology* 1993;**4**:222–230. Copyright 1993 Chapman and Hall.

## CHAPTER 2

**Table 2** from *The Journal of Infectious Diseases* 1992;**166**(suppl 1):S63–S68. Copyright 1992 The University of Chicago Press.

**Figure 1** from Dr Y Asano, Fujita Health University, Toyoake, Japan.

**Table 4** from *Annals of Internal Medicine* 1992;**117**:358–363. Copyright 1992 American College of Physicians.

**Table 7** from Nathwani D, MacDonald T, Davey P. Cost-effectiveness of acyclovir for varicella infections in immunocompetent patients: a British perspective. *Infectious Diseases in Clinical Practice* 1995;**4**(2):1–8. Copyright 1995 Williams & Williams.

## CHAPTER 3

**Table 1** from *Clinical Use of Intravenous Immunoglobulins* 1986:225–267. Copyright 1986 Academic Press Inc (London) Ltd.

**Cell-mediated immunity** Immune responses which are initiated or mediated by T lymphocytes, macrophages or both

**Cost-consequence analysis** A form of economic evaluation where the costs (direct, indirect and intangible) are expressed in monetary terms but where some of the consequences are expressed in other terms (e.g. healthy days of life)

**Cost-effectiveness analysis** An economic evaluation in which the costs of treatment are compared with outcomes

**Direct costs** Costs of medical intervention (e.g. cost of hospitalizations, outpatient care, therapies)

**Immune-altered** An individual with a change in the immune system caused by pregnancy or the physiological changes related to ageing

**Immunocompetent** Possessing the ability to mount a normal immune response

**Immunocompromised** An individual whose immune system is deficient either because of an intervention with immunosuppressive agents or because of an immunodeficiency disorder

**Incidence** The number of new events during a defined period (e.g. number of people infected with varicella in one year)

**Indirect costs** The productivity losses associated with illness or the work time taken up in medical treatment. These costs also include the loss of productivity of family and caregivers

**Intangible costs** The impact of treatment on life expectancy and quality of life

**Nosocomial transmission** Transmission of a disease within a hospital setting

**Pre-exposure prophylaxis** Prevention of disease before anticipated contact with infectious agent

**Post-exposure prophylaxis** Prevention of disease after suspected contact with infectious agent but in the absence of clinical signs or symptoms

**Prevalence** The number of cases in a given population at a specified time

This publication is jointly sponsored by the University of Alabama School of Medicine, University of Alabama at Birmingham and the *International Herpes Management Forum (IHMF)*.

The University of Alabama School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.

This CME activity was planned and produced in accordance with ACCME Essentials.

The University of Alabama School of Medicine designates this continuing medical education activity for 2.0 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

These materials will be evaluated by the University of Alabama School of Medicine, Division of Continuing Medical Education, at a minimum of 3 years to determine that they are currently relevant to the physician.

Use of the University of Alabama School of Medicine (UAB) name implies review of educational format and materials only, and does not constitute product endorsement. Furthermore, the opinions and recommendations expressed by faculty and other experts whose input is included in the programs are their own. They do not represent nor speak for UAB or Glaxo Wellcome plc or PPS Europe Ltd.

In accordance with the Standards for Commercial Support of the Accreditation Council for Continuing Medical Education (ACCME) which require 'the disclosure of the existence of any significant financial interest a faculty member or a sponsor has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation.' Each faculty member completed disclosure information forms for this project. Disclosures are described below:

M Levin, MD

Research grants: Glaxo Wellcome  
Honorarium: Glaxo Wellcome, the *International Herpes Management Forum (IHMF)*

M Oxman, MD

Research grants: Merck  
Consultant: Merck, Glaxo Wellcome, SmithKline Beecham  
Honorarium: Merck, Glaxo Wellcome, SmithKline Beecham, the IHMF

A Sivayathorn, MD

Honorarium: Glaxo Wellcome, the IHMF

R Whitley, MD

Research grants: National Institutes for Health, Glaxo Wellcome, Bristol-Myers Squibb  
Honorarium: The IHMF

MJ Wood, MD

Research grants: Glaxo Wellcome, SmithKline Beecham, Bristol-Myers Squibb  
Consultant: Glaxo Wellcome, SmithKline Beecham  
Honorarium: Glaxo Wellcome, SmithKline Beecham, the IHMF

The following faculty disclosed no financial interests related to the topic of varicella other than honoraria for participation in the IHMF:

G Koren, MD	D Nathwani, MD	J White, MD
S Kroon, MD	K Elliott, MD	T Schwartz, MD
M Myers, MD	E Sandström, MD	Y Asano, MD

Written and produced by PPS Europe Ltd under an educational grant from Glaxo Wellcome plc.

© 1996 PPS Europe Ltd and the University of Alabama School of Medicine, University of Alabama at Birmingham. All rights reserved.

The International Herpes Management Forum (IHMF) World Wide Web site has information on the IHMF, forthcoming meetings and internet versions of *Management Strategies in Herpes*.

Internet address: <http://www.pps.co.uk/ihmf/welcome.htm>.

