Viral infections in children frequently exert their main effects at mucosal surfaces, such as the respiratory and gastrointestinal tracts, and do not have significant systemic effects. For example, rhinovirus is found in children with the common cold and asthma\(^1\); rotavirus is a significant agent in childhood gastroenteritis \(^2\), and enteroviruses \(^3\) cause a wide spectrum of illness in children and are often asymptomatic. Indeed, experiencing some of these viral infections is considered a normal part of childhood.

However, many paediatric viral infections pass beyond the protective mucosal surfaces, enter the bloodstream and may cause more severe disease, significant hematologic sequelae or death (Table 1). Outbreaks of common viruses, such as human enteroviruses, have been recently associated with severe systemic manifestations, including brainstem encephalitis and death \(^4\).

Human cytomegalovirus (CMV) is a common virus which usually causes a mild illness in immunocompetent children, but is associated with long-term complications when it infects the foetus or immunosuppressed child, including organ and bone marrow transplant recipients \(^5\).

Immunisation has led to a significant change in the pattern of agents responsible for systemic viral infections in childhood. Congenital rubella, poliomyelitis, mumps and measles are now rare diseases in children in the developed world, although recent case reports demonstrate that these viruses have not been completely eradicated \(^6\). Surveillance of infectious and vaccine preventable diseases by the Australian Paediatric Surveillance Unit (APSU) since 1993, including CMV and acute flaccid paralysis, has provided national data on the epidemiology, clinical features, current management and short-term outcome of the conditions under surveillance \(^7\) (Table 2).

**Enteroviruses**

There are over 60 serotypes within the Enterovirus genus, including five species that infect humans; Polioviruses and Human Enterovirus A, B, C and D. Congenital infection (resulting in stillbirth and cerebral palsy), neonatal sepsis, meningitis, encephalitis, myocarditis and type 1 diabetes are recognised manifestations of systemic enterovirus infection. Recently identified variants have been numbered enterovirus 68 to 78.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease/clinical syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>Infectious mononucleosis, hepatitis</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>Congenital infection, neonatal sepsis, encephalitis, myocarditis, acute flaccid paralysis, type 1 diabetes</td>
</tr>
<tr>
<td>Epstein-Barr Virus</td>
<td>Infectious mononucleosis</td>
</tr>
<tr>
<td>Human Immuno-deficiency Virus</td>
<td>Acquired immunodeficiency syndrome (lymphopaenia, neutropaenia, anaemia, thrombocytopenia)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Fulminant hepatitis</td>
</tr>
<tr>
<td>Rubella</td>
<td>Congenital rubella syndrome, lymphadenopathy, polyarthritis, chronic infection</td>
</tr>
<tr>
<td>Measles</td>
<td>Lymphadenopathy, mild hepatomegaly, encephalitis, subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>Herpes simplex virus (HSV1 &amp; 2)</td>
<td>Perinatal infection (disseminated HSV infection or encephalitis in neonates or immunocompromised)</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Transient erythroblastopenic crisis, thrombocytopenia, neutropenia, prolonged bone marrow aplasia in immunocompromised</td>
</tr>
</tbody>
</table>

**Table 1. Viruses that may be associated with significant systemic or haematologic manifestations in children.**

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Amongst these, Enterovirus 71 (EV71) has caused several epidemics in Australia and South East Asia, leading to neurologic dysfunction and death. The illness typically began with hand foot and mouth disease, followed by deterioration associated with pulmonary oedema, brainstem encephalitis, or acute flaccid paralysis. The vast majority of this subgroup of patients died during the outbreak, typically within 24 hours of presentation. Seven affected infants and young children with severe EV71 infection survived during an outbreak in Sydney.

All cases received aggressive and early resuscitation; in addition they were treated with intravenous immunoglobulin.

Table 2. Communicable diseases reported to APSU.

- Acute flaccid paralysis
- Congenital cytomegalovirus infection
- Congenital rubella
- HIV AIDS and perinatal exposure to HIV
- Neonatal herpes simplex virus infection
- Hepatitis C virus infection

(n=3), the antiviral agent pleconaril (n=4) and steroids (n=5). Pleconaril has also been used to treat enterovirus infections in neonates and immunocompromised patients.

Enteroviruses are usually identified in stool, nasopharyngeal aspirate, serum and fluid from skin blisters, and EV71 has been detected in brain and spinal cord of autopsied patients confirming its neurotropism. In the Sydney outbreak, EV71 was isolated in serum from most of the affected children using RT-PCR and were typed using heteroduplex mobility analysis. Enteroviruses have also been isolated from serum and lymphocytes from children at the onset of type 1 diabetes, and from healthy control children, indicating that enterovirus RNA can be found in blood without causing symptoms.

Cytomegalovirus

CMV is the most common cause of viral intrauterine infection and has been the major cause of congenital defects in developed countries for over 20 years. The incidence of congenital CMV ranges from 0.5% to 2.2% of all live births in developed countries. The virus may be transmitted in utero during primary maternal infection, or by reactivation or reinfection of seropositive mothers. Infants can also be infected during delivery, or after birth from breast milk, saliva, urine, fomites and other sources.

Rates of CMV seropositivity vary among countries and among social classes within countries; worldwide between 60% to 100% of adults are infected by 40 years of age. Children with CMV infection may have a flu like illness, but are frequently mildly unwell or asymptomatic.

In collaboration with the APSU, active surveillance for congenital CMV commenced in Australia in 1999. From 1993 to 2003, 70 cases of congenital CMV were identified. The most common clinical features reported in infected infants were jaundice, enlarged liver or spleen, low platelet count and bruising. Almost half of the infants had complications affecting the central nervous system, including microcephaly, chorioretinitis, sensorineural hearing loss, developmental delay or seizures. A febrile illness in the mother was noted in over half of the cases. It is of interest that almost half of the infected mothers were in their first pregnancy, whilst another 40% were in their second pregnancy, suggesting that there are two different population groups at risk of primary CMV infection.

The overall risk of transmission of viruses such as CMV through blood and plasma...
products is low, particularly in the immunocompetent recipient, but the risk increases in immunocompromised patients and in those receiving organ transplants. For CMV seronegative recipients, the risk of CMV infection in solid organ transplant recipients is 2% to 3% and in bone marrow transplant recipients between 20% to 50%. This risk can be decreased by seronegative donors and/or the use of leukocyte depletion filters, decreasing to approximately 2% in bone marrow transplant recipients using leukoreduction. In addition to CMV, human polyoma BK virus, BKV, has also been recognised as a potential agent in paediatric renal transplant patients.

Human herpesvirus 6 (HHV6) is another member of the HHV family, along with CMV, that is found in the blood supply in children. HHV6 can be acquired congenitally, is mostly asymptomatic, and was found in 1% of newborns, the same frequency as CMV in a recent study from the USA. HHV6 causes a febrile illness in children. DNA can persist intermittently following primary infection and was unrelated to illness. Reactivation occurred in a small number of cases without apparent illness. HHV6 is an uncommon cause of meningitis in infants.

Many common viral infections may be associated with severe systemic or haematological manifestations in children, particularly in neonates or the immunocompromised child. Immunisation has led to many of these conditions being eradicated; however, ongoing surveillance is needed due to the potential for resurgence of cases, particularly in the non-immunised and if treatment or immunisation is not available.

**References**


3. Craig ME, Howard NJ, Silink M & Rawlinson WD. Reduced frequency of HLA DRB1*03-DQB1*02 in children with type 1 diabetes associated with Enterovirus RNA. *J Infect Dis* 2003; 187:1562-1570.


