

# Parechovirus: an important emerging infection in young infants

Philip N Britton<sup>1,2</sup>, Cheryl A Jones<sup>3,4</sup>, Kristine Macartney<sup>5</sup>, Allen C Cheng<sup>6</sup>

In late 2017, public health warnings were issued about a national epidemic of human parechovirus (HPeV) in young children. Here, we review the epidemiology of HPeV in Australia since 2013, and provide guidance to clinicians on the management of suspected infection.

This narrative review used a PubMed search of original and review articles from 1996 to 2018, supplemented by data from the Paediatric Active Enhanced Disease Surveillance (PAEDS) network. PAEDS is a hospital-based active surveillance system that performs prospective case ascertainment for selected serious childhood conditions at sentinel paediatric hospitals, including encephalitis, vaccine-preventable diseases and adverse events following immunisation.<sup>1</sup>

## Virology and epidemiology

HPeVs were formerly part of the echovirus genus in the 1960s but were assigned their own genus in the 1990s.<sup>2</sup> Of the 17 genotypes,<sup>3,4</sup> HPeV genotypes 1, 3 and 6 are most commonly associated with human disease.<sup>3,5</sup> With the advent of more sensitive molecular assays, HPeV is now recognised as a small but significant cause of illness in infants aged < 3 years. HPeV was detected in 3–8% of children presenting to emergency with undifferentiated fever in European studies<sup>6,7</sup> and appears to be more common in younger children and in children requiring hospital admission, where up to 15–20% of children with fever without source are HPeV-positive.<sup>8,9</sup> Serological data from Europe and Japan show that 90% of infants have been infected with at least one HPeV subtype by the age of 2 years.<sup>5</sup>

More serious disease has been associated with HPeV3 infection, which was first associated with acute flaccid paralysis in a young girl in 2004.<sup>10</sup> It is now recognised as a leading cause of sepsis-like illness and central nervous system infection, particularly in young infants.<sup>5</sup> In Australia, an epidemic of HPeV3 was first noted in the spring and summer of 2013–2014, initially in New South Wales then nationwide.<sup>11,12</sup> Epidemic activity was subsequently observed in the spring and summer of 2015–2016. This 2-yearly pattern is similar to that observed in the United Kingdom.<sup>13</sup> However, in contrast to other countries, epidemics in Australia have been larger and associated with more severe disease (and poorer clinical outcomes).<sup>14,15</sup> Recently, whole genome sequencing has shown that the first Australian epidemic was likely caused by a novel recombinant HPeV3.<sup>16</sup>

Since August 2017, PAEDS has been tracking an increased frequency of HPeV cases through the Australian childhood encephalitis study and acute flaccid paralysis surveillance systems.<sup>1,17</sup> Increased case numbers were initially noted in Victoria, then in Queensland. In early November 2017, with cases being reported across all five PAEDS sites (Box 1), a formal notification was made to the Communicable Diseases Network Australia of a third national epidemic. In December 2017, the PAEDS network had

## Summary

- Epidemics of human parechovirus (HPeV) causing disease in young children have occurred every 2 years in Australia since 2013. HPeV genotype 3 caused the epidemic from late 2017 to early 2018.
- Most HPeV infections cause no or mild symptoms including gastroenteritis or influenza-like illness. Characteristically, young infants present with fever, irritability and on occasions a diffuse rash (“red, hot and angry” babies).
- Severe disease can manifest as meningoencephalitis, seizures or sepsis-like presentations (including septic shock), or less common presentations including signs of surgical abdomen.
- Testing for HPeV by specific molecular tests is indicated in children younger than 6 months of age with characteristic presentations without another confirmed diagnosis including febrile illnesses with other suggestive features (eg, rash, seizures), sepsis syndromes (including shock), and suspected meningoencephalitis (which may be detected by magnetic resonance imaging only).
- There are no effective antiviral therapies. Treatment is primarily supportive, including management of complications.
- Some infants with severe HPeV infection may have adverse neurodevelopment. Follow-up by a paediatrician is recommended.

identified > 200 cases of hospitalised HPeV infection in young infants associated with the current third epidemic.

## Clinical presentation and complications

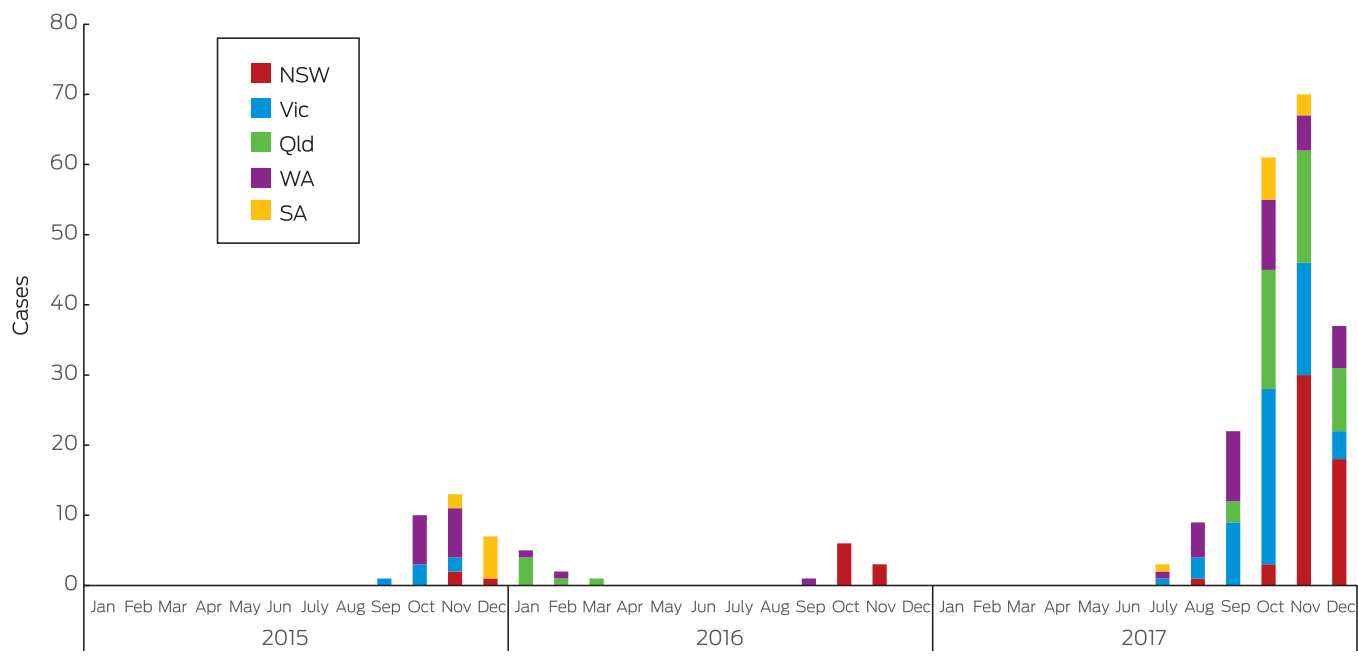
Like enteroviruses, the epidemiology and clinical syndromes associated with HPeV vary by genotype.<sup>5</sup> HPeV1 and HPeV6 are primarily associated with milder gastrointestinal symptoms and presentation in children aged > 6 months.<sup>18,19</sup> HPeV may be isolated from respiratory specimens in children presenting with influenza-like illness<sup>20</sup> and in faecal specimens from children presenting with viral diarrhoea.<sup>21</sup>

HPeV3 causes a range of disease manifestations but primarily fever and irritability, and sepsis-like illness (Box 2).<sup>12,19</sup> Rash is variable,<sup>5</sup> but where present, infants are often described as being “red, hot, angry babies” (Box 3).<sup>12</sup> Occasionally the illness has been mistaken for atypical Kawasaki disease with a palmar-plantar erythema.<sup>12</sup> Young infants (< 3 months) are at highest risk of hospitalisation.<sup>3,5,12,19,22</sup> Neonates (< 28 days) and ex-premature infants may be at higher risk of complications.<sup>14,23</sup> HPeV3 disease can be severe with up to 20–50% of admitted patients with sepsis-like illness requiring intensive care admission.<sup>12,24,25</sup>

Severe manifestations of the acute illness include severe sepsis and meningoencephalitis, which occur in around 10% of hospitalised babies (PAEDS, unpublished data). In a series of 104 children

<sup>1</sup>University of Sydney, Sydney, NSW. <sup>2</sup>The Children’s Hospital at Westmead, Sydney, NSW. <sup>3</sup>University of Melbourne, Melbourne, VIC. <sup>4</sup>Melbourne Academic Centre for Health, Melbourne, VIC. <sup>5</sup>National Centre for Immunisation Research and Surveillance, Sydney, NSW. <sup>6</sup>Monash University, Melbourne, VIC. ✉ [allen.cheng@monash.edu](mailto:allen.cheng@monash.edu)  
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### 1 Monthly case counts of severe hospitalised parechovirus infection identified by PAEDS, 2015–2017\*



PAEDS = Paediatric Active Enhanced Disease Surveillance. \* Before September 2017, surveillance only for suspected encephalitis and acute flaccid paralysis at sentinel sites; enhanced surveillance for all hospitalisations with parechovirus infection commenced in September 2017. ♦

admitted to intensive care units in the United Kingdom and Ireland, 77% required mechanical ventilation and 40% required inotropic support, with similar severe presentations reported elsewhere.<sup>26,27</sup> Seizure activity, including central apnoea, and focal neurological signs may signal meningoencephalitis.

Magnetic resonance imaging of the brain is important to detect characteristic features of meningoencephalitis (peri-ventricular white matter diffusion restriction) that likely has prognostic significance.<sup>14,23</sup> Head ultrasound, widely used in the assessment for meningitis in neonates, is not sensitive to diagnose white matter changes due to parechovirus.<sup>14</sup>

Other less common presentations include an acute abdomen, including intussusception, pseudo-appendicitis and bowel perforation.<sup>3,5,12</sup> Additional unusual manifestations include HPeV3-associated haemophagocytic lymphohistiocytosis and fulminant liver failure.<sup>28,29</sup> Chronic infection in an adolescent with agammaglobulinaemia has also been described.<sup>30</sup>

In adults, HPeV is associated with upper respiratory tract infection and mild diarrhoeal illness, and less commonly with epidemic

myalgia and myocarditis.<sup>31-34</sup> There is currently no evidence to suggest particular concern regarding infection in pregnant women or fetuses.<sup>35</sup>

### Diagnosis of parechovirus

HPeV is not detected by nucleic acid testing for enteroviruses; if suspected, specific polymerase chain reaction testing is required. Testing is generally only available through specialised reference laboratories. The virus can be detected in cerebrospinal fluid (CSF), stool, respiratory secretions, serum and urine. Stool testing appears to be most sensitive (95–98%), followed by CSF testing (84–95%).<sup>12,36</sup> Characteristically, CSF pleocytosis is mild or absent in HPeV3 central nervous system infection, in contrast to other causes of encephalitis.<sup>8,12,14,18,19,23</sup>

Currently, we recommend testing all children aged < 6 months presenting to hospital with clinical features of HPeV infection without another confirmed diagnosis. This includes young infants with sepsis syndromes (including shock), febrile illnesses with other suggestive features (eg, rash, seizures) and suspected meningoencephalitis. Specific testing on stool or CSF for HPeV nucleic acid using polymerase chain reaction should be ordered even in the absence of CSF pleocytosis in these infants. Testing is not generally indicated for children with milder illnesses presenting in the primary care setting. There are as yet insufficient data to define seasonal periods of elevated risk. HPeV infection is not a notifiable disease.

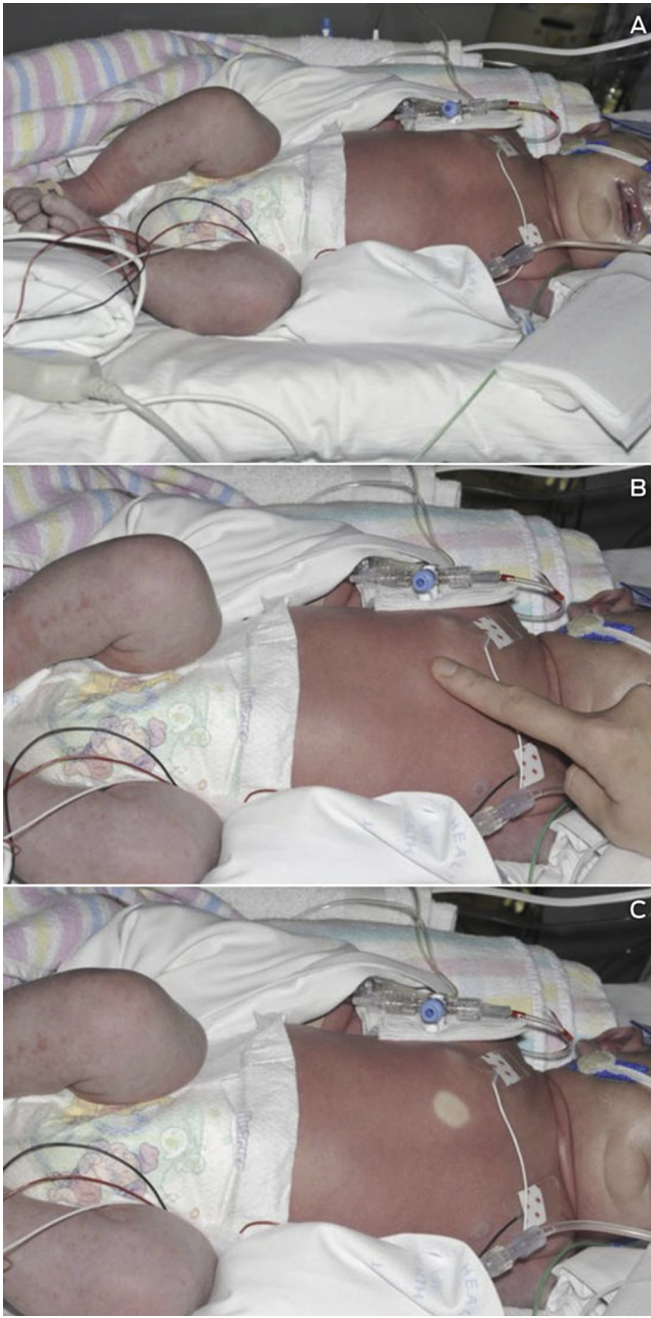
### Managing parechovirus infection

There is no specific antiviral therapy for HPeV infection available at present. Empirical antibiotics should be administered according to local and national guidelines for possible bacterial sepsis or meningoencephalitis, especially in neonates, until this has been excluded by negative sterile site cultures. Once bacterial infection

### 2 Clinical features of parechovirus infection

- Mild disease (especially in children aged > 6 months)
- Gastrointestinal symptoms: diarrhoea
- Respiratory disease: influenza-like illness
- Severe disease (especially in infants aged < 3–6 months): testing may be indicated
- Fever, irritability, rash (“red, hot, angry babies”) in infants aged < 3 months
- Sepsis-like syndromes (including shock)
- Seizures
- Meningoencephalitis, other neurological complications
- Distended abdomen ♦

### 3 Appearance of a young infant with hospitalised parechovirus infection and sepsis-like disease



**A:** Confluent erythroderma of the trunk with an acral erythematous maculopapular rash of the lower limbs (note the presence of cardiorespiratory monitoring, multiple intravenous lines and nasal mask for continuous positive airway pressure ventilation support). **B and C:** Intense erythroderma and prolonged capillary return time. Photographs courtesy of Ameneh Khatami, Brendan McMullan and Julie Huynh. ♦

has been excluded, management is mainly supportive but may require close monitoring and intensive care. Although some case reports suggest benefit, there is no clear evidence to support administration of intravenous immunoglobulin.<sup>37</sup> Physical examination and close observation should exclude acute complications such as shock, apnoea and seizures, and early management should be provided if such complications are detected. Infants with proven HPeV infection and neurological symptoms should undergo magnetic resonance imaging (and not head ultrasound) to exclude encephalitis.

HPeV is transmitted via the faecal–oral route and possibly respiratory droplets. In hospitals, contact precautions are recommended to prevent transmission to other young infants. HPeV3 has been shown to be shed in the stool for a median of 58 days,<sup>38</sup> although the risk of transmission is probably highest during acute symptomatic illness. In the community, non-hospitalised, confirmed cases should avoid contact with other young children (including childcare and school attendance) until symptoms have fully resolved. Contacts of confirmed cases should be made aware that older children and adults may develop mild upper respiratory or diarrhoeal symptoms.<sup>39</sup> There are cases of transmission from mildly symptomatic children to adults resulting in severe acute illness, but these appear to be uncommon.<sup>34</sup> Hand hygiene, cough etiquette and staying away from childcare and school while unwell should be emphasised.

Follow-up studies have shown adverse neurological outcomes in patients with meningoencephalitis, and developmental concern among patients with sepsis-like illness from the 2013–2014 epidemic.<sup>14,15,23</sup> A study of Australian infants hospitalised with HPeV3 in 2013 found that 19% showed significant concern in developmental attainment 12–16 months after infection and an additional 50% had some concern based on standardised tools.<sup>15</sup> An earlier study documented severe neurodevelopmental sequelae, including cerebral palsy, central visual impairment and gross motor impairment.<sup>14</sup> These findings are consistent with those from other countries, where 16% of children hospitalised with confirmed HPeV infection had significant neurological sequelae.<sup>24</sup> These data also appear to be consistent with outcomes from other causes of encephalitis.<sup>40</sup>

Because of the evidence of adverse neurodevelopmental outcomes following severe HPeV infection, we recommend that all children hospitalised with HPeV infection should be followed up by a paediatrician at least until school entry, and preferably afterwards, to monitor development and learning, and manage complications including seizures.

### Future directions

The HPeV epidemics since 2013 highlight the need for surveillance targeted at important syndromes such as encephalitis, to define the disease burden, evaluate strategies and interventions to prevent and manage cases, and to respond to the potential first signals of emerging infectious diseases. The Australian childhood encephalitis study, based on PAEDS data, has already demonstrated capacity for early detection of serious infectious epidemics in children including HPeV and enterovirus 71 (EV71).<sup>17</sup> This would also provide information on all causes of this devastating syndrome that are potentially vaccine-preventable, such as influenza.<sup>41,42</sup>

Many unanswered questions remain regarding the epidemiology and clinical features of HPeV in Australia, and there are unique opportunities to study the evolution of the virus and disease over the three epidemic waves in Australia to date. In addition, the specific pathogenesis of HPeV3 disease needs better elucidation in order to develop specific treatments. There are currently cohort studies underway to better characterise the long term neurodevelopmental outcomes for children with central nervous system infection.

In the Asia–Pacific region, HPeV cases have mainly been reported from developed countries, such as Australia, Japan,<sup>26</sup> Taiwan,<sup>43</sup> Korea<sup>44</sup> and Hong Kong.<sup>45</sup> However, even in high resource settings, the known epidemiology of infection is likely to reflect the

availability of diagnostics.<sup>46</sup> Small case studies suggest that HPeV is an important cause of seasonal febrile illnesses in other settings but its true epidemiology in developing countries is yet to be determined.<sup>47-49</sup>

Vaccines for polio, also an enterovirus, have been highly successful in eradicating the virus from all but three countries in the world. Unfortunately, the antigenic diversity of the enterovirus/HPeV group is a barrier to the development of broadly protective vaccines. A promising strategy is to develop vaccines against specific highly pathogenic enteroviruses, such as EV71 (a cause of complicated hand, foot and mouth disease), which has led to a licenced vaccine in China.<sup>50</sup> As HPeV seems to be associated with similar outcomes as EV71, HPeV3 may be a future target of such

efforts. Although further work to define the global epidemiology of HPeV infection is required to establish the utility of vaccine development, the high morbidity in young children provides a strong case for prevention.

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