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Biographies

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Public health impact of the Enteroviruses and Parechoviruses

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Enteroviruses (EV) comprise viruses originally classified on cell culture replication patterns and clinical manifestations into a number of groups: poliovirus, coxsackievirus A, coxsackievirus B and ECHOvirus. The closely related genus *Parechovirus* has more recently been associated with human disease. EVs are common commensals of the human gut, often found without any ill effects on the person, but are also associated with a wide range of diseases and syndromes including non-specific rash illnesses, hand, foot and mouth disease (HFMD), conjunctivitis, meningitis and encephalitis, myocarditis and polio. This results in a significant burden of disease worldwide, often due to a particular genotype of EV. An estimated 1 billion people are infected with EV every year.

Australia has not seen endemic polio since 1972, and as a result of global eradication efforts, wild poliovirus is now only present in Afghanistan, Pakistan and Nigeria, although cases of paralysis caused by vaccine-derived poliovirus have been detected in the past 1–2 years in the Democratic Republic of the Congo, Syria and the Lao People's Democratic Republic[1]. In Australia, an acute flaccid paralysis surveillance program is conducted in order to support and verify Australia's polio-free status. The laboratory component is coordinated by the Victorian Infectious Diseases Reference Laboratory and the clinical component by the Australian Paediatric Surveillance Unit[2].

Although most EV serotypes typically cause subclinical infection, some can result in serious complications disproportionately affecting neonates and young infants. In high income countries, up to 60% of aseptic meningitis in infants under 3 months of age are caused by EV and human parechoviruses (HPeV). As a single species parechovirus type 3 is the most common cause of viral meningitis in this age group. EV and HPeV manifest seasonally with a peak in summer. This was recently demonstrated in a large New South Wales outbreak with cases of HPeV-3 meningitis and sepsis in infants[3]. The ease of transmissibility, prolonged shedding in stool and respiratory secretions, and the resistance of these non-enveloped picornaviruses to common disinfectants sustain outbreak propagation.

One highly neurovirulent serotype, EV-A71 has been known to cause severe rhombencephalitis in the Western Pacific region including several documented outbreaks in Australia since it was first described in 1969. EV-A71 neurotropism for the midbrain may compromise cardiopulmonary function leading to long term sequelae and death. Devastating outbreaks resulted in the death of 78 children in 1998 in Taiwan and 126 deaths reported in the 2008 outbreak in China[4,5]. In 2013, Sydney experienced a severe EV-A71 outbreak resulting in four deaths in young infants and focal paresis described as the most common persisting functional deficit[6].

More recently, the EV-D68 outbreak in North America underlined the importance of EV surveillance as it was predominantly transmitted through the respiratory route whereas EVs are usually passed on by the faecal-oral route[7]. In response, the Center for Disease Control (CDC) developed an EV-D68 specific assay with a reported sensitivity and specificity of 98% to 100% and 92% to 98% in respiratory samples respectively.

As with most viruses, EV and HPeV diagnosis has shifted from conventional culture to nucleic acid detection (NAD) techniques as they have increased sensitivity and a clinically relevant turnaround time. Current molecular assays for EV and HPeV diagnosis rely on reverse transcriptase PCR (RT-PCR) of highly conserved genomic sequences within the 5'-untranslated region (UTR) present in all known serotypes. Commercial assays have reported sensitivities ranging from 94% to 100% on CSF, blood, respiratory samples and stool. These assays have also been used to detect EV RNA in cardiac and hepatic tissue[8]. In neonates and young infants with sepsis or meningitis, EV or HPeV RT-PCR on blood is often more sensitive than on CSF making combined testing recommended to increase diagnostic yield. In the case of EV-A71, there has been no correlation established between viraemia and the presence of neurological complications nor the severity of clinical presentation[9,10].

Caution is warranted with the interpretation of stool and respiratory sample results as asymptomatic shedding has been reported for weeks to months post infection, rendering the positive predictive value of an affirmative RT-PCR limited. HPeV RT-PCR requires different primers underpinning the need to test for both in case of clinical suspicion. Sharing a high proportion of nucleotides in the 5′-UTR region, cross amplification of common rhinoviruses may occur in EV RT-PCR from respiratory samples. Without sequencing, commercial assays will not be able to differentiate between EV and rhinoviruses.

Speciation and genotyping relies on sequencing of the highly variable VP1 capsid protein. Between 2007 and 2012, Papadakis *et al*. were able to genotype 43% of 729 EV RT-PCR positive CSF samples from patients with aseptic meningitis in Victoria. The four most common genotypes identified were ECHOvirus 6, ECHOvirus 30, ECHOvirus 25, and coxsackievirus A9, comprising 61% of all EVs identified[11].

Current treatment of EVs relies on early recognition by astute physicians and supportive therapy. Based on retrospective data the World Health Organization (WHO) 2011 guide to clinical management and public health response to HFMD recommend the use of IVIG for severe cases of EV-A71 neurological disease[12]. Several capsid-inhibitor compounds targeting the EV capsid-canyon hydrophobic pocket are under investigation. Pleconaril is the only compound that has gone through phase III trials in neonates with EV sepsis, but strong efficacy data are lacking[13]. Several vaccine designs are going through early stages of development, but the most successful approach so far has been with the use of formalin-inactivated EV-A71 vaccines. Phase III trials involving more than 30 000 Chinese infants and children did not reveal any significant adverse events and showed they can prevent 90% of EV-A71 HFMD and 80% of EV-A71 complications[14,15]. Similarly, formalin-inactivated EV-A71 vaccines are being trialled in phase I in Singapore and Taiwan. These inactivated viruses are based on the C4 genotype most commonly causing disease in mainland China. Data collection of Australian aseptic meningo-encephalitis EV genotypes may

elucidate the role of commercially available EV-A71 vaccines in mitigating CNS complications.

Several studies have shown that rapid diagnosis of EV meningitis by RT-PCR results in decreased length of hospitalisation and cost savings, particularly at times of high prevalence such as during seasonal outbreaks[16]. In the absence of pleocytosis, strengthening of laboratory capacity for testing of EV and HPeV RT-PCR can help clinicians to accurately diagnose aseptic meningitis and provide optimal treatment.

Further integration of data on commonly circulating genotypes into Australia's existing EV surveillance networks will prove to be crucial for early recognition and identification of emerging strains such as EV-A71 and EV-D68 as well as more virulent strain variants, thus allowing a timely and effective public health response.

Apart from poliovirus, EVs and associated syndromes are not subject to statutory notification under public health legislation in Australian states and territories. Surveillance of acute flaccid paralysis is currently being undertaken whilst it has been suggested that effort should also be directed to surveillance of infectious causes of encephalitis[17]. More robust nationwide surveillance into common genotypes causing severe disease may also guide policy makers to introduce a targeted vaccine.

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Biographies

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