

## Invited Comment for Lancet Infectious Diseases

### Viral meningitis – epidemiology and diagnosis

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**Text.** The introduction of conjugate vaccines against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* led to a remarkable reduction in the incidence of bacterial meningitis in children, with viral meningitis now being the most common cause of central nervous system (CNS) infections in children.<sup>1,2</sup>

In *the Lancet Infectious Diseases*, Natalie Martin and colleagues<sup>3</sup> describe the changing epidemiological trends in childhood viral meningitis in England between 1968 and 2011. This study is extremely valuable in applying a standardised methodology for very large sets of epidemiological data collected over 40 years and the changes demonstrated in overall incidence and viral aetiologies are remarkable. The study records the virtual disappearance of mumps meningitis following the introduction of the measles-mumps-rubella (MMR) vaccine in 1988. It also describes a dramatic rise in admissions with viral meningitis in infants under one year of

age. Among these cases, an increasing proportion are recognized to be caused by enteroviruses (EV), accounting for only 3% of infant viral meningitis cases in 1968-1985, but rising to 47% in 2007-2011.

This apparent increase in enteroviruses meningitis cases undoubtedly reflects in part the elimination of other bacterial and viral causes of meningitis in this age group but changes in diagnostic technology have also likely contributed. Specifically, the adoption of polymerase chain reaction (PCR)-based screening of CSF and stool samples in suspected viral meningitis cases has undoubtedly increased detection rates through its greater sensitivity compared to virus culture, and its much wider use.<sup>4,5</sup> A recent audit performed by the Clinical Virology Network (CVN) reported that all UK laboratories in 2012 utilized PCR-method for EV detection and most (75%) routinely screened all CSF samples irrespective of clinical picture or biochemical findings (unpublished data). Martin and colleagues<sup>3</sup> indeed describe how such methodology would detect EV infections in a large number of meningitis cases presenting without pleocytosis that would have been previously untested.

PCR-based screening is also effective for the detection of other viral pathogens refractory to previously used viral culture methods. Among these, the most prominent is human parechovirus (HPeV) whose role in neonatal sepsis and CNS complications has been systemically underestimated since its original discovery over 50 years ago.<sup>5,6,7,8</sup> While HPeV is distantly related to EVs, it cannot be diagnosed using the traditional virus isolation methods. However, the recent application of PCR-based screening methods to CSF samples has identified a specific HPeV type (HPeV3) as a major cause of CNS infections and sepsis-like disease in young infants.<sup>5</sup> HPeV3 has been shown to be more common cause of neonatal fever with CNS involvement than any EV type.<sup>5,9</sup>

Its role in viral meningitis is still widely underestimated. According to the CVN audit, only half of the UK hospital laboratories had introduced molecular testing for HPeV by 2012. Furthermore relevant for the purposes of systematic surveillance, HPeV meningitis still lacks a separate ICD code. Even if HPeV3 infections were diagnosed, they would have been reported under the general viral meningitis code in the dataset analysed in the current study.<sup>3</sup> HPeV3 infections have been almost uniformly identified in infants under 3 months of age, and higher frequencies of HPeV3 infection have been mostly reported in even-numbered years in northern Europe since 2008.<sup>5,6,7,8</sup> Remarkably, even without specific diagnosis or reporting, the data presented by Martin and colleagues<sup>3</sup> demonstrated highest rates of neonatal meningitis in 2008 (59.9/100.000), 2010 (67/100.000) and 2011 (70/100.000), a pattern consistent with temporal trends in HPeV3 incidence reported in CSF samples in 2008 and 2010 obtained from children under the age of three months in UK and elsewhere in Europe.<sup>5,6,7,8</sup> As a further potential correlate of the raw epidemiological data, coxsackievirus B5 (CBV5) was one of the most commonly identified EV type in 2011<sup>9</sup> and as it has been previously associated with meningitis in young children<sup>10</sup>, it may well account for the further peak in incidence observed in 2011.

An additional potential explanation for the increasing hospitalisation rate of young children from enterovirus meningitis is its changing epidemiology. For example the proportion of pregnant women lacking antibodies to one enterovirus type (CBV4) increased from 6% in 1983 to 17% in 1995.<sup>11</sup> Similar long term declines in seroprevalence to other enteroviruses associated with viral meningitis are likely to have occurred in parallel. Increasing number of young infants would therefore lack the protective maternal antibodies to viruses circulating in community, and thus have increased likelihood of developing severe CNS-associated EV disease.

It is clear that methods used to identify the etiology of viral meningitis have changed. It would have been interesting to see if there might have been regional differences in reported incidence of enterovirus meningitis, potentially coinciding with different screening strategies or methods used in regional diagnostic centers. As the study by Martin and colleagues<sup>3</sup> was based on reported admission rates for viral meningitis, the findings have to be evaluated with an awareness that diagnostic and surveillance methods have changed over the study period. What is the clinical definition for viral meningitis in young children under the age of three months, especially in the absence of pleocytosis? Are they all true cases of viral meningitis? Does detection of EVs or HPeV in CSF truly identify a viral aetiology of neurological disease?<sup>12</sup>

## References

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