**Title:**

# Heterologous immunity potentially affects the immune response to EV71 infection and vaccine

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Hand, foot and mouth disease (HFMD) is a common children sickness. The major etiological agents of HFMD are enterovirus 71 (EV71), coxsackievirus (CV) A16. Other enteroviruses including CV serotypes A2, A4, A6, A9, A10, B1, B3 and B5, also cause mild HFMD. EV71 is the most pathogenic virus of these causative agents, causing severe HFMD and significant mortality. Although it is reported previously that cross-reactive T cell epitopes exist for enteroviruses, it remains unknown how immunization or exposure to other enteroviruses affect T cell response to EV71 infection of HFMD patients and the efficacy of EV71 vaccine in clinical trial. We used EpiMatrix algorithm to identify promiscuous CD4+ T cell epitopes contained within the sequence of the EV71 polyprotein. We then validated the epitope predictions via ELISpot assays and flowcytometry analysis of intracellular staining. Fifteen epitopes elicited detectable T cell responses in adult donors, and sequence analysis revealed two dominant epitopes that were located in the capsid region. The most dominant eiptope is highly conserved among enterovirus species, including HFMD-related coxsakieviruses as well as echoviruses and polioviruses. We further found that higher levels of Th2 response to the dominant epitope negatively correlated with the slower recovery of HFMD patients. Our findings imply that heterologous immunity mediated by CD4+ T cells to poliovirus following vaccination, or to other enteroviruses to which individuals may be exposed in early childhood, may have a modulating effect on subsequent CD4+ T cell response to EV71 infection and vaccine, and affect the severity of EV71-caused HFMD.