Antibodies were prepared by immunizing mice with empty, immature particles of human enterovirus 71 (EV71). EV71 is a picornavirus that causes hand, foot, and mouth disease. In infants and small children the infection may proceed to encephalitis that can be fatal or result in permanent brain damage. The capsid structure of EV71 empty particles is different from that of the mature virus and is similar to “A” particles encountered when picornaviruses recognize a potential host cell prior to genome release. The “A” particles are expanded relative to the stable form of the virions and are prone to release their genomes. The monoclonal antibody E18, generated by this immunization, induced a conformational change when incubated with mature virus, transforming infectious virions into A particles. Thus, binding of E18 to the virus might correspond to receptor interaction. The resultant loss of genome that was observed by cryo electron microscopy and a verified by fluorescent Sybr-GREEN dye assay. The release of the genome inactivated the virus. As the mechanism for virus inactivation has now been established the E18 has the potential to be developed for anti-EV71 therapy. Antibodies recognizing epitopes similar to that of EV71 could be prepared in mice. The antibody-mediated virus neutralization by the induction of genome release has not been previously demonstrated. Furthermore, the present results indicate that antibodies with genome-release activity could also be produced by immunization with immature particles for other picornaviruses.