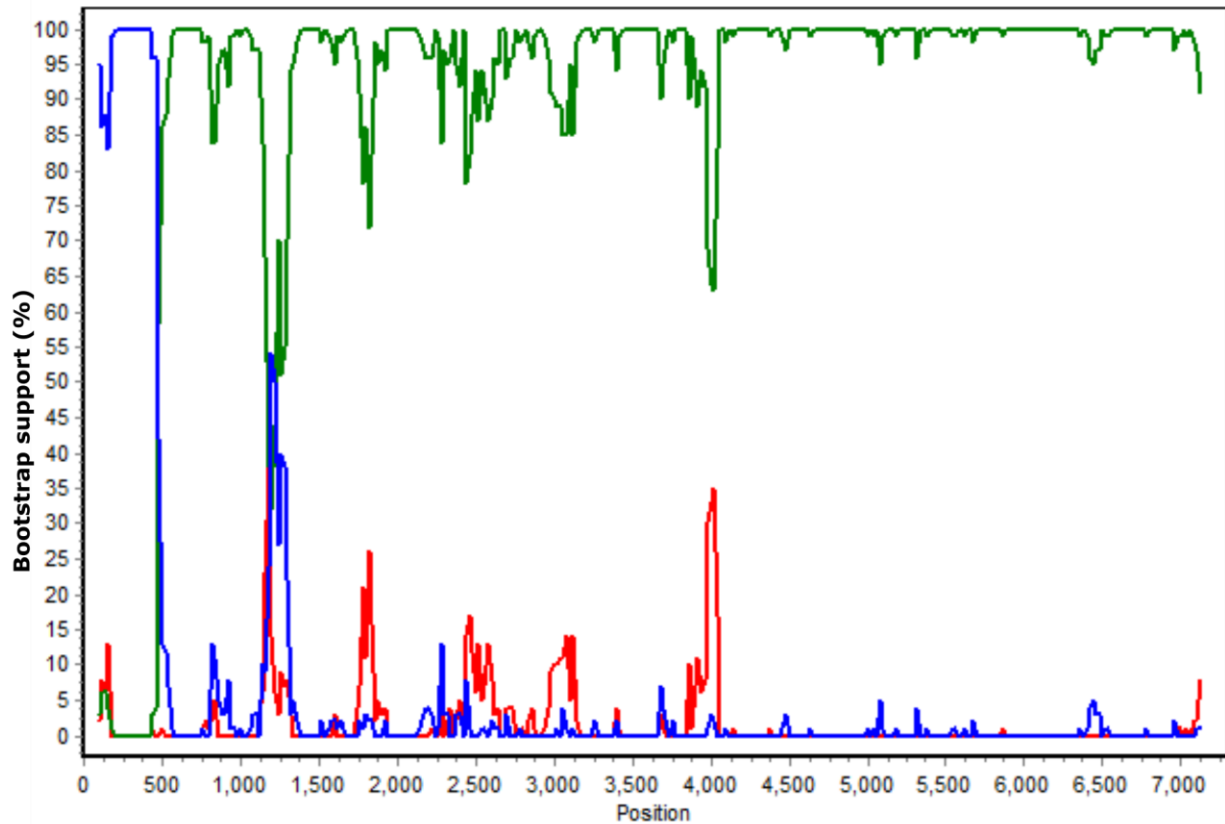


Supplementary Materials

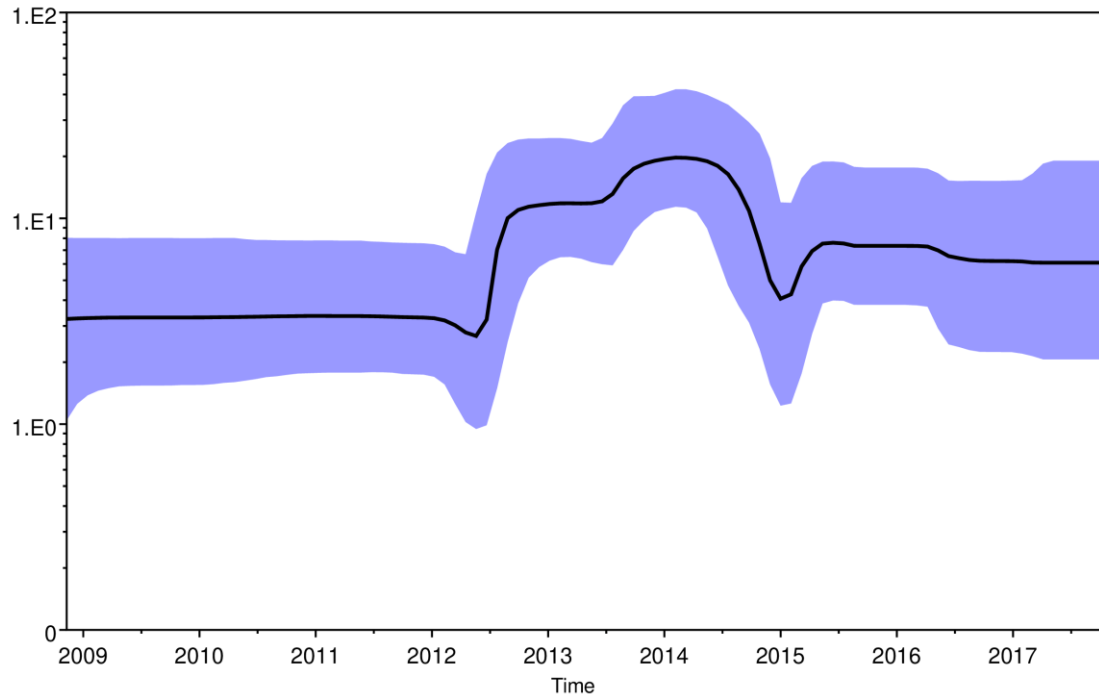
Supplementary Table 1: HFMD management guidelines according to Vietnamese Ministry of Health

	Classification Signs/symptoms	Suggested Management
Grade 1	Oral ulcers and/or vesicular rash on the hands, feet, and/or the buttocks	OPD care, with advice sheet for family Careful observation for warning signs
Grade 2a	Grade 1 AND Myoclonic jerks observed by the family (not witnessed by medical staff) Legarthy, agitation/irritability Fever $\geq 39^{\circ}\text{C}$ for ≥ 48 hours. Vomiting	Hospitalization Oral phenobarbitone Vital Signs Monitoring: every 4-6 hours following standard protocols
Grade 2b1	Grade 1 AND Myoclonic jerks witnessed by medical staff or by the family (2 jerks/30 minutes or 1 jerk and stupor) Resting pulse rate $> 130/\text{min}$ but $< 150/\text{min}$ (adjusted for fever")	Admit to HDU/PCIU IV Phenobarbitone Antipyretics Vital Signs Monitoring: every 1-3 hours for minimum 6 hours until stable
Grade 2b2	Grade 1 AND witnessed myoclonic jerks accompanied by one of the following findings: Continuous limb tremor, limb weakness Or paralysis, or drowsiness (provided no hypoglycemia) Resting pulse rate $> 150/\text{min}$ (adjusted for fever) Fever $\geq 39.5^{\circ}\text{C}$ (rectal) and unresponsive to antipyretics > 4 hours	Give oxygen IV Phenobarbitone Antipyretics Start IVIG - 2g/kg in two divided doses Check: FBC, CRP, blood sugar, and consider lumbar puncture Vital Signs Monitoring every 1-3 hours for > 6 hours
Grade 3	Serious complications in CNS or Cardiopulmonary systems: Pulse $> 170/\text{min}$ Profuse sweating Stage 1 hypertension (SBP $> 95^{\text{th}}$ centile for age) Respiratory abnormalities: tachypnea, labored breathing Muscle hypertonia Coma (Glasgow coma score < 10)	Oxygenation Consider need for ventilation IV Phenobarbitone and IVIG Milrinone if stage 2 hypertension (SBP $> 99^{\text{th}}$ for age + 5 mm Hg) Dobutamine if HR > 170 bpm Consider additional fever control measures Invasive blood pressure monitoring Check: FBC, CRP, blood sugar, and Consider lumbar puncture Vital signs monitoring: every 30-60 minutes for 26 hours
Grade 4	Severe complications: Acute pulmonary edema Cardiac collapse	SpO2 $< 92\%$ with cannula oxygen 6 litres/min) Respiratory arrest or gasping respiration Intubation and ventilation IV Phenobarbitone Dobutamine; Fluid challenge Antipyretics, Access CVC plus invasive BP monitoring Vital signs monitoring: every 15-30 mins for 26 hours



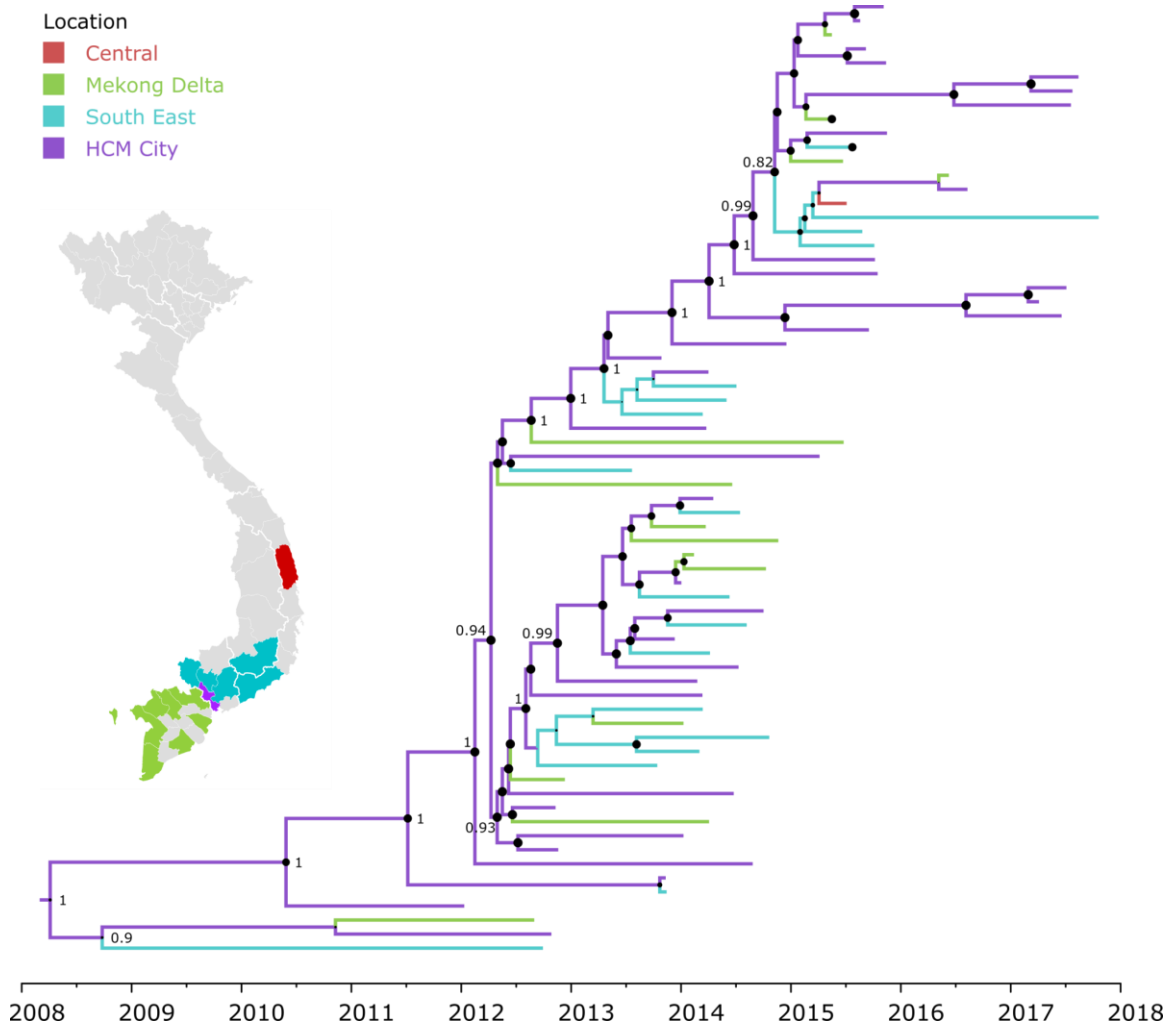
Supplementary Figure 1: Bootscan analysis showing the recombinant CVA16

Note Supplementary Figure 1: Green color indicates the recombinant CVA16 strain obtained from the present study, while red and blue colors indicate reference strains (GenBank accession numbers: KX768156 and KF193624, respectively).



Supplementary Figure 2: Estimated relative genetic diversity of CVA16 in Vietnam by Bayesian skyline plot using CDS dataset

Note to Figure 2: The analysis was done for 68 CDS. The estimated substitution rate was 4.6×10^{-3} ($4.21 - 5.02 \times 10^{-3}$) substitutions per site per year. The estimated time to most recent common ancestor was Apr 2008 (Aug 2007 - Oct 2008)



Supplementary Figure 3: CDS based maximum clade credibility trees demonstrating the phylogeography of CVA16 isolates in Vietnam