

1 **Population based hospitalization burden of laboratory-confirmed**
2 **hand, foot and mouth disease caused by multiple enterovirus serotypes**
3 **in southern China**

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28

29 **Short title:** Hospitalization rates of HFMD in Southern China

30

31 **Abstract**

32 **Background.** Hand, foot and mouth disease (HFMD) is spread widely across Asia, and
33 the hospitalization burden is as yet not well understood. Here, we estimated serotype-
34 specific and age-specific hospitalization rates of HFMD in Southern China.

35 **Methods.** We enrolled pediatric patients admitted to 3/3 county-level hospitals and
36 3/23 township level hospitals in Anhua county, Hunan (CN) with HFMD, and collected
37 samples to identify enterovirus serotypes by RT-PCRs between October 2013 and
38 September 2016. The information of other eligible but un-enrolled patients were
39 retrospectively collected from the same six hospitals. Monthly number of
40 hospitalizations for all causes was collected from each of 23 township level hospitals
41 to extrapolate hospitalizations associated with HFMD among these.

42 **Results.** During the three years, an estimated 3,236 pediatric patients were hospitalized
43 with lab-confirmed HFMD, and among these only one patient was severe. The mean
44 hospitalization rates were 660 (95% CI: 638-684) per 100,000 person-years for lab-
45 confirmed HFMD, with higher rates among CV-A16 and CV-A6 associated HFMD
46 (213 vs 209 per 100,000 person-years), and lower among EV-A71, CV-A10 and other
47 enteroviruses associated HFMD (134, 39 and 66 per 100,000 person-years, $p<0.001$).

48 Children aged 12-23 months had the highest hospitalization rates (3,594/100,000
49 person-years), followed by those aged 24-35 months (1,828/100,000 person-years) and
50 6-11 months (1,572/100,000 person-years). Compared with other serotypes, CV-A6-
51 associated hospitalizations were evident at younger ages.

52 **Conclusions.** Our study indicates a substantial hospitalization burden associated with

53 non-severe HFMD in a rural county in southern China. Future mitigation policies
54 should take into account the disease burden identified, and optimize interventions for
55 HFMD.

56

57 **Key words:** Hand, foot and mouth disease; enterovirus; hospitalization burden;
58 hospitalization rates.

59

60 **Introduction**

61 Hand, foot and mouth disease (HFMD) is a common infectious disease that mainly
62 affects children below 5 years of age [1]. HFMD is caused by multiple serotypes of
63 Enterovirus species A, among which enterovirus 71 (EV-A71) and coxsackievirus A16
64 (CV-A16) are the most frequently detected [2]. EV-A71 is of particular concern as it
65 can cause neurological and systematic complications, and even fatal outcomes [2-4].
66 Coxsackie virus A6 (CV-A6) and Coxsackie virus A10 (CV-A10) have become more
67 prevalent among HFMD outbreaks. Their re-emergence was first identified in HFMD
68 cases in Europe and Singapore between 2008 and 2011 [5-8]. They are also responsible
69 for considerable cases of HFMD in China since 2013 [9, 10]. Severe complications
70 associated with CV-A6 and CV-A10 have also been reported [11, 12]. Currently, no
71 specific antiviral treatments are available for HFMD. Three inactivated monovalent
72 EV-A71 vaccines have been licensed in mainland China, with high efficacy (90.0%–
73 97.4%) against EV-A71-HFMD, but no cross-protection against other enterovirus
74 serotype-associated HFMD [13, 14]. Bivalent and multivalent enterovirus vaccines are
75 under development [15, 16].

76 Since 1997, HFMD has widely spread across Asia, including Malaysia, Japan,
77 Singapore, Vietnam, Cambodia, and China [1]. Understanding the age and serotype-
78 specific burden of HFMD, including the hospitalization burden, is valuable in
79 informing healthcare systems, vaccine strategies and other intervention policies.
80 However, the hospitalization burden of HFMD has not been thoroughly studied in a
81 well-defined catchment population. Indirect estimates of hospitalization rates of HFMD

82 are hampered by limited availability of population level incidence and unknown
83 hospitalization rates among HFMD cases. Population level incidence of HFMD has
84 been estimated in Japan [17], Singapore [18], Malaysia [19], and China [2, 20]. These
85 estimates were based on notifiable surveillance data which may underestimate the true
86 prevalence. The risk of hospitalization for HFMD varied between 1.3% and 24.3% [21-
87 25], possibly due to patients with distinct severity and different causative serotypes of
88 enterovirus in different studies. The number of people that were included in these
89 studies ranged from 6,027 to 1,081,046 [21-25]. Additionally, there is an increasing
90 threat of enterovirus serotypes of non-EV-A71 among both mild and severe HFMD [7,
91 11, 20]. Therefore, the hospitalization burden of HFMD caused by CV-A6, CV-A10,
92 CV-A16 and other enterovirus serotypes requires further assessment.

93 We aim to estimate population level hospitalization rates of HFMD by age and
94 enterovirus serotype in a well-defined catchment population in China between October
95 2013 and September 2016.

96

97 **Methods**

98 **Study setting**

99 This study was conducted in Anhua County, Yiyang Prefecture, Hunan Province, China
100 [26]. The total population residing in Anhua County was 1,017,463 according to the
101 2015 census [27]. A total of 165,050 (16%) of the population were children aged <15
102 years, and of these 61,123 (6%) were aged <5 years [27]. There were three county-level
103 hospitals and 23 township level hospitals in Anhua County where HFMD patients were

104 admitted. According to vaccination records, the EV-A71 vaccine was initiated in Anhua
105 County on July 10, 2016.

106 **Case definitions**

107 A probable case of HFMD was defined as a patient with a rash on their hands, feet,
108 limbs or buttocks, ulcers or vesicles in the mouth, with or without fever. A lab-
109 confirmed case was defined as a probable case with laboratory evidence of enterovirus
110 infection detected by real-time RT-PCR (reverse transcription-polymerase chain
111 reaction) or nested RT-PCR. Hospitalized patients were defined as patients hospitalized
112 during at least 24 hours of admission.

113 **Virological surveillance of HFMD**

114 Virological surveillance of HFMD was conducted among six hospitals, including three
115 county-level hospitals and three township level hospitals between October 2013 and
116 September 2016. The six hospitals were selected as they admitted 87% of the reported
117 HFMD patients from Anhua County during 2010-2012. The methods for the virological
118 surveillance have been described elsewhere [26]. Briefly, the pediatric patients (aged
119 0-14 years) who were hospitalized for HFMD, were enrolled after parents/legal
120 guardians provided verbal consent. Throat swabs and stool samples (or rectal swabs)
121 were collected within 24 hours of enrollment. A standardized form was used to collect
122 data, including basic demographic information, date of illness onset, types of samples
123 (stool, throat swab, or rectal swab), complications, and clinical outcome.

124 Swabs were immediately placed in viral transport mediums, and all samples were
125 stored at -70 °C until testing. Viral RNA was extracted using QIAamp Viral RNA Mini

126 Kit (QIAGEN, Hilden, Germany). RNA from each sample was tested with generic
127 primers and probes targeting pan-enterovirus, and specific primers and probes targeting
128 EV-A71, CV-A16, and CV-A6. If a sample tested positive in the generic and negative
129 in the specific RT-PCRs, nested RT-PCRs were used to amplify VP1 regions. If
130 negative in amplifying VP1 regions, nested RT-PCRs on VP4-VP2 regions were used
131 for further identification of enterovirus serotype.

132 **Estimation of hospitalization burden**

133 Some patients who were admitted to hospital for HFMD during the study period were
134 not captured by the above virological surveillance. Therefore, we retrospectively
135 collected the monthly number of eligible but unenrolled hospitalized patients with
136 diagnosis of HFMD by age group at each of the six hospitals. We extracted data from
137 the electronic Hospital Information System (HIS) at the three county-level hospitals.
138 We manually reviewed the paper-based medical charts at the three township hospitals.
139 We did not visit the other 20 township hospitals to collect the number of HFMD-
140 associated hospitalizations manually. Instead, the number of patients who were
141 hospitalized between October 2014 and September 2016, the cause of their
142 hospitalization and their age was extracted from the Rural Health Information System
143 (RHIS) of Hunan Province (<http://220.170.145.170:8888/chss/>) for each of the 23
144 township hospitals.

145 A multiplier model [28] was used to estimate the hospitalization rates of HFMD in
146 this study (Fig 1). We divided the patients and the population denominators into eight
147 age groups, including <6 months, 6-11 months, 12-23 months, 24-35 months, 36-47

148 months, 48-59 months, 5-9 years, and 10-14 years. We assumed that the age stratified
149 admission rates were comparable among the township level hospitals. We extrapolated
150 the number of HFMD-associated hospitalizations per age group among 23 township
151 level hospitals based on data from the three township hospitals and number of total
152 hospitalizations among all township level hospitals (Fig 1). The total number of
153 hospitalizations for HFMD in each age group in Anhua county was the sum of the
154 number of hospitalizations captured and non-captured in virological surveillance
155 among the county level hospitals, and number of hospitalizations among all township
156 level hospitals. We estimated the number of hospitalizations attributable to lab-
157 confirmed HFMD, EV-A71, CV-A16, CV-A6, CV-A10 and other enteroviruses (non-
158 EV-A71 & non-CV-A16 & non-CV-A6 & non-CV-A10) associated with HFMD in
159 Anhua County. We assumed that the age-specific distribution of enterovirus serotype
160 in the enrolled group was the same as that in the non-enrolled group (Fig 1).

161

162 **Fig 1. Flowchart of estimating age-specific and serotype-specific hospitalization**
163 **burden associated with HFMD.**

164

165 The hospitalization rates by serotype were estimated by dividing the serotype-
166 specific number of hospitalizations by the size of the resident population. The age-
167 specific population denominators of Anhua County from 2013 to 2016 were collected
168 from the National Bureau of Statistics of China [27].

169 **Statistical analysis**

170 The Poisson method was used to estimate 95% confidence intervals (CI) of
171 hospitalization rates. The χ^2 test or Fisher's exact test was used to analyze categorical
172 data. The Mann-Whitney U test was used to analyze ranked data. Student's t test was
173 used to analyze continuous data. Data cleaning and all analysis were conducted using
174 R (version 3.4.2).

175 **Ethical approval**

176 This study was approved by the Institutional Review Board (IRB) at the Chinese Center
177 for Disease Control and Prevention (no. 201224). This study was considered to be part
178 of a continuing public health outbreak investigation by National Health and Family
179 Planning Commission of China and except from institutional review board assessment.
180 Therefore, written informed consents were not obtained from subjects. The IRB
181 approved the use of verbal consent, and agreed that we anonymized the specimens and
182 personal information by permanently removing personal identifiers from the database.
183 Anonymized samples were labeled with a random coding system. Verbal informed
184 consent was obtained form the patients' parents/guardians when sampling and filling
185 out the questionnaire, and documented in forms.

186

187 **Results**

188 **Virological surveillance**

189 During the three-year virological surveillance, 2,836 (85%) of the total of 3,326
190 hospitalized patients with a diagnosis of HFMD were enrolled across the six hospitals.
191 The baseline characteristics were similar between the enrolled and un-enrolled patients,

192 including gender, age, and length of hospital stay [26]. One 27-month old child with
193 detection of EV-A71 had symptoms of neurological involvement (frequent jittering and
194 myoclonic jerks after 4 days of fever), and all others had uncomplicated illnesses.
195 Enterovirus was detected among 2,517 (89%) patients via the real-time RT-PCR
196 targeting pan-enterovirus. Nineteen serotypes of enterovirus were successfully
197 identified in 2,513 (99.8%) patients. The most commonly detected were CV-A16 (33%,
198 819), CV-A6 (31%, 785), EV-A71 (20%, 514), and CV-A10 (6%, 149). CV-A6
199 infections were more frequently identified in patients younger than 2 years, while CV-
200 A16 and EV-A71 accounted for a higher proportion of HFMD among children aged ≥ 3
201 years than CV-A6 ($p < 0.001$) (S1 Table). A seasonal peak in total hospitalizations
202 associated with HFMD was observed between April and June (S1 Fig).

203 **Serotype-specific hospitalization rates of HFMD**

204 Between October 2013 and September 2016, an estimated 3,642 pediatric patients were
205 hospitalized for HFMD in Anhua County. A total of 3,273 (90%) children were
206 admitted in the three county-level hospitals and 369 (10%) children were admitted in
207 the 23 township level hospitals (S2 Table). Among these, 3,236 (89%) patients were
208 estimated to be positive for enterovirus. The mean hospitalization rates of probable
209 HFMD were estimated as 743 (95% CI: 719-768) per 100,000 person-years, and the
210 mean rates of lab-confirmed HFMD were 660 (95% CI: 638-684) hospitalizations per
211 100,000 person-years during the surveillance period (Fig 2A). Both the annual
212 hospitalization rates of probable and lab-confirmed HFMD were highest during the
213 2013-2014 season (1,099 and 1,011 per 100,000 person-years), and lowest during the

214 2014-2015 season (458 and 422 per 100,000 person-years) (Fig 2B).

215

216 **Fig 2. Hospitalization rates of HFMD in Anhua County, China, October 2013 -**

217 **September 2016.**

218 (A) Average hospitalization rates of HFMD, overall and stratified by serotype. (B)

219 Annual hospitalization rates of HFMD, overall and stratified by serotype.

220

221 Based on the assumption of similar distribution of serotypes among the enrolled
222 and un-enrolled groups, 3,236 (89%) patients with lab-confirmed HFMD consisted of
223 1,043 with CV-A16, 1,023 with CV-A6, 657 with EV-A71, 191 with CV-A10, and 322
224 with other enteroviruses. The mean hospitalization rates were comparable between CV-
225 A16-associated HFMD (213 per 100,000 person-years) and CV-A6-associated HFMD
226 (209 per 100,000 person-years) during the surveillance period, and lower for EV-A71-
227 associated HFMD (134 per 100,000 person-years), CV-A10-associated HFMD (39 per
228 100,000 person-years), and other enteroviruses (66 per 100,000 person-years)
229 infections ($p<0.001$) (Fig 2A).

230 In the first year, between October 2013 and September 2014, the hospitalization
231 rates for CV-A16 were the highest (467 per 100,000 person-years). While in the second
232 year, CV-A6 had the largest burden of hospitalizations (248 per 100,000 person-years).

233 The hospitalization rates were similar among CV-A16, CV-A6, and EV-A71 infections
234 in the third year ($p=0.568$) (Fig 2B). The annual hospitalizations varied substantially
235 over years for EV-A71, CV-A16, and CV-A10. However, CV-A6 displayed

236 comparable hospitalization rates over three years (Fig 2B).

237 **Age-specific hospitalization rates of HFMD**

238 The mean hospitalization rates of HFMD varied with age. The highest rates of lab-
239 confirmed HFMD were among children aged 12-23 months (3,594 per 100,000 person-
240 years), followed by 24-35 months (1,828 per 100,000 person-years) and then 6-11
241 months (1,572 per 100,000 person-years). The hospitalization rates were lower among
242 infants younger than 6 months (381 per 100,000 person-years) and among children aged
243 5-14 years (84 per 100,000 person-years) (Fig 3B). Similar age distributions of
244 hospitalization rates were observed for probable HFMD (Fig 3A). The mean rates of
245 probable and lab-confirmed HFMD were 1,829 and 1,638 hospitalizations per 100,000
246 person-years (respectively) among children younger than 5 years. Unlike the
247 distribution of yearly rates for children aged ≥ 12 months, the hospitalization rates
248 decreased over three years for children aged 0-11 months (Fig 3C and D).

249

250 **Fig 3. Age-specific hospitalization rates associated with HFMD in Anhua County,**
251 **China, October 2013 - September 2016.**

252 (A) Average age-specific hospitalization rates of probable HFMD. (B) Average age-
253 specific hospitalization rates of lab-confirmed HFMD. (C) Annual age-specific
254 hospitalization rates of probable HFMD. (D) Annual age-specific hospitalization rates
255 of lab-confirmed HFMD.

256

257 The four common enterovirus serotypes had highest hospitalization rates among

258 children aged 12-23 months (955 for CV-A16, 1,344 for CV-A6, 640 for EV-A71, and
259 267 for CV-A10 per 100,000 person-years) (Fig 4A-D). CV-A6 uniquely had higher
260 rates among children aged 6-11 months than among those aged 24-35 months ($p<0.001$),
261 while CV-A10 had comparable rates between these age groups ($p=0.849$) (Fig 4A-D).
262 Statistical analyses suggested that HFMD hospitalization associated with CV-A6 were
263 evident at younger ages, compared to EV-A71 and CV-A16. The distribution pattern
264 of age-specific hospitalization rates for CV-A16, EV-A71, and CV-A10 were
265 consistent across the three years, between October 2013 to September 2016 (S2 Fig).
266 For CV-A6, the higher hospitalization rates in 6-11 months than 24-35 months was not
267 evident in the third year, between October 2015 to September 2016 ($p=0.777$) (S2 Fig).

268

269 **Fig 4. Age-specific and serotype-specific hospitalization rates associated with**
270 **HFMD in Anhua County, China, October 2013 - September 2016.**

271 (A) Average age-specific hospitalization rates of CV-A16-associated HFMD. (B)
272 Average age-specific hospitalization rates of CV-A6-associated HFMD. (C) Average
273 age-specific hospitalization rates of EV-A71-associated HFMD. (D) Average age-
274 specific hospitalization rates of CV-A10-associated HFMD.

275

276 **Discussion**

277 **Principal findings**

278 This study provides a comprehensive estimate of the hospitalization rates of probable
279 and lab-confirmed HFMD in Anhua County, Hunan Province, China, between October

280 2013 and September 2016. An average of 743 probable HFMD and 660 lab-confirmed
281 HFMD associated hospitalizations were estimated per 100,000 person-years in Anhua
282 County, with the highest annual rates during 2013-2014 and the lowest during 2014-
283 2015. CV-A16 and CV-A6 were associated with most (64%) lab-confirmed HFMD
284 hospitalizations, and had higher hospitalization rates than EV-A71, CV-A10 and other
285 enteroviruses during the study period. Hospitalization rates peaked among children
286 aged 12-23 months, and decreased with age among EV-A71, CV-A16, CV-A6, CV-
287 A10 and other enterovirus associated HFMD. Compared to other non-CV-A6 serotypes,
288 CV-A6 had higher hospitalization rates in children aged 6-11 months than in children
289 aged 24-35 months.

290 **Strength and comparison with previous studies**

291 Because of the high proportion of asymptomatic enterovirus infections (EV-A71, 64.1-
292 71.4%) in children [29, 30], and the relative scarcity (1.1%) of HFMD associated severe
293 illness [2, 29], the burden of HFMD is substantially underestimated if symptomatic case
294 notifications are only used. In this study, we actively captured HFMD-associated
295 hospitalizations in all healthcare facilities in Anhua county instead of relying on passive
296 surveillance. Additionally, our virological surveillance captured 78% of the total
297 HFMD-associated hospitalizations over three years. This allowed us to attain an
298 accurate representation of the enterovirus serotypes that cause HFMD. Samples were
299 collected in a timely fashion; multiple samples were available and intensive methods
300 were used to identify enterovirus serotypes. This enabled us to make a robust estimation
301 of the population-based hospitalization burden stratified by age group and enterovirus

302 serotype.

303 In our study, all children with mild illness (except one) were admitted to hospital.

304 The reasons underlying overuse of healthcare resources for mild illnesses include a low

305 hospitalization threshold applied by local physicians to capture all possible sudden

306 deteriorations [3], parents self-requesting hospital admission and the rural healthcare

307 insurance (New Rural Cooperative Medical Scheme) providing higher reimbursement

308 for inpatient than outpatient care [31]. Proportions of mild patients accounted for 80-

309 99% among HFMD-associated hospitalizations in previous reports [21, 24, 25, 29]. The

310 patients without complications were hospitalized in these reports because of high fever,

311 poor feeding, mouth ulcers, vomiting, or dehydration [24]. This indicates that

312 hospitalizations for non-severe HFMD is common in China.

313 To our knowledge, population-based hospitalization rates for HFMD have not been

314 reported until now. As the threshold for hospitalization of HFMD in our study was

315 relatively low, we made comparisons with the incidence rates estimated using the

316 notifiable surveillance data [2, 17-20]. The hospitalization rates estimated in our study

317 (119/100,000 person-years) were comparable to the incidence rates reported in

318 mainland China during 2008-2015 (127/100,000 person-years) [2, 20]. The rates we

319 estimated were higher than the incidence rates in Malaysia during 2011-2014 (20-

320 90/100,000 person-years) [19], and lower than the incidence rates in Singapore during

321 2001-2007 (126-436/100,000 person-years) [18] , and Japan during 2002-2005 (743

322 vs 2,940-5,740 per 100,000 population) in children aged 0-14 years [17]. The variation

323 in results could be associated with distinct activity intensity of enterovirus serotypes in

324 different study periods, and differences among the surveillance systems. The dual layers
325 of doctor-driven and teacher-driven surveillance make the data on notified symptomatic
326 presentations of HFMD collected by the Singapore's Ministry of Health unusually
327 complete [29]. The surveillance of HFMD in China and Malaysia rely on all hospitals
328 [2, 19]. The surveillance targeted HFMD in Japan are based on sentinel medical
329 institutions according to the guidelines for surveillance of infectious diseases [17].
330 Outpatients were not included in our study, therefore the hospitalization rates we report
331 could be an underestimate of the true incidence rates in Anhua County.

332 The age pattern of HFMD-associated hospitalizations was consistent with previous
333 reports of HFMD-associated incidences [2, 19, 20]. Relatively low hospitalization rates
334 among children younger than 6 months were likely due to protection by maternal
335 antibodies [32]. Compared to older children who may attend kindergartens or nurseries,
336 children aged 6-23 months have a lower intensity of contact with those of similar ages
337 due to limited mobility. The high hospitalization rates among this age group may
338 suggest higher susceptibility and/or possible transmission routes from contact with
339 asymptomatic adults or contaminated environments [20]. Serological surveillance also
340 revealed a low level of sero-prevalence in children aged 6-23 months [32, 33].

341 Our study found that CV-A6 presented a higher burden of HFMD-associated
342 hospitalization than EV-A71. This was consistent with the increasing activity of CV-
343 A6 in China [10, 11, 34-36] and the regional introduction of CV-A6 in 2012. CV-A6-
344 associated hospitalizations were also higher among younger age groups than EV-A71
345 and CV-A16 [37-39]. This may result from lower maternal immunity against an

346 emerging virus. As observed in this study, CV-A6 will likely affect more older children
347 and present a similar age pattern to EV-A71 and CV-A16, since more maternal
348 immunity is attained after introduction and spread of CV-A6, causing the median age
349 of infection to go up. Further studies should be conducted to monitor the potentially
350 changing epidemiology of CV-A6.

351 **Limitations**

352 This study was subject to several limitations. First, due to unavailability of data, the
353 number of HFMD associated hospitalizations in township hospitals was estimated from
354 the proportion of HFMD-associated hospitalizations for all causes rather than from
355 hospitalizations in pediatric or internal medicine departments. Nonetheless, the
356 distribution of hospitalization causes is not expected to vary greatly since the
357 demographics, and economic and living conditions were very similar among the
358 different townships. Second, virological surveillance was not conducted at the 20 other
359 township hospitals where the number of HFMD hospitalizations was very small (9%).
360 Third, the HFMD patients hospitalized outside Anhua County were not captured. Due
361 to low case-severity risk (1.1%) among HFMD patients, few cases need referral to
362 prefecture- or provincial-level hospitals. Therefore, hospitalization rates of HFMD
363 estimated in our study should be robust.

364 **Conclusions**

365 Our study provides a comprehensive analysis of probable HFMD, lab-confirmed
366 HFMD, EV-A71, CV-A16, CV-A6, CV-A10 and other enterovirus associated
367 hospitalization rates in Anhua County, Hunan Province, China between 2013 and 2016.

368 We found a substantial hospitalization burden annually for mild HFMD, caused by
369 multiple enterovirus serotypes in China. During the study period, CV-A16 and CV-A6
370 contributed to more hospitalizations than EV-A71, CV-A10 and other enteroviruses.
371 Our findings suggest that intensive training on how to quickly detect and treat mild
372 HFMD should be provided to clinicians, especially those working at county-level and
373 township-level hospitals. Furthermore, health education on HFMD should be provided
374 to parents/guardians to address their concerns about HFMD.

375

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519

520 **Supporting information**

521 **S1 Fig. Temporal trends of HFMD-associated hospitalizations by enterovirus**

522 **serotype in six surveillance hospitals in Anhua County, China, October 2013 -**
523 **September 2016.**

524

525 **S2 Fig. Annual hospitalization rates associated with HFMD stratified by age and**
526 **enterovirus serotype in Anhua County, China, October 2013 - September 2016.**

527 (A) Annual age-specific hospitalization rates of CV-A16-associated HFMD. (B)
528 Annual age-specific hospitalization rates of CV-A6-associated HFMD. (C) Annual age-
529 specific hospitalization rates of EV-A71-associated HFMD. (D) Annual age-specific
530 hospitalization rates of CV-A10-associated HFMD.

531

532 **S1 Table. The age profile of HFMD-associated hospitalizations stratified by**
533 **enterovirus serotype in 6 surveillance hospitals in Anhua County, China, October**
534 **2013 - September 2016.**

535

536 **S2 Table. Estimated hospitalization rates associated with HFMD by age group in**
537 **Anhua County, China, October 2013 - September 2016.**

538

539 **S1 Checklist: STROBE Checklist**







