# Basic Reproduction Number of Enterovirus 71, Coxsackievirus A16 and A6: Evidence from Outbreaks of Hand, Foot and Mouth Disease in China between 2011 and 2018

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**Summary:** This study estimates the pathogen-specific basic reproduction number based on laboratory-confirmed hand, foot, and mouth disease outbreaks in China between 2011 and 2018. It is the first to compare the changes of $R_0$s before and after the EV-A71vaccines licensure.

**Abstract:**

**Background**: Enterovirus 71 (EV-A71), Coxsackievirus A16 (CV-A16) and Coxsackievirus A6 (CV-A6) are common serotypes causing hand, foot, and mouth disease (HFMD). Analyses on the basic reproduction number ($R_0$) of common pathogens causing HFMD are limited and there are no related studies using field data from outbreaks in mainland China.

**Methods**: We estimated the pathogen-specific basic reproduction number based on laboratory-confirmed HFMD outbreaks (clusters of ≥10 HFMD cases) reported to the national surveillance system between 2011 and 2018. The reproduction numbers were calculated using a mathematical model and the cumulative cases during the initial growth periods.

**Results**: This study included 539 outbreaks, of which 198 were caused by EV-A71, 316 by CV-A16, and 25 by CV-A6. All 10417 cases involved were children. Assuming the outbreaks occurred in closed systems and the incubation period is 5 days, the median $R_0$s of EV-A71, CV-A16, and CV-A6 were 5.06 [2.81, 10.20], 4.84 [3.00, 9.00] and 5.94 [3.27, 10.00] (Median [IQR]). After adjusting for seroprevalences, the $R_0$s for EV-A71, CV-A16 (optimistic and conservative scenarios), and CV-A6 were 12.60 [IQR: 7.35, 25.40], 9.29 [IQR: 6.01, 19.20], 15.50 [IQR: 9.77, 30.40], and 25.80 [IQR: 14.20, 43.50], respectively. We did not observe changes in the $R_0$s of EV-A71 after vaccine licensure ($p$-value = 0.67).

**Conclusions**: HFMD is highly transmissible when caused by the three most common serotypes. In mainland China, it primarily affects young children. Although a vaccine became available in 2016, we have not yet observed any related changes in the disease dynamics.

**Key Words**:

Enterovirus; transmission dynamics; basic reproduction number; vaccine; hand, foot, and mouth disease

## Introduction

Hand, foot, and mouth disease (HFMD) is an infectious disease most commonly observed among children under five years and in Asia-Pacific regions, including Singapore, Taiwan, Hong Kong, Japan and mainland China [1, 2]. In mainland China specifically, more than one million cases involving hundreds of outbreaks have been reported every year since 2008, contributing to a substantial disease burden [3]. Various serotypes of the *Enterovirus* genus of the family *Picornaviridae* can cause HFMD, such as Enterovirus 71 (EV-A71), Coxsackievirus A16 (CV-A16) and Coxsackievirus A6 (CV-A6) [1, 3, 4]. The main clinical manifestations include fever and a rash or blisters on the hands, feet, mouth, and buttocks, and a small number of patients, especially those infected with EV-A71, may develop severe complications [5]. Inactivated monovalent EV-A71 vaccines, which showed high efficacy in preventing EV-A71 related HFMD, were licensed in mainland China in 2016 [3].

Understanding the transmission dynamics of an infectious disease is crucial to public health decision-making. The basic reproduction number ($R_0$), one of the most fundamental parameters that govern the transmission patterns of infectious diseases, measures the average number of secondary cases infected by a typical primary case in a susceptible population. The $R_0$ is determined by the duration of infectiousness and the effective contact rate [6].

However, studies on the $R_0$ of HFMD-related enterovirus are limited. Previous studies have drastically different results, ranging from 1.1 to 27 [7-8], and these results were often not pathogen-specific. Such ambiguity hinders the use of these estimates for further analyses [2]. In mainland China, HFMD outbreaks primarily occur in relatively closed units such as

kindergartens (usually for 3 to 6-year-olds) and elementary schools (usually for 6 to 12-year-olds) [9, 10]. Thus, one of the foci of HFMD prevention and control is to timely intervene at these key locations. Other studies have provided estimates of $R_0$ of EV-A71 and CV-A16 for Hong Kong using outbreak data between 2004 and 2009 [11] and for Singapore between 2007 and 2012 [12]. However, only a small number of outbreaks were identified (34 and 33, respectively) [11, 12]. The $R_0$s of HFMD-related enteroviruses have not been accurately estimated using outbreaks in mainland China, where the largest number of cases are observed in the world [13]. In this study, we estimated the $R_0$s of EV-A71, CV-A16 and CV-A6, and assessed the changes after the licensure of EV-A71 mono-valent vaccines.

## Materials and methods

### Key Terminologies

In mainland China, a public health emergency event (PHEE) of HFMD is defined as an outbreak involving 10 or more cases in a unit such as a kindergarten or a primary school or involving 5 or more cases in a village or a neighborhood block during a seven-day window. In this study, we selected PHEE outbreaks using the ten-case threshold to reduce numeric noises.

The initial growth periods (IGPs) refers to the period from the onset of the primary case to the date when the number of newly onset cases have peaked (or plateaued) or when public health measures were put in place, whichever occurred first.

## Surveillance Systems

HFMD has been classified as a "notifiable infectious disease" in mainland China since 2008. There are currently two systems for HFMD surveillance: (1) the National Notifiable Infectious Diseases Surveillance System (NNIDSS), a subsystem of the China Disease Control and Prevention Information System (CDPCIS), which keeps track of patient information (e.g., clinical categorization); and (2) the National Public Health Emergency Event Surveillance System (PHEESS), also a subsystem of CDPCIS, which focuses on outbreak investigation. All patients included in PHEESS have a linked record in NNIDSS, but not all patients in NNIDSS have confirmed source of infection – thus, they may not all be included in PHEESS. In this study, we rely only on outbreak-specific data from PHEESS, where the source of infection is clear.

An overwhelming majority of HFMD cases in mainland China is clinically confirmed (i.e., based on symptoms). Healthcare providers are required to confirm the first five cases seeking care for mild HFMD symptoms and all cases seeking care for severe HFMD symptoms each county/district each month using laboratory results that lead to the identification of specific pathogens. Healthcare providers may test more patients when laboratory capacity allows. When an outbreak emerges, local public health authorities are required to test at least 5 cases within the cluster.

## Data collection

A retrospective review was conducted on HFMD outbreaks reported to PHEESS from 2011/01/01 to 2018/12/31. The local Centers for Disease Control and Prevention (CDCs) report outbreaks to the web-based PHEESS through a structured database with data items

including but not limited to the timing of first and last cases, outbreak settings (e.g., first-year kindergarten), and the numbers of the exposed (i.e., close contacts identified via outbreak investigation), infected (i.e., all symptomatic individuals), and deaths.

Additional information that does not fit in any specific database items could be included in the unstructured narratives attached to the PHEESS reports. Such information could be epidemic curves (by symptoms onset, as photos), laboratory test results (i.e., EV-A71, CV-A16 and CV-A6), and control measures (e.g., school suspension and environmental disinfection). The completeness and quality of these narratives may vary by municipalities. Note that PHEESS, either in the structured database or the unstructured narratives, cannot capture asymptomatic individuals during outbreaks.

For this analysis, both structured data and non-structured narratives of all HFMD outbreaks between 2011/01/01 and 2018/12/31 were downloaded from PHEESS and analyzed. Note that surveillance lab did not start testing for CV-A6 nation-wide in China until 2017 [3]. Outbreaks need to meet the following three criteria to be included in estimating the $R_0$: (1) there was a single index case (e.g., having multiple cases at the beginning of the time-series indicate that the true primary case was likely never identified); (2) during the outbreak, there were no consecutive periods of longer than 10 days where no cases occur; and (3) all laboratory-confirmed cases involved can be attributed to the same pathogen. Additionally, each outbreak has been assigned an age group based on the outbreak setting. For example, infected individuals in an outbreak that occurred among first-year kindergarteners are assumed to be 3-year-olds.

**Estimating the Basic Reproduction Number**

We applied an existing method, used in [11, 12], to estimate the $R_0$s of EV-A71, CV-A16 and CV-A6 in mainland China. The method was originally introduced by Choi & Pak to study the 2003 SARS-COV outbreak [14]. Each outbreak was assumed to have occurred a closed system during an outbreak. All outbreaks were assumed to be seeded by a single case (i.e., the index case). Assuming complete susceptibility at the beginning of an outbreak, the value of $R_0$ is estimated using the following formula:

$$\sum N_{t*i} = 1+R_0+R_0^2+R_0^3+\ldots+R_0^t=(R_0^{t+1}-1)/(R_0-1)$$

where *i* refers to the incubation period of HFMD-related enteroviruses and *t* the number of transmission generation. The total time elapsed, thus, is *t*i*. The notion $\sum N_{t*i}$ represents the expected cumulative number of cases on day *t*i* of the initial growth period. We assumed the incubation period to be 5 days, consistent with previous studies [11, 12] and presented sensitivity analyses for incubation periods to be 3 to 7 days [15]. This approach looks for the exact analytical solutions given *t*i* and $\sum N_{t*i}$.. We further validated this approach using a stochastic simulation model outlined in the Supplemental Material Section 1.

The analyses were truncated at the end of 2015/ beginning of 2016 when the EV-A71 monovalent HFMD vaccines were licensed [3]. There is currently no vaccine for CV-A6 and CV-A16. Mann-Whitney U test was used to test for statistical difference between estimated $R_0$s before and after the licensure of the EV-A71 vaccines. Kruskal-Wallis test was used to compare the estimated $R_0$s of all three serotypes.

The assumption of complete HFMD susceptibility may not be realistic in mainland China, as the disease is largely endemic [3]. To account for this, we obtained age- and serotype-specific seroprevalence data ($p$) from the existing literature [16-20] and adjust our raw R0 estimates:

$$R_{0.adj} = \frac{R_{0.raw}}{1-p}$$

One seroprevalence estimate is used for each pathogen – we were not able to find literature to capture year-to-year variations in seroprevalence. Two scenarios, optimistic (i.e., the lowest mean seroprevalence identified) and conservative (i.e., the highest seroprevalence identified), were included for CV-A16 as existing literature includes inconsistencies. Between new-borns and six-year-olds, the ranges of seroprevalence in each one-year age group of CV-A16 (optimistic and conservative scenarios), CV-A6, and EV-A71 are 0.34 – 0.6, 0.64 – 0.73, 0.47 – 0.77, and 0.26 – 0.7. Specific values used can be found in the Supplemental Material Section 2.

Additional validation against effective reproduction numbers ($R_e$) are also provided, where $R_e$ is calculated using methods described in Wallinga & Lipsitch [21], White et al. [22], and Cori et al.[23]. We further investigated the association between the estimated $R_0$s and other outbreak characteristics (outbreak duration, number of exposed, and number of infected).

**Data Management and Analysis**

Information provided by unstructured narratives was abstracted for temporal, spatial and demographic parameters indicators before summarized and analyzed. Software R (version 4.0.0) [24] and Microsoft Excel were used for data cleaning and analysis. Code used can be found at [https://github.com/yangclaraliu/HFMDR0_539].

## Ethics Statement

This project involved a retrospective analysis of data on outbreaks reported to PHEESS by local CDCs in mainland China between 2011 and 2018. No identifiable information was included as part of this project.

## Results

Between 2011 and 2018, 2178 outbreaks of HFMD were reported to PHEESS in China, of which 1743 were laboratory confirmed. The three HFMD-related pathogens (i.e., EV-A71, CV-A16, and CV-A6) caused 1653 (94.8%) of these outbreaks. We identified 539 outbreaks that meet the inclusion criteria (Figure 1).

Among these 539 outbreaks, 198 (36.7%) were associated with EV-A71, 316 (58.6%) with CV-A16, and 25 (4.6%) with CV-A6. Inter-annual variability in the number of outbreaks was observed - a relatively larger number of outbreaks occurred every other year (Figure 2, a and c). In years with a larger number of outbreaks, CV-A16 tended to be the dominating serotype; in years with a smaller number of outbreaks, EV-A71 tended to be the dominating serotype (Figure 2, a and c). Within year analyses revealed two peaks (Figure 2, b and d), which was consistent with the surveillance outcomes of all HFMD cases in China. The April-June peaks, however, was much more evident than the September-October peaks.

The 539 outbreaks that met the inclusion criteria occurred in 27 provinces (Figure 3). Provinces with the largest number of outbreaks were Guangdong (88), Chongqing (81),

Guangxi (53), Anhui (51), Jiangsu (36), Yunnan (36) and Shandong (35). These seven provinces were also among the provinces with the highest incidence of HFMD.

There were 479 (88.9%) outbreaks that occurred in kindergartens, affecting 9202 children; 33 (6.1%) outbreaks in primary schools, affecting 635 students; 18 (3.3%) in villages, affecting 400 preschool children; 6 (1.1%) in childcare centers, affecting 121 cases; and 3 (0.6%) in junior middle schools, affecting 59 cases.

Outbreaks caused by EV-A71, CV-A16 and CV-A6 were similar in terms of the number of children infected and duration of outbreaks. However, in CV-A6 outbreaks, more children were exposed on average, leading to overall lower attack rates (Table 1). While there are no significant differences in terms of the school types where HFMD outbreaks occurred (i.e., the distribution of kindergartens, primary schools or that of urban or rural settings), CV-A6 outbreaks were reported primarily in populated areas such as Guangdong, Shanghai, Jiangsu, and Beijing while EV-A71 and CV-A16 have been reported everywhere in mainland China. Higher population density may have contributed to the higher total numbers of exposed children. However, it remains unclear whether the spatial clustering observed is a result of higher testing capacity in populated areas (as CV-A6 is a new pathogen in the surveillance system) or reflects true disease occurrences. This observation, although does not affect our estimates, should be kept in mind as an important context while interpreting pathogen-specific $R_0$s.

Pathogen-specific raw and adjusted $R_0$ estimates are presented in Figure 4. Before the EV-A71 mono-valent vaccines were licensed in mainland China in 2016, the $R_0$s of EV-A71 (Median: 4.64 [IQR: 2.78, 10.10]) and CV-A16 (5.13 [IQR: 3.23, 11.00]) were comparable ($p$-value = 0.37). After vaccine licensure, the $R_0$ of EV-A71 (5.42 [IQR: 3.01, 10.80]) did not change much compared to previously ($p$-value = 0.67). The $R_0$ of CV-A16 declined to 4.80 [IQR: 2.79, 8.69] after EV-A71 mono-valet vaccine licensure. This decline was not statistically significant either ($p$-value=0.09). Using all time-series available, the estimated $R_0$s of CV-A16, CV-A6, and EV-A71 are 4.84 [IQR: 3.00, 9.00], 5.94 [IQR: 3.27, 10.00], and 5.06 [IQR: 2.81, 10.20]. The difference among these three types was not statistically significant ($\chi^2 = 0.38$ , $p\text{-value} = 0.83$). Statistics on the distribution shown in Figure 4 are presented in Supplemental Material Section 3. Sensitivity analyses indicate a longer incubation period is associated with a larger $R_0$ estimate (Supplemental Material Section 4). We were not able to conduct any age-stratified analysis because the sample sizes outside the 3 and 4-year-old age groups are too small (Supplemental Material Section 5).

While validating our results, as expected, we found our raw estimates align with those estimated from various other methods (assuming complete susceptibility, see also Supplemental Material Section 6). After adjusting for age-specific seroprevalence, the estimated adjusted $R_0$s became higher compared to their respective raw estimates (Figure 4, panels b-c, e, and g). The adjusted $R_0$s for CV-A16 (optimistic and conservative scenarios), CV-A6, and EV-A71 are 9.29 [IQR: 6.01, 19.20], 15.50 [IQR: 9.77, 30.40], 25.80 [IQR: 14.20, 43.50], and 12.60 [IQR: 7.35, 25.40], respectively. See Supplemental Material 3 for more details. As a result of drastically different seroprevalence, the differences among the transmissibility were statistically significant after the adjustment ($\chi^2 > 16$ , $p\text{-value} < 0.001$).

Further statistical analyses showed that the estimated $R_0$s were independent of the number of children exposed and infected in the outbreak. Nevertheless, there is a negative and statistically significant association between $R_0$s and outbreak duration (Figure 5).

## Discussion

The provinces most affected by HFMD outbreaks also reported the most HFMD cases in mainland China [25]. Among the three serotypes studied here, CV-A6 has emerged as one of the most common causative agents since 2013 [26], later than EV-A71 and CV-A16 in mainland China. As mentioned before, $R_0$ is not an intrinsic value of a given pathogen, but rather describes the transmissibility of that pathogen within the specific populations and settings [6]. $R_0$ depends not only on the biology of the infectious agent but also the natural environment and socio-demographically dependent factors.

This study estimated the $R_0$ among children in mainland China in outbreak settings. To our best knowledge, this is the first study that estimates the pathogen-specific $R_0$s based on HFMD outbreaks across mainland China and the largest study of its kind in the world. Also, this study is the first to compare the changes of $R_0$s before and after the licensure of the EV-A71 mono-valent vaccines. A wide geographical coverage and a large time span of this study ensure representativeness.

The majority of the HFMD outbreaks we identified were in kindergartens (88.9%), implying that the impacts were predominantly on those between 3 and 6 years of age. The HFMD Prevention and Control Handbook includes specific individual and environmental measures designed to protect children within this age group, including the promotion of hand hygiene, daily sanitation of toys and classrooms, and school suspension in response to confirmed HFMD cases [27].

This study revealed that the transmissibility of CV-A16, CV-A6, and EV-A71 in mainland China are comparable without adjusting for seroprevalence. The incorporation of age- and pathogen-specific seroprevalence introduces some differences in terms of transmissibility. But the over-arching message remains the same – the most common three enteroviruses causing HFMD are all highly transmissible. Local public health agencies need to continue to monitor the serotype distribution among infected cases in the future as it may have implications for clinical severity [28].

The median $R_0$ of EV-A71 in our study is similar to that in Hong Kong (5.48) [11] but larger than that in Singapore (3.50) [12]. The median $R_0$ of CV-A16 was similar to that of EV-A71 in this study, larger than those Hong Kong (2.50) [11] and Singapore (2.42) [12]. Overall, current evidence in this study does not indicate differential transmissibility across HFMD-causing pathogens in mainland China without adjusting for seroprevalence. Comparing to the wide range of uncertainty around $R_0$ of EV-A71 (3.02 to 44.91) estimated by two studies using SIR/TSIR model conducted in Guangdong [8, 29], the mathematical model used in this study are more consistent.

The $R_0$s of EV-A71 and CV-A16 have not significantly changed while comparing pre and post EV-A71 vaccine licensure periods. Although the EV-A71 mono-valent was licensed at the end of 2015, it has not been included in the National Immunisation Programme in China, which means parents need to rely on out-of-pocket payment to vaccinate their children [30]. As a result, vaccine coverage is relatively low. Pan et al. estimated vaccine coverage among 0- to 5-year-olds to be approximately 11% in Fujian, China [31], which may explain why we are not capturing any change in reproduction numbers. Future research should validate this observation when more data (i.e., longer time series post-vaccine licensure) becomes available.

As expected, we found that our raw $R_0$ estimates are consistent with reproduction numbers calculated using other methods [21-23]. After adjusting for seroprevalence found in existing literature [16-20], the $R_0$s becomes significantly higher and in some cases more than doubled. It is important to note that although literature shows relatively high seroprevalence among Chinese children (see Supplemental Material Section 2); the study designs are often at the population level. In other words, seropositive individuals may not be evenly distributed across the population. Patches of susceptible children may exist, leading to potential outbreak risks. In an outbreak setting, it is uncertain how the seroprevalence in the given close system may compare relative to the regional population average.

Some limitations remain. Firstly, the primary (i.e., index) case is hard to identify using the available database. When investigators failed to trace the true primary case of an outbreak, they underestimate the IGPs, leading to an overestimation of $R_0$. This issue may have contributed to the association between larger $R_0$s and shorter outbreak durations (Figure 5).

Secondly, there may be bias introduced by right-censoring of data. Our approach relies on clearly defined initial growth periods. Inevitably, some infections that should have been included in the cumulative incidence calculation may have been left out as IGP cuts off. To assess the magnitude of such bias, we relied on a stochastic simulation model. We found that while the approach we used can well reconstruct $R_0$ while values are low, bias towards the null hypothesis (i.e., underestimation) becomes more severe as true $R_0$ increases (Supplemental Material Section 1). Last but not least, we did not account for asymptomatic infections as they are not tracked by the current surveillance system. Focusing only on symptomatic infections allow our results to be more comparable to existing literature. However, it may have introduced a downward bias to $R_0$ estimates [15].

## NOTES

### Contributors

Zhaorui Chang and Zhongjie Li conceived, designed, and supervised the study. Zhong Zhang and Yang Liu conducted the analysis, visualized and interpreted the results, and wrote the manuscript. Fengfeng Liu, MinruiRen, Taoran Nie, Jinzhao Cui participated in collection and management of data. All authors provided comments and approved the submitted version of the manuscript.


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### Conflicts of interest

All authors declare no conflicts of interest.

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**Table 1** Characteristics of 539 identified HFMD outbreaks in China, 2011-2018.

| Serotype | Number of Outbreaks | Median #children exposed | Median #children infected | Median attack rate （%） | Median outbreaks duration (days) |
|---|---|---|---|---|---|
| EV-A71 | 198 | 280(188-449) | 17(13-22) | 6.5(4.0-10.1) | 15(11-22) |
| CV-A16 | 316 | 299(189-453) | 17(14-22) | 6.1(4.3-10.0) | 16(11-22) |
| CV-A6 | 25 | 408(300-658) | 16(14-20) | 4.2(3.2-5.2) | 14(10-17) |
| Overall | 539 | 297(191-451) | 17(13-22) | 6.1(4.0-10.0) | 15(11-22) |

Values in parentheses are interquartile range. Outbreak duration is the time elapsed between the onset time of the first and last case identified.

**Figure legends:**

**Figure 1** Process used to identify HFMD outbreaks for $R_0$ estimation in China, 2011-2018.

**Figure 2** Between- and within-year variability of HFMD outbreaks (measured by changes in the number of outbreaks and the number of infected children) by serotypes in China, 2011-2018. The corresponding month and year of outbreaks are attributed based on the timing of the first cases.

**Figure 3** Spatial distribution of HFMD outbreaks in China, 2011-2018.

**Figure 4** Basic reproduction numbers of EV-A71, CV-A16 and CV-A6 in China, 2011-2018. The corresponding month and year of outbreaks are attributed based on the timing of the first cases. Adjusted R0 estimates are based on seroprevalence data among Chinese children identified through existing literature (Supplemental Material Section 2). The seroprevalence of EV-A71 is based on the estimated mean in a meta-analysis; the seroprevalence of CV-A6 is based on the estimated mean in the only study identified. We identified several studies on the seroprevalence of CV-A16, yet no meta-analysis – so we include both the conservative (i.e., the highest mean seroprevalence found) and the optimistic (i.e., the lowest mean seroprevalence found) scenarios. Y-axis has been truncated at $R_0$ of 60 so that distributions over smaller values can be displayed. Full statistical summaries of distributions shown here are presented in the Supplemental Material Section 3.

**Figure 5** Scatter plots showing the associations between $R_0$ estimates (y-axis) and other outbreak characteristics (x-axis: the total exposed individuals, total infected individuals, and outbreak duration) in mainland China, 2011-2018. Solid lines are serotype-specific fit of simple linear models (formula: $R_0$ estimates ~ outbreak characteristics). Only $R_0$ estimates within the 2.5 and 97.5 percneitle range for each serotype were included.

Figure 1

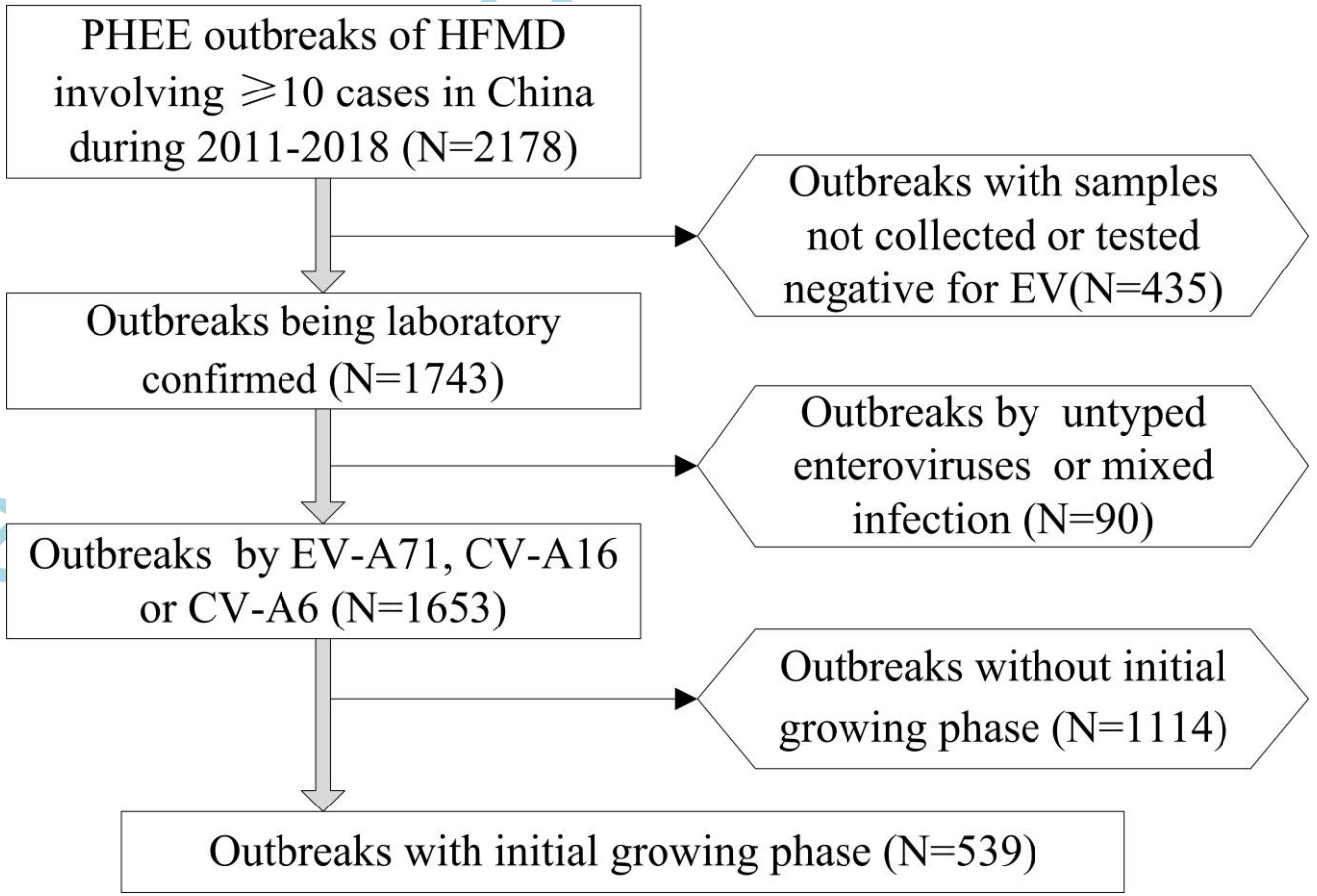

Figure 2

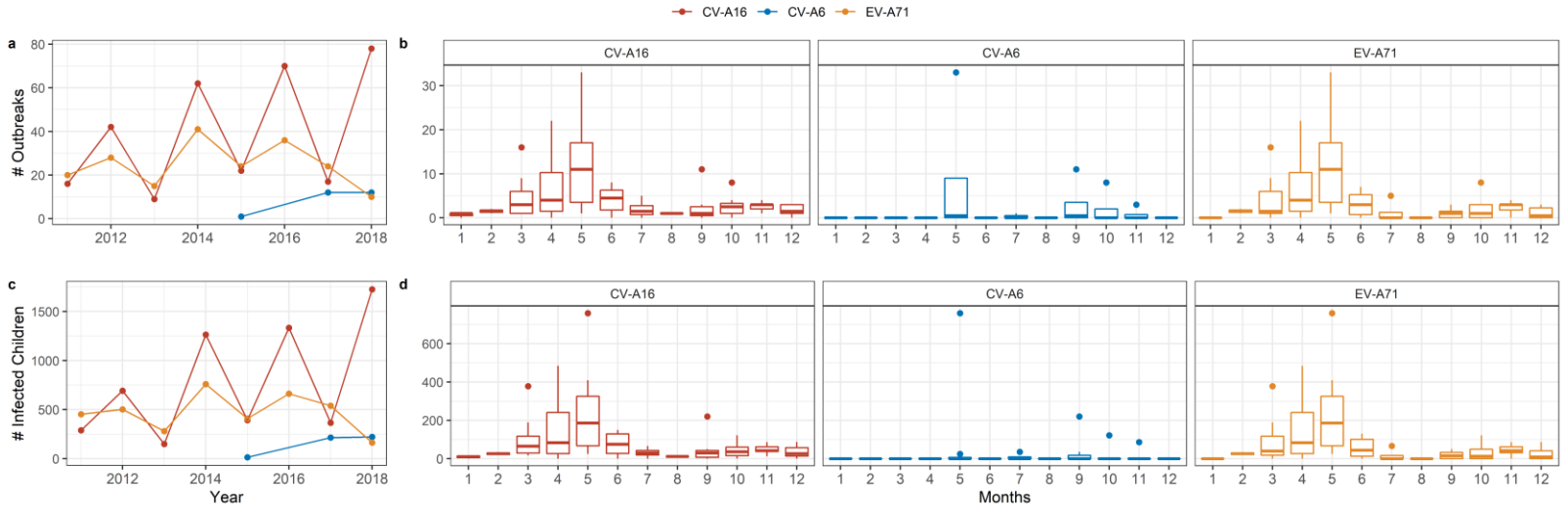

Figure 3

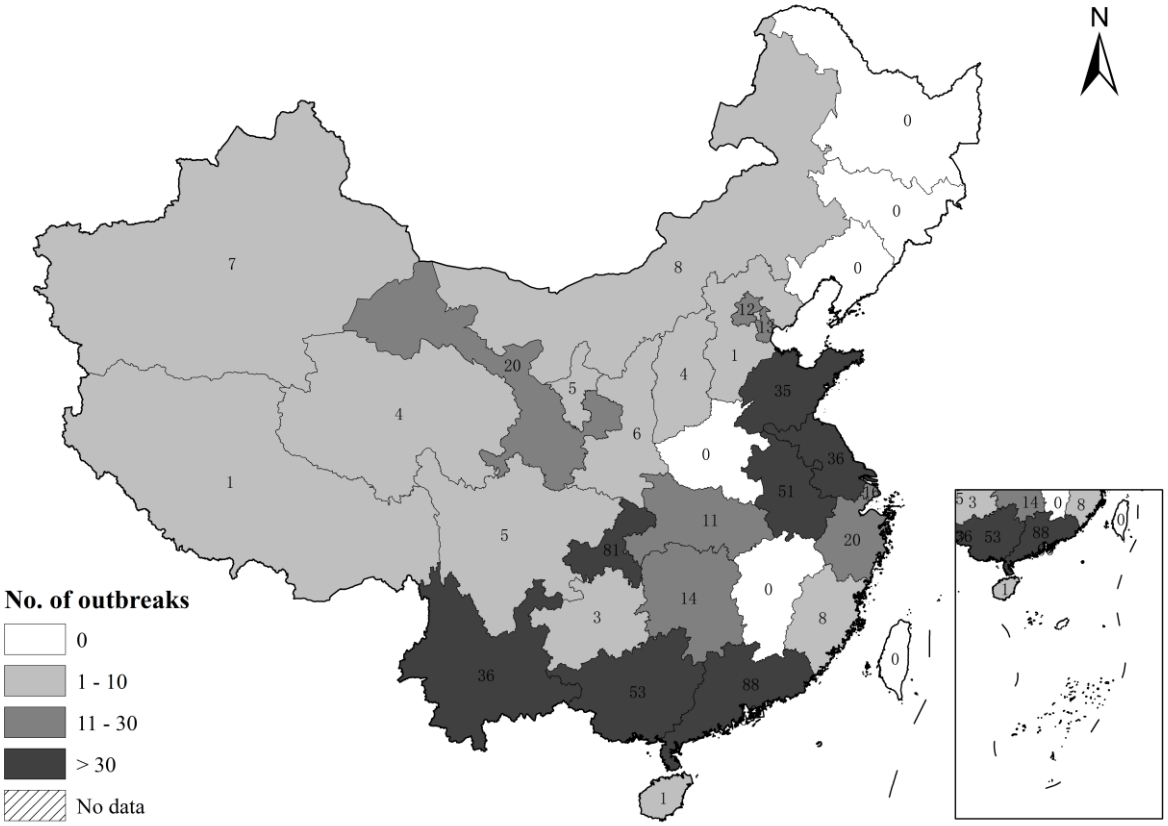

Figure 4

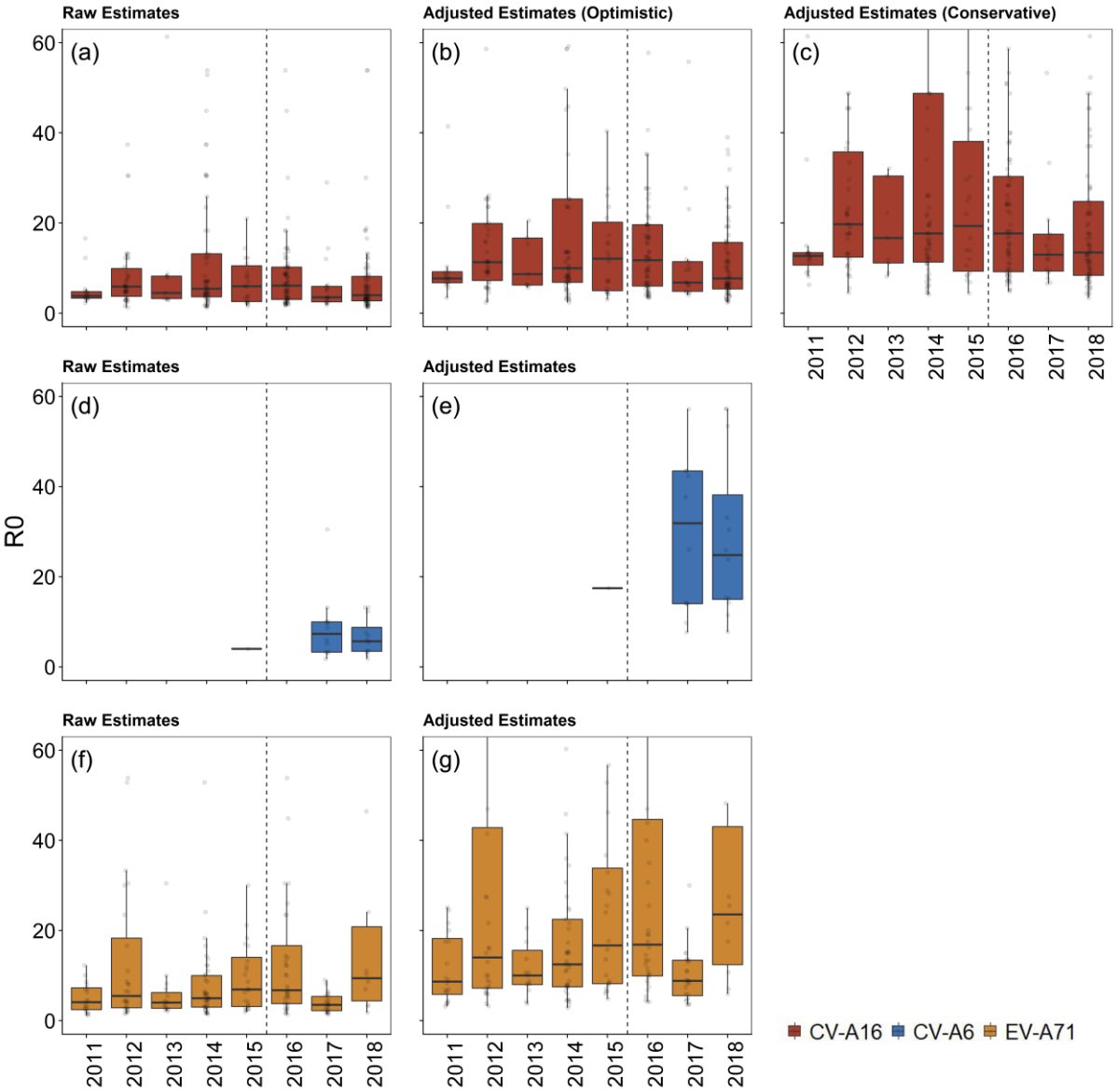

Figure 5