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The Epidemiology of Hand, Foot and Mouth Disease in Asia

A Systematic Review and Analysis

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Context: Hand, foot and mouth disease (HFMD) is a widespread pediatric disease caused primarily by human enterovirus 71 (EV-A71) and Coxsackievirus A16 (CV-A16).

Objective: This study reports a systematic review of the epidemiology of HFMD in Asia.

Data Sources: PubMed, Web of Science and Google Scholar were searched up to December 2014.

Study Selection: Two reviewers independently assessed studies for epidemiologic and serologic information about prevalence and incidence of HFMD against predetermined inclusion/exclusion criteria.

Data Extraction: Two reviewers extracted answers for 8 specific research questions on HFMD epidemiology. The results are checked by 3 others.

Results: HFMD is found to be seasonal in temperate Asia with a summer peak and in subtropical Asia with spring and fall peaks, but not in tropical Asia; evidence of a climatic role was identified for temperate Japan. Risk factors for HFMD include hygiene, age, gender and social contacts, but most studies were underpowered to adjust rigorously for confounding variables. Both community-level and school-level transmission have been implicated, but their relative importance for HFMD is inconclusive. Epidemiologic indices are poorly understood: No supporting quantitative evidence was found for the incubation period of EV-A71; the symptomatic rate of EV-A71/Coxsackievirus A16 infection was from 10% to 71% in 4 studies; while the basic reproduction number was between 1.1 and 5.5 in 3 studies. The uncertainty in these estimates inhibits their use for further analysis.

Limitations: Diversity of study designs complicates attempts to identify features of HFMD epidemiology.

Conclusions: Knowledge on HFMD remains insufficient to guide interventions such as the incorporation of an EV-A71 vaccine in pediatric vaccination schedules. Research is urgently needed to fill these gaps.

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Hand, foot and mouth disease (HFMD) has become an endemic childhood disease in East and Southeast Asia. Its main etiologic agents are human enterovirus 71 (EV-A71) and Coxsackievirus 16 (CV-A16). Although usually mild—with symptoms limited to >38°C fever, malaise, rashes on the volar regions of the hands and feet, herpangina and difficulty eating and drinking—more rarely, infection can lead to complications of the nervous or cardiopulmonary systems. Such cases can result in long-term sequelae such as cognitive and motor disorders[1,2] or death, usually from pulmonary edema or brainstem encephalitis.[3] Although complications are rare, the number of children being infected in high-incidence countries such as China (≈2.7 M cases in 2014[3]) means the death toll can be substantial (384 deaths in China in 2014[3]). The EV-A71 virus seems to be responsible for more severe outcomes, while CV-A16 and other Coxsackieviruses, such as CV-A2, CV-A6 and CV-A10, usually present milder symptoms that resolve within a few weeks.[4–6]

There are nearly 25 years of literature from Asia that describes the epidemiology of HFMD, drawing on pediatric cohorts, national surveillance systems, outbreak investigations and clinical data, and from disparate countries that span stages of economic development and with climates that range from tropical to temperate. This diversity complicates attempts to identify general features of HFMD epidemiology and conceals gaps in the body of knowledge of this important pediatric disease.

The objective of this paper is to provide a robust systematic review of the epidemiology of HFMD that informs public health policy making about HFMD epidemics. The review covers 3 major areas: (1) history and seasonality of HFMD, and the efforts in predictive modeling; (2) risk factors for infection, to guide control and (3) global epidemiologic parameters, such as the incubation period and basic reproduction number, which may determine the effectiveness of control policies.

METHODS

Search Strategy and Selection Criteria

Using a combination of search terms, including "Hand foot and mouth disease," "Hand foot and mouth," "HFMD," "Enterovirus," "Enterovirus 71," "EV-A71," "Coxsackie A16," "CV-A16," "CVA16," we searched PubMed, Thomson Reuters Web of Science and Google Scholar to identify 1305, 1255 and 100 articles, respectively.

Eligibility criteria were articles that: (1) were published in peer-reviewed journals from January 1957 to December 2014; (2) were studies with epidemiologic and/or serologic information (quantitative/qualitative) about incidence and prevalence of

HFMD; and/or (3) contained information about factors associated with prevalence and incidence and/or (4) employed statistical models to derive the above. Articles not in English, not related to HFMD, or HFMD articles that did not cover epidemiologic or clinical factors were excluded.

Two independent readers examined each of the 407 abstracts to determine if specific research questions were answered. The 8 specific research questions were as follows: (1) What time of the year do HFMD outbreaks occur, and with what seasonal factors are outbreaks associated? (2) How long have EV-A71 and CV-A16 been circulating in Asia? (3) What age groups are at higher risk of infection? (4) What risk factors are associated with infection and severe outcomes? (5) Where do infections predominantly occur (home or school)? (6) What is the incubation period? (7) What proportion of infections are symptomatic? and (8) What is the basic reproduction number for HFMD by virus? An article was retained as long as both readers indicated that it answered at least 1 specific research question and was discarded if both readers agreed that no questions were answered. A third independent reader arbitrated when there was a disparity between the original readers.

The 2 original readers each read the full text of half of the articles to identify answers to the questions. A second pair of independent readers read the articles again. Finally, the first author compiled all answers to the specific questions and compared the extracted answers to the original text. Relevant references from these papers were included in the analysis, in particular to identify non-English and early references. In total, information from 242 papers was compiled and 108 papers were used in data synthesis.

Hourly weather data were downloaded from the Weather Underground and aggregated at a weekly scale. Incidence data from Tokyo, Hong Kong, Taiwan and Singapore were extracted from routine surveillance data published by government agencies (the National Institute of Infectious Diseases, Japan[7]; the Department of Health, Hong Kong[8]; the Taiwan National Infectious Disease Statistics System[9] and the Ministry of Health, Singapore).

Nontabular data were extracted from figures using Plot Digitizer.[10] Data on weather and incidence were analyzed using a time series model. Symptomatic proportions were pooled by aggregating denominators and numerators. Other analyses used standard statistical methods and were conducted using R.[11]

RESULTS

Timing and Seasonality of HFMD Outbreaks

Outbreaks of HFMD do not occur uniformly throughout the year across Asia. In Fukuoka, Japan, for example, weekly numbers of HFMD cases have been found to increase with average temperature and humidity, especially among younger children.[12] By digitizing the incidence data from publications on Japan[5,12–14] and North China[15–20] (Fig. 1), we observe that May through July are the months with highest incidence in temperate regions of Asia. However, this relationship is less clear for tropical and subtropical Asia. The extracted data on Southwest China,[15,21] South China,[2,15,22,23] Hong Kong[24,25] and Taiwan[26–28] show that outbreaks typically happen in late spring and fall. No distinct pattern is obvious for tropical regions as seen from data in Thailand,[29–31] Vietnam,[32,33] Malaysia[34] and Singapore,[35–38] where outbreaks occur sporadically throughout the year, although models have been developed for Singapore (≈1° north) that show a positive statistical relationship between maximum daily temperature above 32°C with HFMD incidence in the subsequent 1–2 weeks.[37]

To assess how general the relationship between climate and transmissibility of HFMD was, we took incidence data from Tokyo, Hong Kong, Taiwan and Singapore (Fig. 2, Appendix 1), that is, spanning temperate, subtropical and tropical latitudes, and fitted time series models to them. After controlling for contagion via autoregression terms, the effect of meteorologic factors was weak: a small positive increase in transmissibility with rising absolute humidity/temperature during the current week in Tokyo and Singapore. There was no evidence for temperature and humidity in having the same effect in Hong Kong or Taiwan, although rising relative humidity seems to decrease transmissibility in Singapore.

The earliest recorded cases of HFMD in Asia are from Japan (1967),[30] Singapore (1970),[31] Taiwan (1980)[32] and Shanghai, China (1981).[33] Since then, outbreaks have been reported in many parts of Asia, including mainland China,[12–14,33–52] Korea,[53–55] Japan,[56–70] Taiwan,[6,69,71–74] Hong Kong,[17,18,75] India,[76–81] Thailand,[21,23,82] Vietnam,[24] Malaysia,[26,69,83–87] Singapore[4,88] and Brunei,[89] as summarized in Figure 3. These reported outbreaks are unlikely to reflect the true first outbreaks of HFMD, as serologic studies provide evidence that by the time surveillance systems were established, EV-A71 and CV-A16 were already endemic in many of these countries. Early serologic tests conducted in Japan in 1970 show evidence of EV-A71 and CV-A16 circulation.[90] Serum taken in the late 1990s in Singapore, before the start of surveillance in 2000, shows that around 50% children and 44% cord blood, indicating maternal infection, had already seroconverted to EV-A71.[91] Blood samples from Taiwan (1989–1997) show 3%–11% EV-A71 incidence per year, and up to 68% of children[92] had serologic evidence of EV-A71 infection before the large HFMD outbreak of 1997. Similarly, although China has reported millions of HFMD cases since the beginning of the HFMD surveillance program in 2008, evidence from Anhui[47] shows high seroprevalence of up to 74.6% in older children before the 2008 outbreaks. Retrospective seroepidemiologic tests from blood serum collected in 2005[93] also show that China had positive rates of 32.0% to EV-A71 and 43.4% to CV-A16, indicating that outbreaks happened earlier but were simply not reported in the literature.

Risk Factors

Risk factors for infection are depicted in Figure 4 (Appendix 2) and summarized below.

Hygiene

Evidence from Qiaosi, China,[94] indicates the importance of hygiene for protection against HFMD infection. Children who always wash their hands before meals are about 50 times less likely to contract HFMD, while those whose caregivers wash their hands before feeding are about 25 times less likely. Additional protective habits include washing of hands after play, washing of hands more than 4 times per day, using soap, and not sucking fingers.

A study in Korea[95] revealed that drinking unboiled water [odds ratio (OR): 3.34 (1.59–6.99)], a change in water quality such as color, taste, smell, presence of precipitation or floating materials [OR: 6.93 (2.17–22.15)], using communal toilets/toilets outside the house [OR: 2.77 (1.14–6.74)] and eating outside the home [OR: 37.0 (5.1–269.5)] were risk factors for HFMD.

Rural Versus Urban Areas

All papers[51,96–98] that compared urban with rural areas agreed that the latter conferred a higher risk for HFMD. However, this might be confounded by socioeconomic status and hygiene practices.

Sex

Although most papers show that being male is a risk factor for both mild[4,14,16,23,27,34,37,51,82,98–101] and severe[52,97,102,103] HFMD (OR ranges between 1.2 and 2), surprisingly, serologic evidence does not support this finding: A study from Singapore[104] shows marginal

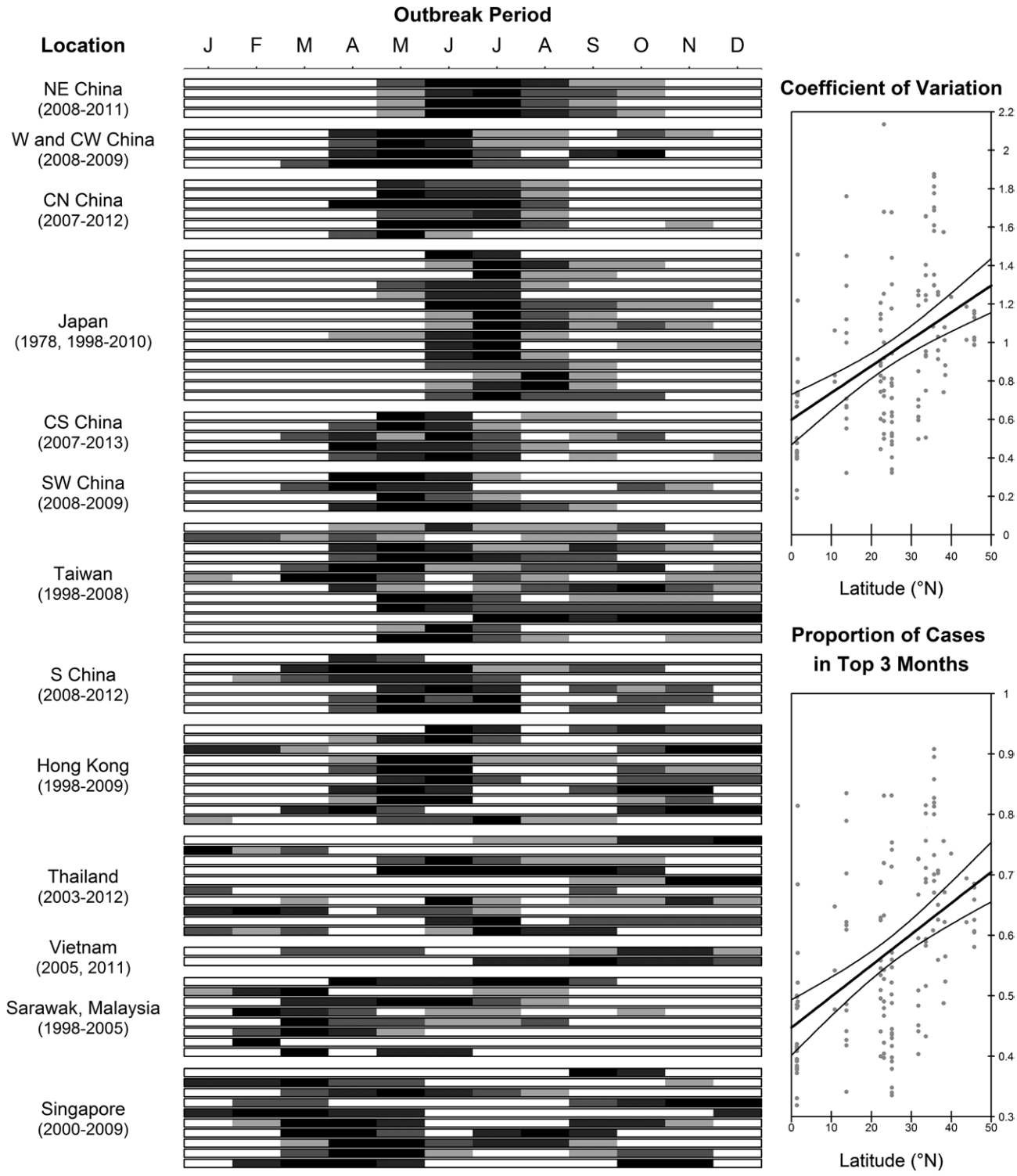


FIGURE 1. Temporal patterns of HFMD outbreaks in Asia, by latitude. Left: Plot Digitizer is used to convert charts into numbers. White boxes are the months where HFMD cases fall below the year's median. The remaining cells are then shaded into 4 darker shades by octiles. The regions of China were based on Wang et al's classification[101](C standing for central). The regions are arranged by latitude. South China, Hong Kong and Taiwan have subtropical climates. Areas further north are temperate, while the Southeast Asian regions are tropical. Right: The coefficient of variation is the ratio of the standard deviation to its mean, and the proportion of cases in top 3 months is the proportion of cases of the 3 months with highest incidence to the annual incidence. Points represent 1 year per region. The lines are obtained from ordinary least squares regression with latitude as the independent variable and show how clearly defined epidemics become the further north from the equator.

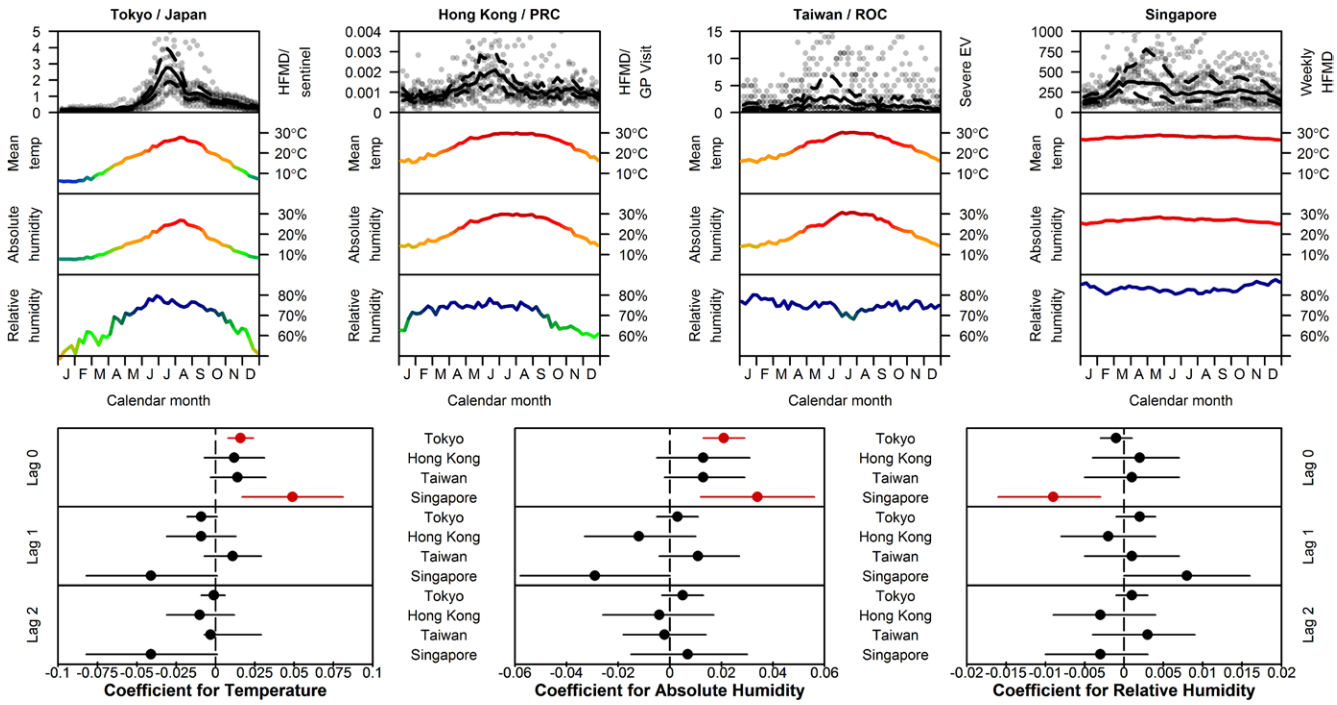


FIGURE 2. Temporal incidence of HFMD or enterovirus and climatic factors for 4 Asian cities spanning temperate, subtropical and tropical latitudes. Top: incidence, temperature, absolute and relative humidity. Top panels indicate incidence (data in gray, mean and 95% interval in black) for the time period Jan 2001 to Mar 2012 (Tokyo), Jan 2001 to Dec 2009 (Hong Kong, Peoples Republic of China), Jan 2001 to Dec 2011 (Taiwan, Republic of China) and Jan 2001 to Jan 2012 (Singapore). Middle and bottom panels show mean daily temperature, absolute and relative humidity at Tokyo Narita, Hong Kong International, Taipei Taoyuan International and Singapore Changi airports, downloaded from the Weather Underground. Bottom: Coefficients of meteorological variables at 0–2 week time lags in autoregressive models of Z-scored HFMD case counts to facilitate comparison between locations. Each city is analyzed separately using a model in which HFMD incidence in week t is (auto)regressed on incidence in weeks t-1 up to t-3 (using the Akaike information criterion to select the order of the autoregression component) and, independently, on each meteorological variable. Weather parameters are not regressed together in a single model because of collinearity. The effect of weather on HFMD incidence can be seen by coefficient mean (points) and 95% confidence intervals (lines), colored red if statistically significant at the 5% level.

evidence that females are more likely to have seroconverted to EV-A71 [OR: 0.79 (0.61–1.01)], while a Taiwanese[96] study shows no statistically significant differences [OR: 0.94 (0.76–1.16)]. Taken together, these suggest that infection rates are comparable, but that boys are more likely to develop symptoms, more involved in propagation of outbreaks or more likely to be brought for medical care than girls.

Other

A case–control study in Xi'an, China,[97] found that breastfeeding may lower the risk of developing severe HFMD [adjusted OR: 0.57 (0.33–0.98)], even though breastfeeding does not apparently lower the chance of being infected by EV-A71 [OR: 1.1 (0.93–1.3)].[96] It further found that patients with a history of Epstein–Barr virus are at greater risk of contracting severe, rather than mild, HFMD [adjusted OR: 2.6 (1.5–4.4)]. A spatial-temporal model of Guangdong[14] showed that sunshine could be protective against HFMD. This is agreed by a matched case-control study of preschoolers in Beijing,[41] which showed that UV radiation in classrooms is associated with lower HFMD attack rate (*P* value of 0.027), and recommended installing UV lamps to sterilize unoccupied classrooms. These findings are, however, inconsistent with the seasonal nature of HFMD, where outbreaks in temperate countries tend to occur in summer, when sunlight and UV exposure are strongest.

Age Distribution of HFMD Cases

The age distribution of HFMD cases in Asia, compiled from a variety of sources including surveillance and cohort data, is summarized in Figure 5. Data from China[12–14,34,49–52,94,100–103,105–107] and Taiwan[5,6,73,108–111] are particularly abundant. Other sources include Hong Kong,[17,18] India,[76,80] Japan,[56,112] Korea,[54,95] Malaysia,[84,113] Singapore,[4,27,88] Thailand[22,23] and Vietnam.[24]

The symptomatic HFMD incidence rate varies widely even within the narrow 0- to 6-year age-band. The greatest proportion of cases occur at ages 1 [18.8% (17.4%–20.2%)] and 2 [17.9% (16.6%–19.2%)]. By the age of formal schooling, from 6 years in most Asian countries, the proportion is substantially lower [8.7% (7.9%–9.5%)]. Overall, 82.6% (82.2%–82.9%) of all cases occur before age 6. The lower rate during the first year of life could be because of lack of contact with other children or to presence of maternal antibodies.[91]

Community Versus School as Medium for Infection

The literature is ambiguous about the importance of locations for transmission. Four studies showed that contact with a case, particularly a household member, is as or more significant a risk factor than preschool attendance.[21,88,96,108] An early study in Singapore observed 60 families with secondary cases and found

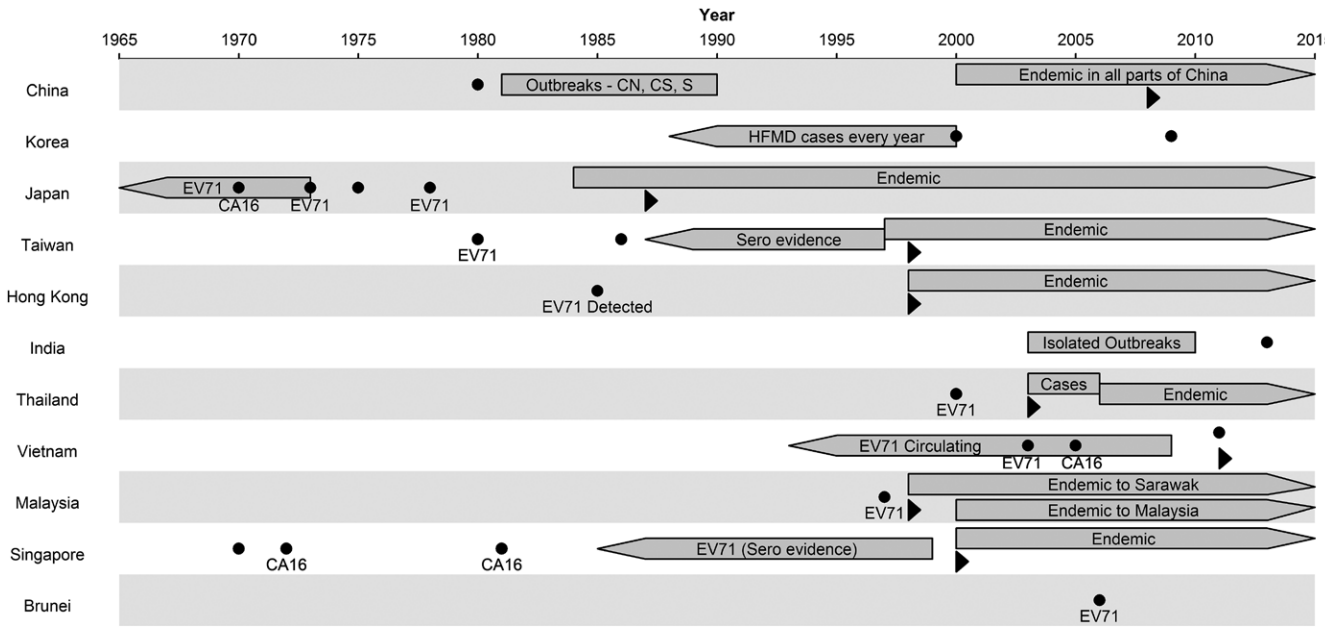


FIGURE 3. Historical establishment of HFMD in Asia. Dots represent a reported outbreak in that year, with the main causal agent written below. Boxes with right arrow indicate endemicity of HFMD, evidenced by repeated reporting of HFMD. Boxes with left arrow indicate seroepidemiologic evidence that the pathogen is already in existence, even if no significant outbreaks were documented previously. Triangles indicate the point where data on HFMD started to be collected systematically, for example, through government surveillance. The length of the left arrows are arbitrary as there is no way to know how long has HFMD been circulating before the tests.

the secondary attack rate amongst children below 12 years old to be 77%.[88] Similarly, in a large seroepidemiologic study of EV-A71 in Taiwanese children,[96] multivariate analysis showed attendance at a preschool imparted a similar magnitude of risk as contact with a case [adjusted ORs: 1.6 (1.2–2.1) and 1.8 (1.3–2.5), respectively], as well as a strong concordance (84%) between seropositivity in younger and older siblings.

Also, a number of studies showed that a higher percentage of diagnoses occurred among children who did not attend a nursery or preschool.[37,51] Liu et al[49] note that about half of symptomatic cases in Nanchang, China, are among children under 3 years, the age at which preschooling starts in China.

Conversely, some studies suggest that preschool attendance is a key risk factor.[4,114] For example, a seroepidemiologic study in 1996 to 1997 in Singapore showed that seropositivity to EV-A71 increases rapidly from age 2 to 5,[91] when attendance at childcare or preschool is the norm. Also, a case-control study in Japan[114] showed that preschool attendance was associated with increased risk of severe disease.

Other studies suggest that both locations are important. In Shanghai, China,[103] there was a marked shift from 2007 to 2008 in the proportion of cases among children in preschools (from 59% to 37%) with a concurrent shift from local to migrant children, suggesting that the importance of routes of transmission can vary over time within the same locale. A case-control study from Zhejiang[94] showed that although attending preschool is a risk factor (OR: 2.1), other factors such as contact with neighbors (OR: 11), going to hospital (OR: 20) and going to parties (OR: 31) impart greater risk. Yet, a Korean case-control study[95] found no significant relationship between infection and school attendance or household size.

Overall, the evidence points to both home and school environments contributing to transmission, but the relative importance of these venues remains murky.

Incubation Period

Several papers describe the incubation period (Fig. 5, Appendix 3) though it is striking that the majority do not provide a source to justify the claimed period. These unsupported claims vary substantially from paper to paper, from the incubation period "is" 3–6 days[115] or 3–7 days,[76] "is usually 3–4 days, but can be ... 10 days or more,"[32] or "is usually 3–5 days (range, 2–12 days),"[111] is "typically" 3–7 days[116] or 3–5 days,[49] ranges from 5 to 7 days[42,98] or 3 to 7 days[113] and the "usual period" is 3–5 days "with longest period of 7 days."[117] Only a few provide evidence to justify the claim: one reports[95] that the incubation period is usually 3–7 days, citing a US Centers for Disease Control and Prevention (CDC) factsheet on aseptic meningitis. Another cites[118] an early study from Singapore,[88] which presented the median and range for the serial interval (3 days [1–7]), not the incubation period. Another early study[119] states that the incubation period is "said to be" 3–5 days, but notes that this is inconsistent with the serial interval observed in the study. It appears that there is no empirical support whatsoever for any distribution of incubation periods.

Symptomatic Proportion

Although several studies report that the asymptomatic rate of EV-A71 infection is high, few studies report data (Table 1). Two studies, from Taiwan and Shanghai, tested sera for evidence of EV-A71 infection and asked patients or their families to recall past HFMD infection, deriving estimates of 29%[120] and 10%[106] of symptomatic infection, respectively. Some HFMD cases may have been caused by other enteroviruses, biasing these estimates upwards, while some may have been diagnosed as another viral illness or forgotten, biasing them downwards.

Two additional studies in Taiwan found much higher symptomatic infection rates. The first[108] study recruited symptomatic cases suspected of having EV-A71 infection, and took throat and

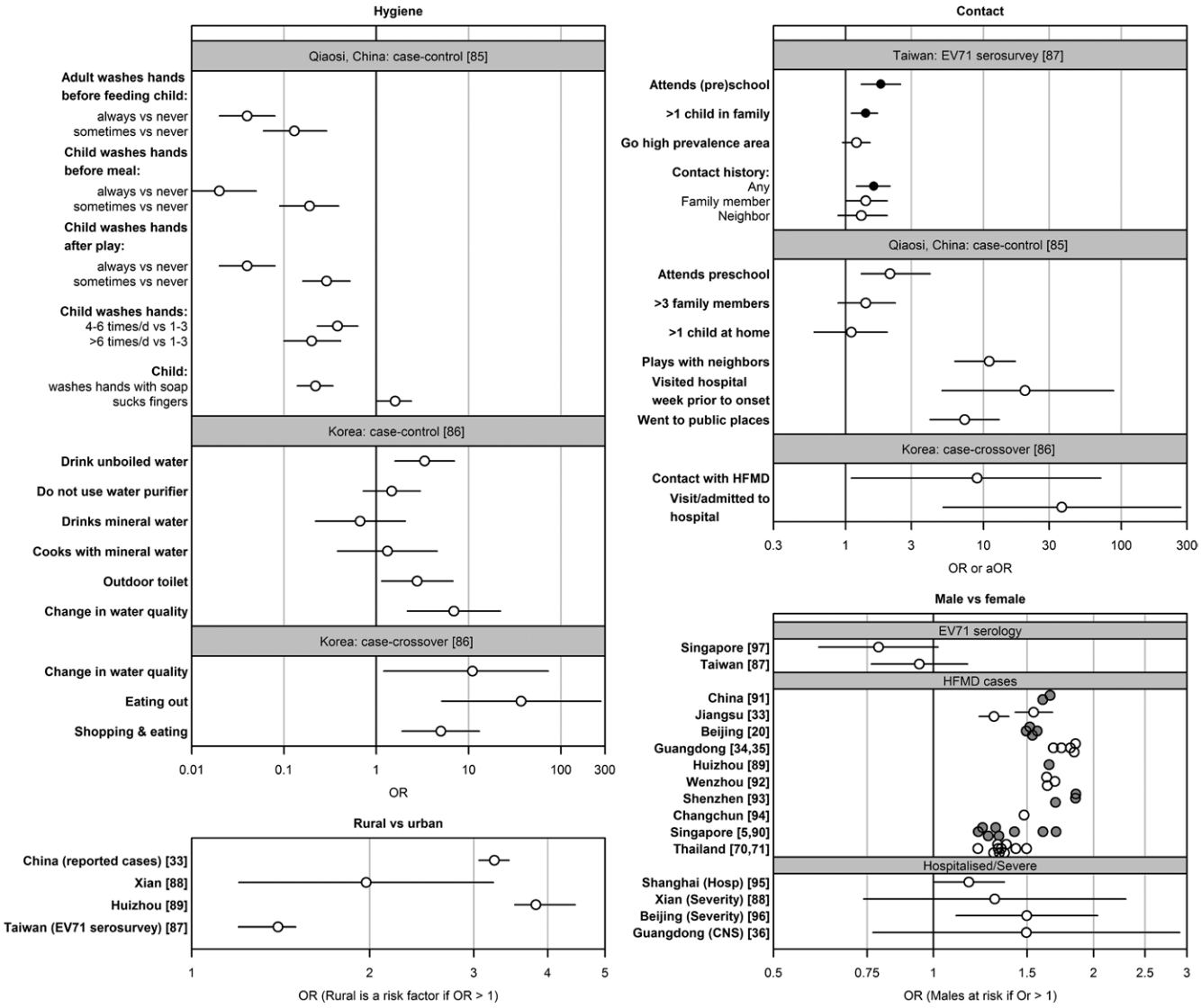


FIGURE 4. Excerpts from studies on risk factors. Ruan et al case-control study in Qiaosi,[94] China, was conducted by taking 273 diagnosed HFMD/herpangina as cases (6 years of age or younger) and 273 stratified random sample as controls. Park et al case-control study uses hospital cases of enteroviral aseptic meningitis (n = 205) and HFMD (n = 116), and nonenteroviral disease controls (n = 170). Their case-crossover design uses only cases. 1–7 days before admission was set as the hazard period, and 22–28 days prior to admission was set as the nonhazard period. Both studies gather data via questionnaires. White points indicate nonadjusted ORs, black points indicate adjusted OR. For the effect of sex (bottom right), confidence intervals are omitted from complete case notifications, and colored gray and white alternately for visual distinction.

rectal swabs or stool samples, of cases and their household members. Signs and symptoms of the entire household were monitored with follow-up telephone interviews. Excluding the 94 symptomatic index cases, 68% of confirmed infections in the household were symptomatic (88% of infected children and 47% of infected adults). A second study[121] prospectively followed a cohort of neonates over 3 years, taking repeat sera, requesting that parents report suspected HFMD and giving reminders during HFMD epidemics. This study found that 71% of serologically confirmed infections were symptomatic, though the sample size is only 28.

The discrepancy between these 2 pairs of papers is substantial, undoubtedly because of differences in methodology. An overall estimate, combining the 4 studies, is 36% (33%–39%), but given the large discrepancy between studies, this estimate does not appear reliable. The latter pair of studies is prospective, thereby circumventing recall bias, and thus appear to provide a more accurate description of the epidemiology of enterovirus infection.

Basic Reproduction Number for HFMD by Virus

Only 3 papers have sought to estimate the reproduction number for HFMD or the viruses that cause it. One paper[101] estimates what they call the "local effective reproduction number" in China—meaning using the average number of secondary cases from a randomly selected index to estimate the cases that would be caused in a fully susceptible population (note, this is substantially different from the effective reproduction number[122] in a partially susceptible population)—using a sophisticated Poisson regression model that incorporated infection from the environment, the prefecture and

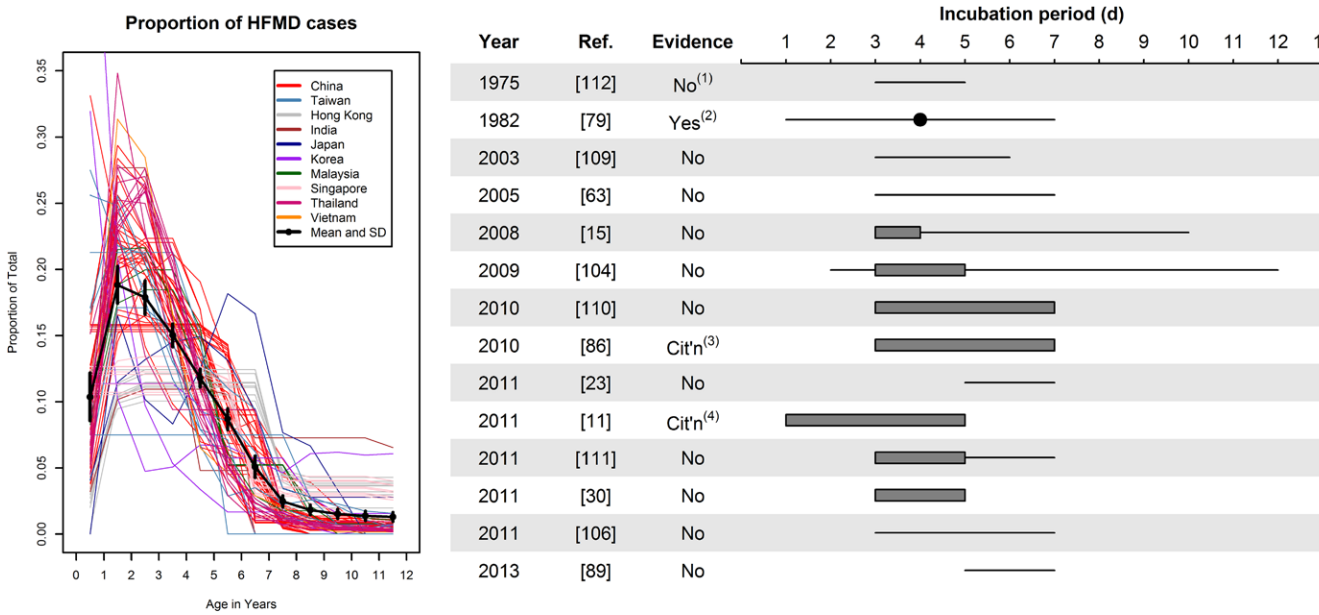


FIGURE 5. HFMD cases by age and estimates of incubation period. Left: Each line indicates a unique data set (total 79 lines). Distributions within age ranges were assumed to be constant. The black dots are average proportion for that age (with 95% CI). Right: Reported incubation periods for HFMD, by year of publication and provision of evidence to support claimed period. Lines indicate that the incubation period "is X days." Gray bars indicate that the incubation period is "usually" or "typically" X days. Gray bars with lines shows an extended interval "can be up to X days." The point indicates a median. *Notes*: (1) provides information within the paper, which is inconsistent in this estimate; (2) uses generation interval distribution as a proxy for incubation period; (3) cites a US CDC factsheet on aseptic meningitis, which in turn provides no supporting evidence and (4) cites Goh et al.[88] CI indicates confidence interval.

TABLE 1. Estimates of Symptomatic Proportion From the Literature

Location	Reference	Year	Inclusion Criteria	Number Symptomatic	Number Infected	Percent Symptomatic (95% CI)
Taiwan	Chang et al[120]	1998	Stratified sampling. Infection determined using serology versus EV-A71 and recall of previous infection history	140	484	28.9 (24.9–33.0)
Shanghai	Zeng et al[106]	2010 to 2011	Routine blood samples and recall of previous infection history	12	122	9.8 (4.6 – 15.1)
Taiwan	Chang et al[108]	2001 to 2002	Household members of hospital symptomatic cases were swabbed for EV-A71	119 (excluding 94 symptomatic index cases)	176 (excluding 94 symptomatic index cases)	67.6 (60.7–74.5)
Taiwan	Lee et al[121]	2006 to 2009	Prospective cohort of neonates with repeat serology (EV-A71) and swabs taken upon subsequent illness	20	28	71.4 (54.7–88.2)
Total				291	810	35.9 (32.6–39.2)

CI indicates confidence interval.

neighboring prefectures. This model did not, however, account for the accumulation of herd immunity and required arbitrary assignment of the infectious period, so the estimated local effective reproduction number of 1.1–1.2 during peak periods may be biased.

A second paper[117] used a method from Choi and Pak[123] to estimate the basic reproduction number to be 5.5 (interquartile range, 4.2–6.5) for EV-A71 and 2.5 (interquartile range, 2.0–3.7) for CV-A16. These estimates are likely inaccurate because the method assumes (i) a known generation time distribution, labeled incubation period in the paper; (ii) a completely immunonaïve population, though applied to groups of individuals for whom past exposure was highly plausible and (iii) an early exponential growth period, despite being applied to complete outbreak data.

The third paper[124] attempted to estimate the reproduction number using a SEIQRS (Susceptible, Exposed, Infectious, Quarantined, Recovered) simulation model and obtained an estimate of 1.1 for the years 2009 to 2012 in China. However, the model used 10% of China population as the initial susceptible population, but did not conduct a sensitivity analysis on this vital parameter.

DISCUSSION

Despite the substantial number of papers on HFMD, this systematic review shows that many fundamental questions about EV-A71 and CV-A16 persist. Both viruses occur year round in tropical Asia, but are epidemic in the summer in Northeast Asia. A role for temperature or humidity therefore seems

plausible,[14,125–128] although given the relative lack of seasonality in equatorial Asia, it is not clear whether prediction of outbreaks is possible there. In Japan, summer temperatures peak after HFMD incidence does, suggesting correlation but not temporality, and that it may not be possible to provide early warning of impending epidemics. This also differs from other human enteric viruses including poliovirus 1 (also an enterovirus), hepatitis A and adenovirus that have been shown to survive longer on colder surfaces.[129]

Urashima et al[125] claimed that enteroviruses experience a more rapid virus decline during dry seasons than during wet seasons, which could explain the seasonality. This result is supported by Wang et al,[130] where they showed that precipitation patterns has the most similar structure as HFMD incidence, more so than other meteorologic variables, albeit with only 11 months of data.

While any causal relationship between climate and HFMD is unknown, speculations include a lower HFMD incidence because of decreased social contact during temperate zones' winter.[118,131] In contrast, increased social contacts during winter have been speculated to facilitate spread of other droplet-borne diseases, such as influenza,[132] which are epidemic in winter. Given the unknowns surrounding this issue, further research is clearly required to ascertain whether meteorologic factors or seasonal social contact patterns is an adequate explanation for the seasonality of HFMD.

The next step to analyzing the dynamics of HFMD seasonality is likely to involve social and environmental factors, another under-researched area for this pediatric disease. For instance, the literature is unclear on the relative importance of school versus community transmission, with evidence to support both, yet knowledge of where HFMD most often is transmitted is important as school closure policies are employed to control outbreaks in some countries. Further, the environment of schools in Asia may vary widely, and attributes such as hygiene practices should be characterized and quantified to allow more definitive results and conclusions in future studies.

Even without being able to determine the relative importance of school versus community transmission, the effectiveness of school closure to prevent large-scale HFMD outbreaks is questionable, as the interruption to social networks cannot be enforced while children are out of school. Additionally, although we know little about the infectiousness of asymptomatic cases of HFMD, the proportion of infections that are asymptomatic is substantial, and so even quite modest school closure attack rate thresholds, such as Singapore's 25%,[133] corresponds to a possible majority of students being infected before the trigger for closure being met. Further, EV-A71 can be found in fecal samples for up to 54 days after infection,[134] and thus continue to be shed after a school is closed, disinfected and reopened.

Studies on risk factors were rare, and we identified only 3 papers that describe risk factors for hygiene and contact patterns, making a meta-analysis of risk factors unfeasible. These typically were only powered to provide unadjusted effect sizes, and so provide evidence of correlation, not causation. One interesting finding was the apparent protective effect of a caregiver "always washing" their hands. This suggests that adult to child transmission might be important, even if adults are mostly asymptomatic with EV-A71 and CV-A16, but may reflect confounding with general hygiene. Future work may elicit hygiene factors at the preschool level and relate these to attack rates.

A recently developed EV-A71 vaccine has undergone phase 3 trials in China.[135–137] To determine the cost-effectiveness of incorporating the vaccine in pediatric vaccination schedules, or of other interventions such as school closure or isolation, would require epidemiologic models that account for the protective effects of herd immunity. However, this review indicates that vital parameters for such models remain unknown. The asymptomatic rate and relative infectiousness of asymptomatic cases are both poorly known, while estimates of the incubation period, although commonly cited as 3–5 days, appear to be based solely on expert opinion. Most importantly, estimates of the basic reproduction number range widely from 1.1 to 5.5. This uncertainty prohibits utilitarian estimation of the necessary vaccine coverage to prevent epidemics of EV-A71.

To reconcile the differences between the disparate estimates, the age distributions of the samples need to be considered. As shown in this review, symptomatic HFMD incidence rate differ greatly even between ages 0 and 6, and thus, studies conducted predominantly on preschoolers may derive higher estimates of R_0 compared with studies in older children. Accordingly, future studies on HFMD should use narrower age bands and also state the distribution clearly to allow adjustments or standardization.

Two final omissions from the literature are quantitative estimates of the impact of infection on complications, child and caregiver absenteeism and costings of complications, and qualitative evidence on the impact of infection and enforced isolation on families and schools. Given the promising direct effects of the EV-A71 vaccine and the huge public health impacts of HFMD in East and Southeast Asia, research is urgently needed to fill these gaps.

The research questions in this systematic review were generally answered only by a limited number of papers, with substantial differences in their study design, and thus, most data were not synthesized through meta-analysis. More research to assess risk factors and measure key epidemiologic parameters is needed. We were also unable to trace the earliest cases of HFMD in Asia as our scope only covers published material on outbreaks, which leads us back to 1967 in Japan. Finally, we limited the scope of this study to exclude virologic characteristics or molecular epidemiology, which have been well reviewed elsewhere,[116,138–141] and clinical manifestations of EV-A71 and CV-A16.[28,116,138,141,142] A recent review of the case-fatality rate has recently been published,[143] as has a review of the epidemiology in Taiwan.[144]

APPENDIX 1. TIMING AND SEASONALITY OF HFMD OUTBREAKS

An autoregressive (AR) model was used to investigate the effect of meteorological variables after correcting for contagion via autoregression.

A lag 2 model can be specified as follows:

$$\mathrm{HFMD}_t = c + A_1\mathrm{HFMD}_{t-1} + A_2\mathrm{HFMD}_{t-2} + B_0\mathrm{WEA}_t + B_1\mathrm{WEA}_{t-1} + B_2\mathrm{WEA}_{t-2} + \in_t$$

The A coefficients are the coefficients for the AR terms, while the B coefficients represent how a change in weather is correlated with changes in HFMD incidence. The number of lag terms is determined by the Akaike information criterion values of the regression models.

This same model was used for 4 countries—Japan (lag 2), Hong Kong (lag 3), Taiwan (lag 3) and Singapore (lag 2)—and for 3 meteorological parameters—temperature, absolute humidity and relative humidity. As this model carries autocorrelated terms, we used generalized least squares for model fitting. Coefficients from the fitted models are presented in Tables A1–A3.

TABLE A1. Coefficients for Autoregressive Model Using Temperature as Predictor

Location	Lag (Weeks)	Autoregression Term (95% CI)	*P* Value	Temperature (°C) Coefficient (95% CI)	*P* Value
Japan	0	-	-	0.016 (0.008, 0.024)	<0.001
	1	1.517 (1.452, 1.582)	<0.001	−0.009 (−0.018, 0.001)	0.07
	2	−0.601 (−0.665, −0.536)	<0.001	−0.001 (−0.009, 0.006)	0.723
Hong Kong	0	-	-	0.012 (−0.007, 0.031)	0.204
	1	0.756 (0.678, 0.835)	<0.001	−0.009 (−0.031, 0.013)	0.415
	2	−0.079 (−0.178, 0.02)	0.116	−0.01 (−0.031, 0.012)	0.388
	3	0.195 (0.117, 0.274)	<0.001	0.017 (−0.001, 0.036)	0.071
Taiwan	0	-	-	0.014 (−0.003, 0.032)	0.108
	1	−0.181 (−0.26, −0.102)	<0.001	0.011 (−0.007, 0.029)	0.222
	2	0.062 (−0.019, 0.142)	0.132	−0.003 (−0.02, 0.015)	0.779
	3	0.192 (0.113, 0.271)	<0.001	0 (−0.018, 0.017)	0.968
Singapore	0	-	-	0.049 (0.017, 0.081)	0.003
	1	1.42 (1.349, 1.491)	<0.001	−0.041 (−0.082, 0.001)	0.054
	2	−0.458 (−0.53, −0.387)	<0.001	0.01 (−0.023, 0.042)	0.564

The outcome variable is the number of reported HFMD cases per sentinel per week (Japan), the number of reported HFMD cases per general practitioner per week (Hong Kong), the number of reported severe enterovirus cases per week (Taiwan) and the number of reported HFMD cases per week (Singapore). To facilitate comparability, the incidence measures were standardized to have mean 0 and variance 1.

CI indicates confidence interval.

TABLE A2. Coefficients for Autoregressive Model Using Relative Humidity as Predictor

Location	Lag (Weeks)	Autoregression Term (95% CI)	*P* Value	Relative Humidity (°C) Coefficient (95% CI)	*P* Value
Japan	0	-	-	−0.001 (−0.003, 0.001)	0.363
	1	1.567 (1.503, 1.631)	<0.001	0.002 (−0.001, 0.004)	0.186
	2	−0.634 (−0.699, −0.569)	<0.001	0.001 (−0.001, 0.003)	0.231
Hong Kong	0	-	-	0.002 (−0.004, 0.007)	0.578
	1	0.942 (0.864, 1.021)	<0.001	−0.002 (−0.008, 0.004)	0.483
	2	−0.242 (−0.349, −0.135)	<0.001	−0.003 (−0.009, 0.004)	0.413
	3	0.215 (0.136, 0.294)	<0.001	0.001 (−0.005, 0.006)	0.753
Taiwan	0	-	-	0.001 (−0.005, 0.007)	0.72
	1	−0.178 (−0.257, −0.1)	<0.001	0.001 (−0.005, 0.007)	0.755
	2	0.062 (−0.018, 0.142)	0.13	0.003 (−0.004, 0.009)	0.426
	3	0.19 (0.111, 0.269)	<0.001	−0.001 (−0.006, 0.005)	0.849
Singapore	0	-	-	−0.009 (−0.016, −0.003)	0.004
	1	1.43 (1.36, 1.501)	<0.001	0.008 (0, 0.016)	0.055
	2	−0.469 (−0.539, −0.398)	<0.001	−0.003 (−0.01, 0.003)	0.349

The outcome variable is the same as the temperature model.

CI indicates confidence interval.

TABLE A3. Coefficients for Autoregressive Model Using Absolute Humidity as Predictor

Location	Lag (Weeks)	Autoregression Term (95% CI)	*P* Value	Absolute Humidity (°C) Coefficient (95% CI)	*P* Value
Japan	0	-	-	0.021 (0.013, 0.029)	<0.001
	1	0.847 (0.766, 0.928)	<0.001	0.003 (−0.005, 0.011)	0.484
	2	−0.141 (−0.221, −0.061)	0.001	0.005 (−0.003, 0.013)	0.228
Hong Kong	0	-	-	0.013 (−0.005, 0.031)	0.153
	1	0.781 (0.703, 0.86)	<0.001	−0.012 (−0.033, 0.01)	0.285
	2	−0.102 (−0.202, −0.001)	0.047	−0.004 (−0.026, 0.017)	0.703
	3	0.195 (0.117, 0.274)	<0.001	0.013 (−0.005, 0.031)	0.156
Taiwan	0	-	-	0.013 (−0.002, 0.029)	0.096
	1	−0.18 (−0.259, −0.101)	<0.001	0.011 (−0.004, 0.027)	0.158
	2	0.064 (−0.016, 0.144)	0.117	−0.002 (−0.018, 0.014)	0.814
	3	0.194 (0.115, 0.273)	<0.001	0.001 (−0.015, 0.017)	0.893
Singapore	0	-	-	0.034 (0.012, 0.056)	0.003
	1	1.42 (1.349, 1.492)	<0.001	−0.029 (−0.058, 0)	0.047
	2	−0.459 (−0.53, −0.388)	<0.001	0.007 (−0.015, 0.03)	0.536

The outcome variable is the same as the temperature model. Coefficients for autoregressive model using temperature as predictor. The AR coefficients are generally statistically significant across models. Significant AR terms indicate that incidence is highly autocorrelated, which is expected as the contagious nature of HFMD is the primary driver of temporal patterns of incidence. The primary parameters of interest are the coefficients of the meteorological variables, which represent how much temperature/humidity affects the Z-score of incidence, after controlling for contagion. The results are tabulated in Tables A1–A3, summarized in Figure 1 and the paper itself. Incidence data are obtained from various sources, summarized in Table A4. For Japan and Hong Kong, "cases per sentinel" and "cases per consultation" are used instead of the actual number of notified cases because these data are from voluntary sentinel reporting. Thus, actual notified cases will increase with an increase of GP sentinel participation rate. CI indicates confidence interval.

TABLE A4. Data Source for Incidence

Country	Data	Source
Singapore	Notified cases (low underreporting, as notification is mandatory and laws are strict)	Ministry of Health, Singapore
Japan	Notified cases, cases per sentinel (not mandatory reporting)	National Institute of Infectious Diseases, Japan (released weekly)
Hong Kong	Notified cases per 1000 GP consultations (not mandatory reporting)	Department of Health (website and digitized from historical documents)
Taiwan	Enterovirus with complications	Taiwan National Infectious Disease Statistics System

APPENDIX 2. ODDS RATIO FROM FIGURE 4

Paper	Type	Location	Details	OR
Ooi et al[91]	Serology	Singapore	1200 serum samples, aged 1–17 yrs. Children were split into 3 equal groups of age 1–6, 7–12 and 13–17	0.788, 0.608, 1.019
Kashyap and Verma[81]	Serology	Taiwan	1800 children between 6 mo to 6 yrs	0.941, 0.763, 1.159
Lum et al[85]	Cases	Whole China	2008 and 2009 reported cases for entire China (almost 1 million cases). Controlled for population male/female ratio of entire population. 632.84 m girls, 667.20 m boys	1.658 (1.648, 1.667) 1.605 (1.599, 1.611)
Tu et al[24]	Cases	Jiangsu, China	2008 and 2009 reported cases for Jiangsu, Zhenjiang. 6324 HFMD cases. Controlled for population male/female	1.543 (1.424,1.673) 1.300 (1.218,1.387)
Zhu et al[102]	Cases	Beijing, China	157k cases in 2008 to 2012, each OR represents a particular year. Not controlled for population male/female	1.568, 1.535, 1.517, 1.493, 1.494
Nguyen et al[25]	Cases	Guangdong, China	48,876 cases in 2008. Do not have denominator for population male/female	1.85
Podin et al [26]	Cases	Guangdong, China	Incidence ratios for 2008 to 2011. Total of 641k cases	1.84, 1.81, 1.74, 1.68
Cardosa et al[83]	Cases	Huizhou	42,012 cases from 2008 to 2011. Incidence ratio	1.65
Shekhar et al[86]	Cases	Wenzhou	103k cases from 2010 to 2012. Not controlled for male/female ratio	1.639, 1.691, 1.633
Ooi et al[87]	Cases	Shenzhen	Total 12,132 reported cases for 2009, 2010 and 2011. Not controlled for male/female ratio	1.851, 1.697, 1.854
Goh et al[88]	Cases	Changchun	17,464 cases reported from 2008 to 2011. Not controlled for male/female ratio in population	1.480
Chen et al[15]	Cases	Singapore	Incidence ratios for 2001 to 2007. All cases in Singapore	1.328, 1.420, 1.607, 1.309, 1.268, 1.236, 1.214
Hooi et al[84]	Cases	Singapore	Year 2000. All cases reported to Ministry of Health, Singapore	1.700
Ishimaru et al[64]	Cases	Thailand	Reported cases in 2012	1.496
Tagaya et al[65]	Cases	Thailand	Reported cases from 2003 to 2012	1.212, 1.297, 1.321, 1.323, 1.330, 1.320, 1.341, 1.360, 1.372, 1.429
AbuBakar et al[89]	Hospital	Shanghai, China	28,058 hospital cases → not reported as case because the other data above are all surveillance data, not hospital. 1.165 is the incidence ratio of severe cases, 473/17,206 boys and 257/10,852 girls	1.1653 (0.999, 1.359)
Puenpa et al[82]	Severe	Xi'an, China	Xi'an Jiaotong University and Xi'an children hospital Apr to Oct 2011. 116 (83m, 33f) severe cases of HFMD. 318 hospital cases (211 m, 107 f)	1.454 (0.8867, 2.3844)
Sudo and Morita[90]	Severe	Beijing, China	Beijing Youan hospital June to Oct 2010, 233 (158m, 75f) severe, 1104 total (667m, 437f)	1.498 (1.103, 2.035)
Chan et al[27]	Central nervous system	Guangdong, China	Zhujiang hospital Mar to Dec 2010. 542 children diagnosed with HFMD. Central nervous system: 34 m, 13 f; total: 349 m, 193 f	1.495 (0.769, 2.906)

APPENDIX 3. DATA SOURCE FOR FIGURE 5 (LEFT)

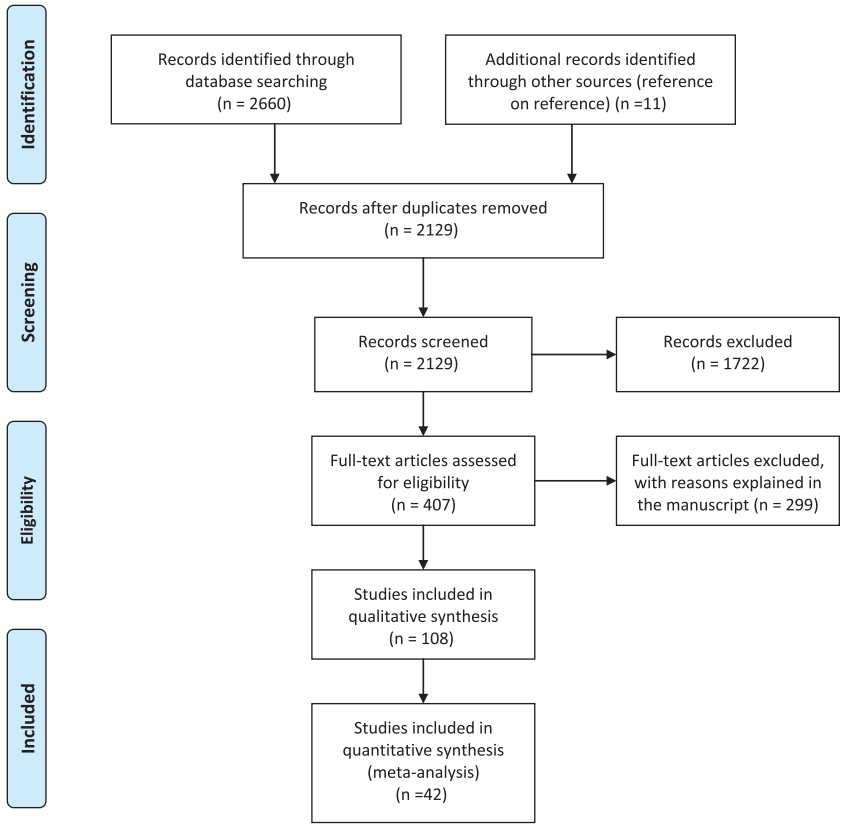
Paper	Date	Data Source	Size	Type	Location	Found in
Chatproedprai et al[21]	Apr 7 to May 11, 2010	9th People's Hospital of Nanchang	109	Hospital cases	Nanchang, China	Page 5, Figure 4 (A)
Linsuwanon et al[22]	May 2008 to Dec 2009	Weekly Reports to China CDC	1,065,000	Surveillance	Mainland China	Figures 1 and 2
Samphutthanon et al[23]	2007 to 2011	China Information System for Disease Control and Prevention	421,488	Surveillance	Shandong, China	Table 1
Tu et al[24]	May 2008 to Oct 2009.	Reported cases to Jiangsu CDC	6324	Surveillance	Jiangsu, China	Figure 3
Nguyen et al[25]	2008	Reported cases to Guangdong HFMD web-based surveillance system (871 clinics)	48,876	Surveillance	Guangdong, China	Figure 2
Podin et al[26]	2008 to 2011	Guangdong surveillance data	641,318	Surveillance	Guangdong, China	Table 1, proportion
Chan et al[27]	2010	Laboratory samples	542	Laboratory	Guangdong, China	Figures 1 and 2
Hii et al[28]	2008 to 2010	Reported cases under Yunnan HFMD web-based surveillance system (871 clinics)	75,109	Surveillance	Yunnan, China	Table 2
Sarma et al[79]	Apr 30 to June 26, 2008	All 6 mo to 6 yr cases from Qiaosi, Zhejiang	273	Case-control	Zhejiang, China	Table 1
Lum et al[85]	2008 to 2009	China surveillance data	1,500,000	Surveillance	Whole China	Table 1
Shekhar et al[86]	2010 to 2012	Reported cases to Wenzhou CDC	103,671	Surveillance	Wenzhou, China	Table 1
AbuBakar et al[89]	2007 to 2010	Cases from Children's Hospital of Fudan University	28,058	Hospital cases	Shanghai, China	Table 1
Sudo and Morita[90]	June to Oct 2010	Cases from Beijing Youan Hospital	1104	Hospital cases	Beijing, China	Figure 2
Lu et al[92]	Jan 2009 to Dec 2010	Cases from Children's Hospital of Fudan University	3208	Hospital cases	Shanghai, China	Figure 3
Zhu et al[93]	2011	Cases from Children's Hospital of Fudan University	8020	Hospital cases	Shanghai, China	Table 1
Ruan et al[94]	May 2008 to Apr 2009	China surveillance data	765,220	Surveillance	China	Figure 4
Lo et al[6]	2008	Laboratory confirmed cases from Chang Gung Children's Hospital	280	Hospital cases	Taoyuan, Taiwan	Table 1
National Institute of Infectious Diseases[7]	Jan 2004 to Dec 2009	Laboratory confirmed CA6 cases from Chang Gung Memorial Hospital	229	Hospital cases	Taoyuan, Taiwan	Figure 3
Mao et al[51]	Apr to Dec 1998	Laboratory confirmed EV-A71 cases from Taiwan MOH passive surveillance	119	Surveillance	Tainan, Chiayi, Taiwan	Figure 3
Park et al[95]	Feb 2001 to Aug 2002	Chang Gung Children's Hospital, ages 0–40	256	Cohort study	Taiwan	Table 2
Chang et al[96]	Mar 1998 to Dec 2005	Taiwan surveillance data, ages 0–15	8000	Surveillance	Taiwan	Figure 4
Li et al[97]	Mar 1998 to Dec 2005	Taiwan surveillance data, severe cases	1584	Surveillance	Taiwan	Figure 2
Qiaoyun et al[98]	Jan 1999 to Dec 2006.	Coxsackievirus confirmed cases from National Taiwan University Hospital	457	Hospital cases	Taiwan	Figure 3
Jee et al[53]	2008	Laboratory confirmed EV-A71 cases from voluntary reporting to Public Health Laboratory of the Department of Health	98	Surveillance	Hong Kong	Figure 2
Baek et al[54]	2001 to 2009	Hong Kong GP-based sentinel surveillance and Public Health Laboratory of the Department of Health	3512	Surveillance	Hong Kong	Figure 4
Gobara et al[57]	Oct 2003 to Feb 2004	Cases from 1 outpatient clinic	81	Clinical cases	Calicut, India	Page 2, Results
Itagaki et al[61]	Sep 2009 to Nov 2009	Hospitals and community in urban areas	78	Clinical cases	Bhubaneswar, Odisha, India	Table 1
De et al[42]	1978	Cases from Gifu Prefectural Hospital	108	Hospital cases	Gifu Prefecture, Japan	Figure 2
Li et al[100]	2004 to 2008	Survey	166	Survey	Yokohama city, Japan	Table 3
Sawada et al[30]	2008 to 2009	Enterovirus-positive cases	1214	Survey	Chungnam, Korea	Figure 2
Kar et al[80]	2002 to 2003	HFMD cases from 3 general hospitals	116	Hospital case-control study	Seoul, Gyeongju, Pohang Korea	Table 1
Bible et al[69]	May 1997 to June 2001	HFMD cases investigated in the University Malaya Medical Centre	467	Laboratory	Malaysia	Figure 1
Zeng et al[103]	1997 to 2008	EV-A71 and CV-A16 confirmed cases	145	Laboratory	Malaysia	Page 7, Host Factors
Chen et al[5]	2001 to 2007	All Singapore cases, GP reporting and laboratory cases	83,970	Surveillance	Singapore	Table 1
Wang et al[74]	Sep to Dec 1981	Notified cases	270	Clinical cases	Singapore	Table 1
Hooi et al[84]	Early Sep 2000 to Mar 2001	Notifications to the Ministry of the Environment	175	Clinical cases	Singapore	Table 1
Tagaya et al[65]	Jan 2003 to Nov 2012	Cases reported to Ministry of Public Health	20,281	Surveillance	Thailand	Table 1
Ang et al[104]	2008 to 2013	Laboratory tested cases from King Chulalongkorn Memorial Hospital	1182	Hospital cases	Bangkok, Thailand	Figure 5
Hosoya et al[66]	2005	Pediatric hospital in Ho Chi Minh city	764	Hospital cases	Ho Chi Minh city, Vietnam	Figure 2B

APPENDIX 4. PRISMA 2009 CHECKLIST

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 5 and Page 19 (Table 1)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Attached as supporting document
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 7 and Page 19 (Table 1)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Data sought answers questions stated in page 19 (Table 1)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Most studies are not synthesized due to small sample size. Potential biases are discussed throughout the paper.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Risk factors: OR, page 10–11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Epidemic patterns: page 21Climate patterns: page 22
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Cumulative evidence that might be biased were not synthesized.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Attached as supporting document
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Details are found in Figures and as supporting doc
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Studies that might be biased are identified throughout the review.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Synthesis of results was avoided when i) data is too sparse; or ii) studies are too different. For these studies, we have summarized the key results into figures for comparison.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Attached as supporting document. (Gender and Age data synthesis)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Cumulative evidence that might be biased were not synthesized.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 1

From Moher D, Liberati A, Tetzlaff J, et al.; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097. For more information, visit www.prisma-statement.org.

APPENDIX 5. PRISMA 2009 Flow Diagram



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