Original Article

# Epidemiology and Control of Hand, Foot and Mouth Disease in Singapore, 2001-2007

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## Abstract

**Introduction: We reviewed the epidemiology of hand, foot and mouth disease (HFMD) in Singapore after the 2000 epidemic caused by Enterovirus 71 (EV71), with particular reference to the cyclical pattern, predominant circulating enteroviruses and impact of prevention and control measures in preschool centres. Materials and Methods: We analysed the epidemiological data from all clinical cases and deaths of HFMD diagnosed by medical practitioners and notified to the Ministry of Health, as well as laboratory data on enteroviruses detected among HFMD patients maintained by the Department of Pathology, Singapore General Hospital, and the Microbiology Laboratory, KK Women's and Children's Hospital from 2001 to 2007. Results: The incidence rate was highest in the 0 to 4 years old age group, with males being predominant. Three deaths were reported between January and February 2001. Nationwide epidemics occurred periodically; the predominating circulating virus was Coxsackievirus A16 (CA16) in the 2002, 2005 and 2007 epidemics, and EV71 in the 2006 epidemic. During the epidemic years between 2005 and 2007, 2 peaks were observed. The number of institutional outbreaks had increased 10-fold from 167 in 2001 to 1723 in 2007, although most of these outbreaks were rapidly brought under control with an attack rate of less than 10%. Conclusion: HFMD remains an important public health problem in Singapore with the annual incidence rate per 100,000 population increasing from 125.5 in 2001 to 435.9 in 2007, despite stringent measures taken in preschool centres to prevent the transmission of infection. A high degree of vigilance should be maintained over the disease situation, in particular, surveillance of EV 71 which continues to cause severe complications and deaths in the region.**

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**Key words: Coxsackievirus A16, Enterovirus 71, Epidemic, Preschools**

## Introduction

Hand, foot and mouth disease (HFMD) is a common childhood viral infection, which is typically mild and self-limiting. It is characterised by a brief prodromal fever, followed by pharyngitis, mouth ulcers and rash on the hands and feet. The disease is caused by numerous members of the Enterovirus genus of the family Picornaviridae e.g. *Coxsackievirus* type A (CA) and *Enterovirus* 71 (EV71), and the clinical features are indistinguishable. Transmission occurs from person to person through direct contact with saliva, faeces, vesicular fluid or respiratory droplets of an infected person and indirectly by contaminated articles.[1]

In Singapore, the first outbreak of HFMD was reported in June to July 1970, but the aetiological agent was unknown.[2] Two other outbreaks associated with CA16 were reported during the period between September 1972 and January 1973, and between September and December 1981.[3] The largest epidemic of HFMD caused by EV71 with 3790 cases and 4 deaths occurred in Singapore between September and December 2000. The main pathological findings at autopsy were interstitial pneumonitis, myocarditis and encephalitis.[4]

The purpose of this study was to review the epidemiology of HFMD after the 2000 epidemic in Singapore, with

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particular reference to determine the seasonality or cyclical pattern, the predominant circulating enteroviruses and the impact of prevention and control measures in preschools.

## Materials and Methods

We reviewed the records of all cases of HFMD notified to the Ministry of Health (MOH) by medical practitioners between 2001 and 2007. The clinical criteria for diagnosis and notification of HFMD are provided in a guidebook that is made available to all medical practitioners.[1]

Childcare centres, preschools and primary schools are also required to notify MOH via facsimile of any HFMD outbreaks in their institutions. An outbreak is defined as 2 or more cases of HFMD with onset of illness occurring within 10 days in the same institution for investigation and management by MOH.

Laboratory notifications of enteroviruses identified in stool samples, throat and rectal swabs and swabs from vesicular fluid and oral ulcers randomly collected from outpatient and inpatient cases of HFMD at KK Women's and Children's Hospital (KKH) and tested at the Virology Laboratory of the Department of Pathology, Singapore General Hospital, were collated. Samples included those obtained from HFMD cases at childcare centres, kindergartens and schools with parental consent.

The classical diagnostic method was adopted; enteroviruses cultured from the samples were typed by micro-neutralisation tests using Lim-Benyesh-Melnick A-H equine antiserum pools (World Health Organization, Statens Serum Institut, Copenhagen, Denmark), equine antiserum pools (Rijksinstituut voor Volksgesondheid en Milieuhygiene, Bilthoven, the Netherlands), rabbit 385JS HEV71-specific polyclonal antiserum (Victorian Infectious Diseases Reference Laboratory, Melbourne, Australia), and rabbit or monkey antisera specific for CA serotypes (National Institutes of Health, Bethesda, MD).[4] Rapid diagnosis for enterovirus polymerase chain reaction (PCR) was performed on nasopharyngeal aspirate/throat swab.[1] The molecular methods used have been described previously.[5,6] Since April 2006, selected stool samples, vesicle and throat swabs were also tested at the Microbiology Laboratory, KKH, using the reverse transcriptase-PCR method for specific identification of EV71.[7]

For the calculation of age-specific and ethnic-specific incidence rates, the denominators used were the estimated mid-year population of the corresponding years from the Singapore Department of Statistics. The attack rates of institutional outbreaks were calculated based on the population of students and staff provided by the affected institutions. Statistical analyses were performed using SPSS Software Version 15.0 (SPSS Chicago, IL). We used $\chi^2$ test for categorical data. Differences between the age-gender-standardised incidence rates of the ethnic groups based on direct method were computed and tested for statistical significance using the Z-test.[8] A $P$ value less than 0.05 was considered statistically significant.

## Results

### *Morbidity*

Nationwide epidemics were reported in 2002, 2005, 2006 and 2007 with 16,228 cases, 15,256 cases, 15,282 cases and 20,003 cases, respectively, compared with 5,187 cases in 2001, 5,603 cases in 2003 and 6,411 cases in 2004. The incidence rates ranged from 125.5 per 100,000 in 2001 to 435.9 per 100,000 in 2007 (Table 1).

The incidence rate was highest in the 0 to 4 years old age group, and this had increased steeply from 1460.5 per 100,000 population in 2001 to 5975.5 per 100,000 population in 2007 (Table 1). A gradual decline in the proportion of cases in this age group was observed during the period of review. It constituted 74.5% of the reported cases in 2001, but dropped to 62.2% in 2007. There was a corresponding shift in the age distribution of the HFMD cases in older children aged 5 to 9 years old. The proportion of cases in this age group increased significantly from 17.0% in 2001 to 26.2% in 2007 ($P$ <0.05, $\chi^2$ test for trend).

There was a male predominance of HFMD cases, with a male-to-female ratio between 1.3:1 and 1.6:1 (Table 2). Males had a significantly higher incidence rate of HFMD compared to females, with the relative risk ranging from 1.2 in 2006 to 1.6 in 2003.

Among the 3 major ethnic groups, the incidence rate among the Chinese was significantly higher than that of Indians (Table 2). The incidence rate of HFMD cases among Malays was higher than that of Chinese in the last 2 years, and the difference between the age-gender-standardised incidence rates was statistically significant.

During the epidemic year in 2002 when CA16 was the predominant circulating enterovirus, there was only 1 single peak in May, whereas in the other epidemic years, 2 peaks were observed in March and October 2005, March and August 2006, and May and August 2007, with the first peak consistently higher than the second (Fig. 1). There were 2 seasonal troughs, one occurring during the school holidays around the middle of the year and the other at the end of the year.

During the EV71-associated HFMD epidemic between March and April 2006, 1.8% of the cases were hospitalised. This was more than twice higher than those epidemics caused by CA16 (0.8% of the cases were hospitalised between March and April 2005, and 0.7% between April and May 2007).

Table 1. Age-Specific Incidence Rates (Per 100,000 Population) of Reported HFMD Cases, 2001-2007

| Age group (y) | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 |
|---|---|---|---|---|---|---|---|
| 0 – 4 | 1640.5 (74.5) | 5256.8 (74.7) | 1830.2 (72.3) | 2111.6 (71.1) | 4807.7 (66.7) | 4649.0 (63.1) | 5975.5 (62.2) |
| 5 – 9 | 330.3 (17.0) | 1127.5 (18.5) | 447.1 (20.7) | 541.4 (21.3) | 1485.8 (24.4) | 1474.1 (24.0) | 2140.8 (26.2) |
| 10 – 14 | 47.1 (2.4) | 165.3 (2.8) | 44.7 (2.2) | 70.8 (3.0) | 194.8 (3.5) | 269.5 (4.8) | 347.4 (4.7) |
| 15 – 24 | 13.0 (1.6) | 33.7 (1.3) | 9.0 (1.0) | 13.9 (1.3) | 33.4 (1.4) | 50.8 (2.3) | 58.2 (2.1) |
| 25 – 34 | 15.7 (2.7) | 31.5 (1.7) | 15.5 (2.3) | 14.2 (1.9) | 43.8 (2.5) | 60.8 (3.6) | 60.6 (2.9) |
| 35 – 44 | 10.2 (1.5) | 19.3 (0.9) | 9.6 (1.3) | 9.0 (1.1) | 26.9 (1.3) | 38.0 (1.9) | 43.0 (1.7) |
| 45 – 54 | 2.6 (0.3) | 3.8 (0.1) | 1.8 (0.2) | 1.7 (0.2) | 3.8 (0.2) | 5.7 (0.2) | 4.9 (0.2) |
| 55+ | 0.4 (0.04) | 0.9 (0.03) | 0.3 (0.04) | 1.0 (0.1) | 1.1 (0.05) | 1.9 (0.1) | 1.1 (0.04) |
| Total | 125.5 (100.0) | 388.6 (100.0) | 136.2 (100.0) | 153.9 (100.0) | 357.6 (100.0) | 347.2 (100.0) | 435.9 (100.0) |

Figures in brackets refer to percentage of total cases in the corresponding year.

Table 2. Gender and Ethnic-Specific Incidence Rates (Per 100,000 Population) of Reported HFMD Cases, 2001-2007

| Residents | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 |
|---|---|---|---|---|---|---|---|
| Chinese | | | | | | | |
| Male | 182.5 | 583.8 | 212.4 | 221.1 | 518.2 | 464.1 | 595.2 |
| Female | 129.1 | 393.0 | 124.7 | 162.4 | 391.5 | 360.1 | 453.6 |
| Malay | | | | | | | |
| Male | 136.6 | 578.9 | 166.4 | 209.5 | 439.3 | 549.8 | 733.5 |
| Female | 104.0 | 392.2 | 108.0 | 170.9 | 332.1 | 442.8 | 562.3 |
| Indian | | | | | | | |
| Male | 37.4 | 181.8 | 51.9 | 64.4 | 137.7 | 173.8 | 270.0 |
| Female | 32.4 | 127.3 | 38.1 | 42.1 | 105.3 | 144.0 | 215.3 |
| Others | | | | | | | |
| Male | 316.0 | 1545.8 | 961.4 | 722.8 | 876.9 | 759.7 | 902.9 |
| Female | 230.8 | 810.7 | 585.4 | 419.9 | 619.4 | 535.9 | 723.8 |
| Foreigners | | | | | | | |
| Male | 58.1 | 40.2 | 16.2 | 6.1 | 75.9 | 93.4 | 124.3 |
| Female | 47.6 | 31.3 | 7.9 | 5.2 | 75.4 | 91.2 | 125.1 |
| Total | | | | | | | |
| Male | 142.5 | 454.5 | 167.4 | 174.2 | 399.3 | 383.2 | 476.8 |
| Female | 107.3 | 320.1 | 104.2 | 133.1 | 315.0 | 310.0 | 392.7 |

### *Mortality*

Three HFMD-associated deaths were reported in January and February 2001 when there was no nationwide epidemic of HFMD.[9] The first death involved a 4-year-old Chinese boy who collapsed suddenly at home and died on arrival at the Emergency Department. Postmortem examination showed brainstem encephalitis. EV71 was isolated from the tracheal swab, brain and intestine. The second death was an 11-month-old Malay boy who vomited and suddenly collapsed at home. The main postmortem findings were myocarditis and pneumonitis consistent with a viral aetiology. EV (untypable) was isolated from the intestine. The last fatal case was an 11-month-old Chinese boy whose condition deteriorated rapidly with poor appetite and lethargy. He vomited and developed a fit on the way to hospital. Clinically, he died of pulmonary and cerebral oedema. No postmortem was done. Since then, no further deaths from HFMD had been reported to MOH.

### *Institutional Outbreaks*

The number of institutional HFMD outbreaks reported in childcare centres, kindergartens and schools increased

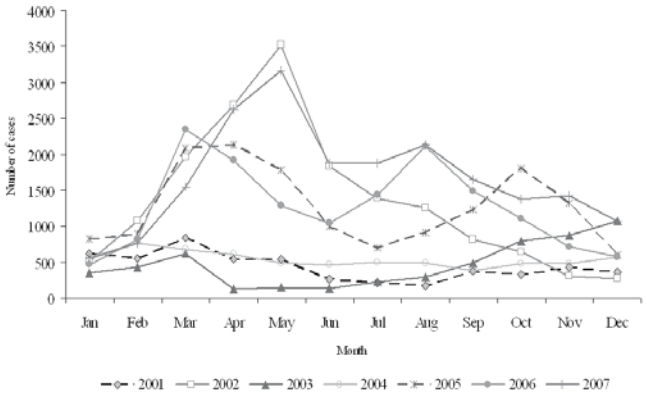


Fig. 1. Monthly distribution of reported cases of HFMD, 2001-2007.

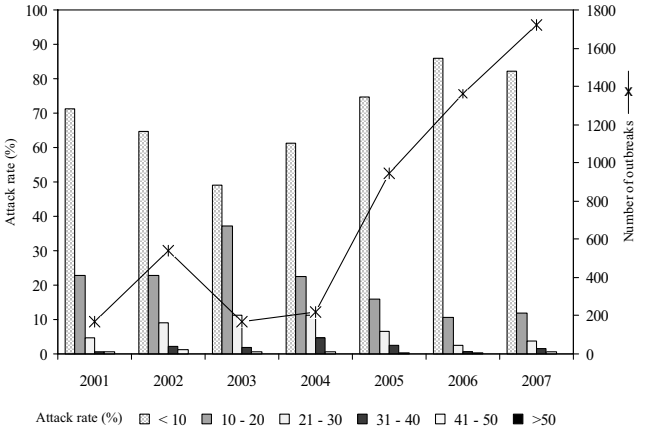


Fig. 2. Institutional outbreaks of HFMD by attack rate (%), 2001-2007.

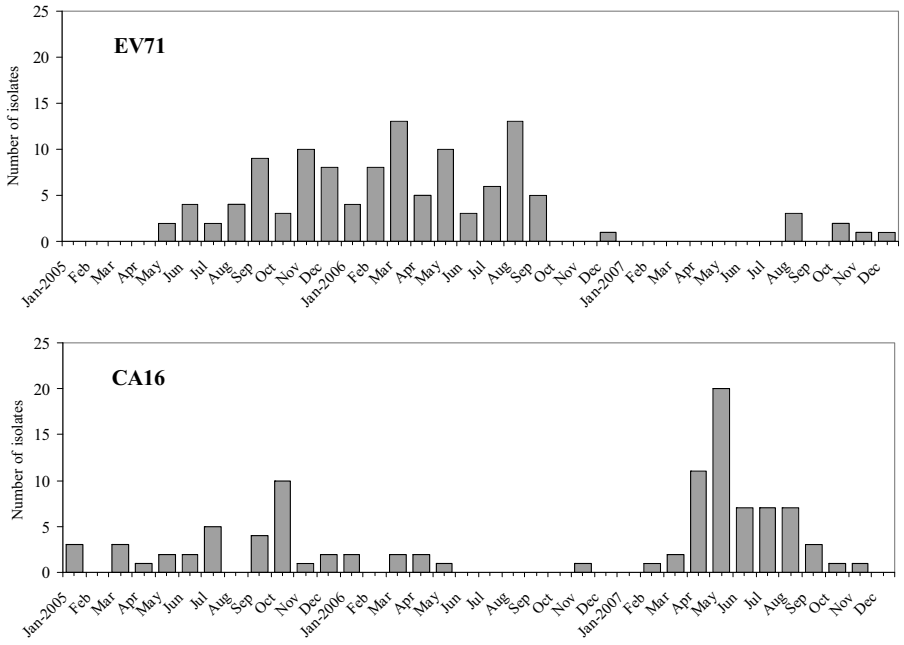


Fig. 3. Monthly isolation/detection of CA16 and EV71, January 2005 to December 2007.

from 167 in 2001 to 539 in 2002, then declined to 169 in 2003, and thereafter increased rapidly to 1723 in 2007 (Fig. 2). Overall, the number of institutional outbreaks increased 10-fold since 2001.

Most of the outbreaks occurred in childcare centres where children aged between 2 and 6 years old congregate (44.8% to 86.4% of the reported cases), followed by kindergartens attended by children aged between 5 and 6 years old (13.0% to 34.1%). While the number of institutional outbreaks had been increasing, the majority had an attack rate of less than 10%.

*Viral Detection*

The majority of the enteroviruses detected from the HFMD cases were CA16 in 2002, 2004 and 2007, while EV71 was predominant in 2001 and 2003 (Table 3). Both CA16 and EV71 were almost equally distributed in 2005, and both CA6 and EV71 were also in almost similar proportions in 2006. In fact, EV71 was detected only in the second half of 2005 and continued into 2006. Other enteroviruses isolated were CA10, CA2, CA4, CA5, CA9, echoviruses, CB3, CB4 and CB5.

Monthly isolation showed that the 2 peaks during the last 3 epidemic years were associated with the same enterovirus; CA16 in 2005 (EV71 came into circulation after the second peak was over), EV71 in 2006 and CA16 in 2007 (Fig. 3).

## Discussion

The 2 main enteroviruses causing nationwide epidemics of HFMD in Singapore were CA16 and EV71. CA16 was the predominant strain circulating during the epidemic in 2002. It re-emerged in 2004 to cause another epidemic in 2005 and 2007. In the case of EV71, although it was the predominant strain detected in 2001, 2003 and 2005/6, it

Table 3. Percent Distribution of Non-polio Enteroviruses Among Positive Isolates from HFMD Cases, 2001-2007

| | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 |
|---|---|---|---|---|---|---|---|
| No. tested | 305 | 255 | 469 | 66 | 183 | 339 | 328 |
| No. positive | 178 | 210 | 50 | 21 | 76 | 145 | 94 |
| Enteroviruses | | | | | | | |
| CA2 | 2.2 | 0.0 | 0.0 | 14.3 | 0.0 | 3.5 | 4.3 |
| CA4 | 10.7 | 0.0 | 6.0 | 4.7 | 0.0 | 2.8 | 0.0 |
| CA5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.7 | 0.0 |
| CA6 | 18.5 | 11.9 | 0.0 | 0.0 | 0.0 | 35.8 | 10.6 |
| CA9 | 0.0 | 0.5 | 0.0 | 0.0 | 0.0 | 1.4 | 0.0 |
| CA10 | 4.5 | 6.7 | 16.0 | 9.5 | 2.6 | 2.8 | 9.6 |
| CA16 | 15.7 | 76.2 | 10.0 | 66.8 | 43.4 | 5.5 | 64.9 |
| CB3, CB4 & CB5 | 0.6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| EV71 | 45.6 | 3.8 | 68.0 | 4.7 | 52.7 | 45.5 | 8.5 |
| Echoviruses | 2.2 | 0.9 | 0.0 | 0.0 | 1.3 | 2.0 | 2.1 |

CA: coxsackie A virus; CB: coxsackie B virus; EV: enterovirus

Table 4. Triggers for Voluntary and Mandatory Closure of Preschools During Epidemic Phase*

| Trigger level | Criteria for trigger | MCYS registered institutions | MOE registered institutions (kindergartens and preschools) | Other non-MCYS/MOE registered institutions |
|---|---|---|---|---|
| 1 | No. of cases ≥2 | MOH to alert institution(s) | | |
| 2 | No. of cases >7 or<br>Attack rate > 9% or<br>Transmission period >9 days | MCYS to conduct field visit and provide feedback to MOH | MOE to conduct field visit and provide feedback to MOH | MOH to conduct field visit |
| 3a | No. of cases >13 or<br>Attack rate >18% or<br>Transmission period >15 days | MOH to conduct investigations and highlight serious hygiene irregularities for actions by NEA | | |
| 3b | Transmission period >15 days | MCYS to implement voluntary closure | MOE to implement voluntary closure | PA/MOH to implement voluntary closure |
| 4 | Transmission period >15 days and<br>(No. of cases >13 or<br>Attack rate >18%) | MCYS to implement mandatory closure | MOE to implement mandatory closure | PA/MOH to implement mandatory closure |

* Revised April 2008

MOH: Ministry of Health; MOE: Ministry of Education; MCYS: Ministry of Community Development Youth and Sports; NEA: National Environment Agency; PA: People's Association

did not cause another epidemic until 2006. A longer time series would be needed to ascertain whether EV71 epidemic occurs on a 2- to 3-year cycle in Singapore. A 2- to 3-year cyclical epidemic of HFMD was noted in the United Kingdom.[10] A 3-year epidemic cycle in 1997, 2000, 2003, and 2006 caused by EV71 with co-circulation of CA16 was observed in Sarawak, Malaysia.[11] In Japan, EV71 re-emerged 3-yearly as the predominant strain after 1994.[12] It is postulated that this cyclical pattern could have been due to the accumulation of immunologically naive preschool children between epidemics until a critical threshold level is breached.[11] Based on a seroepidemiological study on EV71 conducted in 1996/7 at the National University Hospital in Singapore, the infection was largely acquired in the preschool years with an annual infection rate of 12%.[13] The increasing size of the epidemics seen in recent years could be partly attributed to better reporting from preschool centres, as a result of parental concerns and wide media publicity.

The incidence rate of HFMD was highest in preschool children below 5 years of age which comprised 62% to 75% of the reported cases. This is consistent with the findings in other outbreaks.[11,14] Transmission occurred rapidly in preschools with attack rates exceeding 40% in some of the

institutions. There was a male predominance with differences in ethnic-specific incidence rates. The reason for the differences observed in gender and ethnic specific incidence rates is not known.

The number of childcare centres and their capacity has increased over the years. There were 739 childcare centres providing almost 63,000 places as at end 2007, compared to 653 childcare centres providing about 54,000 places in 2003.[15,16] Correspondingly, a larger cohort of 23% of preschool children currently attends childcare centres, up from 16% in 2003. With the emphasis on centre-based care, in the form of infant care, childcare and student care centres as an important continuum of care and development for children, supply and enrollment of childcare centres are expected to rise over the next few years. More children would be congregating in a limited space, which provides a readily available reservoir for rapid circulation of the virus, which could then be transmitted to their families and the rest of the population. Thus, the incidence of HFMD in preschool population is expected to increase further.

Poor feeding and loss of appetite due to mouth ulcers rather than neurological and cardiac complications accounted for admissions to hospital requiring intravenous drip. Of 131 non-fatal cases admitted to KKH during the 2000 epidemic, there were only 2 cases of aseptic meningitis.[17] A higher proportion of children was hospitalised during EV71-associated epidemics of HFMD compared to those due to CA16. In Taiwan, where several enteroviruses have also been circulating in the community, EV71 was found to be more prevalent among the severely ill and hospitalised cases with HFMD.[14,18] In Japan, hospitalised cases also increased when EV71 was the main circulating strain in 2000.[12]

The case fatality rate in 2001 was very low at 0.06% (3/5210 cases) and the 3 deaths in January and February were probably related to the EV71 which caused the 2000 epidemic with 4 deaths between September and October. Based on the genetic sequence of 2 representative EV71 strains isolated from a fatal case and a surviving patient in the 2000 epidemic, the outbreak strains were classified under genogroup B, similar with those previously isolated in Singapore, Malaysia and Japan. It is believed that epidemics of EV71 were caused by closely related genetic variants of the enterovirus giving rise to a wide spectrum of clinical disease severity. There was no evidence to show that these epidemics were due to the emergence of EV71 strains with increased virulence.[19] Another study on molecular epidemiology of EV71 strains isolated during large epidemics in Sarawak, Singapore and Taiwan in 2000 also confirmed that the viruses were from genotype B4.[20]

Although no EV71-associated deaths have been reported since 2001, a high degree of vigilance is maintained on the clinical severity and prevalence of this specific enterovirus through routine laboratory surveillance. MOH together with other relevant agencies have instituted a number of measures to curb the HFMD problem. Public health measures, in particular, personal and environmental hygiene, continue to target childcare centres, kindergartens and preschools where highly susceptible children congregate. These institutions are required to report clusters of 2 or more cases of HFMD and to take appropriate steps to interrupt transmission of infection. Depending on the level of trigger for outbreak management involving cluster notifications, actions taken range from issuing alert letters to the relevant institutions, field investigation including implementation of control measures, to mobilisation of multi-agency efforts to contain further spread. To stem the spread of infection, preschools where transmission persists for more than 2 incubation periods, are recommended for closure with additional trigger criteria for voluntary closure instituted in April 2008 (Table 4). During closure, operators are to thoroughly clean the centres before they are allowed to reopen. In addition, parents are advised to ensure that their children adopt a high standard of personal hygiene and to keep the infected child at home until full recovery.

Despite the stringent measures taken to prevent transmission of HFMD in institutions where young children congregate, outbreaks in these institutions increased 10-fold from 2001 to 2007. However, due to the high degree of vigilance, institutional outbreaks were recognised early and rapidly brought under control with the majority of these outbreaks having an attack rate of less than 10%. Moreover, there had been a significant decline in the proportion of HFMD cases among preschool children aged between 0 and 4 years old over the years compared to older children aged between 5 and 9 years old. This suggests that control measures could have delayed the onset of infection.

The main limitation of the study was the small number of samples tested for enteroviruses. Therefore, virological surveillance data should be interpreted with caution. Moreover, if more EV71 isolated were to be routinely sequenced, we could have a better understanding on the evolution of the virus from one genotype to another and its epidemiological linkage with viruses isolated from other countries in the region.[20] Nevertheless, based on limited data, the predominant EV71 genotype during the 2000 epidemic was B4, and it was B5 during the 2006 epidemic.

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Research is urgently needed to fill these gaps. 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).Â  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. Infectious Diseases of Singapore, 2015. 460 pages, 112 graphs, 1,964 references. Gideon e-books, www.gideononline.com/ebooks/country/singapore/. 3. Gideon graph tool at www.gideononline.com/wp/wp-content/uploads/Gideon-Graphs.pps. Note appears on ProMED. This entry was posted on Friday, March 20th, 2015 at 9:45 pm and is filed under Ebooks, Epidemiology, Graphs, ProMED. You can follow any responses to this entry through the RSS 2.0 feed. Both comments and pings are currently closed. Hand, foot and mouth disease (HFMD) is a common childhood viral infection, which is typically mild and self-limiting. It is characterised by a brief prodromal fever, followed by pharyngitis, mouth ulcers and rash on the hands and feet. The disease is caused by numerous members of the Enterovirus genus of the family Picornaviridae e.g. Coxsackievirus type A (CA) and Enterovirus 71 (EV71), and the clinical features are indistinguishable. Transmission occurs from person to person through direct contact with saliva, faeces, vesicular fluid or respiratory droplets of an infected person and indirect...