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# An Outbreak of Acute Haemorrhagic Conjunctivitis in Melaka, Malaysia

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## ABSTRACT

**This paper reports a second outbreak of acute haemorrhagic conjunctivitis due to coxsackievirus A24 in peninsular Malaysia. Between June 2002 and early October 2003, 10,327 patients, comprising 3,261 children and 7,066 adults, were treated for acute conjunctivitis in 11 government health clinics in the Melaka Tengah district of the state of Melaka. The figure grossly underestimates the size of the outbreak; as no patients treated in private clinics in the same district were included.**

**Institution and household surveillance showed that the commonest presenting clinical feature of the illness was eye-discharge (91.2%), followed by foreign body sensation (81.8%), pain (78.3%) and subconjunctival haemorrhage (74.4%). The mean duration of illness was 6.5 and five days for patients with and without subconjunctival haemorrhage respectively.**

**Keywords: epidemic, conjunctivitis, coxsackievirus A24**

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## INTRODUCTION

Acute haemorrhagic conjunctivitis is an epidemic viral infection of the eyes that was first recognised in Ghana, West Africa, in 1969[1,2]. It was nicknamed as "Apollo 11" disease because this illness emerged at the time of the Apollo 11 moon landing. In West Africa, the disease is still referred to as "Apollo conjunctivitis". Acute haemorrhagic conjunctivitis is characterised by an abrupt onset of ocular pain, swelling of the eyelids, a foreign body sensation or irritation, epiphora (excessive tearing), eye discharge and photophobia[3-7]. A palpebral conjunctival follicular reaction, subconjunctival haemorrhage and congestion are commonly present. The infection is highly contagious and frequently both eyes are involved. Typically, the signs and symptoms follow an incubation period of 24 to 48 hours and persist for three to seven days before resolving spontaneously[5,6].

Epidemics of acute haemorrhagic conjunctivitis have been most commonly caused by enterovirus 70, coxsackievirus A24 variant and less commonly by adenovirus 11[5]. Acute haemorrhagic conjunctivitis due to enterovirus 70 was first reported in 1969 from Western Africa[1,2]. From 1969 to 1972, the disease spread as a pandemic from Ghana across tropical and subtropical western and central Africa to the Middle East and other parts of Asia[3,7,8]. The disease was first reported in the Western Hemisphere in 1981 when the pandemic that originated in Kenya in 1980 reached South America, Central America, the Caribbean islands and the United States of America[6-9]. On the other hand, the first isolate of coxsackievirus A24 variant causing acute haemorrhagic conjunctivitis was obtained during an outbreak in Singapore in 1970[10,11], and had not been isolated outside Southeast Asia and the Indian subcontinent until 1986 when an outbreak was reported in American Samoa and subsequently spread to the Caribbean islands and other parts of America[12-20]. The coxsackievirus A24 variant was implicated in four of six major acute haemorrhagic conjunctivitis outbreaks in Singapore since its discovery in 1970 till 1993[21,22]. In Malaysia, the first report of outbreak of acute conjunctivitis caused by coxsackievirus A24 was in 1978 where 2,133 patients were infected[23]. This is a report of another outbreak of acute haemorrhagic conjunctivitis caused by CA24 in peninsular Malaysia.

## MATERIALS AND METHODS

### Background

Patients who attended all government outpatient polyclinics in the Melaka Tengah district of Melaka, peninsular Malaysia, for complaints of acute conjunctivitis from 6 June 2002 to 17 October 2002 were examined and recorded. Relevant epidemiological data of the patients such as age, gender, ethnic group, date of symptoms and residential addresses were also obtained.

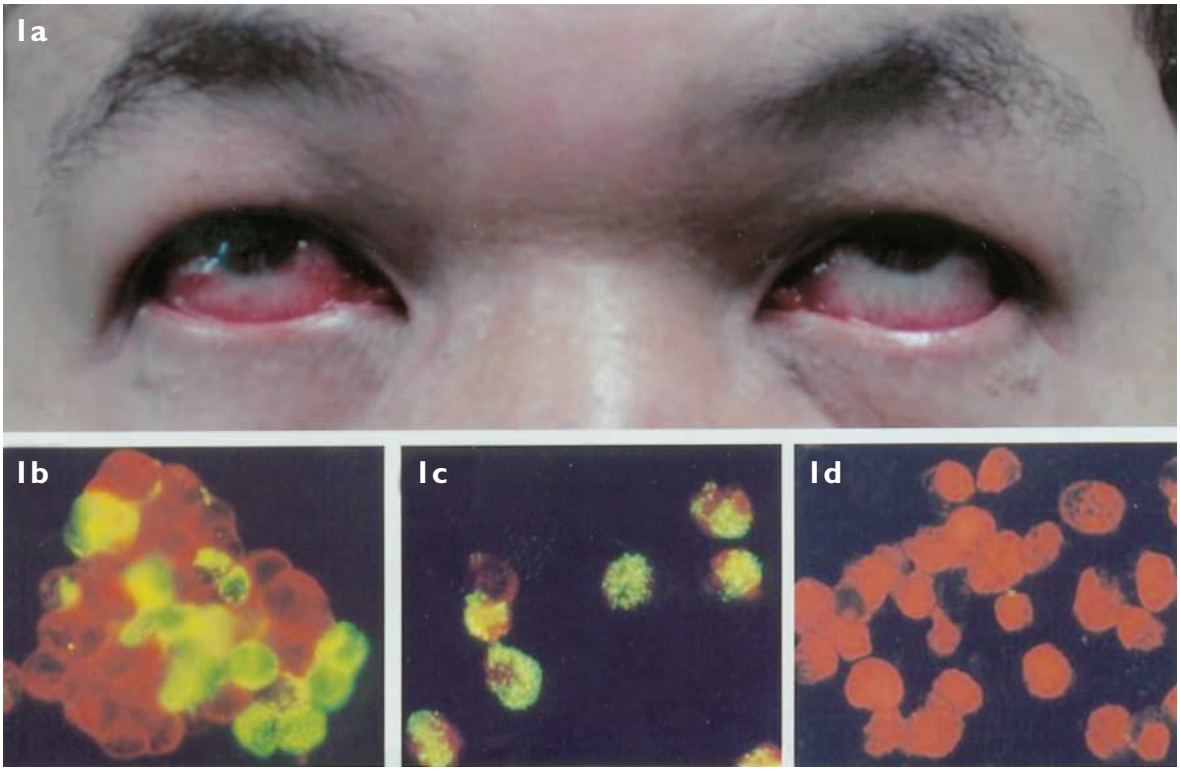


**Fig. 1** A composite photograph showing acute haemorrhagic conjunctivitis (a), Hep-2 cells infected with the isolated virus from patients with acute haemorrhagic conjunctivitis giving positive immunofluorescence staining with pen-entero blend monoclonal antibody (b), echovirus blend monoclonal antibody (c) but negarive with enterovirus blend monoclonal antibody (d).

**Virus isolation and identification**

Sterile cotton swabs were used to soak up the tears and eye discharges and immediately individually broken off into 2 ml of viral transport medium (VTM) [1X Hank's balanced salt solution (ICN Biomedicals, Inc., USA) containing 1% bovine albumin hydrolysate, penicillin G (100 units/ml) and streptomycin (50 µg/ml), pH 7.4] in a Bijou bottle. The inoculated VTM was kept cold by placing it in an Esky box containing frozen ice-packs and transported to the laboratory in Kuala Lumpur for virus isolation.

In the laboratory, three types of tissue culture cell-lines, namely RD (a clone line of a human rhabdomyosarcome cell-line), Hep-2 (a human laryngeal carcinoma cell-line), and A549 (a human colonic adenocarcinoma cell-line) were used for virus isolation. The eye-swab in VTM inside each Bijou bottle was lightly vortexed and 200 µl of the VTM was each separately inoculated into three different wells of a 24-well flat-bottom tissue culture plate. Each separate well contained a suspension of 1 x $10^5$ cells of the respective cell-type in a mililitre of Dulbelcco modified Eagle essential medium supplemented with 10% foetal calf serum, 100 units/ml of penicillin and 50 µg/ml of streptomycin. The 24-well culture plates were incubated in a 37ºC incubator with 5% $C0_2$ and examined daily for cytopathogenic effects (CPE) over a period of nine to 10 days. Each CPE-negative specimen was "blindly" passaged once before they were discarded as virus negative.

Virus isolates were preliminarily identified by indirect immunoflourescence test on the infected cells using commercial enterovirus and adenovirus typing monoclonal antibodies (Chemicon, USA). The virus isolate was identified as enterovirus by reverse transcriptase-polymerase chain reaction (RT-PCR) amplification of a 500 base pairs fragment of the viral 5'-untranslated region using the primer pair; 5'-GTAMCYTTGTRCGCCWGTTT-3', 5'-GAAACACGGACACCCAAA-3' followed by nucleotide sequencing and sequence analysis of the amplified product[24,25]. The final identity of the virus isolate type was confirmed by a similar process of RT-PCR amplification of the 5'-half of the viral VP1 gene using the primer pair; 5'-ACIGCIGTIGARACIGGNG-3' (188), 5'-CICCIGGIGGIAYRWACAT-3' (222)[26].

**Epidemiological Survey**

An epidemiological survey was carried by public health officers of the Melaka Tengah district in late August 2002, to study the characteristic features of the outbreak on 16 families and two schools; SMMS (Sekolah Menengah Muzaffar Shah) and SMSM (Sekolah Menengah Sultan Muhammad) in the Melaka Tengah district of Melaka. The two schools

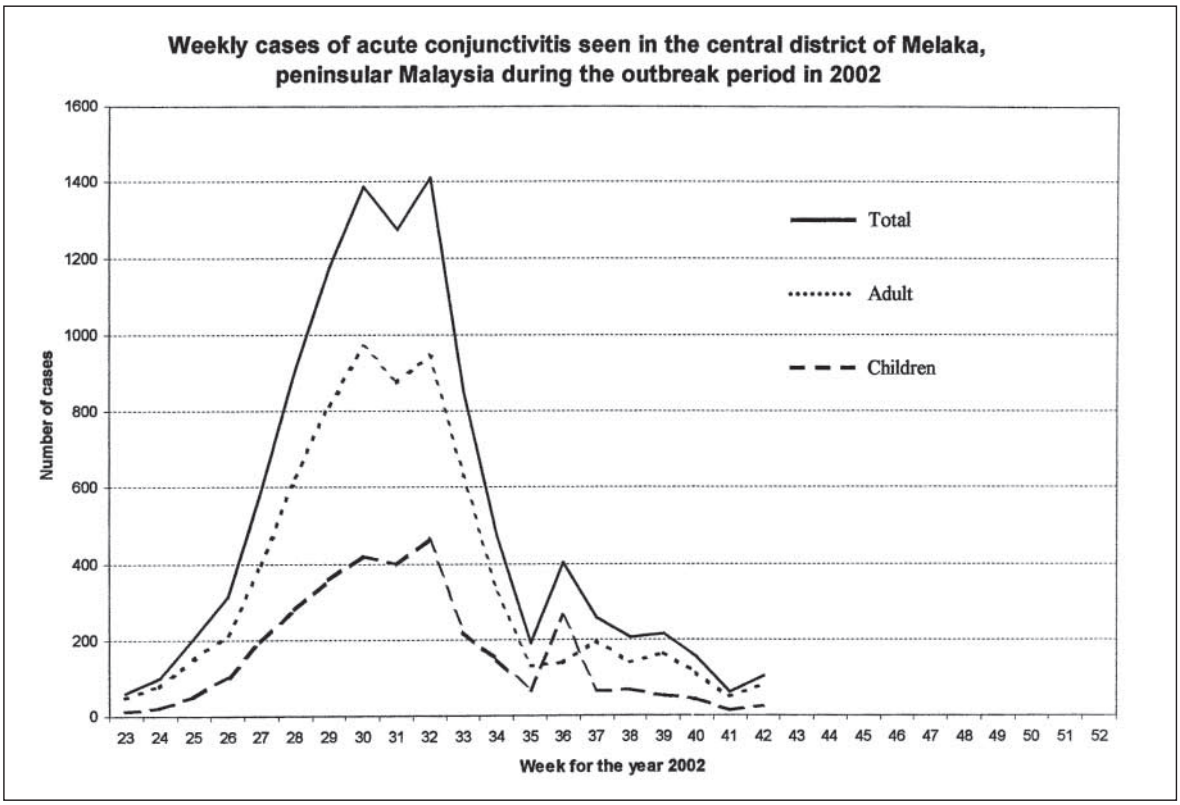


**Fig. 2** Weekly cases of acute conjunctivitis seen in the central distral district of Melaka, peninsular Malaysia during the outbreak period in the year 2002.

were chosen because both were residential schools with excessive cases of acute conjunctivitis treated in the government outpatient polyclinics during the period. Face-to-face interview was carried out with every student in each school and filled-in questionnaires were used to collect data on the clinical features of the illnesss (such as foreign body sensation, pain, photophobia, haemorrhage, eyelid swelling, eye discharge, fever and headache). Relevant epidemiological characteristics such as age, gender, racial group, family size, history of contact, date of onset and date of recovery from the illness were also obtained during the interview.

### Statistical analysis

Statistical analysis was performed using the Epi Info 6, a word processing, database and statistical programme for public health, Center of Disease Control and Prevention (CDC), Atlanta, USA. The results of the study were subjected to chi-square test and student's t-test for any statistical significant association. A p-value of 0.05 or less was taken as the level of significant association for each ordinal variable with the relevant adjusting variables.

## RESULTS

Melaka is one of the 14 states of Malaysia, situated in the central western part of peninsular Malaysia. The state is divided into three districts (Melaka Tengah, Jasin and Alor Gajah) and the Melaka Tengah district is the most populous district among the three and contains the state capital, the city of Melaka. There are 11 government health clinics providing outpatient health services in the central district. From 6 June 2002 to 17 October 2002 (20 weeks) a total of 10,327 patients, comprising 3,261 children and 7,066 adults, were treated for acute (with and without haemorrhage) conjunctivitis (Fig. 1a). The distribution of the number of cases of acute conjunctivitis in each week from week 23 to week 42 of the year 2002 is shown in Fig. 2. The outbreak was characterised by a huge peak reaching its maximum number of cases per week within six weeks of onset and a second small peak of shorter duration at 13 weeks after its onset.

During the outbreak, 86 eye-swab samples from 86 patients with acute conjunctivitis seen in the outpatient health clinics were collected for virus isolation. Sixty-one virus isolates causing cytopathic effect (CPE) in tissue culture cells were obtained. Two of the isolates reacting positively with anti-adenovirus monoclonal antibodies (Chemicon, 5,000) were isolated in A549 cell-line and 59 of the isolates from Hep-2 cells strongly with pan-entero blend monoclonal antibodies (Fig. 1b) and echovirus blend monoclonal antibodies (Fig. 1c) (Chemicon, 3,360, 3,311) but were non-reactive with enterovirus blend

**Table I. Distribution of cases of acute conjunctivitis and attack rates with respective to gender in various categories.**

| Category | SMMS school | | | SMSM school | | | Family | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | @No. | *Cases | ^A.R. | @No. | *Cases | ^A.R. | @No. | *Cases | ^A.R. | @No. | *Cases | ^A.R. |
| Gender | | | | | | | | | | | | |
| Male | 231 | 93 | 40.3 | 484 | 247 | 51.0 | 48 | 38 | 79.2 | 763 | 378 | 49.5 |
| Female | 150 | 48 | 32.0 | | | | 39 | 31 | 79.5 | 189 | 79 | 41.8 |
| Total | 381 | 141 | 37.0 | 484 | 247 | 51.0 | 87 | 69 | 79.3 | 952 | 457 | 48.0 |
| Statistical test | | | | | | $\chi 2 = 36.23$, $p<0.0001$ | | | | | | |

@No. = Number of people surveyed.
*Cases = Number of cases of acute conjunctivitis.
^A.R. = Attack rate in percent.

**Table II. Distribution of patients with acute conjunctivitis in each category with respect to the presence of various clinical features.**

| Category | SMMS *(141) | | SMSM (247) | | Family (69) | | Total (457) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable | Presence | Absence | Presence | Absence | Presence | Absence | Presence(%) | Absence | $\chi 2$ | p-value |
| Eye-discharge | 124 | 17 | 228 | 19 | 65 | 4 | 417 (91.2) | 40 | 3.03 | 0.1494 |
| Irritation | 110 | 31 | 203 | 44 | 61 | 8 | 374 (81.8) | 83 | 3.41 | 0.1818 |
| Pain | 112 | 29 | 192 | 55 | 54 | 15 | 358 (78.3) | 99 | 0.15 | 0.9263 |
| Haemorrhage | 98 | 43 | 193 | 54 | 49 | 20 | 340 (74.4) | 117 | 4.00 | 0.1352 |
| Swelling (eyelid) | 85 | 56 | 168 | 79 | 51 | 18 | 304 (66.5) | 153 | 4.40 | 0.1106 |
| Photophobia | 61 | 80 | 99 | 148 | 34 | 35 | 194 (42.5) | 263 | 1.92 | 0.3826 |
| Headache | 55 | 86 | 110 | 137 | 24 | 45 | 189 (41.4) | 268 | 3.75 | 0.1531 |
| Fever | 51 | 90 | 70 | 177 | 17 | 52 | 138 (30.2) | 319 | 3.80 | 0.1494 |
| History of contact | 92 | 49 | 209 | 38 | 68 | 1 | 369 (80.7) | 88 | | |

*(.....) = Number of cases of acute conjunctivitis.

**Table III. Duration of recovery in patients with acute conjunctivitis with respect to the presence or absence of subconjunctival haemorrhage in various categories.**

| Category | SMMS | | SMSM | | Family | | Total | |
|---|---|---|---|---|---|---|---|---|
| Days | Haemorrhage | | Haemorrhage | | Haemorrhage | | Haemorrhage | |
| of illness | *Presence | ^Absence | Presence | Absence | Presence | Absence | Presence(%) | Absence |
| 2 | | 1 | | | | 1 | | 2 |
| 3 | 8 | 7 | 16 | 3 | 1 | 8 | 25 | 18 |
| 4 | 12 | 10 | 26 | 9 | 9 | 5 | 47 | 24 |
| 5 | 23 | 6 | 44 | 28 | 9 | 4 | 76 | 38 |
| 6 | 13 | 10 | 35 | 8 | 6 | 1 | 54 | 19 |
| 7 | 10 | 4 | 24 | 3 | 9 | 1 | 43 | 8 |
| 8 | 14 | 2 | 21 | 2 | 5 | | 40 | 4 |
| 9 | 4 | 1 | 7 | 1 | 2 | | 13 | 2 |
| 10 | 4 | 2 | 6 | | 2 | | 12 | 2 |
| 11 | 5 | | 9 | | 3 | | 17 | |
| 12 | 3 | | 1 | | 2 | | 6 | |
| 13 | | | 1 | | | | 1 | |
| 14 | 1 | | 1 | | 1 | | 3 | |
| 15 | | | 2 | | | | 2 | |
| 16 | | | 1 | | | | 1 | |
| 17 | 1 | | | | | | 1 | |
| Total | 98 | 43 | 193 | 54 | 49 | 20 | 340 | 117 |
| #Mean | 6.6 | 5.3 | 6.3 | 5.2 | 6.8 | 4.0 | 6.4 | 5.0 |

*Presence = Number of patients with acute conjunctivitis with subconjunctival haemorrhage.
^Absence = Number of patients with acute conjunctivitis without subconjunctival haemorrhage.
#Mean = Mean duration of illness in days.

monoclonal antibodies (Chemicon, 3,321) (Fig. 1d) that covered enterovirus 70 and enterovirus 71. Analysis of the 500-bp non-translated nucleotide sequence derived from the PCR-amplified products confirmed that the identity of the 59 viral isolates belonged to the same type of enterovirus. Sequence analysis of their 5'-half of the VPI gene confirmed the enterovirus isolated as coxsackievirus A24 (CA24). Coxsackievirus A24 were also isolated in Hep-2 cells from the two eye-swab samples containing adenovirus isolates in A549 cells. Hep-2 cell-line was a better cell-line for the isolation of CA24 in this study though a similar virus was also isolated in some RD cells.

In studying the characteristic features of the outbreak, three categories of populations were selected, consisting of two schools and a family group of 16 families. Both schools chosen for the surveillance study were boarding schools: one with both male and female (SMMS) while the other had only male students (SMSM). The mean age of the study populations in the SMMS school, SMSM school and the family group was 14.5 years (range 12-17, SD 1.24), 14.3 years (range 12-17, SD 1.27) and 23.8 years (range 1-63, SD 17.02) respectively. The mean age of patients with acute conjunctivitis in the respective schools and family group was 14.2 years (range 12-17, SD 1.34), 14.0 years (range 12-17, SD 1.10) and 20.4 years (range 1-58, SD 15.49) respectively. Table I shows the distribution of cases of acute conjunctivitis and attack rates with respect to gender in each group. The attack rate of acute conjunctivitis was higher in the all-male school (SMSM, 51.0%) than the mixed gender school (SMMS, 37.0%). However, the highest attack rate was noted in the family group (79.3%). There was a significant difference in the attack rates between the two schools($\chi^2$ = 16.39, p = 0.0001) and between the schools and the family group ($\chi^2$ = 36.23, p<0.0001). However, there was no significant gender difference in the attack rates in both the family group ($\chi^2$ = 0.05, p=0.8186) and the SMMS school ($\chi^2$ = 2.32, p=0.1278). The family group consisted of 16 families; six families had a family size of four members or less, five families with a family size of five peoples and the rest had a family size of six people or above. The attack rates with respect to different family sizes were 71.5%, 80.0% and 82.0% respectively. There was no significant difference in the attack rate with respect to size of the family ($\chi^2$ = 1.13, df = 2, p=0.5686).

Table II shows the distribution of the clinical features of the illness in each category of population group. Overall, the commonest presenting clinical feature was eye-discharge (91.2%), followed by foreign body sensation (81.8%), pain (78.3%), and subconjunctival haemorrhage (74.4%). About 41% pf patients presented with headache and 30% presented with the constitutional symptom of fever. More than 80% of the patients gave a history of contact with people of similar illness. There was no significant difference in the presenting features of the illness between the various categories of selected population groups (Table II).

Table III shows the duration of illness with respect to the presence of subconjunctival haemorrhage in each group. Overall, the mean duration of illnes for patients without subconjunctival haemorrhage was five days (range 2 to 10, SD 2.69) and the mean duration of illness for patients with subconjunctival haemorrhage was 6.5 days (range 3 to 17, SD 2.51). Statistically, there was no significant difference in the duration of illness with respect to the presence or absence of subconjunctival haemorrhage (t-test, p=0.4920).

## DISCUSSION

Acute haemorrhagic conjunctivitis is clinically characterised by a sudden onset of bilateral conjunctival injection, irritation, epiphora, ocular pain, eye-lid oedema, eye discharge and subconjunctival haemorrhage in varying degrees of severity[5,6]. The disease was highly contagious and spread rapidly among close contacts[5,6]. Enterovirus 70 and CA24 were the main causative agents responsible for such epidemics though adenovirus was implicated for a couple of smaller outbreaks[5-7]. In this outbreak of acute haemorrhagic conjunctivitis in Melaka, peninsular Malaysia, CA24 was identified as the aetiological agent responsible for the epidemic though two isolates of adenovirus were isolated. though the data presented here described the outbreak that occurred in the Melaka Tengah district of the state of Melaka, the disease subsequently spread to other parts of the state. We had also isolated similar virus from patients with acute conjunctivitis from other states of peninsular Malaysia (unpublished data).

This is the second outbreak report of acute conjunctivitis due to CA24, the first report being in 1978 by Tan et al[23]. However, this may not represent the true number of epidemics of CA24 acute conjunctivitis that had occurred in Malaysia, since for a similar time period, four epidemics of acute conjunctivitis due to CA24 had been described in Singapore, which is a close neighbour[21,22]. Furthermore, the number of case of acute conjunctivitis reported in this study probably grossly under – estimated the actual number of cases since patients treated in the private medical clinics were not included.

In comparison with the first outbreak, the results of this study confirmed that most patients presented

with bilateral eye involvement (80.1% vs 86.7%) with eye discharge (90.0% vs 91.2%) as the commonest presenting clinical feature of the illness. However, a higher percentage of patients in this study presented with subconjunctival haemorrhage took a longer duration to recover. Unlike the findings in the first epidemic, in which pain was inconspicuous, a higher proportion of patients in this study complained of pain (78.3%) and photophobia (42.5%). Similarly, a fairly high proportion of patients developed constitutional symptoms such headache and fever. As with the finding reported in the first outbreak, up to date, all patients recovered fully without any complication including neutological complication.

Data from this epidemiological surveillance showed that there were more males than females being affected with acute conjunctivitis in both the SMMS school and family group, with a male-to-female ratio of 1.9:1 (93/48) and 1.2:1 (38/31) respectively. This finding is in concordance with the results reported in the first epidemic in Malaysia and other studies[10,12,22,23]. However, there was no significant difference in the attack rates with respect to gender in both the school and family groups presented earlier (Table I), which is compatible with a finding by Sawyer et al in an epidemic of acute haemorrhagic conjunctivitis in American Samoa[15]. The increase in the male-to-female ratio in this study was probably due to the unintentional inclusion of more males than females in the studied populations (Table I). On the other hand, a significantly higher attack rate was noted in the family group compared to students in the boarding school. This is probably due to a closer and longer duration of contact among members in the family.

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