

# Emergence of Cytomegalovirus Mononucleosis Syndrome Among Young Adults in Hong Kong Linked to Falling Seroprevalence: Results of a 14-Year Seroepidemiological Study

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**Background.** Cytomegalovirus (CMV) mononucleosis is a manifestation of primary CMV infection. This study aims to establish the link between long-term population CMV seroepidemiological trends and incidence of CMV mononucleosis requiring hospitalization. Furthermore, by analyzing serial laboratory data of patients hospitalized with CMV mononucleosis, we aim to provide insights into the natural history of this syndrome.

**Methods.** We conducted a 14-year observational study in a tertiary hospital in Hong Kong. Cytomegalovirus immunoglobulin G data of 2349 adults were analyzed for trends in CMV susceptibility during the study period. The clinical features, risk factors, antiviral treatment data, and laboratory findings of 25 adult patients presenting with CMV mononucleosis during this period were retrieved.

**Results.** Susceptibility to CMV infection among the adult population aged 18–45 in Hong Kong increased from 14.5% in 2004 to 32.2% in 2012–2017 ( $P < .001$ ), and this led to doubling of observed CMV mononucleosis incidence among inpatients in our center during the study period. All patients with CMV mononucleosis were hospitalized for investigation of fever of unknown origin. Household contact with young children was the most common risk factor followed by recent overseas travel. Derangement of liver function tests was universally observed and was more severe than in previously published western CMV mononucleosis patient cohorts. Most patients showed clinical improvement within the third week of illness.

**Conclusions.** We conclude that increasing CMV susceptibility among young adults in Hong Kong has resulted in a rising observed incidence of CMV mononucleosis, which is typically a self-limited illness characterized by anicteric hepatitis.

**Keywords.** cytomegalovirus; hepatitis; seroepidemiological study.

Cytomegalovirus (CMV) is an enveloped double-stranded deoxyribonucleic acid (DNA) virus that, like other herpesviruses, establishes life-long latency after primary infection. Most morbidity attributed to CMV is due to reactivation of the virus in immunocompromised patients [1]. Primary infection in early childhood, which is ubiquitous in many Asian countries, is often asymptomatic. However, primarily infected adults may present with CMV mononucleosis syndrome: a syndrome complex of prolonged febrile illness, sore throat, cervical lymphadenopathy, atypical lymphocytosis, and anicteric hepatitis [2].

The objective of this study was to analyze seroepidemiological trends in CMV susceptibility among adults in Hong Kong over a 14-year period and to test the public health significance of such trends by linking long-term CMV seroprevalence shifts to incidence of CMV mononucleosis among adults at our center. Because the natural history of CMV mononucleosis is poorly defined, we also aim to fill in knowledge gaps regarding the clinical course, liver function test (LFT), and viral load kinetics of CMV mononucleosis by analysis of CMV mononucleosis patients seen during the study period.

## MATERIALS AND METHODS

### Study Design

#### *Cytomegalovirus Seroprevalence Study*

This retrospective observational study was conducted in Queen Mary Hospital, a 1700-bed tertiary referral hospital offering transplantation services in Hong Kong. For CMV seroprevalence analysis, data of 4047 patients with CMV immunoglobulin (Ig)G testing performed by the microbiology laboratory at Queen Mary Hospital between the years 2004 and 2017 were retrieved from the laboratory information

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system. Individuals tested were immunocompetent potential organ donors, solid organ transplant recipients, or patients planning to receive immunosuppressive therapy. After exclusion of patients younger than 18 years of age and patients with equivocal CMV IgG results, a total of 2349 individual patients were included in the seroprevalence analysis. These patients were divided into 4 groups based on the year of testing (Figure 1). Group A comprised 524 patients sending serum in 2004, group B comprised 834 patients sending serum in 2005 and 2006, group C consisted of 457 patients sending serum between 2007 and 2011, and group D consisted of 534 patients sending serum between 2012 and 2017. Because more samples were received annually between 2004 and 2006 compared with the latter part of the study due to logistics reasons, division into these 4 groups was performed to ensure that the groups were as congruent as possible in terms of size, average age, and gender distribution for subsequent analysis of CMV susceptibility. There was no significant difference in the population being tested or indications for CMV IgG testing during the study period. Patients were defined as being CMV susceptible if they were CMV IgG negative.

#### Cytomegalovirus Mononucleosis Study

For the analysis of CMV mononucleosis incidence, adult patients admitted between September 16, 2004 and September 15, 2017 with CMV mononucleosis were included in this study. Patients were diagnosed to have CMV mononucleosis if they fulfilled all of the 6 clinical and virological criteria listed in Table 1. The virological criteria used for diagnosis of CMV infection were as per the UK Standards for Microbiological

Investigations for CMV serology in immunocompetent hosts [3]. Patients with risk factors for latent CMV reactivation such as critical illness, underlying malignancy, autoimmune disease, human immunodeficiency virus (HIV) infection, and intake of immunosuppressants including corticosteroids were excluded from the study. Clinical details of patients were retrieved from the electronic patient record and patient charts. This study was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster.

#### Serological Testing

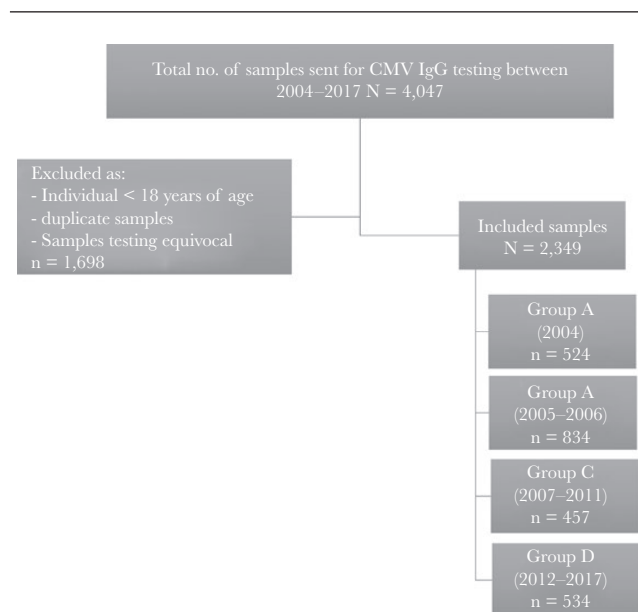
Serum samples from patients were tested for CMV IgM using the VIDAS CMV IgM assay (bioMérieux, Marcy-l'Étoile, France). Serum testing for CMV IgG was done using the Abbott ARCHITECT chemiluminescent enzymatic immunoassay system (Abbott, Chicago, IL). Serological testing for Epstein-Barr virus (EBV) was performed by testing for IgM antibodies against the viral capsid antigen using a commercial enzymatic immunoassay (Shenzhen YHLO Biotech Co., Ltd., Shenzhen, China). Antibodies against HIV were tested using the VIDAS Duo Ultra fourth-generation assay (bioMérieux), which is capable of detecting both HIV p24 antigen, antibodies against HIV-1 groups M and O, and antibodies against HIV-2.

#### Cytomegalovirus pp65 Antigenemia Assay

Quantitative detection of CMV in blood was performed using a standard CMV pp65 antigenemia assay as described previously [1, 4]. This assay has been shown to have excellent sensitivity for the diagnosis of primary CMV infection [5]. In brief, a preparation of  $2 \times 10^5$  polymorphonuclear cells from patients' whole blood sample were concentrated onto a glass slide by cytocentrifugation. The cells were then fixed with formaldehyde and stained with an antibody against the CMV pp65 matrix protein antigen, which is expressed inside the nuclei of abortively infected polymorphonuclear cells. After a rinsing step, the slide was stained with a secondary fluorophore-labeled antibody and then washed again. The slide was then examined using a fluorescent microscope, and the number of polymorphonuclear cells with nuclear immunofluorescence staining was counted manually. The result was reported as number of positive cells per  $2 \times 10^5$  polymorphonuclear cells.

#### Cytomegalovirus Polymerase Chain Reaction

Patients who were suspected to have CMV mononucleosis were tested using CMV polymerase chain reaction (PCR) if specimen quantity or quality was not suitable for antigenemia assessment. In brief, DNA was extracted from ethylenediaminetetraacetic acid-treated whole blood using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) and subjected to CMV-specific PCR. Before February 2014, a nested conventional CMV PCR assay targeting the CMV morphological transforming region II gene was used [6]. From February 2014 onwards, this assay was replaced by an in-house developed quantitative real-time PCR assay targeting the UL111A gene using primers



**Figure 1.** Flowchart showing details of recruitment, application of exclusion criteria, and division of study population into 4 groups. CMV, cytomegalovirus; IgG, immunoglobulin G.

**Table 1. Diagnostic Criteria for Cytomegalovirus Mononucleosis**

Clinical and Hematological Criteria (All of the Following)
1. Immunocompetent patients aged >18 years
2. Presenting with febrile illness
3. Peripheral blood smear showing at least one of the following reactive changes suggestive of infectious mononucleosis-like syndrome:
a) >5 atypical lymphocytes per 100 lymphocytes in blood, and/or
b) Lymphocytosis >50% of total white blood cell count
Virological Criteria (All of the Following)
1. Detection of CMV-specific IgM antibodies in serum
2. Detection of CMV in blood by CMV pp65 antigen or CMV PCR assay
3. No evidence of other causes of infectious mononucleosis such as primary EBV or HIV infection

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; Ig, immunoglobulin; PCR, polymerase chain reaction.

(CMV63F: 5'-GATAAAGAATACAAAGCCGCAGTGT-3'; CMV134R: 5'-AAGGTGACGCGGAGATCTTG-3') and probe (FAM 5'-TCCRGAGGAYTACGCGASCAGATTG-3' BHQ1).

**Statistical Analysis**

Linear and multiple regression analyses were performed using the Microsoft Excel Analysis ToolPak. The  $\chi^2$  tests of independence, goodness-of-fit, and Welch's analysis of variance (ANOVA) test were performed using Microsoft Excel add-ons.

**RESULTS**

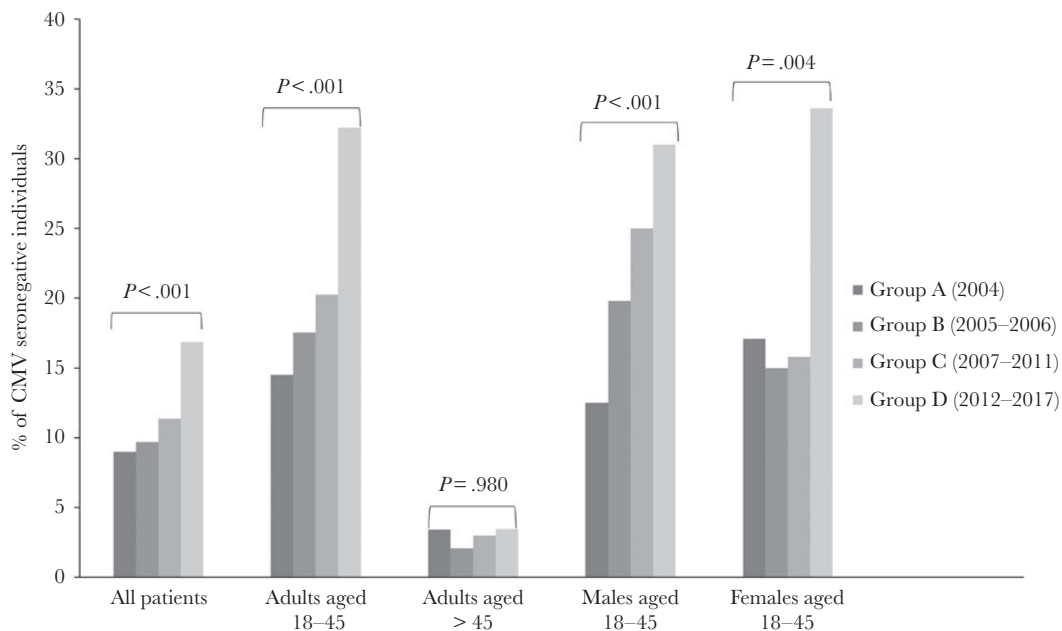
**Cytomegalovirus Seroepidemiology and Incidence of Mononucleosis-Hepatitis Syndrome**

The mean age of patients was 44.67 in group A, 44.33 in group B, 44.20 in group C, and 46.08 in group D. The population mean ages were not statistically different by Welch's ANOVA

test ( $P = .070$ ). The female/male ratio was 0.63 in group A, 0.64 in group B, 0.79 in group C, and 0.68 in group D; differences were not statistically significant ( $P = .264$ ).

Cytomegalovirus IgG-negative patients accounted for 8.97% (47 of 524) of group A patients, 9.69% (81 of 836) of group B patients, 11.38% (52 of 457) of group C patients, and 16.85% (90 of 534) of group D patients showing a stepwise increase over time (Figure 2). The difference in CMV susceptibility between groups A and D was statistically significant ( $P < .001$  by  $\chi^2$  test). Cytomegalovirus susceptibility in the young adult population (18–45 years old) was further examined. Cytomegalovirus susceptibility was 14.56% (38 of 261) among young adults in group A, 17.54% (70 of 399) in group B, 20.23% (45 of 222) in group C, and 32.24% (79 of 245) in group D. The difference in CMV susceptibility was significantly different among young adults in groups A and D ( $P < .001$ ). In contrast, CMV susceptibility did not increase among adults aged older than 45 years old across the study period. Among adult males aged 18–45 years old, susceptibility rose from 12.50% (18 of 144) in group A to 31.00% (40 of 129) in group D ( $P < .001$ ). Likewise, for women aged 18–45 years old, susceptibility rose from 17.09% (20 of 117) in group A to 33.62% (39 of 116) in group D ( $P = .004$ ).

For analysis of CMV mononucleosis incidence, we divided the 12 complete years of the study (2005–2016) into 4 blocks. We found that the incidence rate of CMV mononucleosis was 9.54 per million patient discharges for the period 2005–2007, 8.51 per million patient discharges for the period 2008–2010, 12.42 per million patient discharges for the period 2011–2013, and 19.52 per million patient discharges for the period 2014–2016.



**Figure 2.** Cytomegalovirus (CMV) susceptibility among the adult population of Hong Kong. "P" indicates P value calculated using the  $\chi^2$  test; all P values are calculated between group A and group D.

Cytomegalovirus IgG susceptibility in the young adult population (18–45 years old) was again examined in these 4 blocks. Susceptibility rose from 12.5% (93 of 743) in 2005–2007 to 21.18% (18 of 85) in 2008–2010 to 31.78% (34 of 107) in 2011–2013. Susceptibility remained static at 31.91% (45 of 141) for the period 2014–2016. Figure 3 shows the trend of CMV mononucleosis incidence and increasing CMV susceptibility among the young adult population during each period.

#### Patient Characteristics

During the study period, 25 patients fulfilled the study inclusion criteria for confirmed CMV mononucleosis (Table 1). Their median age was 32 years (interquartile range, 28.5–39). The oldest individual was 61 years of age. Eighty percent (20 of 25) of the patients were male. All patients were of Chinese ethnicity and residents of Hong Kong.

Clinical characteristics of the cohort are described in Table 2, whereas individual patient profiles are listed in Table 3. All patients required inpatient care, and the mean time between symptom onset and admission was 13 days. All patients presented with nonremitting fever. Mild sore throat, urticarial, and maculopapular rashes were the most commonly observed accompanying symptoms. In 22 patients (88%), the diagnosis was made by clinical microbiologists or infectious disease specialists consulted for pyrexia.

Contact with young children was the most common risk factor for primary CMV infection in this cohort followed by travel outside Hong Kong within the last 3 months (Table 2). Most travelers

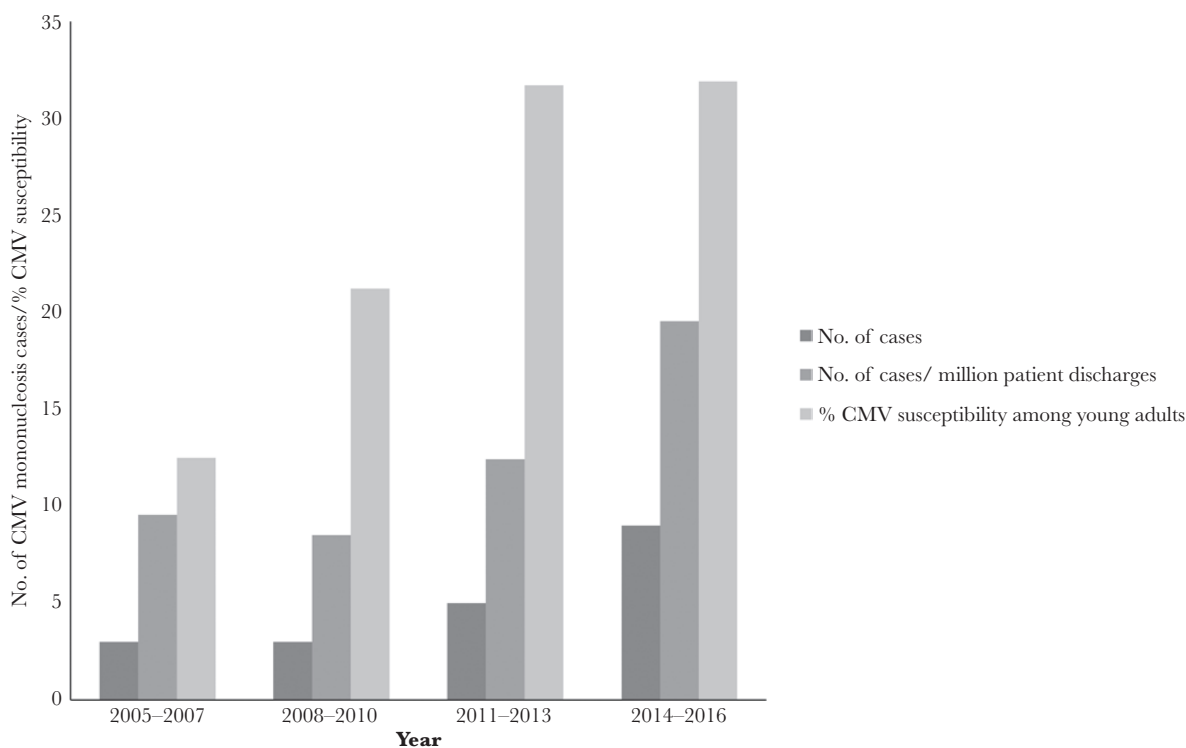
had returned from domestic travel in China. Two patients reported homosexual contact with a new partner. The observed male-to-female ratio significantly departed from a theoretical 1:1 expectation using an exact test of goodness-to-fit ( $P = .004$ ).

#### Virological Parameters

Eighty-eight percent (22 of 25) of patients had CMV pp65 antigenemia. Twenty-one of these patients had detectable CMV pp65 antigen in the first sample collected for the test. The level of antigenemia ranged from 1 to 30 positive cells/ $2 \times 10^5$  neutrophils. There was no significant correlation between time since symptom onset and blood CMV pp65 antigen level by linear regression ( $R^2 = 0.125$ ). In 4 CMV-IgM positive patients, the presence of CMV DNA in peripheral blood was confirmed by PCR.

#### Liver Function Test Parameters

All patients had deranged LFTs on presentation (Table 2). Alanine aminotransferase (ALT) was elevated at presentation in 96% of patients and ranged from 25 to 713 U/L (reference range, 8–58 U/L). The mean elevation in ALT was 4.7 times the upper limit of normal (ULN). On linear regression analysis, there was no significant correlation between ALT at presentation and patient age, time since symptom onset, admission lymphocyte count, and first CMV pp65 antigen measurement ( $R^2 = 0.013, 0.105, 0.016, \text{ and } 0.033$ , respectively). Multiple regression analysis using combinations of age, gender, time since symptom onset, CMV pp65 antigen levels, and total lymphocyte count as predictors did not find a model that could successfully explain the variance of ALT at presentation.



**Figure 3.** Rise in cytomegalovirus (CMV) mononucleosis incidence and CMV susceptibility among young adults between 2005 and 2016.

**Table 2. Clinical Features and Laboratory Investigations of Patients With Cytomegalovirus Mononucleosis Syndrome**

Clinical or Laboratory Characteristics	No. (%) <sup>a</sup>
<b>Clinical</b>	
Fever	25 (100)
Sore throat	7 (28)
Rash	8 (32)
Cervical lymphadenopathy	3 (12)
Splenomegaly	5 (20)
<b>Epidemiological</b>	
Household contact with children	17 of 21 (81)
Travel outside Hong Kong within 3 months	9 (36)
Men who have sex with men	2 (8)
No identifiable risk factor	2 (8)
>1 risk factor	5 (20)
<b>Liver Function Tests<sup>b</sup></b>	
ALT >58 U/L	24 (96)
ALT >2 × ULN	21 (84)
AST >38 U/L	25 (100)
AST/ALT ratio <1	24 (96)
ALP >110 U/L	14 (56)
Direct bilirubin elevation	0 (0)
<b>Hematological Tests</b>	
Atypical lymphocytes	21 of 22 (95)
Lymphocytosis >50% of total white cell count	13 (52)
PT >13.5 seconds	3 of 21 (14)
APTT >33.7 seconds	8 of 21 (38)
<b>Virological Tests</b>	
CMV pp65 antigenemia	22 (88)

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CMV, cytomegalovirus; PT, prothrombin time; ULN, upper limits of normal.

<sup>a</sup>Denominator is 25 unless otherwise indicated.

<sup>b</sup>Values indicated are the ULN reference range of the respective assays unless otherwise indicated.

Aspartate aminotransferase (AST) was elevated at admission in all patients (range, 40–496 U/L; reference range, 15–38 U/L). The mean AST elevation at admission was 4.3 times ULN. The ductal enzyme alkaline phosphatase was elevated in 56% of patients and the mean elevation was 1.8 times ULN (reference range, 42–110 U/L). Gamma-glutamyltransferase (GGT) was measured in 12 patients, 11 of whom (91%) had elevations with a mean GGT rise of 4.3 times ULN. Total bilirubin levels were normal in all patients. None of the patients underwent liver biopsy. No other cause of viral hepatitis was identifiable in any patient with the exception of 1 patient (patient no. 18), who was known to have chronic inactive hepatitis B carriage.

#### **Clinical Progress, Kinetics of Liver Function Tests, and Cytomegalovirus pp65 Antigenemia**

Vital sign charts of 19 patients could be retrieved for detailed examination. The mean duration of fever was 17 days after symptom onset. Seventy-four percent of patients achieved defervescence in the third week after symptom onset (Figure 4), usually coinciding with decline in LFTs. Alanine aminotransferase levels peaked during the second and third week of illness (range 7–20 days based

on an analysis of 11 patients for whom sufficient ALT measurements were available). This was either at presentation or within a few days of admission in 10 patients. The peak ALT levels ranged from 1.5 to 15.7 times ULN with a mean of 6.3 times ULN. The highest recorded ALT was 908 U/L. The ALT was monitored in 8 patients until levels subsided to <2 times ULN, and this took place during the third week after symptom onset in 7 patients and at the end of the fourth week in 1 patient (Figure 4). Serial monitoring of CMV pp65 antigen at intervals of 7 days or less until negativity was performed for 9 patients. Seven patients cleared the virus from the blood stream in the third and fourth weeks after symptom onset.

## **DISCUSSION**

In this 14-year retrospective study, we demonstrate a significant rise in CMV susceptibility among adults aged 18–45 years. This trend is particularly striking when compared with a local study, conducted in 1994, which found that no individual was susceptible to CMV by the age of 21 [7]. Increasing age of seroconversion is likely due to improving socioeconomic conditions in Hong Kong. Breast feeding has previously been implicated as an important vehicle of CMV transmission, and a generational shift to formula feeding may result in decreased CMV acquisition in early life [8]. However, in Hong Kong, breast feeding actually increased between the 1987 and 1997 birth cohorts, both in terms of percentage of babies receiving breast feeding as well as duration of breast feeding [9]. Therefore, changes in feeding practices could not account for the increasing CMV susceptibility observed among individuals reaching adulthood during this study.

Such an epidemiological shift of the entire adult population is a rarely reported phenomenon: a Japanese study found a similar decrease in CMV seroprevalence among pregnant women in Sapporo city between 1988 and 2000, whereas a Spanish study found a small increase in the proportion of seronegative females between 1993 and 1999 [10, 11]. We believe that the CMV seroprevalence in the Hong Kong adult population will continue to decline to levels currently prevalent in Europe and North America [12–14].

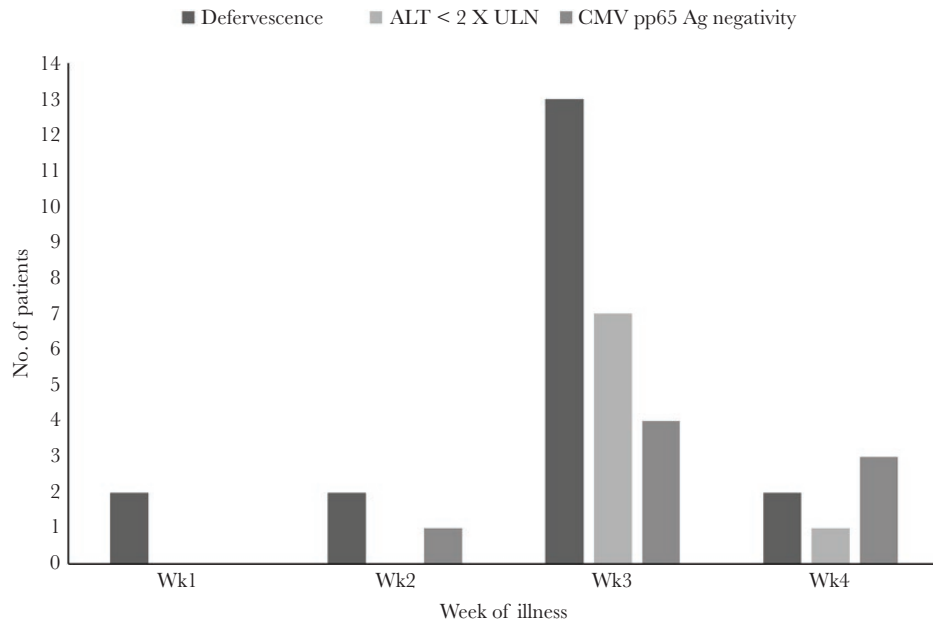
We suspect that the declining seroprevalence in young adults was probably the reason behind increasing incidence of CMV mononucleosis observed at our center. Other possible explanations for rising incidence such as increased clinician awareness of the diagnosis could be discounted as almost all cases were diagnosed by clinical microbiologists or infectious disease specialists consulted for pyrexia of unknown origin, which highlights the importance of infectious disease physicians in making the diagnosis and reducing unnecessary investigations and hospitalization [15, 16]. There was no significant increase in CMV IgM laboratory testing during the study period. There have been no major changes in the scope of services or the population served by the hospital over the study period that might otherwise account for rise in incidence of CMV mononucleosis. We acknowledge that many patients with primary CMV infections may be asymptomatic or do not need inpatient management, so our observed incidence

**Table 3. Characteristics of Cytomegalovirus Mononucleosis Patients**

No.	Gender/ Age (Years)	Risk Factors for Acquiring CMV Infection			Symptoms and Signs at Presentation					Time From Symptom Onset to Admission (Days)	Hematological Parameters at Presentation		
		Contact With Children	New Sexual Partner	Recent Travel	Fever	Sore Throat	Rash	Lymph Nodes	Splenomegaly		WBC Count	TLC Count	%Atypical Lymphocytes
1	M/49	+	-	-	+	-	-	-	-	15	7.19	4.49	Not quantified
2	F/50	Not available	-	-	+	-	-	-	-	15	10.8	6.59	7
3	M/32	+	-	-	+	-	-	-	+	13	7.45	4.04	Not quantified
4	M/24	+	-	-	+	+	-	-	+	5	8.50	3.32	100
5	M/33	+	-	+	+	+	-	-	-	10	9.68	4.26	25
6	M/29	+	-	+	+	+	-	-	+	17	7.59	2.96	44
7	M/42	Not available	Not available	+	+	-	-	-	-	17	11.2	5.95	32
8	M/26	-	+	-	+	+	+	-	-	14	10.36	6.63	11
9	M/37	+	-	-	+	+	+	-	-	13	8.74	4.20	6
10	M/28	-	-	+ <sup>a</sup>	+	-	-	-	-	8	13.33	6.93	6
11	M/40	+	-	-	+	-	-	-	-	8	8.17	1.96	63
12	M/27	+	-	-	+	-	-	-	-	20	9.37	3.89	25
13	M/36	+	-	-	+	-	-	-	-	7	7.19	4.31	13
14	M/25	-	+	-	+	+	-	-	-	6	6.78	2.58	10
15	F/27	-	-	-	+	+	+	-	+	15	5.90	3.84	6
16	M/30	+	-	-	+	-	-	-	-	5	9.88	4.94	12
17	M/37	Not available	Not available	+	+	-	-	-	-	14	10.18	3.87	13
18	F/38	+	-	-	+	-	-	-	-	5	12.40	9.20	Not quantified
19	M/31	+	-	+	+	-	-	-	+	11	7.28	4.08	11
20	M/44	+	-	+	+	-	-	-	-	14	11.64	4.66	25
21	F/38	+	-	-	+	-	-	-	-	0	5.71	1.88	9
22	M/31	+	-	+	+	-	-	-	-	16	7.70	3.39	16
23	F/61	Not available	-	+ <sup>a</sup>	+	-	-	-	-	17	12.82	8.33	11
24	M/31	+	-	-	+	-	-	-	-	11	7.26	4.28	3
25	M/32	+	-	-	+	-	-	-	-	21	11.63	5.12	38

Abbreviations: CMV, cytomegalovirus; TLC, total lymphocyte count; WBC, white blood cells.

<sup>a</sup>Travel to multiple destinations within a 3-month period (China and Malaysia for patient 10; China and United Arab Emirates for patient 23).



**Figure 4.** Duration from symptom onset to defervescence, alanine aminotransferase (ALT) decline to  $<2 \times$  upper limits of normal (ULN), and cytomegalovirus (CMV) pp65 antigen negativity. Analysis was performed based on 19 patients with available fever chart data, 8 patients with sufficiently frequent liver function test measurements, and 8 patients with sufficiently frequent CMV pp65 antigen measurements.

may only represent the tip of the iceberg of CMV infection in the community. Further liaison with community health clinics is required to bolster testing for CMV infection in outpatients with compatible clinical features.

The most common risk factor for acquiring primary CMV infection in this study was household contact with young children. This is consistent with previous studies, which find that children shed CMV for prolonged periods placing susceptible adults in the household at risk [17, 18]. Transmission between children and from children to susceptible adults in daycare center settings has previously been reported, and working in daycare settings is considered a risk factor for CMV infection among educators [19, 20]. Daycare is common practice in Hong Kong; children contracting CMV in daycare and kindergarten could subsequently transmit the virus to their susceptible parent at home. Recent travel to CMV hyperendemic destinations was also reported by a significant proportion of patients, confirming previous reports that CMV is an important cause of mononucleosis in returning travelers [16, 21]. Uniquely, we identified 2 HIV-negative men who have sex with men (MSM) who had primary CMV infection without any other risk factors. The presence of CMV in genital secretions has been described [22], and the CMV seroprevalence in the MSM population is higher than the general population [23, 24]. Therefore, MSM may be at increased risk for acquiring primary CMV infection in regions of declining CMV endemicity. Our cohort was characterized by a male/female ratio of 4:1; several other cohorts have also reported skewed male gender distribution among CMV mononucleosis-hepatitis patients [15, 16, 25]. Whether

males are more likely to have symptomatic primary CMV infection than females requires further study.

The clinical features of CMV mononucleosis in our cohort were similar to descriptions in previously published series [2, 26]. The lack of prominent pharyngitis and diffuse lymphadenopathy rendered clinical differentiation from adults with EBV-infectious mononucleosis straightforward in most cases. Of 22 patients with measured atypical lymphocytes, 21 had atypical lymphocytosis of  $>5\%$  of total lymphocyte count (range, 3%–100%), indicating a diagnostic sensitivity of 95.4% for CMV mononucleosis. Thirteen of twenty-five patients had lymphocytosis  $>50\%$  of total leucocyte count including the 3 patients with undetermined atypical lymphocytosis, indicating a diagnostic sensitivity of 52%. Derangement of LFTs was observed in all patients. Indeed, the derangement appeared to be more severe than CMV mononucleosis patient cohorts described in Western populations. The mean ALT elevation at presentation in our study was 4.7 times ULN with a subsequent nadir of 6.3 times ULN; these were higher than the mean elevations of 3.3 times ULN derived from data reported in German and North American case series [15, 25]. Furthermore, in 3 other studies conducted in Belgium, Italy, and the United Kingdom, a significant proportion of patients with primary CMV infection had no derangement of LFTs at presentation [16, 21, 26]; all of these studies were conducted in tertiary referral centers, and therefore the observation of normal LFTs could not be attributed to earlier patient presentation. Whether CMV hepatitis in Asian patients is more severe in terms of liver biochemistry compared with Western cohorts requires further

examination of comprehensive datasets. Link of clinical disease severity with CMV envelope glycoprotein genotypes and ORF79 mutants, which we have found previously in immunocompromised patients [27, 28], may also be worth exploring.

Using multiple measurements of ALT and CMV pp65 antigen, we were able to delineate the LFT and blood virus kinetics in a subset of our cohort. Fever resolution was closely linked to ALT improvement and CMV pp65 antigen decline and occurred in the third week of illness in most patients.

Due to the retrospective nature of this study, certain clinical, epidemiological, and laboratory data points were missing or unrecorded. Liver function test and CMV pp65 antigen measurements were conducted at physician discretion and, therefore, were not at the same intervals in all patients. As a result, not all patients could be included in the analysis of liver function and virus kinetics due to inadequate testing frequency. We also did not have precise surveillance data on the number of patients admitted to our unit with pyrexia of unknown origin over the study period. Therefore, the incidence rate of CMV mononucleosis among such patients, which would be the best measure to estimate incidence rate ratios and statistical analysis, could not be calculated.

## CONCLUSIONS

In summary, we demonstrate that CMV mononucleosis is an emerging cause of acute hepatitis in Hong Kong, probably due to rapidly declining seroprevalence in the young adult population. Further studies are required to demonstrate the effect of decreasing seroprevalence on the incidence of antenatal CMV infection, congenital CMV infection, and CMV infection in immunocompromised patients. In our study cohort of CMV mononucleosis, the disease is typically a 3-week illness characterized by anicteric hepatitis as the prominent laboratory abnormality [2, 15, 21].

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