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Risk factors for transmission of chikungunya virus infection in Singapore, 2008

Introduction

Chikungunya virus disease is a self-limiting illness caused by an arbovirus of genus *Alphavirus* and family *Togaviridae*. [1] This disease was first described by Robinson[2] and Lumsden[3] following an outbreak in 1952. Chikungunya is a Makonde term translated as "that which bends". It is spread between persons via the bite of an infected vector and infection confers life-long immunity to this disease[4] . There are three strains of chikungunya: the East-Central-South African, the West African and the Asian strain[5]. The incubation period of chikungunya ranges from 3 –12 days[6]. This paper reviews the 2008 experience of chikungunya virus infection in Singapore, describes the risk factors for transmission and the evidence implicating *Aedes albopictus* as the primary vector of chikungunya in Singapore.

Materials and methods

A laboratory-confirmed case of clinically diagnosed disease was defined as a patient with either a chikungunya virus genome detected following reverse transcription and amplification via reverse transcriptase polymerase chain reaction (RT-PCR), or a four-fold rise in chikungunya virus IgG antibody titres between paired samples taken at least 14 days apart. To increase the specificity of case detection, cases who were IgM positive, had single IgG samples positive or with only clinical symptoms were excluded.

Age, gender, type of residential premises, occupation, nationality and ethnicity of the cases were collected via questionnaires. Indigenous

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cases were considered part of a cluster if they did not travel abroad during the 12-day period prior to onset of illness, resided within 300 metres of each other and had their illness onset dates not more than 24 days apart. Clusters were classified as urban, sub-urban or rural based on their location in the island. In the cluster area, mosquito surveys were carried out by the National Environment Agency (NEA) concurrent with epidemiological investigations. Mosquito larvae found during vector control operations were identified.

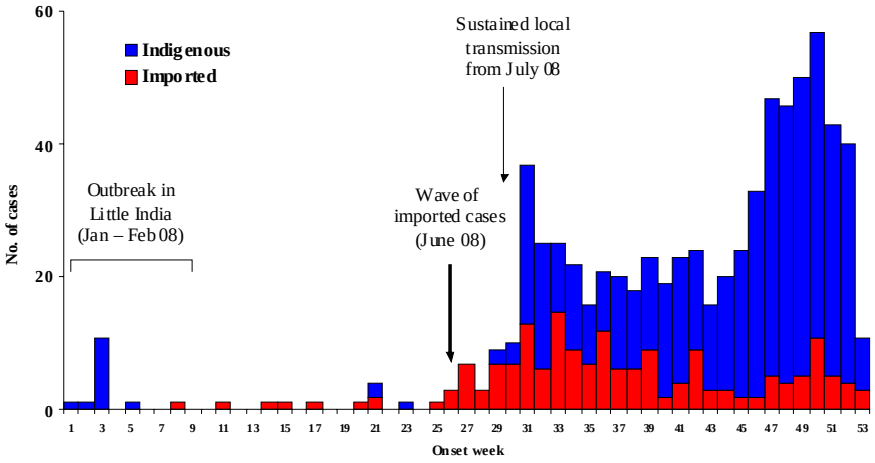
In the statistical analysis, the locations of identified clusters of cases were entered into a geographic information system with ArcView version 3.3 (ESRI). The demographic profiles of the cases were characterised by age, gender, type of residential premises and occupation. Difference in demographic characteristics between indigenous and imported cases were analysed by chi-square tests or Fisher's exact test for proportion. Incidence rates and risk ratios (RR) were calculated based on the population data provided by the Singapore Department of Statistics. All statistical analyses were performed with the SPSS version 15.0. A p-value of <0.05 was considered as statistically significant.

Results

A total of 718 laboratory-confirmed cases of chikungunya virus disease comprising 537 indigenous and 181 imported cases were identified in 2008. After excluding 34 cases inclusive of tourists arriving in Singapore for medical treatment, the overall incidence rate of chikungunya virus disease was 14.1 cases per 100,000 population. There were two separate episodes of indigenous transmission of chikungunya. The first episode (Jan - Feb 08) occurred in Little India while the second episode of indigenous transmission (Jun – Dec 08) began with a wave of imported cases from epidemiological (e)-week 25 – 28 (*Fig. 1*).

Using data from e-week 25 onwards, the population profiles and the relative risks of acquiring the infection of imported and indigenous cases were found to be different: indigenous cases involved mainly males, non-residents or labourers while imported cases

Figure 1
Time distribution of 718 chikungunya cases in Singapore, 2008



were more frequent amongst Singaporean Malays (*Table 1*).

For imported cases, a high proportion involved those on social visit or tours in Malaysia (*Table 2*). For indigenous cases, the geographical distribution (*Fig. 2*), the types of residential premises in the clusters (*Table 3*) and the type of mosquito found in the clusters (*Table 4*) showed that people living in rural or sub-urban areas were at high risk of infection and indicated that *Aedes albopictus* was the main vector responsible for transmission in most clusters.

Discussion

In contrast to the Little India outbreak from Jan – Feb 08[7], indigenous transmission in the second half of the year was sustained and of larger magnitude. The population profile suggests that this outbreak was probably first initiated by Singaporean Malays returning from social visits or tours in Malaysia during e-week 25 -28. Most of them had visited rural villages in Johor which reported outbreaks of chikungunya virus disease from April 2008 onwards. After introduction of the virus into the local vector population,

Table 1

Demographic characteristics of imported and indigenous chikungunya cases, 2008

	Indigenous cases (n=520)			Imported cases* (n=142)		
Mean age (yrs) (SD)	38.2 (14.0)			43.3 (15.7)		
	Number (%)	Incidence rate+	RR	Number (%)	Incidence rate+	RR
Age group (yrs)						
0 - 14	13 (2.5)	1.8	0.1	6 (4.2)	0.8	0.3
15 - 54 (ref)	431 (82.9)	12.9	1.0	102 (71.8)	3.1	1.0
55+	76 (14.6)	9.8	0.8	34 (23.9)	4.4	1.4
Gender #						
Female (ref)	106 (20.4)	4.6	1.0	61 (43.0)	2.6	1.0
Male	414 (79.6)	16.4	3.6	81 (57.0)	3.2	1.2
Ethnicity #						
Singaporeans						
Chinese (ref)	164 (31.5)	6.1	1.0	78 (54.9)	2.9	1.0
Malay	5 (1.0)	1.0	0.2	30 (21.1)	6.1	2.1
Indian	16 (3.1)	5.6	0.9	4 (2.8)	1.2	0.4
Others	8 (1.5)	7.8	1.3	1 (0.7)	1.0	0.3
Non-residents	327 (62.9)	28.3	4.6	29 (20.4)	2.4	0.8
Occupation #		Number (%)			Number (%)	
Labourers		277 (53.3)			12 (8.5)	
Administrative		59 (11.3)			27 (19.0)	
Domestic		88 (16.9)			47 (33.1)	
Sales & services		20 (3.8)			17 (12.0)	
Students		15 (2.9)			9 (6.3)	
Technical		54 (10.4)			30 (21.1)	
Others		7 (1.3)			0 (0.0)	

* excludes 31 cases among foreigners seeking medical treatment in Singapore + expressed per 100,000 population
# P value (indigenous against imported) < 0.05.

Table 2.

Country of origin of 173 imported chikungunya cases and reasons for travel, 2008

	Cases (%)
Malaysia	162 (93.6)
Indonesia	4 (2.3)
India	4 (2.3)
Cambodia	1 (0.6)
The Maldives	1 (0.6)
Sri Lanka	1 (0.6)
Reasons for travel	
Social visit	73 (42.2)
Tourism	55 (31.8)
Medical treatment	31 (17.9)
Weekend visits to Malaysia from Singapore	7 (4.0)
Work	7 (4.0)

Table 3

Incidence rates and relative risk (RR) by type of residential premises of reported indigenous chikungunya cases, 2008

Residential premises	Number (%)	Incidence rates per 100,000	RR
Public high-rise apartments (ref)	130 (25.0)	3.7	1.0
Private high-rise apartments	32 (6.2)	9.7	2.6
Landed properties	111 (21.3)	30.4	8.3
Temporary housing	247 (47.5)	40.3	11.0

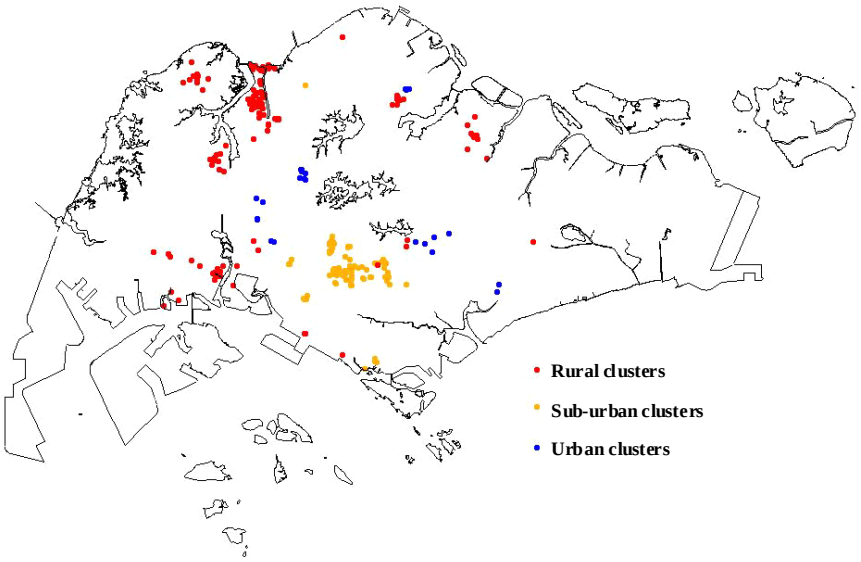
Table 4

Predominant *Aedes* mosquitoes detected in 34 chikungunya cluster areas, 2008

Cluster location	*Ae. aegypti*	*Ae. albopictus*	Mixed
Rural	0	15	0
Sub-urban	0	16	0
Urban	0	0	3

Source: National Environment Agency

Figure 2
Geographical distribution of reported indigenous chikungunya cases in Singapore, 2008



transmission of infection was sustained amongst male non-resident labourers. Majority of these were foreign nationals (Indian, Chinese, Bangladeshi and Thai) who are mainly deployed in outdoor jobs such as construction workers, odd-job labourers or gardeners.

Given that *Aedes aegypti* is an indoor mosquito[4], the population profiles of both imported and indigenous cases of chikungunya virus disease suggested that the outbreak was initiated and maintained by exposure to infected *Aedes albopictus* mosquitoes in an outdoor environment. Clusters were mostly found in the rural and sub-urban areas of the north, southwest and central parts of Singapore, but in the eastern part of Singapore, where vector control was traditionally focused on the dominant *Aedes aegypti* mosquitoes, there were relatively few clusters. Another observation was a higher risk of infection among those living in landed properties and temporary housing premises. These findings pointed to *Aedes albopictus* as the primary vector, supported by evidence that this was the main vector detected in 31 (91.2%) of the 34 clusters identified.

Prior to the regional outbreaks since 2005, the virus was believed to spread only between humans and the mosquito vector *Aedes aegypti*[4] as the virus normally has a low infectivity for *Aedes albopictus*[8]. In recent years, there was an A226V mutation that improved the vector competence in *Aedes albopictus* mosquitoes without compromising transmission by *Aedes aegypti* mosquitoes[8] . Viral sequencing of the initial cases by the Environmental Health Institute (EHI) confirmed that the 2008 outbreak in Singapore was caused by the A226V mutant. This mosquito-mutant combination was responsible for the re-emergence of chikungunya in Malaysia[9] and India [10] and for the colonisation of new habitats in Italy[11]. It also explains why *Aedes albopictus* was able to cause an epidemic of such severity in Singapore.

(Contributed by Tan BH, Lai F, Wu R, James L, and Ooi PL, Communicable Diseases Division, Ministry of Health)

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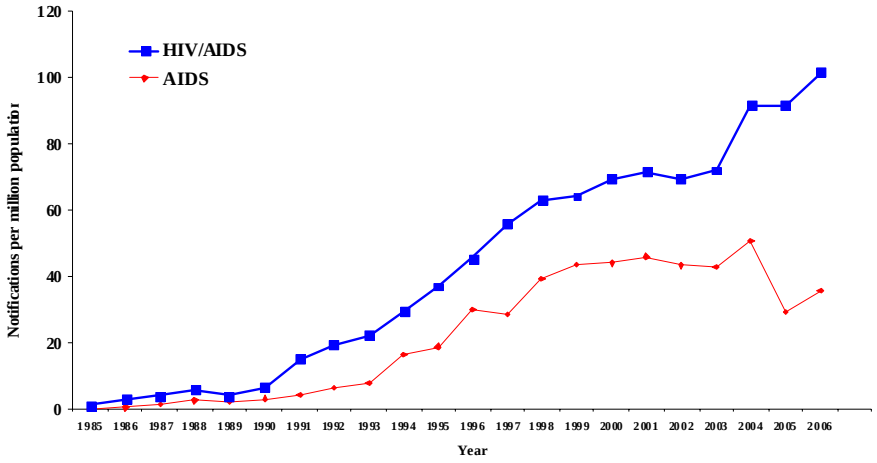
Survival of AIDS patients based on their AIDS-defining illnesses

The notification rate of human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) in Singapore has been on the rise from 0.8 per million population in 1985 to 71.9 per million population in 2003, and further increased to 101.3 per million population in 2006 (*Fig.* 3). The notification rate of AIDS at first diagnosis increased from 0.4 per million population in 1986 to 50.7 per million population in 2004. This was followed by a decrease in the notification rate to 28.8 per million population in 2005, and a subsequent increase to 35.7 per million population in 2006. More than half of the newly diagnosed HIV-infected patients had late-stage infection (defined as CD4 cell count of less than 200 per mm^3 or AIDS-defining opportunistic infections at first diagnosis or within one year after HIV infection at diagnosis).

The prognosis of AIDS patients is known to be determined by various factors.[1-3] These factors include

Figure 3
Notification rate of HIV/AIDS (per million resident population), 1985-2006



the AIDS-defining illnesses, which has been suggested to be a significant determinant of survival in patients with AIDS in some studies.[4,5]

We carried out a retrospective study to examine the survival of AIDS patients based on their AIDS-defining illnesses, for the purpose of evaluating the use of these illnesses as a parameter in the clinical assessment, prognostication and management of AIDS patients.

Materials and methods

The data for the retrospective study was obtained from the national HIV registry. We included 1077 HIV-infected patients who were diagnosed with AIDS at first diagnosis in Singapore from 1987 to 2006. These patients were infected sexually via heterosexual, bisexual or homosexual mode of transmission, or through intravenous drug use.

To describe the survival pattern of patients, we used Kaplan-Meier estimation of median survival time to carry out the ranking of AIDS-defining illnesses. Cox's proportional hazards models were used to determine the mortality risk of the AIDS-defining illnesses after adjustment for potential confounders, such as age at diagnosis of AIDS, CD4 cell count and number of AIDS-defining illnesses. The adjusted hazard ratios (HR) were then ranked, first based on the initial AIDS-defining illness and then repeated on subsequent AIDS-defining illnesses.

Results

Of the 1077 AIDS patients, 81% were infected via the heterosexual route. Homosexual/bisexual transmission and intravenous drug use accounted for 17% and 2%, respectively. 62% of the patients were aged 30—49 years at the time of diagnosis. Lymphoma (non-Hogkins) and HIV encephalopathy were ranked amongst the top three initial and subsequent AIDS-defining illnesses which corresponded with the shortest median survival times (*Table 5*).

The relative risk of mortality was significantly raised ($p < 0.05$) in the Cox model for the initial AIDS-

defining illness of HIV encephalopathy, Kaposi's sarcoma, lymphoma (non-Hogkins), unspecified pneumonia and toxoplasmosis (*Fig.* 4). Only the relative risk of mortality for HIV encephalopathy and unspecified pneumonia remained significantly raised in the analysis of subsequent AIDS-defining illnesses (*Fig.* 5).

Comments

The AIDS-defining illnesses were ranked based on their corresponding median survival time and adjusted HR. The results showed that clear ranking had been generally maintained for unspecified pneumonia, lymphoma (non-Hogkins), HIV encephalopathy and Kaposi's sarcoma for the shortest median survival times and highest relative risk of mortality. The adjusted HR for HIV encephalopathy was noted to be the highest for both initial and subsequent AIDS-defining illnesses. This is consistent with the findings of other studies which observed significant association of HIV encephalopathy with high mortality in AIDS patients[4,6,7]. Unspecified pneumonia was noted to correspond with short median survival times for both initial and subsequent AIDS-defining illnesses, ranking

Table 5

Ranking of shortest median survival time (months) for specific AIDS-defining illness

AIDS-defining illness	Initial			Subsequent		
	Median survival	95% CI	Ranking	Median survival	95% CI	Ranking
Unspecified pneumonia	0*	-	1	13	10—16	4
Lymphoma (non-Hogkins)	7	0—17	2	13	8—18	3
HIV encephalopathy	7	1—14	3	5	3—7	1
Mycobacterium avium intracellulare infection	11	0—31	4	23	15—31	5
Kaposi's sarcoma	15	2—28	5	7	4—10	2
Toxoplasmosis	26	11—41	6	24	8—40	6

CI: Confidence interval
* 9% of AIDS patients diagnosed with unspecified pneumonia as their initial AIDS-defining illness were still alive 21 months later.

Figure 4
Five highest adjusted hazards ratios of initial AIDS-defining illness

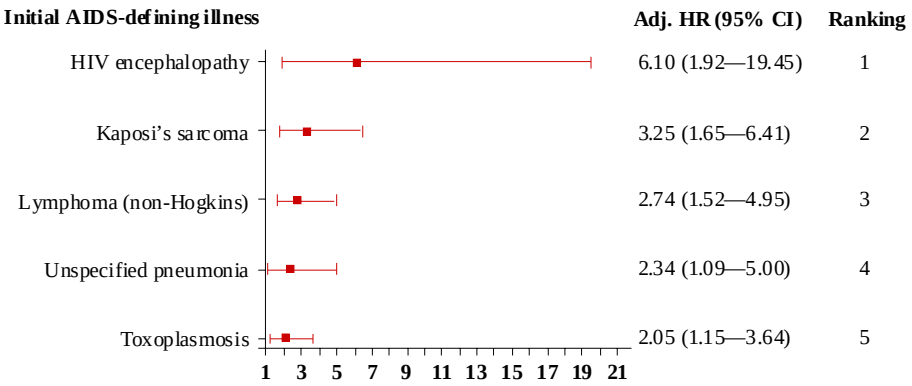
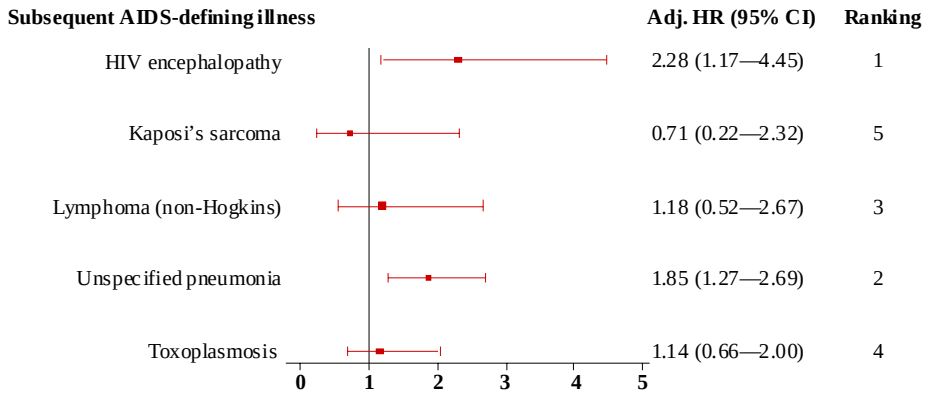


Figure 5
Five highest adjusted hazards ratios of subsequent AIDS-defining illnesses



first and fourth place in the two analyses, respectively. Further research to study the effects of antibiotic prophylaxis, anti-retroviral therapy as well as pneumococcal vaccination on the local population with AIDS [People Living with AIDS (PLWA)] would be important in reducing avoidable mortality and improving their overall survival.

Accurate diagnosis and reporting of the sequence of initial and subsequent AIDS-defining illnesses are essential in ensuring the robustness of the study findings. This study serves as a reference in evaluating the use of AIDS-defining illnesses as a parameter in the clinical assessment, prognostication and management of AIDS patients.

(*Reported by Ang LW and Tey SH, Communicable Diseases Division, Ministry of Health*)

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Seroprevalence of hepatitis B virus infection in adults in Singapore

Hepatitis B constitutes a major public health concern, and its significance lies in the considerable number of hepatitis B virus (HBV) carriers in the Singapore population. At least 50% of HBV infections are asymptomatic.[1] While most of the adult cases recover completely from acute HBV infection, approximately 5% progress to become asymptomatic HBV carriers or develop chronic hepatitis that could result in cirrhosis and/or liver cancer. Rarely, some may develop fulminant hepatitis.

In Singapore, the HBV control programme includes surveillance, hepatitis B immunisation, universal precautions, public education and routine screening of voluntary blood donors for hepatitis B surface antigen (HBsAg) carriers. The hepatitis B immunisation programme was first introduced in mid-1983 for high-risk groups such as health care workers. A mass immunisation programme against hepatitis B for babies born to HBsAg carrier mothers was incorporated into the national childhood immunisation programme on 1 October 1985, and subsequently extended to cover all newborns on 1 September 1987.[2]

In Singapore, a number of hepatitis B seroprevalence studies have also been carried out to determine population immunity to HBV and the HBV carrier rates in Singapore. The findings would help to identify population groups requiring more targeted control strategies and contribute to the assessment of need for strengthening the national hepatitis B prevention and control programme.[3-5] Based on the findings from the hepatitis B seroprevalence study (HBSS) 1999, the School Health Services implemented a 4-year 'catch-up' hepatitis B immunisation programme (2001-2004) for students in secondary schools, junior colleges, centralised institutes, institutes of technical education, polytechnics and universities. As these students were born before 1987, they were likely to have missed the national childhood hepatitis B immunisation programme. A mass media education programme was also launched in Feb 2001 to educate the public on the risks of hepatitis B infection and to encourage members of the public who have not been immunised to be screened and immunised against HBV infection.

We determined the prevalence of HBV markers among adults aged between 18 and 69 years in 2005, and evaluated the impact of the 4-year 'catch-up' hepatitis B immunisation programme.

Methods and materials

Sera were obtained from 4,034 participants of the National Health Survey (NHS) 2004 aged 18-69 years. All these participants had given consent for their blood specimens to be tested for future research. The population sample was selected by a combination of disproportionate stratified sampling and systematic sampling, and was representative of the Singapore resident population by age, gender and ethnicity.

The sera which had been collected and stored at –80°C at the Department of Pathology, Singapore General Hospital, were sent to the Department of Laboratory Medicine, National University Hospital, for screening of HBV markers using electrochemiluminescence immunoassay. The stored blood sera were first tested

for HBsAg. Sera of subjects found to be HBsAg positive were further tested for heptatitis B e-antigen (HBeAg). Those found to be HBsAg negative were screened for antibody to HBsAg (anti-HBs). Immunity to HBV was based on the titres of anti-HBs: <10mIU/ml, non-immune; >10mIU/ml, immune.

Statistical analysis was performed using the statistical software package, Statistical Package for Social Sciences (SPSS) 15.0. The survey sample data was adjusted to the age, ethnic group and gender distribution of the 2004 Singapore resident population, to ensure that the characteristics of the sample conformed to that of the general population.

To determine the changing prevalence of HBV infection, the results were compared with those from a similar study conducted in 1999 involving 4,698 participants of the NHS 1998. Age-standardisation of prevalence of HBsAg, HBeAg, and anti-HBs was calculated by the direct method, using the 2000 census resident population as the standard. Differences between the age-gender-standardised incidence rates of the 3 ethnic groups were computed and tested for statistical significance using the Z-test.[6] Statistical significance was taken as p <0.05.

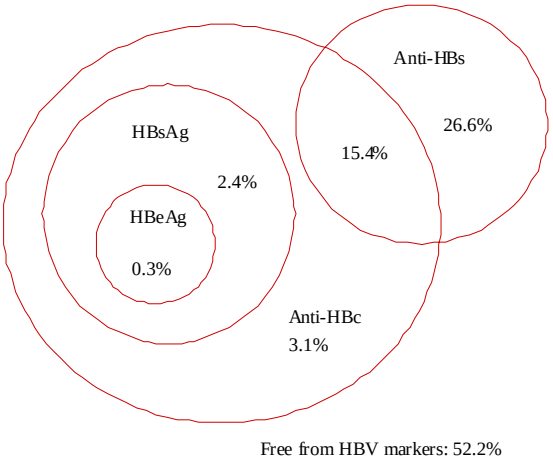
Results

The overall prevalence of HBsAg among Singapore residents aged 18-69 years was 2.7% in 2005, significantly lower than the 4.1% in 1999. HBeAg was detected in 11.9% of those who were HBsAg positive, not significantly different from the 13.0% in the previous study. Overall, about 42.0% of the population had immunity to HBV, an improvement from the 39.5% in 1999. About 15.4% of the adults had natural HBV infection in view of their concurrent anti-HBs and anti-hepatitis B core antigen (anti-HBc) positivity (*Fig. 6*).

Immunity to HBV

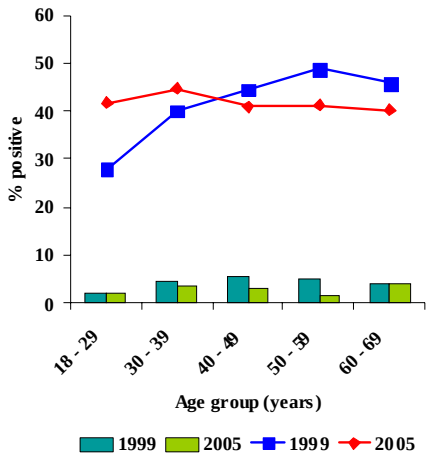
Adults in the 18-29 years (41.7%) and 30-39 years (44.7%) age-group had the highest immunity in 2005, whereas these two age groups had the lowest immunity in the 1999 study (27.9% and 39.9%, respectively) (*Fig. 7*).

Figure 6
Prevalence (%) of HBV markers among adults aged 18-69 years, 2005



Free from HBV markers: 52.2%

Figure 7
Age-specific seroprevalence of HBV infection in adults 18-69 years of age, 1999 and 2005



There was no gender difference in the prevalence of anti-HBs (*Table 6*). The proportion with immunity to HBV was comparable among Chinese (42.3%), Malays (41.5%) and Indians (40.5%) in 2005. This was a stark contrast to the 1999 study, with Chinese having significantly higher proportion of immunity to HBV (44.3%) compared to Malays (19.7%) and Indians (22.1%). The age-standardised immune status of Malays increased significantly from 19.5% in 1999 to 41.9% in 2005; the corresponding figures for Indians were 21.8% and 40.9%, respectively.

HBV carrier rate

The HBV carrier rate was lowest among young adults aged 18-29 years (2.1%) and highest in the oldest age group of 60-69 years (4.0%) (*Fig. 7*). The prevalence of HBsAg in the 40-49 years age group (2.9%) was halved that of the 1999 study (5.5%). In the 50-59 years age group, it dropped from 4.9% in 1999 to 1.6% in 2005. The proportion of HBV carriers who were HBeAg positive remained highest among those aged 18-29 years in 2005 (15.8%), with a decline in proportion in the older age groups. None of the HBV carriers 50-59 years of age had a positive HBeAg test.

There was no gender difference in the prevalence of HBsAg (2.7%) in 2005, unlike in 1999 when there was a significant difference between males (4.9%) and females (3.3%) (*Table 7*). The HBeAg positivity among female HBsAg carriers in the reproductive age group 18-44 years was lower in 2005 (12.8% of HBV carriers) compared to the 1999 study (18.2%).

The age-standardised prevalence of HBsAg in males decreased significantly from 4.9% in 1999 to

Table 6
Comparison of prevalence (%) of anti-HBs (>10 mIU/ml) by gender and ethnic group, 1999 and 2005

	1999		2005		Difference in age-std prevalence [2005 – 1999]
	Crude prevalence	Age-std prevalence (95% CI)	Crude prevalence	Age-std prevalence (95% CI)	
All	39.5	39.7 (38.2, 41.1)	42.0	42.1 (40.5, 43.7)	2.5*
Gender					
Male	38.5	38.6 (36.5, 40.8)	41.1	41.1 (38.8, 43.5)	2.5
Female	40.5	40.7 (38.7, 42.6)	43.0	43.1 (40.9, 45.3)	2.4
Ethnic group					
Chinese	44.3	44.5 (42.8, 46.3)	42.3	42.3 (40.4, 44.2)	-2.3
Malay	19.7	19.5 (16.9, 22.2)	41.5	41.9 (38.5, 45.3)	22.4***
Indian	22.1	21.8 (18.6, 25.0)	40.5	40.9 (37.0, 44.8)	19.1***

* $0.01 < p < 0.05$
** $0.001 < p < 0.01$
*** $p < 0.001$

2.8% in 2005 (*Table 7*). Among the three major ethnic groups, the HBsAg prevalence was highest among Chinese (2.8%), followed by Malays (2.7%) and Indians (1.8%). The age-standardised prevalence of HBsAg in Chinese decreased significantly from 4.7% in 1999 to 2.8% in 2005. The prevalence of HBeAg among those who were HBsAg positive was highest among the Malays (21.4%), followed by Chinese (11.2%). There was no case with HBeAg positivity among the Indians. The age-standardised prevalence of HBeAg by gender and ethnic group did not show any statistical difference in 1999 and 2005 (*Table 8*).

Comments

The national hepatitis B prevention and control programme in Singapore has been largely successful, as evidenced by the decline in HBV carrier rate and sustained decline in liver cancer incidence (age-standardised incidence rate was 18.5 per 100,000 population per year in men and 4.6 per 100,000 population per year in women during 1998-2002).[7] The significant increase in immunity among young adults in the age group 18-29 years from 1999 (39.7 %) to 2005 (42.1 %) could be attributed to the successful implementation of the 4-year 'catch-up' hepatitis B immunisation programme between 2001-2004 and the mass media education publicity.

However, a large proportion of the adult population remains susceptible to HBV infection. In addition to routine infant immunisation, hepatitis B vaccination should continue to be actively promoted among adults and 'catch-up' immunisation strategies targeting at older age groups or groups with risk factors for acquiring HBV infection be reviewed periodically.[8]

Table 7

Comparison of prevalence (%) of HBsAg by gender and ethnic group, 1999 and 2005

	1999		2005		Difference in age-std prevalence [2005 – 1999]
	Crude prevalence	Age-std prevalence (95% CI)	Crude prevalence	Age-std prevalence (95% CI)	
All	4.1	4.0 (3.4, 4.6)	2.7	2.8 (2.2, 3.3)	-1.3**
Gender					
Male	4.9	4.9 (3.9, 5.9)	2.7	2.8 (2.0, 3.6)	-2.1**
Female	3.3	3.2 (2.5, 3.9)	2.7	2.8 (2.0, 3.5)	-0.4
Ethnic group					
Chinese	4.7	4.7 (3.9, 5.4)	2.8	2.9 (2.3, 3.5)	-1.8***
Malay	2.1	2.1 (1.1, 3.1)	2.7	2.8 (1.7, 3.9)	0.7
Indian	0.5	0.5 (0.0, 1.0)	1.8	1.6 (0.6, 2.6)	1.1*

* $0.01 < p < 0.05$
** $0.001 < p < 0.01$
*** $p < 0.001$

Table 8

Comparison of prevalence (%) of HBeAg by gender and ethnic group, 1999 and 2005

	1999		2005		Difference in age-std prevalence [2005 – 1999]
	Crude prevalence	Age-std prevalence (95% CI)	Crude prevalence	Age-std prevalence (95% CI)	
All	0.5	0.5 (0.3, 0.7)	0.3	0.4 (0.2, 0.6)	-0.1
Gender					
Male	0.5	0.5 (0.2, 0.8)	0.3	0.4 (0.1, 0.6)	-0.1
Female	0.5	0.5 (0.2, 0.8)	0.3	0.4 (0.1, 0.6)	-0.2
Ethnic group					
Chinese	0.6	0.6 (0.3, 0.9)	0.3	0.4 (0.1, 0.6)	-0.2
Malay	0.2	0.2 (0.0, 0.6)	0.6	0.6 (0.1, 1.1)	0.3
Indian	0.0	0.0	0.0	0.0	-

* $0.01 < p < 0.05$
** $0.001 < p < 0.01$
*** $p < 0.001$

(Reported by Ang LW, Communicable Diseases Division, Ministry of Health)

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Risk assessment and horizontal scanning scenario builder: developing a systematic approach to assess risk of importation of avian influenza (H5N1)

Introduction

The risk of importation of human H5N1 infection from an infected area is determined by a few key decision makers based on their expert knowledge on the disease characteristics and the prevailing global situation. This may not be ideal as it overly relies on the subjective knowledge of the various experts. The risk assessment and horizontal scanning (RAHS) scenario builder seeks to translate this decision-making process into a systematic approach[1] of assessing importation risk by identifying risk factors that will have an impact on the importation of human H5N1 infections.

Materials and methods

The scenario builder is a module in the risk assessment and horizon scanning (RAHS) system. (The RAHS system is a network of tools developed for whole-of-government approach to risk assessment and horizon scanning in helping the analysts to anticipate strategic threats). This module uses systems thinking and morphological analysis[2] to develop a model to assess the risk of importation of human H5N1 into Singapore.

Scenario builder

A workgroup which consisted of members with expert knowledge in infectious diseases and contingency planning, and consultants from RAHS was formed to develop this model.

The workgroup identified important risk factors that could contribute to the potential of importation of H5N1 into Singapore and included them as individual factors in the scenario builder. Using the modified Delphi method, the workgroup decided on the causal relationships among these factors, linking them up to produce a model known as the system map (*Fig. 8*). (The Delphi method is a systematic, interactive forecasting method which relies on the opinion of a panel of independent subject experts. It is based on the principle that forecast from a structured group of experts are more accurate than those from unstructured groups or individuals).

From the causal relationships among the factors in the system map, an influence map (*Fig. 9*) can be generated to identify the most influential factors in the model. These are the factors that had the greatest impact on the risk of importation of human H5N1 cases into Singapore and were taken into consideration when selecting the factors to be included for further analysis using the scenario option space function.

For each factor, options depicting the possible scenarios in which the factor may manifest itself in a particular point of time were created (*Fig. 10*). The consistency matrix (*Fig. 11*) cross-tabulates the options of two linked factors and allows the user to perform a consistency check to suppress inconsistent pairwise scenarios. This will prevent opposing scenarios

Figure 8
System map depicting the key risk factors and their interrelationship
Legend: AC = affected country; H to H = human to human

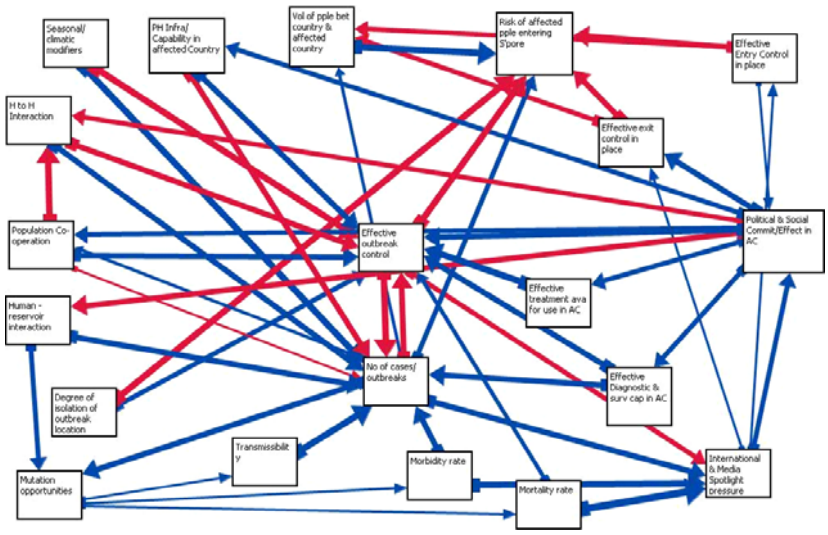


Figure 9
Influence map showing the most influential factors in red

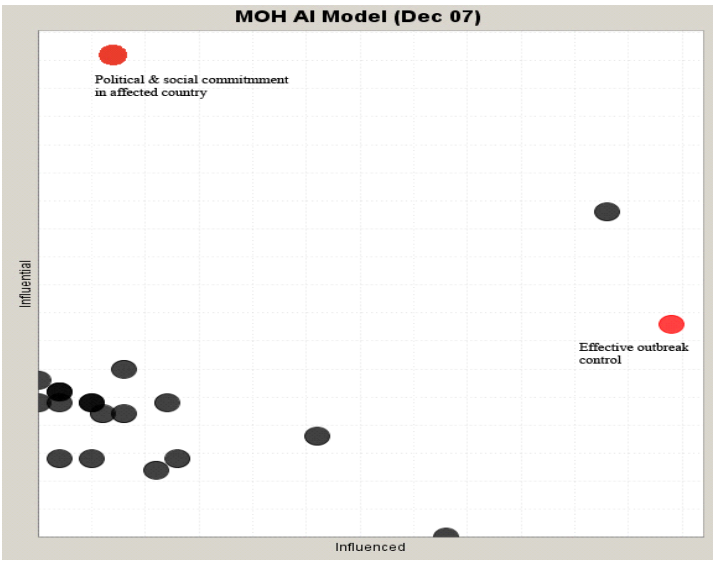


Figure 10
Possible scenario options of a risk factor

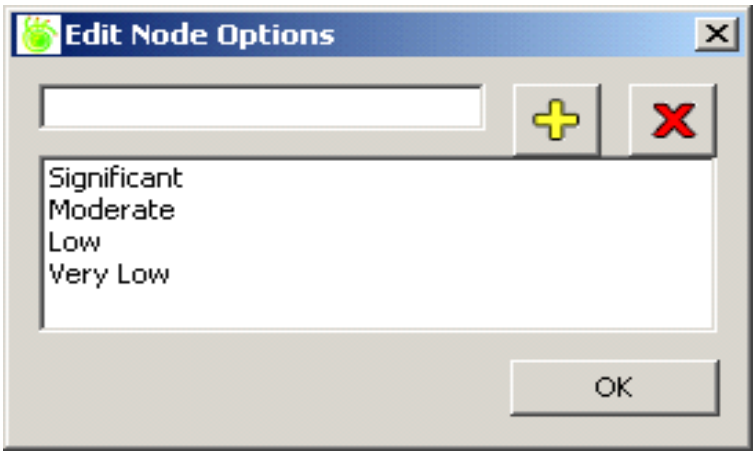


Figure 11
Consistency matrix to suppress inconsistent pair-wise scenarios

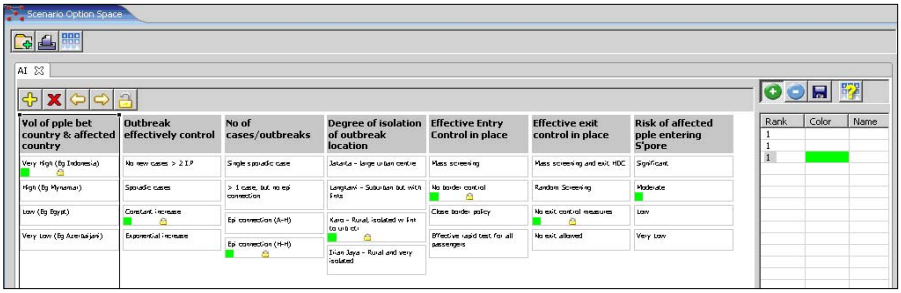
		Risk of affected pple entering S'pore			
		Significant	Moderate	Low	Very Low
Outbreak ef..	No new cas..	-1	-1	-1	1
	Sporadic cas..	-1	-1	1	1
	Constant inc..	-1	1	1	1
	Exponential ..	1	1	1	1

which could not happen from being analysed at the same time.

The scenario option space (*Fig. 12*) was used to analyse and determine the risk level of an outbreak and its impact on Singapore. We identified the node which will determine the risk of importation of a human H5N1 infection into Singapore and included it in the scenario option space as the determining factor. Thereafter, we defined the key factors affecting the risk level as those that have direct linkages to the determining factor and included them into the scenario option space together with the determining factor.

To analyse the risk level for an outbreak episode, the known scenario option for each factor for the outbreak was locked and the scenario option space would simulate the risk based on the information en-

Figure 12
Scenario option space depicting the scenarios of a particular outbreak



tered. The importation risk of human H5N1 case for the episode was interpreted as the highest risk level the scenario option space generated.

Validation of model

The model was tested using past incidents of outbreaks of human H5N1 avian influenza cases in Karo, Indonesia in May 2006, Garut, Indonesia, in August 2006, Azerbaijan in March 2006, and Egypt in December 2006. The results obtained were consistent with previous analysis of the situations provided by the opinions of the experts. This result is not unexpected as the risk factors considered in the model were obtained from the inputs of the various experts. Nonetheless, the interaction of the various risk models could potentially throw up unexpected scenarios which the experts may not think of in the first instance. This exemplifies the value in developing a scenario builder model. The model thus provides an objective and systematic approach to determine the risk of an avian influenza outbreak to Singapore.

Conclusion

As demonstrated in our study, morphological modelling can be a useful tool in semi-quantifying importation risk of H5N1. This model can be applied for future risk assessments on the importation of human H5N1 avian influenza cases based on the prevailing global situation. Nevertheless, the validity of our model rests on the correct interpretation of the effects of disease characteristics, its transmission dynamics, population movements, and more importantly, the accurate identification of the linkages of the risk factors which determine their inter-relationship.

(Reported by Low YJ, Koh KWB*, Choo SB*, Leng CY*, James L*, Oh LM# and Wong RF#; *Ministry of Health, and #RAHS Experimentation Centre)*

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Human bocavirus: significance of discovery and the proof of causality

Introduction

In the January 2009 issue of the Journal of Medical Virology, Tan *et al*.[1] published a study that examined the incidence of human bocavirus (HBoV) in a local paediatric hospital. The paper described the molecular detection of HBoV using anonymized nasopharyngeal swabs collected from paediatric patients admitted for acute respiratory infections. HBoV was found in 8.0% of the children tested. A majority of them presented with lower respiratory tract infection (LRTI). The presence of other common respiratory pathogens like parainfluenza viruses, respiratory syncytial viruses (RSV) and rhinoviruses (RHV) were also detected in 42.5%. This was the first time the incidence of HBoV infections amongst children has been established in the setting of a developed Southeast Asian country; i.e. Singapore.

Discovery of HBoV and its significance

HBoV is the newest member added to the *Bocavirus* genus which comes under the *Parvoviridae* family[2]. Its name has its origins from the other two members of the genus, bovine parvovirus and canine minute virus, which HBoV shares similarities in structure and sequence.

Using a novel technique termed molecular virus screening, HBoV was discovered from pooled respiratory aspirates obtained from hospitalized paediatric patients in Sweden. This approach involved the purification of viral DNA from clinical samples with amplification using randomly designed primers. The amplified DNA products were then subsequently sequenced before carrying out bioinformatics analysis to reveal the presence of a previously unknown parvovirus.

While the aetiology of some respiratory infections can be accounted for by relatively well-characterized agents like influenza viruses, parainfluenza viruses, adenoviruses, RSV and RHV, there remains a considerable percentage of respiratory tract illnesses that are undiagnosed even with comparatively exhaustive usage of several virus detection techniques[3-8]. Based on a prevalence study of respiratory viruses in paediatric patients, the aetiology of at least 28.1% of samples tested remained undiagnosed [unpublished data; study done by the National Public Health Laboratory (NPHL), Ministry of Health (MOH) and Health Service Development Project, Tan Tock Seng Hospital].In fact, new respiratory viruses continue to be discovered around the world including the human metapneumovirus[9] in 2001, coronavirus HKU1[10] in 2005, polyomavirus KI[11] and WU[12] (Karolinska Institute and Washington University, respectively) in 2007.

The discovery of HBoV reminds us of the presence of undiscovered respiratory pathogens and potential importance these undiscovered agents can have in the circulation and incidence of respiratory diseases. This is especially significant if one is to consider that LRTI was ranked as one of the top leading causes of global disease burden and deaths, especially for children[13].

In view of the severe acute respiratory syndrome[14] (SARS) experience in 2003, MOH needs to build capability in virus discovery. The lesson from SARS is that diagnostic tests should not be confined to targeting known viruses but also unknown ones. While HBoV is not likely to be as pathogenic as SARS, it is important to have demonstrated capability to identify and characterize (albeit limited initially) an unknown virus. In addition, while the discovery of HBoV was via molecular screening techniques, a multipronged strategy (incorporating traditional approaches like electron microscopy and virus isolation, etc) in viral discovery should be adopted because no single approach would work all the time.

Causality

Since its discovery in 2005, HBoV has been detected in children all over the world including Australia, Canada, China, Japan, Hong Kong, South Korea , Thailand[15-24], and Singapore. Though the majority of the HBoV positive patients exhibited LRTI in the study, the lack of control groups in many studies (including this one) makes causality hard to establish.

Definitive evidence of disease causation can no longer be solely dependent on Koch's postulates and we need to be cognizant that there exist pathogenic agents which do not fulfill these postulates and that animal models are not always available or suitable. For instance, the phenomenon of sub-clinical infection defies Koch's postulates when it comes to pathogens like *Mycobacterium tuberculosis*, *Neisseria meningitidis* and *Vibrio cholerae*. Having only a specific host (e.g humans only) also violates Koch's postulates because of the unfeasibility of infecting other hosts. This is not tantamount to declaring that Koch's postulates are no longer useful or needed in today's world of emerging and re-emerging infectious diseases. Koch's postulates and its subsequent revisions will continue to provide a valid framework for us to establish infectious disease causation and we will continue to enhance and revise it as science and technology advances[25]. For HBoV, it is not culturable and so poses additional problems in proving causation. Evidence for causation may need to take into account some or all of the following: presence associated with disease state vs. non-disease state, high viral load correlating with disease, decline in viral load after resolution of disease, antibody response in acute and convalescent phases, and histological evidence of tissue invasion. The last criteria of reproducing the disease in an animal model will not likely be achievable for a non-culturable virus.

While we have fully sequenced the HBoV genome, we have not answered, possibly the only question that matters: does HBoV cause respiratory illness in children or humans for that matter? The logical flow of associated questions (not exhaustive) would be as below. If the above is true, what then is the severity of the illness? Is it more severe in children or in adults? Or is it just a childhood illness? Could it also be the case that HBoV is being carried asymptomatically and that subclinical infection is the norm, thus accounting for its wide-geographical spread? Or it may just turn out to be another commensal microorganism found as part of normal respiratory tract flora?

A significant level of co-infection was also detected for the Singapore study. This is consistent with other studies which also found co-infection with other common respiratory viruses[15-24]. In addition, the study also found 47% of those with HBoV coinfections hav-

ing LRTIs compared to 52% of those being infected with HBoV only. This alone does not indicate that HBoV alone is required to cause LRTI but points to the need for future studies for corroborative support. Indeed, as elaborated by Tan and colleagues, the clinical implications of HBoV co-infections have yet to be fully understood and a more robust study involving a larger sample size and longer study period will be needed to better understand the dynamics between HBoV and its co-infectants.

There have also been reports of the association HBoV may have with gastroenteritis and excreted in faeces[24-26]. The presence of HBoV has also been found in the serum of HBoV positive patients suggesting that viremia occurs during infection. This was observed in at least two independent studies[21,27]. In short, the full HBoV disease spectrum remains to be elucidated and so far, its effects appear to be restricted to the respiratory and intestinal systems.

Conclusion

The discovery of HBoV and the confirmation of its incidence in Singapore serves as a reminder to public health professionals (clinicians, microbiologists and epidemiologists) that we must remain both aware of the constraints that our diagnostic capabilities will always have and also be vigilant of the fact that new respiratory viral entrants will continued to be uncovered. MOH will continue to develop and enhance national capability within NPHL to identify novel pathogens rapidly with the best possible science. However, it is together with clinical epidemiology and laboratory studies can one firmly establish causation and the importance of new viruses.

(Reported by Teo J X and Lin R V T P,
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