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Singapore's first chikungunya outbreak – surveillance and response

Introduction

The chikungunya virus is transmitted by the bite of an infected *Aedes aegypti or Aedes albopictus* - similar to that of dengue. Chikungunya fever has been documented as early as 1824 in India and elsewhere, though the *alphavirus* which belongs to family *Togaviridae*, was only first isolated from an outbreak in Tanzania in 1952 [1]. The virus is believed to have originated in Africa, where it is maintained in sylvatic cycle involving wild primates and forest-dwelling mosquitoes. It was subsequently introduced into the urban setting, where human-to-human transmission is maintained by *Aedes aegypti* and *Aedes albopictus* [2].

The disease is characterized by abrupt onset of high fever, arthralgia, myalgia, headache, and sometimes rash. The symptoms are generally self-limiting, lasting 1-10 days. However, arthralgia may last for months or years. Chikungunya is an African Makonde word meaning "the one which bends up", describing the posture of an infected patient suffering from excruciating joint pains.

Chikungunya outbreaks have been reported in Asia; e.g. Philippines, Malaysia, India, Indonesia [3-7] and Africa; e.g. Congo, Uganda, Senegal [8-10]. Major epidemics appear and disappear cyclically, usually with an inter-epidemic period of 7-8 years and sometimes as long as 20 years. However, due to an unprecedented outbreak in the Indian Ocean in the beginning of 2005, the disease has more recently grabbed international attention [11-13]. More than 1 million cases have been reported from Comoros, Mayotte, Seychelles, Reunion Island and Mauritius. The huge epidemic potential of the disease is demonstrated by the seroconversion rate of 35% of the Reunion population of 770,000 [14]. The epidemic has

since moved to Sri Lanka and India in the beginning of 2006 [5]; and Italy in 2007 [15].

Surveillance in Singapore

In view of the outbreaks in the Indian Ocean islands, India and Sri Lanka, a surveillance system was initiated at the end of 2006. The medical community was apprised by the Ministry of Health (MOH) to look out for cases of chikungunya fever. At the Environmental Health Institute (EHI), National Environmental Agency, laboratory diagnosis capacity was established, and active laboratory-based surveillance that involved polymerase chain reaction (PCR) and serology testing was set up. The active surveillance involves a network of general practitioners (GPs) who are encouraged to consider chikungunya fever as a differential diagnosis when dengue was suspected (due to similar initial symptoms for both diseases). It also involves testing of dengue-negative blood samples from hospitals and general practitioners.

Out of about 1800 samples tested since the start of the surveillance, 10 cases were detected at EHI between Dec 2006 and Dec 2007. All these cases were classified as imported.

On 14 Jan 08, a 27 year-old foreign national residing in Little India was notified by a general practitioner in the area to have chikungunya fever. Epidemiological investigations revealed that this was likely a case of local transmission as he had not travelled out of Singapore for several months.

Outbreak control

As soon as local transmission was suspected, active case finding was immediately conducted by MOH among the residents and workers in the vicinity of the case and within the Little India enclave. Blood samples were also collected after consent had been obtained. The medical community was alerted through a MOH circular. Clinics in the vicinity of the residential premises and workplaces of the cases were further alerted through telephone communications. The monthly number of chikungunya tests requested by GPs and hospitals increased sharply from 18 in Dec 2007 to 200 in Jan and Feb 2008. A total of 2626 persons in the area consented to have their blood samples taken With this enhanced surveillance, another 12 local cases were detected (*Fig 1*).

The initial cases resided within the same row of shop houses at Clive Street, but subsequently one case was reported at Norris Road and 2 cases at Mackenzie Road. All the 13 cases were epidemiologically

Figure 1
**Time distribution of 13 chikungunya cases in Singapore,
5 – 28 January 2008**
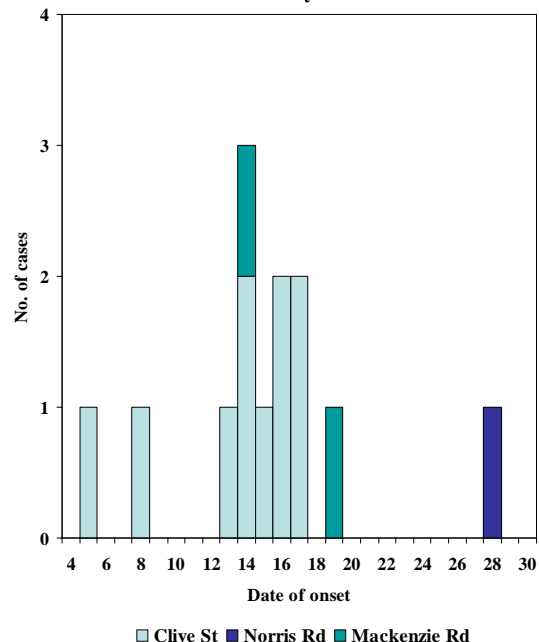
Source: Ministry of Health, Singapore

linked to an area of about 0.3 km^2 in the vicinity of Little India (*Fig 2*).

Viraemic patients that were tested positive by PCR were isolated and managed at the Communicable Disease Centre (CDC), Tan Tock Seng Hospital. These patients were closely monitored with daily blood tests to ensure that they were well and no longer viraemic before they were discharged.

Aggressive 'search and destroy' vector control measures were concurrently implemented. These included mass ground operations involving 95 field officers who inspected more than 4800 premises for mosquito breeding, as well as indoor insecticide misting, outdoor ultra low volume thermal fogging and residual spraying of workers' quarters. A total of 77 breeding sites were detected and destroyed. These operations were also extended to places visited by the cases prior to their onset of illness. A number of agencies such as Urban Renewal Authority, Land Transport Authority, Public Utilities Board, Ministry of Manpower and Singapore Contractors Association Limited were also involved in sprucing up the affected area and in community outreach. Media publicity, including advisories to residents and shop owners in the vicinity and foreign workers, was intensified.

The last case was a Singaporean who lived at Mackenzie Road She was admitted to hospital on 16 Jan 2008 for suspected dengue, but later found to have chikungunya fever. Her date of onset of fever was 28 Jan 2008. The outbreak was declared over on 21 Feb 2008 (2 incubation periods) when no further cases were reported despite the high level of vigilance. A key to the successful control of this outbreak was the close interagency coordination and the public-private partnership.

Figure 2
Red frame in the Singapore map shows the area with the chikungunya cluster.
Street map shows the location of cases
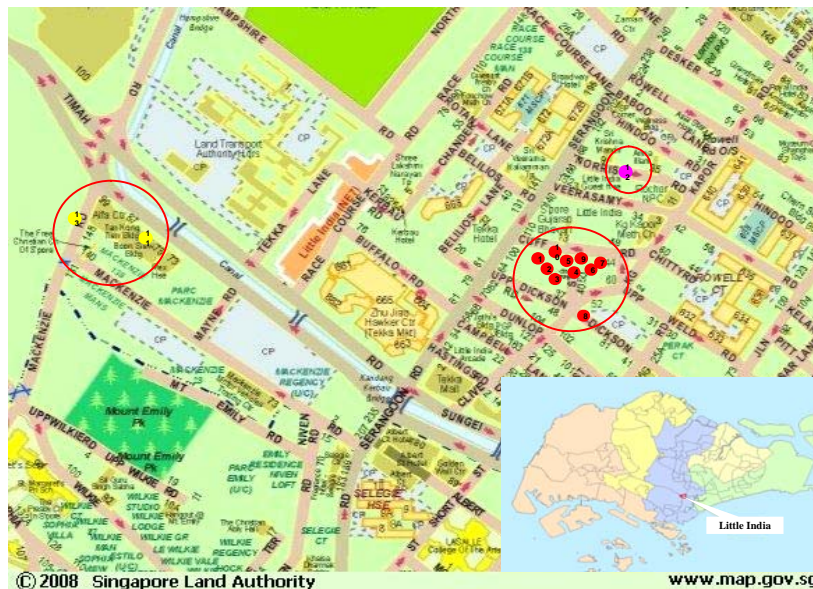
● **Clive St**   ● **Norris Rd**   ● **Mackenzie Rd**   Source: Ministry of Health, Singapore

Further surveillance and research

Surveillance for chikungunya infection continues. 5 more imported cases have been detected at EHI since the outbreak was brought under control.

Sequencing of the viruses responsible for the local outbreak has revealed that the local viruses are different from the ones that have been circulating in Indonesia and Malaysia in the last few decades, but are very similar to the ones that caused the Indian Ocean outbreak in 2006 (accession no EU441882 and EU441883). Together with similar analysis from other studies in the world, this shows that this group of virus, which spread from Africa to the Indian Ocean islands in 2005, has moved East to India and Sri Lanka in 2006, north to Italy in 2007, and now to Singapore in 2008. This demonstrates the rapid spread of this disease in the highly globalised world. A mutation (A226V) in the genome that could have resulted in the high epidemic potential of the chikungunya virus in Reunion Island[16] and its high replication rate in *Aedes albopictus* is not found in our virus. Owing to the wide distribution of *Aedes albopictus* in Singapore, transmission caused by the virus with that mutation could pose even bigger challenges.

(Reported by Ng L C, Environmental Health Institute, National Environmental Agency)

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Surveillance and control of malaria in Singapore

Singapore was certified free from malaria by the World Health Organization in Nov 1982[1]. This followed a thorough review of the effectiveness of malaria surveillance operations, with particular reference to the comprehensiveness and efficacy of the case detection mechanism, reliability of the microscopic diagnosis of blood smears, thoroughness of epidemiological investigations and satisfactoriness of the epidemiological situation, adequacy of preventive and remedial action taken on discovery of cases, and adequacy of the general health services and of the system of notification and epidemiological follow-up for the prevention of the re-establishment of malaria[2]. The confirmation of malaria eradication refers not only to the situation at a given point of time, but more importantly it is concerned with the probability that the malaria-free status can be maintained in the infinite future. The WHO was confident that this state could be maintained in view of Singapore's comprehensive health service networks in the urban setting and its effective malaria vigilance mechanisms.

Epidemiological situation

During the period 2003-2007, between 118 and 181 malaria cases were reported annually. Most of the infections were caused by *Plasmodium vivax* (64%-71%), followed by *P. falciparum* (26%-34%). Infection by *P. malariae* was uncommon (*Table 1*).

All age groups were affected with the highest proportion of cases between 25 and 34 years of age (*Table 2*). There was a male predominance with males outnumbering females by 3.3 to 5.9 times.

Majority of the reported cases (55%-70%) were foreigners (*Table 3*). Among local residents, the mean annual incidence rate was highest in Malays (3.0/100,000), followed by Indians (2.6/100,000) and Chinese (0.8/100,000).

Based on travel history, majority of the reported cases were classified as imported, mainly from Southeast Asia and the Indian subcontinent (*Table 4*). Local

Table 1

Distribution of malaria parasite species, 2003-2007

Parasite species	2003 (%)	2004 (%)	2005 (%)	2006 (%)	2007 (%)*
Plasmodium vivax (P.v).	76 (64.4)	108 (71.1)	107 (64.5)	123 (68.0)	103 (68.2)
Plasmodium falciparum (P.f.)	40 (33.9)	41 (27.0)	54 (32.5)	47 (26.0)	43 (28.5)
Mixed (P.v. & P.f)	2 (1.7)	1 (0.7)	3 (1.8)	7 (4.0)	2 (1.3)
Mixed (P.v. & P.m.)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)
Plasmodium malariae (P.m).	0 (0)	2 (1.3)	2 (1.2)	4 (2.0)	2 (1.3)
Total	118 (100.0)	152 (100.0)	166 (100.0)	181 (100.0)	151 (100.0)

* excludes 3 *P. knowlesi* infections

Table 2
Age distribution of reported malaria cases*, 2003-2007

Age group	2003 (%)	2004 (%)	2005 (%)	2006 (%)	2007 (%)
0 - 4	0 (0.0)	2 (2.2)	1 (0.8)	1 (0.9)	0 (0)
5 - 14	2 (2.5)	4 (4.4)	6 (4.8)	6 (4.8)	1 (1.1)
15 - 24	18 (22.2)	22 (23.9)	38 (30.6)	24 (19.4)	23 (25.0)
25 - 34	26 (32.1)	33 (35.9)	43 (34.7)	49 (39.5)	37 (40.2)
35 - 44	13 (16.0)	7 (7.6)	15 (12.1)	22 (17.7)	12 (13.0)
45 - 54	11 (13.6)	12 (13.0)	11 (8.9)	18 (14.5)	15 (16.3)
55+	11 (13.6)	12 (13.0)	10 (8.1)	4 (3.2)	4 (4.4)
Total	81 (100.0)	92 (100.0)	124 (100.0)	124 (100.0)	92 (100.0)

* Figure excludes foreigners seeking medical treatment and tourists

Table 3
Ethnic distribution of reported malaria cases*, 2003-2007

Ethnic group	2003 (%)	2004 (%)	2005 (%)	2006 (%)	2007 (%)
Chinese	21 (25.9)	20 (21.7)	10 (8.1)	31 (25.0)	20 (21.7)
Malays	15 (18.5)	13 (14.1)	19 (15.3)	18 (14.5)	7 (7.6)
Indians	7 (8.6)	11 (12.0)	11 (8.9)	6 (4.8)	3 (3.3)
Others	0 (0)	3 (3.3)	6 (4.8)	1 (0.9)	3 (3.3)
Foreigners	38 (47.0)	45 (48.9)	78 (62.9)	68 (54.8)	59 (64.1)
Total	81 (100.0)	92 (100.0)	124 (100.0)	124 (100.0)	92 (100.0)

* Figure excludes foreigners seeking medical treatment and tourists

Table 4
Classification of reported malaria cases, 2003-2007

Classification	2003 (%)	2004 (%)	2005 (%)	2006 (%)	2007 (%)**
Indigenous+	0 (0)	1 (0.7)	0 (0)	12 (6.6)	1 (0.7)
Introduced*	4 (3.4)	0 (0)	0 (0)	2 (1.1)	0 (0)
Induced	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.3)
Imported#	113 (95.8)	150 (98.6)	165 (99.4)	166 (91.7)	148 (98.0)
Cryptic^	1 (0.8)	1 (0.7)	1 (0.6)	1 (0.6)	0 (0)
Total	118 (100.0)	152 (100.0)	166 (100.0)	180 (100.0)	151 (100.0)

+ a malaria infection which has been proved or cannot be disproved to be due to recent local transmission;
* directly secondary to a known imported case;
# as shown by tracing the case to its origin in a malarious area outside Singapore;
^ isolated and not associated with secondary cases, as determined through appropriate epidemiological investigation, including a mass blood survey after the expiry of the incubation period;
** Excluding 3 cases caused by *P knowlesi*

residents who contracted the disease in the endemic countries constituted 29% - 34% of the imported cases. The other population groups with imported malaria were work permit/ employment pass holders, foreigners seeking medical treatment in Singapore and tourists from other countries (*Table 5*). More than 92% of the local residents did not take personal chemoprophylaxis while they were away for social visit, business or vacation.

Localised outbreaks

An outbreak occurred at Pulau Tekong between July and Aug 2003[3]. The index case was a foreigner with relapsing vivax malaria. His onset of illness after arrival in Singapore was 29 July 2003. The infection subsequently spread to four local residents who were confirmed to have vivax malaria between 10 Aug and 19 Aug 2003. *Anopheles* vector breeding habitats were detected in the island.

Another localised outbreak of 13 cases of vivax malaria, including one with asymptomatic infection, was reported at Jurong Island/ Pulau Busing from March – Aug 2006[4]. All of them were foreign construction workers. The initial cluster of four cases among this group of workers with onset of illness be-

tween 20 March 2006 and 20 May 2006 was originally classified as imported. Transmission continued until the last case was notified on 11 Sept 2006. No *Anopheles* vectors were detected despite extensive larval surveillance and adult trapping.

A cluster of 3 cases of simian malaria was detected among a group of local residents who had no recent travel history outside Singapore. The first case developed generalised body aches, fever and joint pains on 25 Apr 2007 and was admitted to the Communicable Disease Centre (CDC), Tan Tock Seng Hospital on 28 Apr 2007. He was earlier diagnosed to be suffering from *P. malariae* but laboratory test by polymersase chain reaction (PCR) later confirmed it to be *Plasmodium knowlesi*. Two more cases from the same work place subsequently developed fever, chills, body ache, myalgia and giddiness on 26 and 27 May 07. They were admitted to CDC on 2 Jun 2007. As their clinical presentation was similar to that of the first case, further laboratory investigations were conducted and they were confirmed to be infected with *P. knowlesi*. These three cases probably acquired the infection in the forested areas where macaques have been sighted. A total of 230 blood slides (for

Table 5
Classification of imported malaria cases by population group, 2003-2007

Classification	2003		2004		2005		2006		2007	
	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
Local residents who contracted malaria overseas	38	33.6	43	28.7	46	27.9	55	33.2	28	18.9
Tourists from other countries	13	11.5	15	10.0	19	11.5	19	11.4	13	8.8
Foreigners seeking treatment from Singapore	24	21.2	45	30.0	23	13.9	38	22.9	49	33.1
Work permit and employment pass holders	33	29.3	36	24.0	46	27.9	46	27.7	51	34.5
Others	5	4.4	11	7.3	31	18.8	8	4.8	7	4.7
Total	113	100.0	150	100.0	165	100.0	166	100.0	148	100.0

microscopy) and 208 venous samples (for PCR) taken from 230 people living within the area were tested negative for malaria parasite.

Prevention of reintroduction of malaria

A high degree of vigilance is maintained over the malaria situation in Singapore as the country is still receptive and vulnerable to the re-introduction of malaria. Favourable vector breeding habitats for *A maculatus* and *A sundaicus* are still present in some specific localities and there is a constant influx of malaria parasite carriers (both foreign workers and tourists) from malaria endemic countries.

All notified cases are thoroughly investigated. Whenever a case which could not be classified as imported is detected, epidemic control measures including active and passive case detection, mass blood survey and vector surveillance and control are imple-

mented. During the period 2003-2006, between 1555 and 3730 blood films were collected and tested for malaria parasites.

Vector surveillance and control

Surveillance and control of *Anopheles* mosquitoes is undertaken by the National Environmental Agency (NEA). Environment management and source reduction are the key strategies of Singapore's anti-malaria programme. The former is to render potential breeding habitats unfavourable for the vector to breed. In the case of source reduction, *Anopheles* breeding and potential breeding sites are eliminated.

Malaria receptive areas (*Fig 3*) i.e. areas where *Anopheles* vectors have been known to be present and whose environment is conducive for the breeding of such vectors, are identified and reviewed annually. A dedicated team of officers is deployed to conduct rou-

Figure 3
Malaria receptive area in Singapore
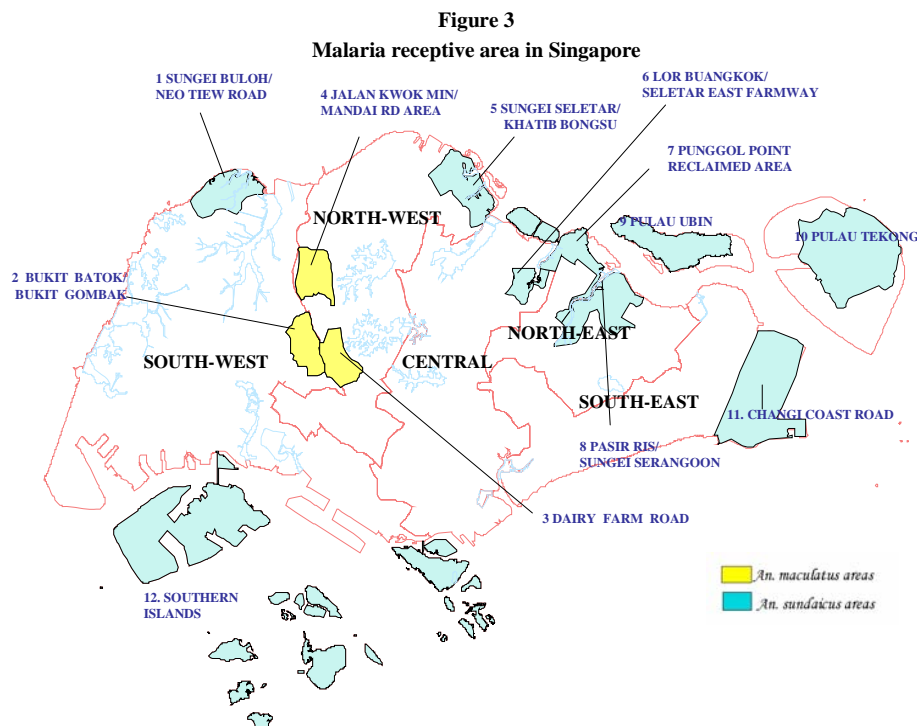
tine vector surveillance and treat potential breeding sites with anti-malarial oil on a weekly basis. If *Anopheles* breeding sites are detected, NEA will carry out thermal fogging at the affected vicinity for 3 consecutive nights (from 10.00 pm onwards). Light trapping (7.00pm to 7.00am) will also be conducted once a week from the fifth day onwards for 3 consecutive weeks (with larvae surveillance) to assess the situation.

The management of any worksite situated in the vicinity where *Anopheles* vectors are detected is required to carry out weekly larvicidal oiling/spraying and night fogging of their premises, and monthly residual-spraying of both the interior and exterior walls of all bangsals (workers' living quarters) and site offices. As a precautionary measure, the Ministry of Health conducts blood screening on all foreign workers residing in the vicinity. All operations will cease when there is no more *Anopheles* mosquito detected.

Environmental control measures such as construction of proper drainage system (with surface drains and subsoil pipes) to minimize water stagnation that are favourable for *Anopheles* breeding , removal of vegetation and variation of water salinity are carried out in identified areas.

When a suspected/confirmed case of imported malaria is reported in a receptive area, *Anopheles* surveillance is immediately carried out within 2 km from the case's address. If breeding sites are detected, they will be destroyed and all potential breeding habitats oiled/sprayed. Thermal fogging will also be conducted within 2 km from the case's address for 3 consecutive nights. Thereafter, daily light trapping (7.00pm to 7.00am) one day after the last fogging will be carried out and this will be continued for 3 weeks. In addition, weekly night fogging will be carried out for the next 2 weeks.

The same measures are also taken for a suspected/confirmed case of local malaria in an area not known to be receptive to malaria. If the case is a foreign worker either working or residing in a worksite in the area, its employer will be required to carry out the above-mentioned control measures at the worksite and advised to provide insect repellent or mosquito nets for all the workers who stay within the worksite at night. Chemoprophylaxis will also be recommended.

If one or more local malaria cases (suspected/confirmed) are reported in a receptive area, regardless of whether any *Anopheles* breeding is detected or not, all the measure described above will be carried out. Besides daily light trapping, human baiting will be set up. If *Anopheles* vector is trapped, the entire operation will continue until the light trapping or human baiting shows that there is no more *Anopheles* mosquito in the vicinity. Residents and visitors to the outbreak area will be advised to use insect repellent and other personal protection measures from evening through the night.

(Reported by Lee A, Communicable Diseases Division, Ministry of Health, and Tang CS, Environmental Health Department, National Environmental Agency)

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Missed opportunities for tuberculosis contact screening in Singapore – a retrospective case-control study

Introduction

Screening close contacts of infectious tuberculosis (TB) cases to identify active and latent TB for treatment constitutes a key TB control and elimination strategy and is utilized by many low TB burden countries [1-5]. Prior to 1998, contact investigation by the Singapore TB Control Programme comprised chest radiograph screening for active disease in household / family contacts of notified TB cases. Tuberculin skin test (TST) screening for latent TB infection (LTBI) and its treatment with isoniazid was only carried out in household contacts under the age of 5 years. With the launch of the Singapore TB Elimination Programme (STEP) in 1997, a national policy of TST screening of close contacts (regardless of age) of sputum TB culture-positive cases for the purpose of LTBI detection and treatment was implemented [6,7]. Screening was also extended to close contacts at the workplace, schools, and congregate settings (eg. prisons, nursing homes and the Institute of Mental Health). We believe that this strategy, in parallel with the other key STEP activities of directly observed therapy or DOT (ie. the administration of TB medications under supervision at the patient's nearest polyclinic) and treatment surveillance of all TB cases treated in Singapore, has contributed to the sustained decade-long decline in Singapore's annual TB incidence rate, from 57 new cases / 100,000 resident population in 1998 to 35 new cases / 100,000 population in 2006 [8].

While contact investigations in congregate settings such as prisons, nursing homes, mental institutions and schools are performed on an outreach basis, screening of close contacts in the household, family and workplace has been carried out largely on an invitational basis, in which contacts identified by the index cases are invited to the TB Control Unit (TBCU) Contact Clinic for screening. Although it is the policy to invite the close contacts of all sputum culture-positive TB cases for screening, our efforts and resources are prioritized towards contact investigations for sputum acid-fast bacilli (AFB) smear-positive cases as these cases are the most infectious, and their contacts should therefore be accorded priority for screening [9]. An audit of the TB Control Programme's contact investigation outcomes over the past five years revealed that approximately 30% of sputum AFB smear-positive TB cases did not have any contacts screened [10].

We performed a retrospective, case-control study to determine the characteristics of sputum smear-positive TB cases for whom no contacts were screened and to identify the points of "failure" in the contact investigation process. We sought to identify specific areas and socio-demographic groups in which initiatives may be needed to provide all TB contacts with the opportunity to be screened and to improve the performance of our contact screening programme.

Methods

TB is a notifiable disease in Singapore. All bacteriologically positive (ie. sputum AFB smear / culture-positive) pulmonary / laryngeal TB cases ("index" cases) are sent a letter inviting them to the TBCU

Contact Clinic for an index interview. This interview serves to ascertain the infectious period (taken as the duration of cough), the environment of exposure and to identify persons exposed during this period. Contact investigations are not carried out for cases of extra-pulmonary TB (with the exception of laryngeal TB) and bacteriologically negative pulmonary TB. Index cases treated at the TBCU (which treats approximately 60% of the country's TB cases) are interviewed at the treatment clinic, which is adjacent to the Contact Clinic. Index cases treated at other treatment centres who are unable or unwilling to attend the Contact Clinic are interviewed via phone by the Contact Clinic staff. The Contact Clinic is electronically linked to the TB Notification registry and receives information pertaining to the demographic and disease characteristics of the notified infectious TB case in readiness for the index interview. Where necessary, site visits are carried out in workplace contact investigations.

Persons deemed to have been exposed to the infectious case in a closed environment for at least 8 hours are invited for screening at the Contact Clinic at no charge. Household and family contacts are verbally invited by the index case to present themselves for screening. If the identified contacts do not self-present for screening, no further attempt is made to reach them, with the exception of children under five years of age or those with known medical factors which render them vulnerable to disease progression if latently infected. In 2002 (the year of the study), contacts without any history of TB or LTBI underwent TST using 1 TU RT 23 PPD (Serum Statens Institut, Copenhagen, Denmark). All contacts were questioned for symptoms of active TB. Chest radiographs were performed in those with positive TST or who were symptomatic, regardless of TST reading.

Contact screening records in the TBCU Contact Clinic were retrospectively reviewed. Although contact screening is performed for sputum culture-proven cases regardless of smear status at our centre, we focused the present analysis on the subset of sputum smear-positive cases, as these are the most infectious cases. All sputum smear-positive pulmonary / laryngeal TB cases notified in 2002 with no contact screened were matched for date of starting TB treatment with two control subjects (ie. sputum smear-positive cases who had at least one contact screened). Those who had no contact screened were subcategorized according to: (1) those who had no index interview (2) those who underwent index interview but did not identify any contacts, and (3) those who had identified contacts, but whose contacts did not turn up for screening.

The following information regarding the index cases' and controls' demographic characteristics were extracted from the TB notification registry for analysis: age, sex, ethnicity, marital status, employment status and housing type according to private or public housing, and the number of rooms in the latter instance. Housing type was taken as a surrogate marker of socio-economic status. (Eighty-five percent of the Singapore population lives in public housing apartments. The number of rooms in these housing units is taken as an indicator of the person's economic status as the eligibility to purchase public housing is linked to household income.) Disease characteristics captured were the presence and duration of cough, cavitary disease and co-morbid conditions (ie. diabetes mellitus, end-stage renal failure, malignancy, immunosuppressive conditions and use of immunosuppressive drugs). For cases in whom index interviews were performed (i.e. categories 2 and 3), additional information per-

taining to the degree of social support as indicated by whether the index case was living alone, with friends or family, was captured. Characteristics of the cases with no contact screened were compared with that of the controls.

Statistical analysis

The data collected was analyzed using SPSS version 13. Subjects' demographic data and background characteristics were summarized by descriptive statistics and presented by study groups. Subgroup analyses were also done. Chi square or Fischer's exact tests were used to determine the association between background characteristics and missed opportunities. Odds ratios together with 95% confidence intervals were presented for significant factors. To provide a more comprehensive analysis, multivariate logistic regression (logit) was also performed. Lastly, multinomial logistic regression (mlogit) was carried out for further analysis of the subgroups. All statistical tests were conducted at 5% level of significance.

Results

There were 658 sputum AFB smear-positive cases out of the 1,141 culture-positive pulmonary / laryngeal TB cases notified in 2002. Of the smear-positive cases, 132 (20%) did not have any contacts screened: 32 (24%) had no index interview performed, 49 (37%) failed to identify any contacts at their interview, while 51 (39%) had identified contacts, but none of these contacts presented for screening. For the case-control analysis, 244 index cases matched for the date of starting TB treatment were selected from the 526 smear-positive cases for whom at least one contact was screened. We were unable to achieve exact matching of 2 controls per index cases as there were some

cases with only one (or no) control who started treatment on the same date.

The demographic and social characteristics of the cases and controls are shown in *Table 6*. Univariate analysis identified living in one or two-room public housing units, living alone, having co-morbid conditions and not having completed treatment as factors associated with no contact screened (*Table 6*). Multivariate analysis revealed non-Chinese ethnicity, living in one or two-room public housing apartments, living alone and having co-morbid conditions as index case factors associated with no contact screened (*Table 6*).

Multinomial logistic regression subgroup analysis

Subgroup analysis of the index cases with no contacts screened (those with no index interview, those with no contacts identified and those with none of the identified contacts turning up for screening) was done, with the controls serving as the reference group for comparison. The multinomial logit model (*Table 7*) shows that contacts of non-Chinese index cases were more likely to fail to turn up for screening (adjusted OR: 4.37; 95% C.I. 1.63-11.76) when compared with contacts of Chinese index cases. Other things being equal, index cases who lived alone were significantly more likely not to have identified any contacts (adjusted OR: 325.33; 95% C.I. 15.40-6871.60), when compared with contacts who lived with family or friends. The model was found to be satisfactory (Nagelkerke: 0.47).

Discussion

Our study revealed index case factors of living alone, lower socio-economic status (taking housing

Table 6

Comparison of characteristics of cases with no contacts (n=132) screened versus controls (n=244)

Characteristic	Cases N (%)	Controls N (%)	Univariate analysis		Multivariate logit analysis	
			OR (95% Cl)	P value	OR (95% Cl)	P value
Age						
• < 60 yr	81 (61)	159 (65)	1.0			
• >=60 yr	51 (39)	85 (35)	1.18 (0.76-1.82)	0.46	1.06 (0.41-2.72)	0.90
Sex						
• Female	35 (27)	79 (32)	1.0			
• Male	97 (73)	165 (68)	1.32 (0.83-2.12)	0.24	1.78 (0.68-4.71)	0.24
Ethnicity						
• Chinese	81 (61)	167 (68)	1.0			
• Non-Chinese	51 (39)	77 (32)	1.37 (0.88-2.12)	0.17	2.75 (1.16-6.52)	0.02
Marital status						
• Married	84 (64)	177 (73)	1.0			
• Not married	48 (36)	67 (27)	1.51 (0.96-2.38)	0.07	0.94 (0.38-2.32)	0.89
Housing Type						
• Private / 5 room	12 (9)	42 (17)	1.0			
• 3 – 4 room	59 (45)	143 (59)	1.45 (0.71-2.93)	0.31	1.44 (0.71-2.94)	0.39
• 1 – 2 room	19 (14)	13 (5)	5.13 (1.79-13.33)	<0.01	5.12 (1.97-13.27)	0.01
• Data NA*	42 (32)	46 (19)				
Living arrangement						
• Lived with family / friends	71 (54)	222 (91)	1.0			
• Lived alone	28 (21)	6 (2.5)	14.59 (5.81-36.66)	<0.01	14.84 (3.50-62.91)	0.01
• Data NA	33 (25)	16 (6.5)				
Employment status						
• Employed	48 (36)	110 (45)	1.0			
• Unemployed	61 (46)	97 (40)	1.44 (0.90-2.29)	0.12	0.96 (0.37-2.49)	0.94
• Data NA	23 (17)	37 (15)				
Co-morbidity						
• No	24 (18)	82 (34)	1.0			
• Yes	70 (53)	114 (46)	2.09 (1.22-3.61)	0.01	2.53 (1.06-6.04)	0.04
• Data NA	38 (29)	48 (20)				
Cavitary disease						
• No	74 (56)	120 (49)	1.0			
• Yes	58 (44)	124 (51)	0.76 (0.49-1.16)	0.20	0.77 (0.35-1.72)	0.53
Treatment outcome						
• Completed	88 (67)	189 (77)	1.0			
• Not completed	44 (33)	55 (23)	1.72 (1.07-2.75)	0.02	1.37 (0.51-3.68)	0.53

*NA = not available

Table 7

Multinomial subgroup analysis*

	No index interview OR (95%)	No contact identified OR (95%)	Identified contacts did not turn up OR (95%)
Ethnicity			
• Chinese	1.0	1.0	1.0
• Non-Chinese	0.85 (0.09-8.46)	0.41 (0.02-10.55)	4.37 (1.63-11.76)
Marital status			
• Married	1.0	1.0	1.0
• Not married	6.15 (0.65-57.74)	1.93 (0.16-23.82)	1.86 (0.52-6.69)
Housing			
• Private/5 room	1.0	1.0	1.0
• 3-4 room	1.16 (0.09-14.42)	0.10 (0.01-1.41)	2.87 (0.58-14.19)
• 1-2 room	2.52 (0.07-89.93)	0.29 (0.01-10.41)	6.00 (0.83-43.70)
Living arrangement			
• Lived with family/friends	1.0	1.0	1.0
• Lived alone	13.57 (0.47-396.04)	325.33 (15.40-6871.60)	2.07 (0.26-16.67)
Employment status			
• Employed	1.0	1.0	1.0
• Unemployed	0.11 (0.01-1.98)	1.04 (0.09-11.49)	0.83 (0.27-2.54)
Co-morbidity			
• No	1.0	1.0	1.0
• Yes	10.95(0.88-135.61)	7.44 (0.63-87.41)	1.91 (0.69-5.24)

* control group as reference
* adjusted for age, sex, marital status, occupational status, presence of cavitary disease and treatment outcome.

status as a surrogate marker), non-Chinese race and presence of co-morbid conditions to be independently associated with having no contact screened. Non-identification of contacts during index interview was significantly more likely in those who lived alone; while non-Chinese index cases were more likely to have identified contacts who did not subsequently turn up for screening.

This study was subject to several limitations. As the data were obtained from the TB registry and retrospectively from the contact screening records, much of the missing information could not be veri-fied. Index interviews done via telephone would have not been as effective as a face-to-face interview. The small sample size would also render the multivariate and multinomial analyses less statistically precise.

Lower socio-economic status and presence of comorbidity, which were associated with having no contact screened in the overall analysis, were not iden-tified as significant factors in the subgroup analysis. This may be due to the large number of missing data in these two fields. Subgroup analysis of cases in whom no index interview was performed also failed to identify any significant associated factors, and this

may be also be due to the large number of missing data in this subgroup and its small sample size. A fair proportion of cases who did not have any index interview either died (21.9%) or left the country (18.8%). Nonetheless, these factors should still not have prevented contact identification by means of proxy interview of a household or close family member, or human resource manager in the instance of workplace exposures.

It was not surprising that index cases who failed to identify any contacts were more likely to be (or claim to be) living alone. It is, however, very unlikely that they did not expose any persons and put any one at risk during their infectious period. We have noticed a general reluctance among index cases to identify their non-household / non-family contacts, possibly for fear of any repercussion or stigmatization. This emphasizes the need for community education towards the destigmatization of TB patients, so that these patients will be more willing to reveal their diagnosis and identify their contacts. Other general measures include honing the interview skills of our Contact Clinic staff and improving the rapport between the healthcare workers and patients, so that the patients will be more willing to identify their contacts. Treating physicians also play a crucial role in reinforcing to their patients the importance of contact screening, and in encouraging their contacts to undergo screening.

We found that identified contacts of Malay and Indian index cases were less likely than the Chinese to present themselves for screening. This may reflect the cultural beliefs and health attitudes of these ethnic communities. We had also previously found that Malay and Indian TB patients were more likely to default their TB treatment [11,12]. The Malay ethnic group also

has the highest TB incidence among the ethnic groups in Singapore (50 per 100,000 versus 33 /100,000 among the Chinese in 2006) [8]. This is thus an important community for which increased educational and outreach activities are needed.

In the United States (US), where targeted screening for LTBI treatment is a key TB elimination strategy, the Centers for Disease Control and Prevention (CDC) has set the target for contact screening to be performed for 95% of sputum smear-positive TB patients [13]. Notwithstanding the obvious need for our programme to increase the proportion of smear-positive TB cases with contacts screened, it is gratifying that, of those who underwent screening, 80 to 90% completed the screening protocol and accepted the recommended LTBI treatment, and over 70% completed their course of treatment [10]. This compares favourably with the LTBI treatment completion rates of 30% to 60% reported by US TB control programmes [14-17] and may be due to our invitational approach such that contacts who are motivated to present for screening are more likely to adhere to the screening protocol and complete LTBI treatment. This observation might argue against expending resources towards the screening of persons who are reluctant in the first place, and who are therefore less likely to achieve completion of LTBI treatment. Nonetheless, we believe that all persons deemed to have had significant exposure to an infectious TB case should be accorded the opportunity to be screened.

In conclusion, this study provides an insight into the factors associated with non-contact screening of sputum AFB smear-positive TB cases in Singapore. This information will be useful to guide future initiatives to strengthen our country's TB control efforts.

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Prevention of introduction of avian influenza into Singapore

Introduction

Avian Influenza (AI) is a highly infectious disease of birds. AI viruses are negative single-stranded enveloped RNA viruses that belong to the influenza A genus of the *Orthomyxoviridae* family. AI viruses maybe further divided into subtypes on the basis of the antigenic properties of their haemagglutinin (H1-H16) and neuraminidase (N1-N9) surface glycoproteins. All highly pathogenic AI viruses that cause generalized rather than respiratory disease belong to either the H5 or H7 subtypes [1]. The most virulent form of AI is known as highly pathogenic avian influenza (HPAI) which is a highly contagious disease of domestic fowl

The greatest variety of AI viruses has been isolated from wild birds particularly from waterfowl (ducks, geese and swans) and (gulls and shorebirds) [2]. Migratory waterfowl of the world are the natural reservoirs of AI viruses of all known subtypes [3]. Available evidence suggests that each of the 16 H and 9 N subtypes combinations exist in harmony with their natural hosts, cause no overt disease and are shed predominantly in the faeces [3].

AI viruses of all 16 H subtypes can cause low pathogenicity avian influenza (LPAI) in susceptible birds [1]. This is usually a mild respiratory disease with low mortality rates in poultry. In contrast HPAI is a systemic disease with high mortality rates approaching 100% in many gallinaceous birds [1]. Current theories suggest that HPAI viruses emerge from H5 and H7 subtypes of low pathogenicity by mutation [4,5] although there must be more than one mechanism by which this occurs [6]. It appears that such mutations occur only after the viruses have moved from their natural wild bird hosts to poultry. However the mutation to virulence is unpredictable and may occur soon after introduction to poultry or after the LPAI virus has circulated for several months [1,5].

Before 1997, there was no evidence to indicate that H5 AI viruses could infect humans and cause fatal disease [7]. The H7 influenza viruses were known to cause conjunctivitis in humans[8,9], and serologic studies provided evidence of subclinical human infection with the subtypes prevalent in avian live poultry markets[10]. The precursor of the H5N1 AI virus that spread to humans in 1997 was first detected in 1996 in Guangdong, China [11]. In the H5N1 outbreak in Hong Kong in 1997, the AI virus infected 18 people resulting in 6 deaths and the total depopulation of the poultry population of 1.3 million birds [12].

The current H5N1 outbreak that started in Asia in 2003 is unprecedented in scale and geographic distribution. The H5N1 AI viruses are now panzootic across 3 continents leading to huge economic losses and have also been transmitted to humans [12]. As at 28 May 08, the World Health Organization (WHO) has recorded a total of 383 human cases of H5N1 infection with 241 deaths [13]. The expansion of intensive poultry husbandry is likely to be facilitating the increased frequency and scale of HPAI outbreaks. Furthermore the present commercialized large-scale poultry industry is now shipping poultry and poultry products over long distances, facilitating the transmission of infection [12].

Singapore is free from HPAI. Given the devastating consequences of an HPAI H5N1 outbreak, the Agri-Food and Veterinary Authority of Singapore

(AVA) has adopted a series of measures to keep the AI virus out of the country. AVA's approach maybe described as a multi-layered control strategy for the prevention and control of HPAI. The strategy consists of several layers of control measures comprising control measures at source; border control measures; local control measures; and emergency preparedness

Control measures at source

Prohibiting import from HPAI infected countries

Under the Animals and Birds Act, the import of any poultry, bird, egg or avian product requires a permit from the AVA. Singapore uses this import requirement as its first line of control against HPAI. AVA officers frequently scan media reports, Food and Agricultural Organization (FAO) and OIE websites and reports for any occurrence of HPAI outbreaks. Where outbreaks are reported, AVA takes immediate steps to suspend import of poultry, birds and avian products from the infected country.

Establishing disease-free zones

Malaysia is an important source of live poultry and table eggs. Accredited poultry farms in Malaysia are allowed to export poultry and eggs to Singapore. In Sep 04 when an outbreak of HPAI was reported in the Malaysian state of Kelantan, AVA suspended all imports of poultry, eggs and ornamental birds from Malaysia. This disrupted the supply and caused a shortfall of poultry and eggs in Singapore. To ensure safety of poultry and egg supplies at source and prevent frequent disruptions to our supply, AVA worked closely with its Malaysian counterpart, the Department of Veterinary Services (DVS), to create disease-free zones (DFZs) in the states of Johor, Perak, Selangor, Malacca, and Negri Sembilan. As an added level of safety all accredited poultry farms are located in DFZs. The DFZs, together with the introduction of enhanced control and surveillance programmes, enabled exports to resume in Jan 05 without compromising animal or public safety.

The rationale for establishing and maintaining the DFZs is to allow the export of poultry and eggs from the DFZs to continue should there be another HPAI outbreak in Malaysia outside the DFZs. Subsequently, when Malaysia reported an outbreak of HPAI in chickens in Sungei Buloh, Selangor on 2 Jun 07, Singapore was able to continue import of poultry products from the DFZs of Johor, Malacca, Negri-Sembilan and Perak.

Border control measures

AVA officers inspect all imports of poultry, birds, eggs and avian products at the port of entry. Poultry and birds are inspected for any overt signs of HPAI. In particular AVA inspects all consignments of poultry from Malaysia. Each consignment is accompanied by a health certificate issued by DVS. In addition all consignments of ducks must be tested negative for AI by polymerase chain reaction (PCR) before they can be exported to Singapore. Randomly selected consignments of poultry and eggs are also sampled and tested for HPAI. During any HPAI alerts, AVA carries out enhanced inspection and surveillance at the checkpoints.

AVA also works closely with the Immigration and Checkpoints Authority (ICA) to curb smuggling especially of birds and avian products, at borders and checkpoints.

Local control measures

AVA employs a variety of local control measures against HPAI. These include biosecurity, biosegregation, surveillance, vaccination, removal of backyard poultry, improvement of diagnostic laboratory capability and public education. However, the

corner stones for AVA's control measures are biosecurity and enhanced surveillance.

Biosecurity

Biosecurity is considered the most important tool to prevent and control AI [1, 14]. The key is to keep migratory wild birds (especially water fowl) away from poultry and commercially bird breeding operations. AVA emphasizes biosecurity at all local poultry farms, poultry slaughterhouses, bird holding and breeding premises, zoological gardens and bird parks.

AVA defines biosecurity measures as measures to keep disease (specifically HPAI) out of local poultry farms, slaughterhouses and bird breeding premises. AVA has imposed strict biosecurity measures for local poultry farms and poultry slaughterhouses. For poultry farms, biosecurity measures are mandatory and annual farm licenses are only issued if the farm can demonstrate adequate biosecurity measures.

Biosegregation

AVA has also encouraged local poultry farms to adopt biosegregation measures. AVA defines biosegregation measures as measures to achieve minimal or no contact between poultry farms to minimize the risk of spread of disease. The adoption of biosegregation measures by poultry farms has allowed AVA to isolate local farms (4 layer and 2 quail farms) into bio-segregated clusters.

Surveillance for HPAI

In tandem with enforcement of biosecurity measures, AVA also carries out extensive surveillance for HPAI. These include surveillance on local poultry, imported poultry and eggs, migratory wild birds, pest and urban birds, ornamental birds, birds in wildlife reserves (e.g. Singapore Zoological Gardens and Jurong Birdpark) and birds at reservoirs and parks such as the Botanic Gardens. To date no HPAI positive bird has been detected.

Risk-based vaccination

Vaccination has been shown to be a powerful tool to support eradication programmes in situations in which a stamping-out policy is neither pursuable nor desirable [15]. AVA has implemented a limited risk based vaccination programme for high-risk species as well as birds kept in open exhibits in the Singapore Zoological Gardens and Jurong Birdpark. Swans and ducks in the Singapore Botanic Gardens have also been vaccinated.

In the Singapore Zoological Gardens, some of the species that were vaccinated include peafowl, bar–headed geese, spotted wood ducks, Egyptian geese, guinea fowl and domestic ducks [16]. The vaccine used is an inactivated avian influenza type A H5N2. This vaccine was evaluated and used to vaccinate poultry flocks in Hong Kong [17].

Improvement of diagnostic laboratory capability

AVA's Animal and Plant Health Laboratory (APHL) carries out tests for AI. To significantly shorten the test-turnover time, APHL decided to adopt molecular techniques to expedite the diagnosis of HPAI. A series of real-time reverse transcriptase polymerase chain reaction (RRT-PCR) assays offers a much more rapid alternative to virus isolation, with results available within 7 hours. APHL has also introduced genetic sequencing and analysis to determine the pathogenicity of AI isolates based on the amino acid sequence at the haemagglutinin gene cleavage site [18]. The new laboratory capability has significantly reduced the test turnover time from an average of 2 months to 2.5 days.

Public education

AVA has embarked on a public education campaign to educate the public to keep pet birds and pet poultry properly caged to avoid contact with wild birds. The AVA web-site has a series of useful frequently asked questions (FAQs) on "bird flu" or Avian Influenza [19] These range from what is bird flu, how is it spread, can it be transmitted to humans, etc.

For pet birds, the public has been advised to take precautionary measures such as keeping their birds in a bird-proof enclosure (e.g. cage, hen house or a netted area in their gardens) so that they do not come into contact with wild birds. In addition owners should not introduce birds of unknown origin to their existing pet birds. Owners or anyone who handles pet birds should also practise good hygiene, such as washing hands thoroughly with soap after handling their pets [19].

Removal of backyard poultry

In conjunction with AVA's public education campaign on "bird flu", AVA has also taken steps to remove backyard poultry from Pulau Ubin. This is in recognition that backyard poultry are difficult to biosecure or keep caged and the presence of such flocks is a risk factor for HPAI. It has been shown in several Asian countries that once the HPAI virus is entrenched it is extremely difficult to eradicate [20] .

In addition, AVA has passed legislation that prohibits the keeping of more than 10 pet poultry (in non-commercial premises) and these must be caged. AVA also prohibits the keeping of pet poultry within 1 km of any commercial poultry farms.

Emergency preparedness

Contingency plans

AVA has drawn up its contingency plans to prepare for an outbreak of HPAI in local poultry farms or bird holding premises. In addition, AVA has carried out preparatory measures to stockpile personal protective equipment (PPE), Oseltamivir tablets for prophylaxis and supplies and equipment for culling operations. AVA has also drawn up contracts with the private sector to provide services such as disposal, logistics and supply of labour.

Training and exercises

AVA has an ongoing training programme to train its officers in biosafety including how to wear PPE, decontamination and mask fitting. In addition AVA also carries out exercises (code named *Exercise Gallus*) once or twice a year to test its contingency plans. Exercises are carried out in situations that simulate an actual HPAI outbreak. These exercises test AVA's readiness to handle an outbreak in areas such as activation and recall of personnel, outfitting of staff with PPE, logistic support, coordination with other agencies, decontamination procedures and culling of poultry. To date AVA has carried out 5 exercises since Feb 2004.

Emergency vaccination

Vaccination has been shown to be useful tool to prevent and control AI in poultry. The primary goal of vaccination is to prevent or reduce clinical disease from an infectious agent [21]. Other than disease control, vaccination has 2 other important benefits. First, if vaccinated animals become infected, there is reduced virus shedding into the environment. This reduction in virus shedding would mean fewer viruses in the environment and would result in more rapid elimination of the virus from the environment . Second, vaccination increases the minimum dose of virus that is required to infect an animal. The increased resistance to infection coupled with reduced virus shedding greatly increases the chance of breaking the infection cycle.

AVA has stockpiled the Nobilis Influenza H5N2, Intervet, inactivated vaccines for emergency vaccination of local poultry farms if the threat of HPAI is imminent. An imminent threat refers to widespread uncontrolled HPAI outbreaks in neighbouring countries' provinces or states in close proximity to Singapore, HPAI detected in wild birds in Singapore and the threat of HPAI infecting humans. AVA will assess the threat before making a decision whether to vaccinate local poultry farms. AVA will also assess other AI vaccines for their effectiveness against H5N1.

Conclusion

Countries all over the world adopt various strategies best suited to their needs and poultry production systems to prevent and control HPAI. A strong veterinary service with adequate technical manpower and financial resources to devise strategies and implement surveillance and control programmes, and a well developed poultry industry with high standard of biosecurity are key success factors in combating HPAI. Some are very successful while others less so. Countries like Malaysia and the UK do not rely on vaccination but adopt import control and biosecurity to keep out HPAI [22]. They have also successfully stamped out occasional incursions of HPAI. Hong Kong has opted for universal vaccination and culling to contain the disease with some degree of success [17]. After stamping out a major outbreak of H7N7 HPAI in 2003, the Netherlands has adopted a preventive, voluntary vaccination programme in the face of the current threat of H5N1 [23]. AVA has applied the key elements of disease control principles in developing an appropriate strategy and put in place a series of control measures to prevent the introduction of HPAI. To control any potential outbreak, AVA has also drawn up its contingency plans and taken preparatory measures through simulation exercises. This strategy has been effective in keeping the disease out of Singapore which remains free from HPAI.

(Based on Leong HK, Goh CS, Chew ST, Lim CW, Lin YN, Chiang SF, Yap HH and Chua SB. Prevention and control of avian influenza in Singapore. Ann Acad Med Singapore 2008; 37: 524-9)

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