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CONTENTS

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Epidemiological and clinical features of melioidosis in Singapore (Jan 2002 – Jul 2004)

Melioidosis is a disease of the tropics caused by *Burkholderia pseudomallei*, a free-living soil organism. The disease is endemic in Southeast Asia and northern Australia with some regions of Thailand and northern Australia being considered hyperendemic.[1]

In endemic areas, the organism could be isolated from agricultural soils, stagnant water and paddy fields. The most common mode of transmission is through direct inoculation of contaminated soil and water through skin cuts or lacerations. Other possible modes of transmission include inhalation of contaminated dust, ingestion or aspiration of contaminated water. Sexual transmission in the presence of prostatic abscesses has been documented. The clinical presentations of the disease vary widely from chronic sub-clinical infections to acute localized or systemic suppurative infections and fatal septicaemic pneumonia. Studies have also shown that an individual's increased susceptibility to acute episodes as well as progression to more severe form of the disease is usually associated with various clinical determinants.

Although the first case of melioidosis in Singapore was reported in 1920, it was not recognized as an important health threat until three fatal septicemic cases among healthy young adults were reported in 1989. The disease was made administratively notifiable in October 1989[2]. The average annual number of cases reached the highest in 1998 with 114 reported cases. Since then, the incidence has been declining steadily and only 40 cases were reported in 2003. The annual incidence of melioidosis in 2002 and 2003 was 0.84/100,000 and 0.96/100,000 population, respectively. However, the number of melioidosis notifica-

tions has increased in Jan – Jul 2004. During this period, 58 cases were notified to the Ministry of Health compared to 13 and 14 cases reported for the same period of 2002 and 2003, respectively. In addition, higher case fatality was reported in 2004, particularly among patients with concurrent illnesses. The demographic and clinical determinants associated with the poor clinical outcomes are reviewed in this study.

In 2004, majority of the cases had onset of illness between February and May. Similar increase in cases was observed in August 2002 (9 cases) and July 2003 (10 cases) (*Fig. 1*). The possible association between heavy rainfalls and increase in incidence of melioidosis has been reported elsewhere[3]. In Singapore, the potential impact of rainfall has been studied and reported in this issue of the bulletin[4,5].

Demographic characteristics

Of 132 cases included in the review (Jan 2002 – Jul 2004), 57 (43%) were reported in the first seven months of 2004. (One case involving a foreigner who came to Singapore for medical treatment was excluded). The overall mean age of patients was 51.4 years (range 2 years – 91 years). The older patients in the 45 years and above age group represented 72% of the total cases. Those affected were predominantly males (81%) (*Table 1*). Most patients were Chinese although a higher proportion of Indian patients (16%) were reported in 2004. No clustering was found for any specific occupation (*Table 2*). It is technically difficult to differentiate between the local and imported cases due to the chronic nature of the disease as well as its endemicity in Singapore. There were no changes in demographic characteristics of the cases reported during the period of review (*Table 1*).

Clinical presentations

Most patients presented with fever (83%), cough (46%) and soft tissue abscesses (24%). Other common presenting symptoms were gastrointestinal symptoms (abdominal pain, vomiting and diarrhoea). An increase in patients presenting with cough was found in 2004 (58% in 2004 vs. 30% in 2003 and 46% in 2002). Patients presenting with soft tissue abscess(es) represented over 30% of cases in 2002

Figure 1
Trend of melioidosis in Singapore, January 2002 – July 2004

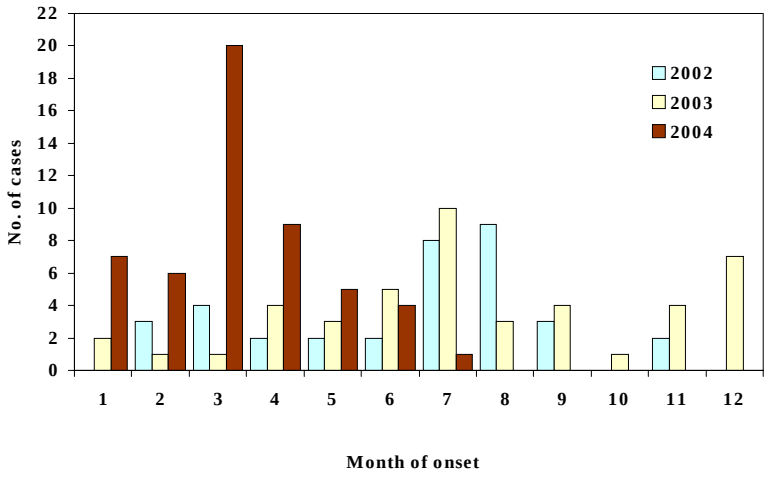

Table 1
Demographic characteristics of reported melioidosis cases (Jan 2002 – Jul 2004)

Patients' characteristics	Year			Total N = 132 (%)
	2002 N = 35 (%)	2003 N = 40 (%)	2004 (Jan-Jul) N = 57 (%)	
Age (Years)				
Mean (SD)	49.9 (20)	52.2 (16)	51.9 (15)	51.4 (17)
Age group				
Less than 35	7 (20)	7 (18)	6 (11)	20 (15)
35 – 44	6 (17)	6 (15)	5 (9)	17 (13)
45 – 54	6 (17)	4 (10)	20 (35)	30 (23)
55 – 64	8 (23)	13 (33)	15 (26)	36 (27)
65+	8 (23)	10 (25)	11 (19)	29 (22)
Gender				
Male	25 (71)	35 (88)	47 (83)	107 (81)
Female	10 (29)	5 (13)	10 (18)	25 (19)
Ethnic Group				
Chinese	19 (54)	26 (65)	35 (61)	80 (61)
Indians	3 (9)	3 (7)	9 (16)	15 (11)
Malays	9 (26)	9 (23)	10 (18)	28 (21)
Others	0	0	1 (2)	1 (1)
Foreigners	4 (11)	2 (5)	2 (4)	8 (6)

Table 2
Occupation of reported melioidosis cases (Jan 2002 – Jul 2004)

Occupation	Year			Total N = 132 (%)
	2002 N = 35 (%)	2003 N = 40 (%)	2004 (Jan-Jul) N = 57 (%)	
Musician	1 (3)	0	0	1 (1)
Businessman/Sales person	2 (6)	1 (3)	3 (5)	6 (5)
Storekeeper/Cashier	0	0	2 (4)	2 (2)
Officer worker	0	3 (8)	1 (2)	4 (3)
Technician	0	2 (5)	2 (4)	4 (3)
Engineer	0	1 (3)	1 (2)	2 (2)
Student	3 (9)	1 (3)	3 (5)	7 (5)
Hawker/Cook	1 (3)	0	3 (5)	4 (3)
Housewife	2 (6)	1 (3)	3 (5)	6 (5)
Infant	1 (3)	0	0	1 (1)
Kindergarten student	1 (3)	0	0	1 (1)
Driver	3 (9)	2 (5)	4 (7)	9 (7)
Operator	0	0	2 (4)	2 (2)
Delivery man/Postman	2 (6)	0	1 (2)	3 (2)
Meter reader	0	0	1 (2)	1 (1)
Security/Police guard	1 (3)	3 (7)	2 (4)	6 (5)
Labourers and related worker	0	1 (3)	0	1 (1)
Cleaner	2 (6)	0	2 (4)	4 (3)
Construction worker	2 (6)	2 (5)	3 (5)	7 (5)
SAF regular/NS man	0	2 (5)	2 (4)	4 (3)
Sports coach	0	0	1 (2)	1 (1)
Gardener/Home gardening	3 (9)	0	1 (2)	4 (3)
Retiree	7 (20)	15 (38)	17 (30)	39 (30)
Unemployed	2 (6)	3 (8)	3 (5)	8 (6)
Self-employed	0	2 (5)	0	2 (2)
Others	2 (6)	1 (3)	0	3 (2)

and 2003, but declined to 12% in 2004. However, those presenting with systemic abscesses increased from 5% in 2003 to 21% in 2004. In 2004, 40 (70%) of the patients were diagnosed with pneumonia compared to 40% in 2002 and 33% in 2003. Bacteremia was a common feature with over 60% having positive blood cultures for *B. pseudomallei*. The remaining patients were diagnosed with positive cultures of the specimens collected from other sites (i.e. pus, respiratory aspirate, sputum and urine) (*Table 3*).

Three quarters of the patients had one or more concurrent illnesses such as cardiac diseases (17%), hypertension (33%), diabetes mellitus (54%) and renal diseases (23%). The proportion of patients with concurrent diseases was higher in 2004, in particular diabetes mellitus (70%).

Case fatality

The case fatality rates due to melioidosis in 2002 and 2003 were 6% and 10%, respectively. During the first seven months of 2004, the case fatality rate has increased to 40% (*Table 4*). This increase was observed in all age groups including teenagers and young adults.

Table 3

Clinical presentations of melioidosis patients (Jan 2002 – Jul 2004)

Clinical findings	Year of notifications			Total N = 132 (%)
	2002 N = 35 (%)	2003 N = 40 (%)	2004 (Jan-Jul) N = 57 (%)	
Constitutional symptoms				
Fever	25 (75)	34 (85)	51 (89)	110 (83)
Chills	25 (75)	6 (15)	18 (32)	49 (37)
Respiratory symptoms				
Cough	16 (46)	12 (30)	33 (58)	61 (46)
Shortness of breath	5 (14)	5 (13)	23 (40)	33 (25)
Gastroinstinal symptoms				
Abdominal pain	3 (9)	3 (8)	9 (16)	15 (11)
Vomiting	2 (6)	2 (5)	6 (11)	10 (8)
Diarrhoea	3 (9)	0	7 (12)	10 (8)
Abscess (soft tissue/systemic)				
Soft tissue abscess(es)	13 (37)	12 (30)	7 (12)	32 (24)
Systemic abscess(es)	6 (17)	2 (5)	12 (21)	20 (15)
None	16 (46)	26 (65)	38 (67)	80 (61)
Pneumonia	14 (40)	13 (33)	40 (70)	67 (51)
Bacteremia (blood culture positive)	23 (66)	24 (60)	38 (67)	85 (64)
One or more concurrent medical conditions	19 (54)	29 (73)	51 (89)	99 (75)
Cardiac diseases	5 (14)	4 (10)	14 (25)	23 (17)
Hypertension	16 (46)	10 (25)	17 (30)	43 (33)
Diabetes mellitus	13 (37)	18 (45)	40 (70)	71 (54)
Renal diseases	6 (17)	8 (20)	17 (30)	31 (23)

The case fatality rate among patients with concurrent renal diseases was consistently high, ranging from 25% in 2003 to 59% in 2004. Similarly, high case fatality was found in those with concurrent cardiac diseases. On the other hand, the case fatality rate among patients presenting with soft tissue abscess(es) was consistently lower (0% in 2002, 8% in 2003 and 14% in 2004). Overall, case fatality among patients presenting with pneumonia was 33%; however, higher case fatality rate (48%) was reported in 2004. The case fatality for patients with bacteremia was 9% in 2002, 17% in 2003 and 53% in 2004 (*Table 5*).

Comments

There was an increase in melioidosis cases in the first seven months of 2004 compared to 2002 and 2003. It was also associated with a higher case fatality rate. There were no changes in the demographic characteristics of the cases that could have accounted for the higher mortality. The higher case fatality in 2004 could be attributed to a higher proportion of patients presenting with pneumonia and with concurrent medical conditions, particularly cardiac and renal diseases. Patients with these clinical features are known to be associated with a higher mortality.

Table 4

Demographic characteristics and case fatality of reported melioidosis cases (Jan 2002 – Jul 2004)

Demographic characteristics	Case fatality (%)			Total (%)
	2002 (%)	2003 (%)	2004 (Jan-Jul) (%)	
All patients	2/35 (6)	4/40 (10)	23/57 (40)	29/132 (22)
Age groups				
Less than 35	1/7 (14)	0/7	2/6 (33)	3/20 (15)
35 – 44	0/6	0/6	2/5 (40)	2/17 (12)
45 – 54	0/6	0/4	6/20 (30)	6/30 (20)
55 – 64	0/8	1/13 (8)	7/15 (47)	8/36 (22)
65+	1/8 (13)	3/10 (30)	6/11 (55)	10/29 (34)
Gender				
Male	1/25 (4)	4/35 (11)	18/47 (38)	23/107 (21)
Female	1/10 (10)	0/5	5/10 (50)	6/25 (28)
Ethnic group				
Chinese	2/19 (11)	3/26 (12)	18/35 (51)	23/80 (29)
Indian	0/3	0/3	2/9 (22)	2/15 (13)
Malay	0/9	1/9 (11)	2/10 (20)	3/28 (11)
Others	0/0	0/0	1/1 (100)	1/1 (100)
Foreigners	0/4	0/2	0/2	0/8

Table 5

Clinical characteristics and case fatality of reported melioidosis cases (Jan 2002 – Jul 2004)

Clinical characteristics	Case fatality (%)						Total N = 132 (%)	
	2002 N = 35 (%)		2003 N = 40 (%)		2004 (Jan-Jul) N = 57 (%)			
Concurrent medical conditions*	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Cardiac diseases	1/5 (20)	1/30 (3)	1/4 (25)	3/36 (8)	11/14 (79)	12/43 (28)	13/23 (57)	16/109 (15)
Diabetes mellitus	1/13 (8)	1/22 (5)	1/18 (6)	3/22 (14)	17/40 (43)	6/17 (35)	19/71 (27)	10/61 (16)
Renal disorders	2/6 (33)	0/29	2/8 (25)	2/32 (6)	10/17 (59)	13/40 (33)	14/31 (45)	15/101 (15)
Hypertension	1/16 (6)	1/19 (5)	3/10 (30)	1/30 (3)	7/17 (41)	16/40 (40)	11/43 (26)	18/89 (20)
Abscess (soft tissue/systemic)								
Soft tissue abscess(es)	0/13	2/16 (13)	1/12 (8)	3/26 (12)	1/7 (14)	21/38 (55)	2/32 (6)	26/80 (33)
Systemic abscess(es)	0/6		0/2		1/12 (8)		1/20 (5)	
Pneumonia	1/14 (7)	1/21 (5)	2/13 (15)	2/27 (7)	19/40 (48)	4/17 (24)	22/67 (33)	7/65 (11)
Bacteremia	2/23 (9)	0/12	4/24 (17)	0/16	20/38 (53)	3/19 (16)	26/85 (31)	3/47 (6)

* A case could have more than 1 concurrent medical condition

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(Reported by Low YJ, Ye T, Chua LT, Ho YM, Chow A and Chew SK, Communicable Diseases Division, MOH)

Epidemiological investigations into an epidemic of melioidosis, January – July 2004

Introduction

Melioidosis is endemic in Southeast Asia and Northern Australia. It was made administratively notifiable in Singapore in October 1989[1]. The causative agent, *Burkholderia pseudomallei*, is an ubiquitous free-living soil bacterium and the disease is acquired by direct contact through skin cuts or abrasions, by aspiration/ingestion or by inhalation. The incubation period is from 2 days to several years.

In March 2004, an excess occurrence of melioidosis was noted, with 20 cases reported as compared to a single case in March 2003. The excess occurrence of melioidosis in March coincided with the wettest spell in Singapore since 1913 with the occurrence of flash floods and rainfall received throughout the island exceeding 85 - 270% above that of past years. This report presents the findings of epidemiological investigations into the epidemic.

Epidemiological findings

A total of 58 cases were notified to the Ministry of Health (MOH) from Jan to Jun 2004, of which 52 cases were classified as of local origin and had onset dates falling between Jan and Jun 2004, as compared to 14 local cases fitting the same criteria for the same period in 2003 (*Fig. 2*).

The cases were notified by the Singapore General Hospital, Changi General Hospital, National University Hospital, Tan Tock Seng Hospital, Alexandra Hospital and Gleneagles Hospital. The diagnosis was mainly confirmed by culture of *Burkholderia pseudomallei* from sputum, blood, urine and pus, and in some cases, by serology.

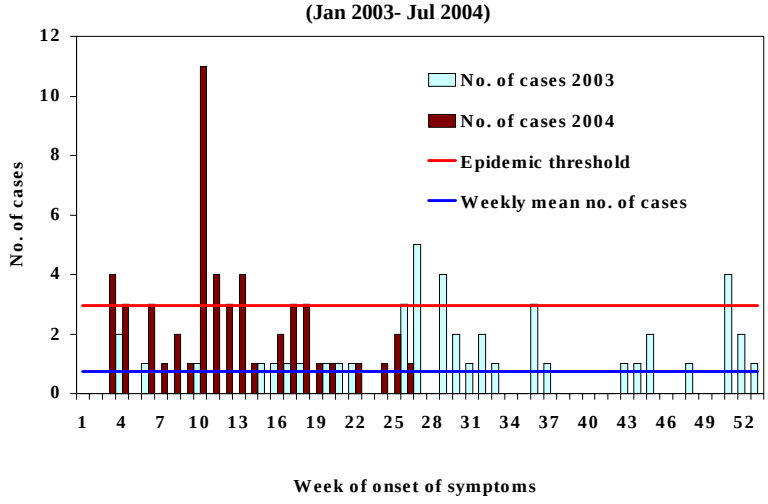
The cases were aged from 14 to 91 years, with 65% of the cases reported in the those aged 45 years and above. The male to female ratio was 5.5: 1. Among the three major ethnic groups, Indians (3.1 per 100000) had the highest incidence rate as compared to Malays (2.1 per 100000) and Chinese (1.2 per 100000) (*Table 6*).

The overall case fatality was 42.3%, with the highest case fatality reported in those above 55 years of age (59.1%).

Clinical findings

Of the 52 cases reported from Jan-Jun 2004, 38 cases (73.1%) presented with pneumonia. 16 of these pneumonia cases had no known previous cutaneous

Figure 2
Distribution of melioidosis cases by epidemiological week
(Jan 2003- Jul 2004)



inoculation event (e.g. abrasions or cuts). Ten of the 20 cases reported in March presented only with pneumonia, with no septicemia or abscesses observed.

92.3% of the cases had some concurrent medical condition, the most common of which was diabetes mellitus, with 73% of the patients suffering from it. The other associated medical conditions were hypertension (30.7%), renal impairment (32.7%) and cardiac conditions such as ischaemic heart disease (25%). (*Table 7*)

Environmental findings

Cases occurred sporadically throughout the island (*Fig. 3*). Possible sources of infection were elicited through interviews with patients and their family members. Prior exposure to soil in occupational or recreational activities was found not to be a significant risk factor.

Environmental sampling was carried out at 24 locations throughout the island but all were negative for *B. pseudomallei.*

A comparison of the incidence of melioidosis with monthly rainfall did not show a definitive association between amount of rainfall and incidence of melioidosis, incidence of cases with pneumonia and number of deaths (*Table 8*).

However, cumulative daily rainfall over 7 days preceding the onset of illness was significantly correlated with the incidence of cases (p<00001), with a quarter of variability in incidence attributable to rainfall in the 7 days preceding onset of illness (*Table 9*).

Table 6

Age-gender-ethnic distribution of 52 reported cases of melioidosis, January –July 2004

Age group	Male				Female				Total
	Chinese	Malay	Indian	Other	Chinese	Malay	Indian	Other	
5-14	1	0	0	0	0	0	0	0	1
15-24	2	0	1	0	0	0	0	0	3
25-34	1	0	0	0	0	0	0	0	1
35-44	1	0	0	1	1	0	1	0	4
45-54	7	6	5	0	1	0	0	0	19
55-64	8	2	2	1	1	1	0	0	15
65+	5	1	0	0	3	0	0	0	9
All ages	25	9	8	2	6	1	1	0	52

Table 7

Concurrent medical conditions of 52 reported cases of melioidosis, January –July 2004

Concurrent medical condition	Present	Absent
Cardiac condition	13 (10)	39 (12)
Diabetes mellitus	38 (16)	14 (6)
Hypertension	16 (6)	36 (16)
Renal impairment	17 (11)	35 (11)

Figure in ( ) denotes no. of deaths

Figure 3
Geographical distribution of 52 reported melioidosis cases, Jan - Jul 2004

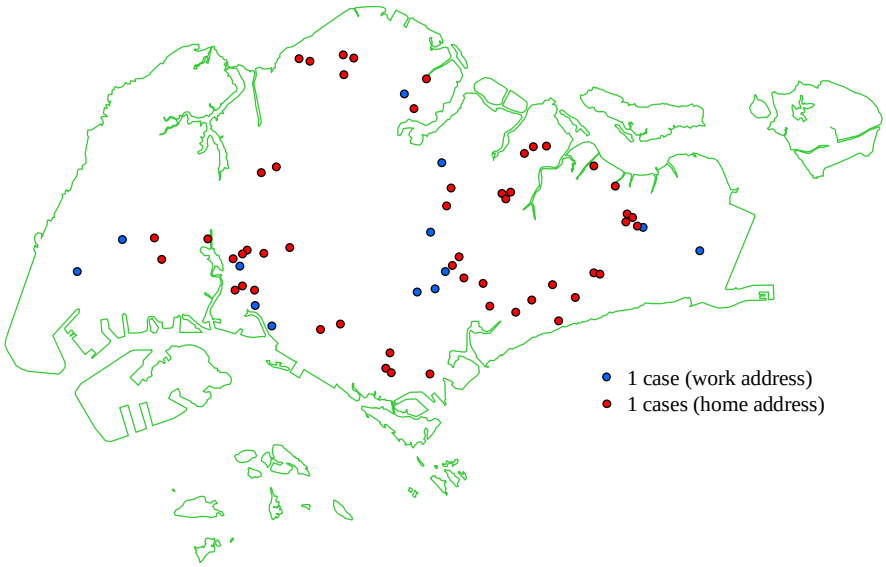


Table 8

Relationship between rainfall and melioidosis, Jan-June* 2004

Month	Total rainfall (mm)	Mean rainfall (mm)	No. of non-rain days	Total no. of cases	No. of cases with pneumonia(%)	No. of cases with pneumonia as the only presentation (%)	No. of deaths	Case fatality (%)
Jan	443	15.82	12	7	5 (71.4)	3 (42.9)	4	57.1
Feb	36	1.86	21	6	4 (66.7)	1 (16.7)	2	33.3
Mar	426	14.19	5	20	16 (80.0)	10 (50.0)	11	55.0
Apr	246	7.3	5	10	8 (80.0)	0	3	30.0
May	159	5.68	14	5	3 (60.0)	2 (40.0)	2	40.0
Jun	131	3.45	21	4	2 (50.0)	0	0	0

***** Combined analysis was performed for June and July cases

Table 9

Incidence of melioidosis and cumulative rainfall 7 days preceding onset of illness

	Pearson's correlation		
	Jan-June 2004 (n = 52)	Jan - Mar 2004 (n=32)	Apr-Jun 2004 (n=20)
Incidence of melioidosis cases	0.384 (p<0.0001)	0.419 (p<0.0001)	0.132
Incidence of melioidosis cases with pneumonia	0.399 (p<0.0001)	0.438 (p<0.0001)	0.174
Incidence of deaths	0.435 (p<0.0001)	0.448 (p<0.0001)	0.134

Comments

Epidemiological and clinical features that distinguished the melioidosis cases this year from those of 2003 were: (1) the significant correlation of incidence with rainfall (mean monthly rainfall of 240mm compared to 211mm in 2003 for the first half of the year); (2) the high percentage of patients presenting with the pneumonic form of melioidosis (73.1% compared to 36.4% in the same period in 2003); and (3) the high case fatality (42.3% compared to 13.6% in the same period in 2003).

A temporal relationship was demonstrated in the correlation between disease incidence and cumulative rainfall 7 days preceding onset of illness. It is postulated that flash flooding events and high wind speeds associated with heavy rainfall could have had a more direct impact on the incidence of melioidosis[2,3]. The former provides a mechanism where the rising water table could have moved *B. pseudomallei* from deeper soils to surface soils and water, while the latter could have enhanced aerosolization of the bacterium, leading to the inhalation of the bacteria.

The high percentage of cases presenting with pneumonia in 2004 also supports inhalation as the possible route of infection. Further, majority of the cases did not have evidence of prior inoculation events or septicaemia/disseminated melioidosis. In fact, most of them were elderly and non-ambulant with minimal outdoor contact, leaving inhalation as the most likely mode of transmission. This reasoning is consistent with findings for other diseases which can be transmitted by both inoculation and inhalation (e.g. anthrax and tularensis). For these diseases, the inhalational mode of transmission also results in pneumonia and a higher case fatality.

To confirm our hypothesis, further studies would need to be carried out to identify the agent in the air after heavy rainfall and occurrence of flash flooding. In the meantime, as Singapore is endemic for melioidosis and experiences occasional heavy rainfall and flooding, persons engaging in higher risk outdoor activities, especially those with diabetes mellitus and other medical conditions should avoid areas of flooding or water-logged soils during periods of heavy rainfall. Preventive measures such as covering of all open wounds with water-proof dressings and wearing of boots and gloves should also be practised.

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(Reported by Lim J, Ng J, Low C, Rasidah N, Low YJ, Lim S, Ooi PL, Disease Control Branch, Ministry of Health)

A study on rainfall and melioidosis in Singapore using case-crossover design

Melioidosis is a disease of humans and animals caused by *Burkholderia pseudomalle* and is endemic in sub-tropical and tropical regions. In Singapore, melioidosis was first documented in 1920. Since the disease was made administratively notifiable in October 1989, the reported incidence has been gradually increasing.

B. pseudomallei is an environmental bacterium of soil and surface water in disease-endemic locations. New infections are primarily acquired from exposure to the organisms in the environment. Contaminated swamps and muddy water are important sources of infection. Soil-borne infections are generally associated with heavy rainfall or flooding in areas with high humidity or temperature.

In the literature, the association between rainfall and melioidosis has long been recognoised, with 75% and 85% of cases occurring in the wet season in northeast Thailand and northern Australia[1]. In Singapore, an increased incidence of melioidosis cases was observed in March 2004 and appeared to coincide with the historical-high volume of rainfall. A local study using temporal correlation analysis reported there was no significant correlation with rainfall during the period 1989 to 1996 [2]. The association could be masked because there was no adjustment for those potential time-varying confounding factors such as age, concurrent medical illness (especially diabetes mellitus) and occupational or recreational exposure to soil.

The case-crossover design, which was first proposed by Maclure to study the transient effect of an intermittent exposure[3], has been used to study the short-term health effects of air pollution. The case-crossover approach is a design in which cases serve as their own controls. Risk estimates are based on within-subject comparisons of their exposures at the time of their onset of illness with exposures at some time before that specific onset of illness. This approach only requires exposure data for cases and can be regarded as a special type of case-control study in which the case serves as his/her referent. Therefore the case-crossover design has the advantage of controlling for potential confounding factors of each individual case. Hence, a total of 107 cases of melioidosis with onset between Jan 2002 and Mar 2004 were used to examine the possible association with rainfall using the case-crossover design.

The preliminary findings showed that greater correlation was found for the number of melioidosis case with the preceding 3 days rainfall (Pearson's $r=0.44$; $p<0.000$). With an unidirectional 3 control sampling approach (using 3 reference periods: 7, 14 and 21 days before the case period), the result from a conditional logistic regression model controlling for weather conditions showed that each 1 mm increase of rainfall corresponded to an odds ratio (it can be interpreted as relative risk in this study since the prevalence of melioidosis is rare) of 1.007 (95% confidence interval 1.002—1.010) in the incidence of melioidosis.

In summary, it seems clear that rainfall was related to an increased daily incidence of melioidosis. The evidence is strengthened when the preceding 3 days rainfall was considered. This study also suggests that the principle of the case-crossover approach is a useful tool in studying the association between melioidosis and rainfall. This to our knowledge is its first application in the study of this disease.

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(Reported by Ma S, Epidemiology and Disease Control Division, MOH)

Staphylococcocal endocarditis following intravenous abuse of crushed buprenorphine tablets (Subutex)

Buprenorphine is a commonly prescribed analgesic. It is a powerful narcotic and a partial agonist at the mu-opioid receptor. Besides pain relief, it is approved for detoxification and maintenance therapy of opoid-dependence in the US and in Europe. Because of a significant hepatic first-pass metabolism, it is given sublingually for dosing. In Singapore, buprenorphine is not a controlled drug and is indicated for moderate to severe pain relief.

Buprenorphine tablets can be diverted for illicit use by crushing the tablet and injecting it intravenously, as has been widely reported in France and other countries where the drug is commonly prescribed[1]. Complications with intravenous usage of crushed buprenorphine tablets reported in the literature include skin reactions, presumed ocular candidiasis, peritonitis, hepatitis, myocardial infarction and deaths[2-7].

In this report, we present a case of staphylococcal endocarditis associated with intravenous abuse of crushed buprenorphine tablets and discuss aspects of this drug abuse phenomenon.

Case report

The patient was a 29 year old female with a history of inhaled heroin abuse. She started using crushed buprenorphine tablets intravenously six months prior to admission. She initially obtained her tablets from a general practitioner but eventually turned to a drug peddler as it was cheaper. Her practice was to dissolve the tablet in hot water either in a pot or a syringe prior to intravenous injection.

She presented to Tan Tock Seng Hospital with a two-week history of lower back pain and three days of fever with sweats. On examination, she had a temperature of 37.8 ^{o}C and had tenderness over the lumbar region of her back, without any stigmata of infective endocarditis. Her blood cultures taken on admission grew *Staphylococcus aureus* and an MRI of her lumbar spine revealed an abscess over the right paraspinal muscles from the level of L4 to S1 vertebral bodies. A trans-oesophageal echocardiogram showed a 1.2 cm by 0.7 cm tricuspid valve vegetation. The chest X-ray was normal. She was treated with intra-

venous cloxacillin and gentamicin and experienced rapid defervescence with improvement in her back pain. Repeat blood cultures taken after five days of intravenous antibiotics had no growth of organisms.

Comments

Infective endocarditis (IE) is a well recognized complication of intravenous drug use[8]. *Staphylococcus aureus* is the most common cause of IE in intravenous drug users (IVDU). Thirty to seventy percent of IVDU-associated endocarditis is right-sided with principal involvement of the tricuspid valve; septic pulmonary emboli are a commonly associated complication[9,10].

In the month of August 2004, a cluster of local cases of staphylococcal endocarditis involving intravenous injection of buprenorphine tablets was noted. A total of seven cases (including this case) with a similar presentation and history were admitted to various hospitals in Singapore. No common epidemiological links have been established among the cases but investigations are still on-going.

This trend in buprenorphine abuse mirrors the situation in other countries. In Europe and the United States, buprenorphine is used for chronic maintenance therapy and detoxification of opoid-dependent individuals. Unlike methadone, buprenorphine used for the indication mentioned above can be prescribed by primary-care physicians in the office setting (outside of licensed narcotic treatment programmes)[11]. As a consequence of this loose framework for prescription, lack of training among general practitioners and the complexities in the behaviour of drug users, a high prevalence of misappropriation and abuse among its users has been reported in other countries[8, 11, 12].

As highlighted by this case, buprenorphine tablets have a substantial potential for misuse. Locally, medical practitioners need to be alert to this ongoing phenomenon. Although not a controlled drug, prudent prescription of buprenorphine is strongly encouraged.

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(Reported by Ling L M and Ong A ,Dept of Infectious Disease,Tan Tock Seng Hospital)

Surveillance of murine typhus in Singapore, 2003

In 2003, a total of 16 cases of murine typhus were reported, compared to 31 cases in 2002 (*Fig. 4*). All cases were laboratory confirmed by rickettsia-specific serology and were classified as locally acquired.

The majority (81.2%) of the reported cases in 2003 occurred among foreigners (*Table 10*). The ages of the notified cases ranged from 20 to 67 years. The overall incidence rate was 0.33 per 100,000 population with the highest age-specific incidence rate in persons aged 15-24 years. The male to female ratio was 7:1 (*Table 11*).

More than half of the notified cases (56.3%) were labourers or related workers in the construction and manufacturing industry (*Table 12*). Occupants of 'bangsals', containers or make-shift worker's quarters accounted for 62.5% of cases (*Table 13*). Cases occurred sporadically throughout the year (*Fig. 5*).

Figure 4
Annual notified cases and incidence rates of murine typhus in Singapore 1999-2003

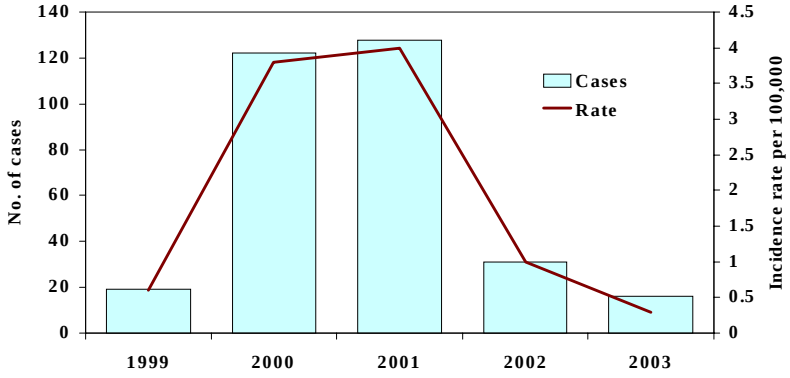

Figure 5
Notified cases of murine typhus by epidemiological week, Singapore, 2003

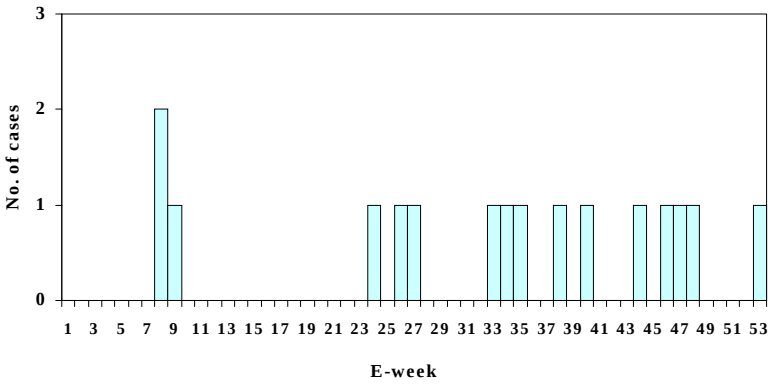

Table 10

Ethnic-gender distribution and ethnic-specific incidence rates of reported murine typhus cases, 2003

Ethnic group	Gender			Incidence rates per 100,000*
	Male	Female	Both (%)	
Chinese	1	0	1 (6.3)	0.04
Malays	0	1	1 (6.3)	0.21
Indians	0	1	1 (6.3)	0.35
Foreigners	13	0	13 (81.1)	1.74
Total	14	2	16 (100)	0.39

* Rates are based on 2003 estimated mid-year population.
(Source: Department of Statistics, Singapore)

Table 11

Age-gender distribution and age-specific incidence rates of reported murine typhus cases, 2003

Age-group	Male	Female	Total (%)	Incidence rates per 100,000*
0 - 4	0	0	0	0
5 – 14	0	0	0	0
15 – 24	5	0	5 (31.2)	0.81
25 - 34	5	0	5 (31.2)	0.58
35 - 44	4	1	5 (31.2)	0.65
45 - 54	0	0	0	0
55+	0	1	1 (6.4)	0.17
Total	14	2	16 (100)	0.33

* Rates are based on 2003 estimated mid-year population.
(Source: Department of Statistics, Singapore)

Table 12

Classification of notified murine typhus cases by occupation, 2003

Occupation	Cases	%
Construction labourer and related worker	8	50.0
Housewife	2	12.5
Manufacturing labourer and related worker	1	6.3
Ship and shipyard cleaner	1	6.3
Computer engineer	1	6.3
Sales promoter	1	6.3
Unknown	2	12.5
Total	16	100.0

Rodent surveillance and control

The National Environment Agency (NEA) is responsible for the surveillance and control of rodents in Singapore. Information on murine typhus cases notified to Ministry of Health are routinely forwarded to NEA for further action. NEA's rodent control programme includes wet markets/food centres and bin centres, as well as airports, seaports and shipyards. It recently launched an 8-month 'rat attack' pilot project in conjunction with town councils and the community. It is a two-pronged control strategy involving reduction and control of rodent population, and effective refuse management and housekeeping to cut off the rodents' food supply and habitat.

Table 13

Classification of notified murine typhus cases by housing type, 2003

Housing type	Cases	%
'Bangsals', containers or worker's quarters	10	62.5
HDB apartments	5	31.3
Condominium and private apartments	1	6.3
Total	16	100.0

Comments

Murine typhus (also known as endemic typhus) is a rickettsial disease caused by *Rickettsia typhi*, and it is a common cause of PUO throughout South East Asia [1, 2]. The disease is transmitted by infective rat fleas although a history of rat exposure is seldom elicited [3, 4]. Unlike scrub typhus (which is caused by *O.tsutsugamushi*), murine typhus tends to occur in more urban environments and runs a milder clinical course. The disease is non-specific in presentation and diagnosis is difficult unless specifically looked for [2]. Increasing travel to endemic areas [5], poor housekeeping in worksites and newer and more specific diagnostic tests [6] have led to more cases being diagnosed. In Singapore, although the burden of cases occurs in foreign immigrant workers living in poorer housing situations, Singapore residents are not completely spared [3] and comprised one fifth of all notified cases last year. Murine typhus remains an important endemic disease in Singapore and continued physician awareness and stringent rodent control measures remain essential in its control.

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(Reported by Kita Y, Communicable Diseases Division (Surveillance), Ministry of Health and Ong A, Tan Tock Seng Hospital)

Review of malaria diagnostic tests

Introduction

Malaria is a vector-borne disease that causes significant morbidity and mortality worldwide. The vector involved in malaria transmission is the female *Anopheles* mosquito. Vector control by environmental management contributes significantly towards the control of malaria by breaking the chain of transmission. On the other hand, fast and accurate diagnosis coupled with treatment is the key to addressing morbidity and mortality associated with malaria[1-3].

Review of currently available malaria diagnostic tests

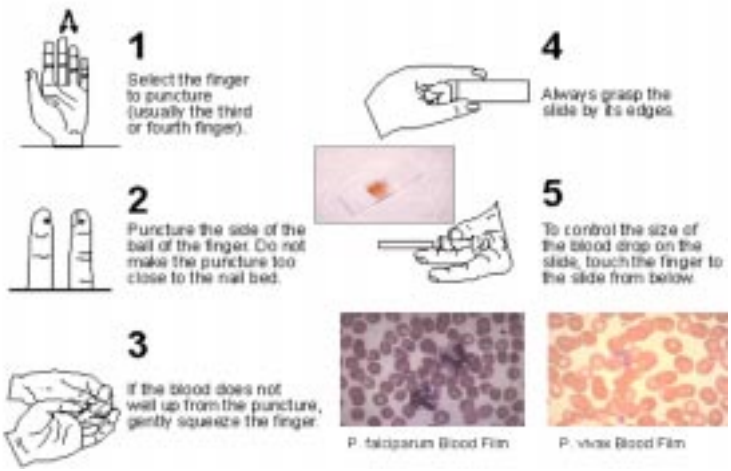
Currently, the two most commonly used diagnostic approaches do not allow a satisfactory diagnosis of malaria. Clinical diagnosis, the most widely used approach, is unreliable because of the non-specific symptoms associated with malaria. On the other hand, the accuracy of blood film microscopic diagnosis is linked to the professional competence of the laboratory staff and available equipment. A number of other tests such as fluorescence microscopy with quantitative buffy coat (QBC), polymerase chain reaction (PCR)-based detection of malarial parasite specific nucleic-acid sequences and rapid diagnostic tests (RDT) are now available.

Blood film microscopy

The accepted laboratory practice and "gold standard" for the diagnosis of malaria is the preparation and microscopic examination of blood films stained with Giemsa, Wright's or Field's stain. Blood obtained by pricking a finger or earlobe is the ideal sample because the density of developed trophozoites or schizonts is greater in blood from these capillary-rich areas[4]. The technique is illustrated in *Fig. 6*.

The strengths and limitations of blood film microscopy are summarised in *Table 14*.

Figure 6
Blood collection for thin or thick blood film



Source: CDC, MMWR 1997; Vol 46 (SS02): 46, Centers for Disease Control and Prevention, Atlanta

Table 14
Review summary of diagnostic test for malaria parasites

Diagnostic test	Principle	Strengths	Limitations	Remarks
Thick/thin blood film microscopic examination	Blood film obtained from fingerprick stained with Giemsa stain	1) Thick blood film detection sensitivity of 50 parasite/ul blood. 2) Thin blood film enables species identification, provides greater specificity than thick film examination.	1) Time-consuming 2) Labour-intensive 3) Interpretation requires expertise 4) Maintenance of equipment required 5) Parasite may be sequestered in spleen, liver or bone marrow, avoiding detection	1) WHO "gold standard"
Fluorescent microscopy with centrifugal Quantitative Buffy Coat (QBC)	Acridine Orange (AO)-coated capillary and internal float separating WBC layer and platelets using centrifugation	1) Faster diagnostic test than blood film microscopy.	1) More technically demanding 2) Requires centrifugation, good fluorescence microscope 3) AO is non-specific and stains nucleic acids of all cell types. 4) Inability to differentiate between *Plasmodium* spp.	1) Higher technical expertise required.
PCR detection of *Plasmodium* specific nucleic acid	DNA/RNA amplification using specific primers	1) Highest detection sensitivity of 5 parasite/ul of blood. 2) Able to detect all *Plasmodium* spp. in nested or multiplex assays. 3) 100% sensitivity and specificity can be achieved. 4) Ability to detect subpatent infection.	1) False positive as PCR yield positive results for 144 hrs (compared with 66 hrs for microscopy) after successful clearance of parasite by therapy. 2) Technical expertise in molecular techniques required. 3) Time consuming	1) Ideal for research on strain variations, mutations and drug resistance genes in parasite. 2) Valuable as supportive diagnostic tool. 3) Limited field application currently.
ParaSight F, ICT Pf and PATH Falciparum Malaria (HRP-2 based RDT dipstick)	Detection of HRP-2 antigen in *P. falciparum*	1) Easy to use in the field. 2) Rapid diagnosis (15-20 mins) 3) Sensitivity of >100 parasites/μl of blood. 4) Permits diagnosis of *P. falciparum* only.	1) Possibility of false negative due to low level or absence of HRP-2 secretion by sexual forms of parasite. Samples with <100 parasites/μl yield false negative results 2) HRP-2 persists after parasite has been cleared, leading to false positive. 3) Cross reactivity with serum rheumatoid factor yields false positive results. 4) Sensitivity drops drastically for parasitemia <100/μl 5) Cannot detect non-falciparum spp. Since HRP-2 is only expressed by *P. falciparum*.	1) Negative results inadequate to exclude parasitemia of <300/ul
OptiMAL (pLDH based RDT dipstick)	Detection of pLDH (soluble glycolytic enzyme expressed by the four human malaria species).	1) pLDH activity can be detected from viable sexual and asexual parasites of *P. falciparum* and *P. vivax* infections. 2) Can differentiate between *P. falciparum* and *P. vivax*. 3) No evidence of cross-reactivity has been found (high specificity). 4) Able to monitor therapy efficacy, since decline in activity parallels decline of viable parasites during therapy in clinical trials. 5) Upon comparison with microscopy, OptiMAL has a sensitivity of 100% and a specificity of 95% for *P. falciparum* samples. Same for *P. vivax*	1) Unable to identify mixed infection when compared with PCR. 2) Cannot detect <50 parasites/ul. 3) Cannot visualized parasite growth stages.	1) Fast assay with good sensitivity and specificity. Could be considered as a viable supportive test to microscopy if rapid diagnosis is critical. 2) Useful tool in monitoring antimalarial therapy.

The blood film technique has undergone very little improvement since its development in the early 1900s. A combination of thin and thick blood film examination does have the combined benefits of specificity and sensitivity in malaria diagnosis. However, this technique is time-consuming (takes up to 60 minutes of preparation time to produce a stained film on slide),and labour-intensive[5], Moreover, it requires expertise in interpreting the findings[6], and the equipment has to be properly maintained.. It is also not able to detect parasite sequestered in the deep capillaries (spleen, liver, bone marrow). Hence, a negative result on blood film examination does not exclude possibility of malaria infection. Therefore, microscopic diagnosis should not be taken in isolation but complemented with clinical diagnosis. In addition, multiple collection and screening of blood film at intervals may be required to identify malaria cases that escape detection of the first screen. This technique is more effective in malaria diagnosis upon onset of fever (circulation of parasite in blood) and its effectiveness in screening of asymptomatic malaria cases is limited due to low parasitemia.

Florescence microscopy with QBC

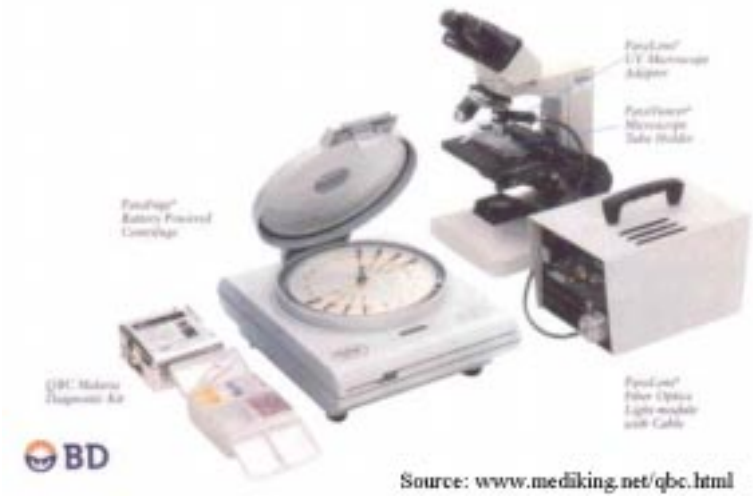
This technique is based on the affinity of certain fluorescent dyes such as acridine orange (AO) and benzothiocarboxypurine (BCP) for the nuclei acid in the parasite nucleus. The documented sensitivity of this method for <100 parasites/µl ranges from 41% to 93%[7] and the specificity for infection with *P. falciparum* is above 93%. But, for infection with other non-*P.falciparum* infection specificity is only 52%[8]. The equipment required for this technique is shown in *Fig. 7*.

The strengths and limitations of this technique are summarised in *Table 14*.

PCR detection of specific nucleic-acid sequences

PCR is basically an amplification system that detects for malarial specific nucleic acid sequences by virtue of specific primers directed against the various *Plasmodium spp.* Conventional PCR cannot be regarded as a rapid technique for initial diagnosis of

Figure 7
Equipment required for fluorescence microscopy with QBC



Source: www.mediking.net/qbc.html

malaria but its value lies in its sensitivity, with the ability to detect as low as 5 parasites/µl of blood[9]. The equipment used for PCR is illustrated in *Fig. 8*.

The major advantages and limitations of PCR detection is summarised in *Table 14*.

The high sensitivity of PCR is a "double-edge sword", the amplification process is prone to false positive results if cross- contamination of blood samples occurred during blood collection, transport or processing. Therefore, extreme caution must be exercised to prevent cross- contamination in these processes and may have limited usefulness in field applications. The time lag between sample collection, transportation, processing and dissemination of results back to the physician limits the application of PCR in routine clinical practice[10].

However, further advances in PCR technology may allow distinction of DNA from viable and non-viable parasites and thus facilitate use of PCR-based procedures in the field[6]. Progress in rapid DNA extraction methods and in thermocycler development in real-time PCR, may enable the amplification of malaria parasite DNA to be performed within a time frame that is clinically relevant for acute diagnosis in both field and laboratory settings. Progress and trials are currently underway locally and overseas, but all of these developments are still in-house technologies and have yet to be accepted by WHO. Meanwhile, microscopy remains as the mainstay for diagnosis for majority of clinical diagnostic centres[5].

Non-microscopic rapid diagnostic tests (RDT)

The principles of RDTs is based on immunochromatographic capture of malarial specific antigens from peripheral blood using immobilized monoclonal antibodies on a dipstick strip. Some examples of RDT kits are shown in *Fig. 9*.

The strengths and limitations of RDT usage is summarised in *Table 14*.

A WHO document[11,12] concluded that results from these test devices should be as accurate as results derived from microscopy performed by an average technician under routine field conditions. In ad-

Figure 8
Equipment used in PCR

Source: Roche Applied Science Light Cycler Online Resource Site

dition, the sensitivity should be above 95% compared to microscopy, and the reliable detection of parasitemia at levels of 100 parasites/µl (0.002% parasitemia) with a sensitivity of 100%. Various published field trials have cast doubts on the accuracy of RDT-based diagnosis in remote areas[13-17]. In these trials, reported sensitivity and specificity for *P. falciparum* is well below that required for operational use and sensitivity for non-falciparum species is generally lower. There is little consistency in results obtained for individual products and direct comparative studies often give widely conflicting results for the same product.

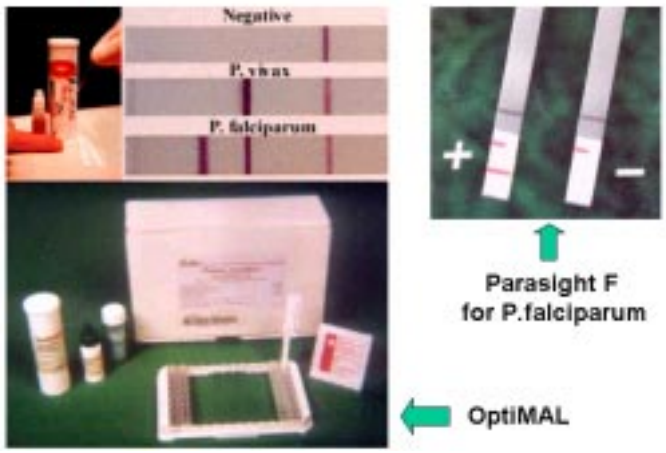
RDTs have been employed on a large scale in the public sectors in parts of South America, Southern Africa and South East Asia (predominantly in areas without microscopy services and they have been used for prevalence surveys). Although RDTs have also been integrated into routine practice in several malaria control programmes (e.g. Thailand, Cambodia, South Africa), significant problems with sensitivity have been reported in both Asia and South America.

Discussion

With reference to *Table 14* it is evident that currently there is no ideal diagnostic test for malaria parasites. However, each method has its unique strengths which could have specific applications in particular settings, depending on the purpose and location of testing, and other factors such as cost effectiveness, desired sensitivity, specificity, speed and ease of use.

Quality blood film microscopy examination remains the recommended method and current gold standard for malaria diagnosis. It should be the main procedure at tertiary medical facilities and the main tool of epidemiological surveys[18]. In the context of Singapore, we do possess a good network of experienced medical technologists. A good quality assurance (QA) programme is currently in place whereby diagnostic laboratories are evaluated on a regular 6-month intervals by an independent body (i.e. NUS-Malaria Reference Centre).

Figure 9
Some examples of rapid diagnostic test (RDT) kits



Source: www.malariasite.com/malaria, courtesy of Dr. B. Srinivas Kakkilaya

The use of fluorescence microscopy may have improved sensitivity but not the specificity. In addition, this technique is still unable to differentiate between the four *Plasmodium spp*., thus limiting its clinical value in diagnosis.

PCR presents itself as a promising complementary technique to the conventional blood film microscopic diagnosis by virtue of its ability to detect subpatent infections (otherwise missed in blood film examination). Its sensitivity also exceeds that of microscopic examination and enables detection of less than 5 parasites/ml of blood. In addition, the ability to provide identification to the species level makes it an excellent technique against which to compare against other non-microscopic techniques. However, due to the length of time and the technical expertise required; it is not practical to use PCR in routine acute malaria diagnosis. The persistence of positive results in PCR even after the patient has been cleared of the parasite also hinders its clinical application. Currently, various research efforts in improving the PCR method is underway but these developments have remained as in-house technologies and have yet to be accepted by WHO. Some of these advances include rapid DNA extraction methods and the use of real-time PCR which may enable the process to be performed within a time frame that is clinically relevant for acute diagnosis in both field and laboratory settings.

The Defence Medical and Environmental Research Institute in Singapore (DMERI) has developed a diagnostic technique using real-time fluorescence-based PCR for detection of malaria parasites and results have been published[19]. This study reported a sensitivity of 0.002pg of *P. falciparum* DNA which is equivalent to 0.1 parasite and specificity for all four human malarial parasites. In addition, the use of real-time PCR will also be useful in monitoring of antimalarial therapy efficacy, especially in situations where drug-resistance strains of the parasites are prevalent. This technique provides an objective method for determining the parasitemia in the samples (in contrast to the subjective elements inherent in blood film microscopy), It is also useful in countries that are non-endemic for malaria and where there is a lack of skilled medical technologists. This method is capable of high throughput rapid screening of hundreds of samples with sensitivity and specificity comparable to the microscopic method. In the report, this method manages to detect a positive malaria case that escaped detection by blood film examination.

Immunochromatographic dipsticks or RDTs provide possibility of more rapid, non-microscopic methods for malaria diagnosis, enabling saving on training and time. RDTs are relatively easy to perform with minimal training to interpret the results. However, the use of RDTs is plagued by several issues discussed in two WHO documents[11,12]. Sensitivity for RDT remains a problem, particularly for non-immune populations. The clinical and epidemiological significance of RDTs in recognizing gametocytes of *Plasmodium* is important. At present, a negative RDT cannot be accepted at face value and will need to be coupled with clinical diagnosis and confirmation by microscopic examination. At present, none of the commercial tests have been approved by the US Food and Drug Administration (FDA).

In summary, RDTs do offer the possibility as an attractive complement to the conventional microscopic examination but its lack of stability and consistency in its performance in field conditions hinder its widespread application in non-endemic countries. The Real-Time Fluorescence-Based PCR method developed by DMERI seems to be an alternative method worthy of further evaluation.

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