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Human immunodeficiency virus (HIV) infection in Singapore

Introduction

The first case of HIV infection in Singapore was detected in May 1985. This was followed by the first case of acquired immunodeficiency syndrome(AIDS) in September 1986. The number of new cases of HIV infection and AIDS reported to the Ministry of Health increased steadily until 1990[1]. From 1991 till 1998, the number of reported cases of HIV infection/AIDS increased rapidly, from 42 cases (1.5 per 100,000 population) in 1991 to 199 (6.3 per 100,000) in 1998. The number of new cases appeared to stabilize during the period 1999 - 2003 with between 200 and 240 new cases reported annually. In 2003, 242 new cases of HIV infection/AIDS were reported, representing an incidence of 7 per 100,000 persons (*Table 1, Fig 1*). However, up to the end of October 2004, 257 new cases have already been reported.

Epidemiology of HIV infection in Singapore

Epidemiological information on HIV infection/AIDS in Singapore is obtained from various surveillance systems; namely, (i) a legally-required HIV infection/AIDS notification system supplemented with additional information collected during interview of cases; (ii) periodic unlinked HIV sentinel surveillance; and (iii) voluntary unlinked anonymous testing.

Modes of transmission

The mode of HIV transmission at the beginning of the epidemic had been predominantly homosexual or bisexual[2]. Heterosexual transmission however, has been the main reported mode of HIV transmission

Table 1

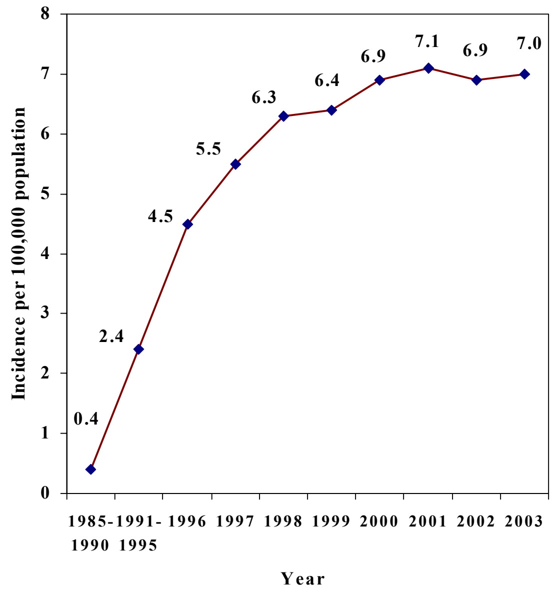
Incidence of new HIV infection and AIDS cases in Singapore, Jan 1985-Oct 2004

Year	Number		Incidence per 100,000 population
	New HIV infection	New AIDS*cases	
1985 - 1990	47	14	0.4 (#)
1991 - 1995	250	108	2.4 (#)
1996	75	64	4.5
1997	105	68	5.5
1998	114	85	6.3
1999	101	105	6.4
2000	118	108	6.9
2001	134	103	7.1
2002	140	94	6.9
2003	144	98	7.0
Jan-Oct 2004	154	103	-

* first diagnosed as AIDS

average annual incidence

Figure 1
Incidence of new HIV infection and AIDS cases per 100,000 population, 1985 - 2003



in Singapore since the early 1990s. Of the 1145 new cases reported during the five year period from 1999 – 2003, 79% reported that they were heterosexual while only 18% stated that they were homosexual or bisexual. There is a possibility that a proportion of men choose not to reveal their true sexual orientation as homosexual and bisexual practices are generally not accepted by the wider community. The contribution from homosexual and bisexual transmission could then be under-reported. Infection via intravenous drug abuse is uncommon, accounting for just 2% of infections. Perinatal infection made up the remaining 1%. There were two cases who were infected in 1977 through blood transfusion which involved a donor who gave blood during the "window period" before antibodies were detectable in his blood[3].

Distribution by gender, age, marital status, ethnic group and employment sector

The vast majority of infections occurred among men, with the ratio between men and women being 7: 1. This could be partially explained by under-reporting of true sexual orientation by homosexuals and bisexuals. Almost 80% of cases were between the ages of 20 and 49 at the time of diagnosis. Less than 2% of cases were below the age of 20 years (*Table 2*). Over half (60%) of men were single while the majority of women (63%) were married at the time of diagnosis. Reflecting the ethnic distribution of the resident population, most of the cases occurred in Chinese (84%), followed by Malays (8%) and Indians (5%). One quarter of cases were employed in the manufacturing and

Table 2

Age distribution (%) of HIV-infected cases by age and gender (Jan 1985 – Oct 2004)

Age at diagnosis (years)	Male (n=2053)	Female (n=279)	Total (n=2332)
< 10	0.5	3.6	0.9
10-19	0.6	1.4	0.7
20-29	15.8	37.3	18.4
30-39	36.4	26.9	35.3
40-49	26.1	16.5	24.9
50-59	11.4	9.3	11.1
60 and above	9.2	5.0	8.7
Total	100.0	100.0	100.0

technical industries, while another 20% were in the service or sales sector.

Status at time of diagnosis

A significant proportion of reported cases were either symptomatic at the time of diagnosis (40.7%) or progressed to AIDS within one year after the diagnosis (9.4%). Considering all cases reported in the period Jan 1985 – Oct 2004, the reported number of HIV-infected/AIDS cases peaked in the 30 – 39 year age group (35.3%). The long latency period between acquisition of HIV infection to the first diagnosis in the majority of cases may explain this observation.

Our data also suggests that older patients are more likely to be diagnosed with HIV infection late in the course of their illness; i.e. in the form of AIDS. Half or more of persons who were aged 40 years or older at the time of diagnosis first presented as AIDS compared to 37% among persons aged 30 to 39 years and 20% among those aged 20 to 29 years (*Table 3*) (unpublished data, Ministry of Health, Singapore). This is again partly explained by the long period between infection and onset of AIDS.

In contrast to their male counterparts, the age distribution of female HIV-infected /AIDS patients peaked in the 20 – 29 year age group (37.3%). This may partly be explained by a significant proportion of female cases (22%) being diagnosed mainly through contact tracing and thus being identified at an earlier stage of infection.

Overall, the age and gender distribution patterns of HIV-infected/AIDS cases in Singapore indicates that the majority of reported HIV-infected/AIDS cases were middle-aged male patients. This male preponderance in Singapore stands in sharp contrast to other countries where heterosexual transmission dominated generalized HIV epidemics with almost half of HIV-infected/AIDS cases reported in women[4].

Unlinked sentinel HIV surveillance

Since 1989, the Ministry of Health has initiated regular unlinked sentinel HIV surveillance to complement the epidemiological information collected through HIV infection/AIDS notification system. The HIV seroprevalence rates among selected sentinel groups such as antenatal care attendees seem very low

Table 3

Presentation of HIV infection by age at time of diagnosis (Jan 1985 – Oct 2004)

Age at diagnosis (years)	No.	Proportion first presenting as AIDS (%)
Under 20	38	15.8
20 – 29	429	20.3
30 – 39	823	37.3
40 – 49	580	49.0
50 – 59	260	54.6
60 & above	202	61.4
Total	2332	40.7

Table 4

Unlinked surveillance for HIV infection, 1989 – 2003

Population group	No. tested	% positive
Antenatal cases	13,281	0.02
Hospital patients[1]	10,875	0.05
Hepatitis B carriers	9,149	0.19
Tuberculosis patients[2]	3,455	0.72
Sexually transmitted infection patients	18,558	0.58

[1] from 1990
[2] from 1992

(0.02%). On the other hand, relatively high HIV prevalence was detected among patients with sexually transmitted infections (STIs) (0.6%) and tuberculosis (TB) (0.7%) (*Table 4*).

Other epidemiological information used to assess and monitor the HIV infection/AIDS situation in Singapore include seroprevalence data among blood donors and those attending voluntary anonymous testing sites. In 2003, over 2600 anonymous tests were carried out with a HIV positive rate of 1.4% (internal communication).

Intervention strategies

In 1985, around the time when the first HIV-infected case was detected, the Ministry of Health drew up a National AIDS Control Programme to prevent and control its spread. Various government agencies and community groups were involved as the government realized early that combating HIV infection would require a multi-sectoral approach. The government also appointed an expert advisory committee (the AIDS Task Force) to advise it on medical and scientific matters relating to HIV infection and AIDS.

Singapore's multi-pronged control programme comprised public education and education of high-risk groups, legislation, protection of the national blood supply through screening of blood and blood products, management of cases, counselling those with high risk of infection, scaling up the prevention and control of conventional STIs and epidemiological surveillance.

Public education

A key feature of the National AIDS Control Programme in Singapore is public education. This is carried out by the Health Promotion Board, the national agency for health promotion. The central message has been that AIDS is deadly and that the only sure way of avoiding AIDS is to remain faithful to one's spouse and avoid casual sex. Another message has been that HIV-infected persons cannot be identified by appearances. This was combined with the message to avoid casual sex. These educational messages are disseminated via the newspapers, magazines (especially those that cater to male readers) and TV, and usually intensified during the month of December to coincide with World AIDS Day. In schools, topics on sexually transmitted infections including HIV are included in sex education programmes run by the Ministry of Education. AIDS education programmes are also given to 18 year-old male youths who are recruited for compulsory National Service. To reach out to the blue-collar workers, *getai* (a popular Chinese entertainment road show) was used for the first time in 1998 to spread AIDS education messages. A recent initiative to reach out to blue-collar workers is talks on HIV infection and STIs at workplaces, especially those from the manufacturing industry.

Information and counselling via the internet and telephone

Information on HIV infection and AIDS is provided through the Internet; e.g. at the website of the Health Promotion Board (http://www.hpb.gov.sg) and the Department of STI Control (http://dsc-sexualhealth.com.sg). Telephone counselling services are provided by the Health Promotion Board, the Department of STI Control and Action for AIDS (a non-governmental organization). The latter two telephone helplines are available 24 hours a day. The Department of STI Control also provides information to questions on HIV infection and STI risks in relation to sexual practices submitted via email at its website.

Education of high risk groups

The use of condoms is promoted among sex workers[5,6] and also in places where such activities may potentially take place; e.g. in lounges, nightclubs and massage parlours[7]. Sex workers are taught about the risks of HIV infection and AIDS and its modes of transmission. They are also taught negotiation skills to persuade clients to use condoms. Some evidence of the success of this programme can be seen with the extremely low rates of HIV infection and STIs like gonorrhoea among sex workers[8]. In each of the last 5 years, only 0 to 0.2% of approximately over 1000 sex workers attending the public STI surveillance clinic have tested positive for HIV infection; in absolute numbers there are about 0 - 2 new cases each year (unpublished data, Ministry of Health, Singapore).

Educational activities for the MSM (Men-who-have-sex-with-men) community are carried out by Action for AIDS (AfA) as it would be difficult for government agencies to reach out to this group. MSM activities are not generally accepted by the community at large. AfA's programme aims to raise awareness of HIV infection/AIDS and to decrease high risk behaviour in the MSM community. The programme consists of distribution of postcards containing messages on reducing risk behaviour and the distribution of condoms at places frequented by MSMs. There are limited specific HIV infection/ AIDS education programmes for intravenous drug users (IDUs). This is also a difficult to reach group as drug abuse is illegal in Singapore. However, IDUs account for only 2% of HIV-infected/ AIDS cases reported.

Legislation

Legislation in the form of provisions under the Infectious Diseases Act covers several areas of importance in the control of HIV infection. Firstly, the Infectious Diseases Act provides additional safeguards (in addition to common law principles on medical confidentiality) to protect the medical confidentiality of persons infected with HIV. This is important to encourage persons to come forward for HIV testing despite having a strong social stigma associated with the disease. Secondly, the Act is used to help minimize the risk of disease transmission. Legislative amendments were last made in 1999 to help strengthen control of HIV infection. Among these was an amendment allowing doctors to inform sexual contacts of cases of the person's HIV status if he or she has refused to inform his or her contacts despite counselling. This provision has helped to minimize the risk of HIV transmission as understandably, there can be a strong reluctance among cases to disclose their condition to their spouses and sexual partners. The other legislative amendments were aimed at further reducing the risk of transmission through blood transfusion.

Protection of the national blood supply

The blood transfusion service in Singapore already practises stringent measures to ensure the safety of transfused blood. This includes a comprehensive donor interview to exclude donors who may be at risk of HIV infection and serological and antigen testing for HIV. Following the unfortunate incident of transfusion-related transmission in 1997, legislative amendments were made in 1999 to increase the penalties for making a false declaration at the Blood Bank so as to increase the deterrence to persons with high-risk sexual behaviour from donating blood. Since October 2000, the Blood Bank employs nucleic acid amplification testing for HIV in addition to serological testing.

Anonymous testing

Anonymous testing is provided by AfA and is publicized as a service to persons who fear that they may have been infected but who also fear going for tests in medical clinics. Persons who attend such anonymous testing receive counselling from trained AfA staff.

Prevention and control of sexually transmitted infections

The Department of STI Control (DSC) is responsible for providing clinical services, epidemiological surveillance, public education, training and research activities related to STIs. (http://dsc-sexualhealth.com.sg). The Ministry of Health funds the activities of the DSC.

Issues of concern

HIV is a largely preventable disease. A simple low-cost and effective prevention method (the condom) exists. Education campaigns have been ongoing for more than 15 years and knowledge about the disease and its modes of transmission should be well established among the public. However, more than 200 new cases each year were reported in Singapore since 1999. A weakness in public education activities in Singapore has been the inability to promote condom usage more openly due to a lack of consensus among community leaders in the past. There are some concerns that such activities would promote promiscuous behaviour. Education activities for the general public have thus focused on avoidance of casual sex. A key challenge is to move beyond knowledge dissemination of HIV infection and its modes of transmission to engaging people at risk so that they modify their behaviour to reduce their risk to HIV.

Freelance and "indirect" sex workers are important potential sources of infection. The prevalence of HIV and other STIs as well as inconsistent condom use among freelance sex workers has been consistently higher than brothel-based sex workers[5] (unpublished data, Ministry of Health). There has also been recent media reports of foreign women involved in vice activities. Contact with sex workers outside Singapore is another potentially important source of infection. Effective strategies are needed to promote safe practices in these groups.

Another major issue of concern is the persistently high proportion of cases who are first diagnosed with HIV infection only when they present with AIDS symptoms. In the five-year period from 1998 to 2002, between 40 and 50% of new cases of HIV infection were first diagnosed with AIDS symptoms. These persons had presumably been living with undiagnosed HIV infection for several years. We need to understand the barriers that prevent persons from undergoing HIV tests so that we can dismantle these barriers as much as possible. It will also provide opportunities for implementing targeted intervention programmes for those who come forward for testing and counselling due to their perceived risk for HIV infection.

The number of undiagnosed cases is a concern for every country, including Singapore. The Ministry of Health has been conducting unlinked surveillance among selected groups in the population since 1989 to assess the extent of undiagnosed HIV infection. The prevalence of positive tests among general population groups has been extremely low – well below 0.1%. As expected, the prevalence of positive tests among higher-risk populations e.g. patients attending the STI clinic is higher – 0.6%.

Communities that are difficult to reach such as MSMs and IDUs are a concern as interventions cannot be delivered openly. It is also difficult to evaluate the effectiveness of interventions delivered. Nonetheless, new and better ways must be found to ensure that high risk behaviour in these communities are minimized. An urgent priority is to improve our understanding of the sexual networks in the MSM community so that more targeted interventions could be designed.

The future

The Ministry of Health has set a target of keeping the incidence of HIVinfection/ AIDS to less than 10 per 100,000 in 2010. The target is above the projected incidence of more than 8 per 100,000 in 2004 to take into account the possible numbers of undiagnosed cases in the population. However, this target may not be achieved if high risk sexual behaviour is not adequately addressed. The number of cases reported in 2004 look set to be the highest number so far. There may also be silent epidemics in the MSM community. The challenge will be to find innovative new approaches to put across the "old" message of prevention through avoidance of casual sex and risk reduction through consistent condom usage. The general community has to accept more open education activities aimed at promoting condom usage rather than worry that such programmes would increase promiscuity.

The focus of these prevention messages has been predominantly on men in view of the high male to female ratio of HIV and AIDS cases. We should increase the spotlight on women as well so that women are encouraged to play a stronger role in promoting safe sexual behaviour[4]. Better information on current sexual practices and attitudes in the general population as well as special groups such as youths and MSMs are also urgently needed to better identify at risk groups for targeted intervention. Towards this end, the Health Promotion Board is planning a survey to address this information gap. Fresh approaches are especially urgently needed to significantly reduce the proportion of cases that are diagnosed only when they present with symptoms of AIDS.

[Reported by Dr Jeffery Cutter, Deputy Director, Communicable Diseases (Policy) Division, Ministry of Health]

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Epidemiology of sexually transmitted infections (STIs) in Singapore

STI surveillance systems

The compulsory reporting of newly diagnosed cases of STIs by health facilities is the mainstay of STI surveillance in Singapore. The sources of notification include the Department of STI Control (DSC), the National Skin Centre (NSC), government and restructured hospitals, private hospitals, diagnostic laboratories, as well as other organizations such as the Singapore Armed Forces (SAF) and general practice clinics.

The surveillance definition for 'STI' includes all sexually transmitted bacterial, protozoal, fungal and viral (except HIV/AIDS) infections. In 1999, laboratory testing for chlamydial infections was introduced. Historically, STIs were diagnosed and reported as gonorrhoea, non-gonococcal urethritis (NGU), syphilis (congenital, infectious and non-infectious), chancroid, genital herpes and genital warts. The remaining STIs including vaginal discharges were included in the 'others' category.

Regular analysis of combined data from the DSC clinic and compulsory notification forms was done. However, it is important to note that significant variations in quality and completeness of data may exist between the two systems.

Information on anti-microbial resistance of gonococci was made available through ad-hoc testing of specimens collected at the DSC.

Trends of STIs

There has been a steady decline in the incidence of STIs in Singapore from 1977 to 1996. STIs in the population declined from an incidence rate of 678 cases per 100,000 population in 1977 to 152 cases per 100,000 population in 1996 (*Fig. 2*).

Between 1997 and 2003, the incidence of STIs in Singapore was noted to increase. The total number of cases of STIs notified in 2003 was 8173. This was a 19% increase compared to that notified in 2002 (6891). There was a 28% increase in the incidence rate of STIs in 2003 (195 cases per 100,000 population) compared to that in 1996 (152 cases per 100,000 population) (*Fig 3*).

Demography of STIs

Gender

In the last decade, majority of the new STI cases occurred in men. Between 1993 and 2003, 62% – 77% of new STI cases were reported in men. In 2003, the male to female ratio for new STI cases was 2.4:1. The lowest incidence rates of STIs for men and women were reported in 1996 (205 cases per 100,000 population) and 2000 (73 cases per 100,000 population), respectively. By 2003, the incidence rate of STIs in men had increased by 32% in males and 21% in females since 1996, when the lowest incidence of STI was reported in Singapore (*Fig 4*).

Figure 2
STI notifications and STI incidence per 100,000 population in Singapore, 1977 - 2003

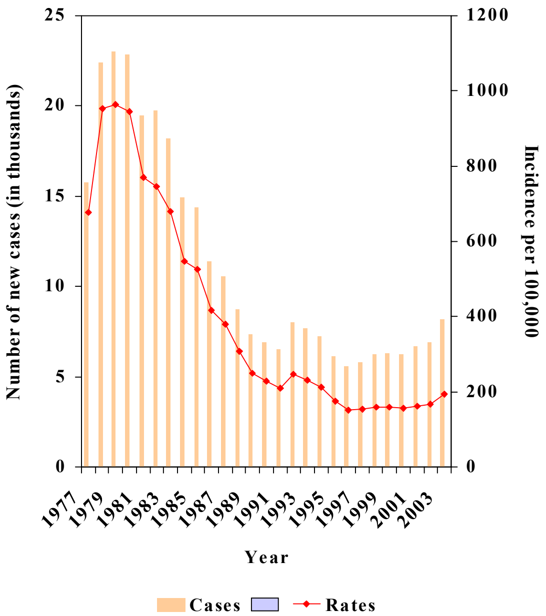


Figure 3
STI notifications and STI incidence per 100,000 population in Singapore, 1993 - 2003

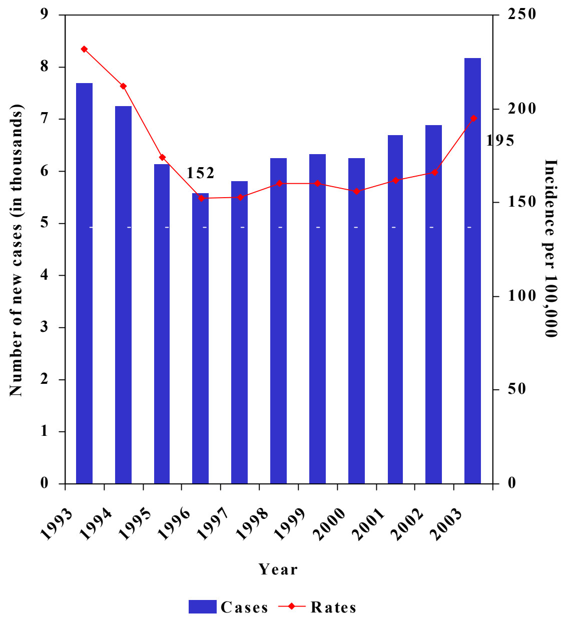
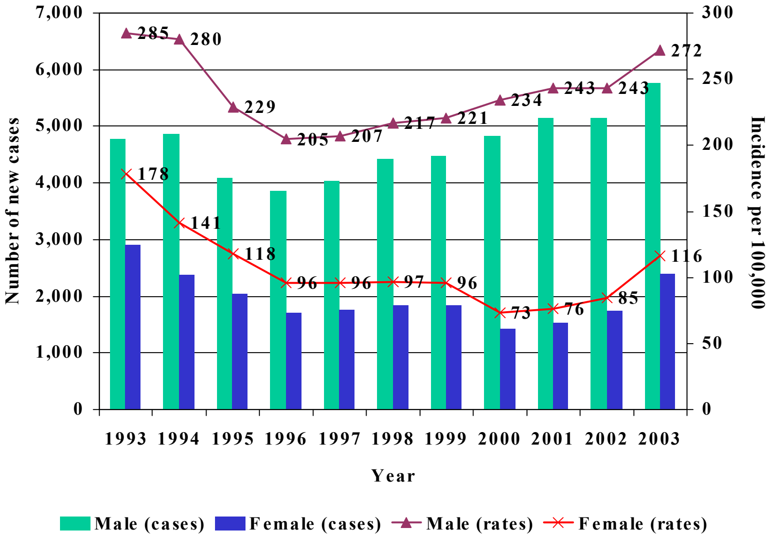


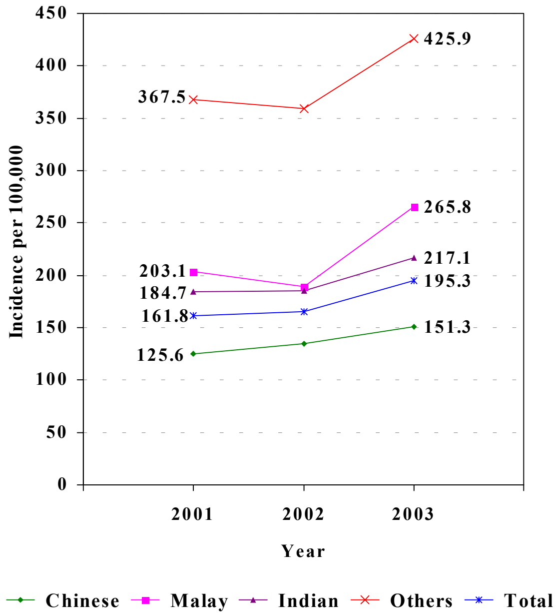
Figure 4
Gender specific STI notifications and STI incidence in Singapore, 1993 -2003



Ethnicity

In the last 3 years, the overall burden of STIs amongst the different ethnic groups in Singapore corresponded to the ethnic composition in the population, with majority of the STI patients being Chinese (58%), followed by Malays (16%), Indians (10%) and other races (16%). In 2003, among the three major ethnic group, the ethnic-specific incidence rate of STIs was the highest in Malays at 266 cases per 100,000 population. This was followed by Indians and Chinese with the incidence rate at 217 cases per 100,000 population and 151 cases per 100,000 population, respectively (*Fig 5*).

Figure 5
Ethnic-specific STI incidence in Singapore, 2001 - 2003



Age

The age-specific incidence rate for STIs among females was highest in the 20-24 year age group. Amongst the males, the highest age-specific incidence rate was in the 25-29 year age group. Overall, the incidence rate was highest in the 20-24 year age group. For the last decade, majority of the STI cases occurred in the 20-29 age group (*Fig 6*).

The lowest STI incidence rate for males in the 20-24 age group was reported in 1997 (293 per 100,000 population), and in 2000 for females in the same age group (196 per 100,000 population) (*Fig 7*). In 2003, the increase of STIs rates were noted in both males and females of most age groups.

Figure 6
Age specific STI incidence in Singapore, 1993 - 2003

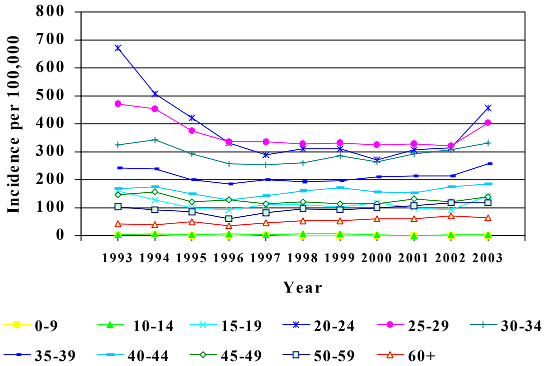
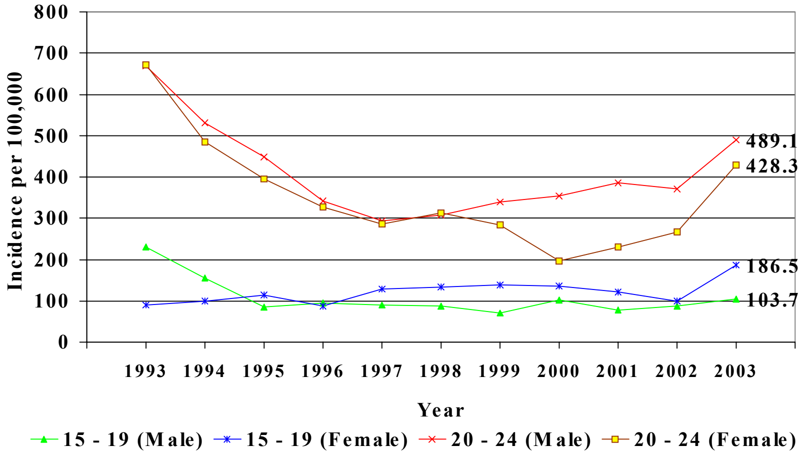


Figure 7
Gender specific STI incidence for the 15-19 and 20-24 age groups, 1993 - 2003



A similar trend was also observed for the 15-19 year age group. In 1993, the overall STI incidence rate among the 15-19 year age group was 162 per 100,000 population. The incidence rate in males was 231 per 100,000, and was much higher compared to that for females in the same age group (88.7 per 100,000 population). The lowest overall STI incidence rate for the 15-19 age group was in 1996 at 92 per 100,000 population. Similar to the 20-24 age group, an increase of STIs in both males and females in the 15-19 age group was also observed in 2003. In addition, the incidence rate among females in this age group was higher compared to their male counterparts.

Aetiology of STIs

In 1980, gonorrhoea was the most common STI with a total of 15,190 reported cases, representing 62.2% of the total burden of STIs. The number of reported cases of gonorrhoea rapidly declined in the

1990s, and reached the lowest level of 1357 cases (23.4% of the total STI burden) in 1997. In the period between 1998 and 2003, there was an increase of gonorrhoea in the community. A total of 2041 new cases were reported in 2003 at an incidence rate of 48.8 per 100,000 population. This constituted 26% of the total STI burden in Singapore for 2003.

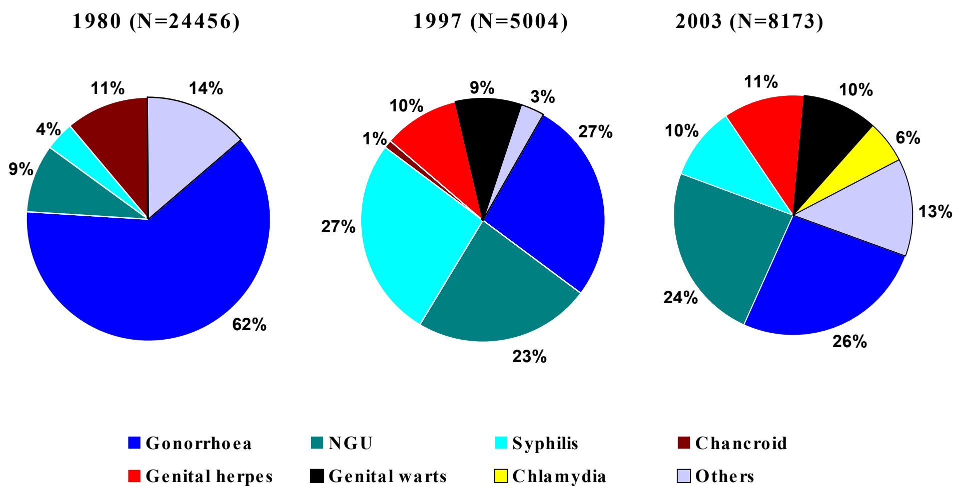
However, it is important to note that the relative burden of infections due to asymptomatic bacterial STIs such as chlamydia and other viral STIs such as the herpes simplex virus (HSV) and human papilloma virus (HPV) has increased in recent years (*Fig 8*) (Chlamydial infections are asymptomatic mainly in women; they are estimated to cause at least 50% of cases of NGU, and are thus less likely to be asymptomatic in men). In 2003, the incidence rates of genital herpes and viral warts were 22.3 and 18.9 per 100,000 population, respectively. Both HSV and HPV also contributed 11% and 10%, respectively to the total STI burden in Singapore in 2003.

After a rapid decline in incidence in the 1980s, a stable incidence trend was observed for syphilis (all types). An annual average of 185 cases of infectious syphilis cases had been diagnosed in the past 10 years. This is a relatively high number when compared to other developed countries with similar socioeconomic conditions. In 2003, the incidence rate of infectious syphilis was 5.1 per 100,000 population. 3 cases of congenital syphilis were reported in the same year.

Antimicrobial resistance surveillance

Rapid and effective treatment of STIs is the key programme element for preventing further spread of infection. This is particularly true for highly infectious and curable STIs like gonorrhoea, chancroid, chlamydia and infectious syphilis. Therefore, ongoing monitoring of the trend in antimicrobial resistance pattern for certain causative organisms is necessary. The World Health Organisation Western Pacific Regional Office (WHO/WPRO) has established a re-

Figure 8
Percentage distribution of the different STIs in Singapore, 1980, 1997 & 2003



gional gonococcal resistance surveillance network, which reveals a growing resistance of *Neisseria gonorrhoea* to penicillin and quinolone in Singapore (*Figs. 9 - 12*). Therefore, the potential spread of the gonococcal strains which have a reduced sensitivity to commonly used antibiotics such as spectinomycin and ceftriaxone should be closely monitored.

Comments

There has been significant achievement in the control of STIs in Singapore in the 1980s and early 1990s. This is evident by the steady decline in the incidence of STIs in Singapore from 1977 to 1996. However, between 1997 and 2003, there was an increase in the STI incidence rate and this was observed in all age groups, including the youths (15 to 24 years old). Gonorrhoea was the leading cause of STI in Singapore with an incidence rate of 48.8 per 100,000 population in 2003.

One of the most sensitive markers of changes in high-risk sexual behaviours is the resultant increase in transmission and diagnosis of STIs. In view of the fact that public access to the healthcare service has not undergone great changes in recent years, the increase in the local STI incidence rate could be an indication of an increase in unsafe sexual practices in the community, and this trend could be extended to all age groups.

STIs cause considerable reproductive morbidity and poor health outcomes, including pelvic inflammatory disease (PID), infertility, ectopic pregnancy, cervical cancer, neonatal disorders and deaths[1]. WHO has also identified curable STIs as an important indicator of potential exposure to human immunodeficiency virus (HIV) infection, both because they are co-factors for infection and because they indicate unprotected sex with non-monogamous partners[2,3]. High levels of STIs can act as a warning system for HIV even in populations where the HIV incidence remains low.

Figure 9

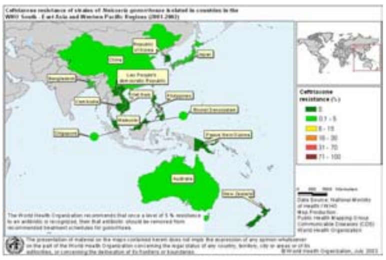


Figure 10

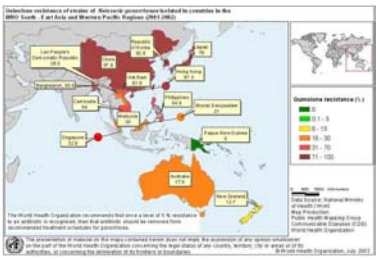


Figure 11

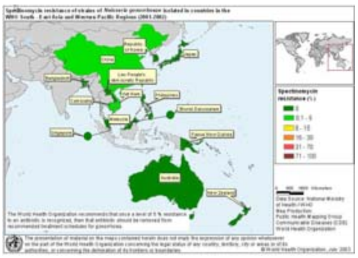
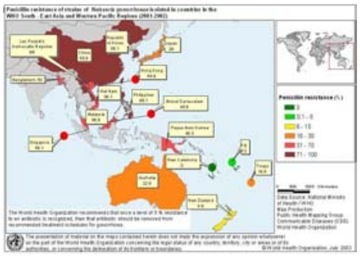


Figure 12



STIs generally reflect risk behaviours in the relatively recent past better than HIV prevalence data, because curable STIs are usually of relatively short duration. HIV infection may indicate risk behaviour in the recent past, but it may equally capture the risk behaviours of several years previously. An increase in safe sexual behaviours is therefore reflected much more quickly in lower STI rates than it is in lower HIV rates. Nevertheless, it should be borne in mind that lower STI rates may reflect improvements in the quality and coverage of treatment as well as changes in risk behaviour. Therefore, good STI incidence and prevalence data can contribute significantly to tracking trends in risky sex and potential exposure to HIV infection, and to monitoring the success of measures aimed at promoting safer sex.

In Singapore, the increase in STI incidence rates for the past few years corresponded with the increase in the local HIV incidence rate as well. In response to this trend, sexual health education and STI/HIV prevention programmes targeted at the various age groups and at risk populations will be planned and carried out to increase public awareness and to promote the adoption of safer sexual practices in our effort to control STI/HIV in Singapore.

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(Acknowledgements : A/Prof Roy Chan, Head DSC and Dr Tan Hiok Hee, Deputy Head, DSC)

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Avian influenza

Introduction

Avian influenza (AI) is a contagious viral infection that can affect all species of birds (chickens, turkeys, guinea fowl, pet birds and wild birds). Wild birds may carry influenza viruses without becoming ill due to natural resistance. Wild waterfowl present a natural reservoir for these viruses and can be responsible for the primary introduction of infection into domestic poultry. The disease can range from a mild infection with no symptoms to a severe epidemic that kills up to 100 percent of infected birds.

Aetiology

Influenza viruses are segmented, negative strand RNA viruses in the family *Orthomyxoviridae*. They are divided into three types of influenza virus, A, B and C. Only influenza A viruses have been reported to cause natural infections of birds.

Influenza A viruses are classified into subtypes on the basis of their surface antigens, haemagglutinin (H) and neuraminidase (N) which are glycoproteins. At present, 15 H subtypes (H1–H15) and 9 N subtypes (N1–N9) are recognized.

Each virus has one H and one N antigen, apparently in any combination. Although the range of subtypes and combinations occurring naturally in mammals appear to be restricted, all subtypes and the majority of possible combinations have been isolated from avian species.

Low pathogenic versus highly pathogenic avian influenza viruses

Influenza A viruses infecting poultry can be divided into two distinct groups, either highly pathogenic avian influenza (HPAI) or low pathogenic avian influenza (LPAI) on the basis of genetic features of the virus and their ability to cause disease. HPAI is usually associated with high mortality in poultry. HPAI viruses can kill 90% to 100% of infected chickens, whereas LPAI viruses cause less severe or no illness if they infect chickens. However, LPAI viruses can evolve into HPAI viruses and therefore need to be closely monitored by veterinary authorities.

To date, the highly virulent influenza A viruses that produce acute clinical disease in chickens and turkeys have been associated only with the H5 (H5N1, H5N2, H5N8 & H5N9) and H7 (H7N1, H7N3, H7N4 & H7N7) subtypes with the exception of two H10 subtypes and more recently H9N2. Many viruses of H5 and H7 subtype isolated from birds have been of low virulence for poultry.

There have been 21 outbreaks of HPAI worldwide in domestic poultry since 1959 (*Table 5*). All other viruses cause a much milder disease consisting primarily of mild respiratory disease, depression and egg production problems in laying birds.

Clinical signs of avian influenza

The incubation period is usually 3 to 7 days depending on the strain, the dose of inoculums, the species and age of the bird. Infections in poultry result in:

Table 5

Primary HPAI virus isolates from poultry since 1959

1.	A/chicken/Scotland/59 (H5N1)
2.	A/turkey/England/63 (H7N3)
3.	A/turkey/Ontario/7732/66 (H5N9)
4.	A/chicken/Victoria/76 (H7N7)
5.	A/chicken/Germany/79 (H7N7)
6.	A/turkey/England/199/79 (H7N7)
7.	A/chicken/Pennsylvania/1370/83 (H5N2)
8.	A/turkey/Ireland/1378/83 (H5N8)
9.	A/chicken/Victoria/85 (H7N7)
10.	A/turkey/England/50-92/91 (H5N1)
11.	A/chicken/Victoria/1/92 (H7N3)
12.	A/chicken/Queensland/667-6/94 (H7N3)
13.	A/chicken/Mexico/8623-607/94 (H5N2)
14.	A/chicken/Pakistan/447/94 (H7N3)
15.	A/chicken/NSW/97 (H7N4)
16.	A/chicken/Hong Kong/97 (H5N1)
17.	A/chicken/Italy/330/97 (H5N2)
18.	A/turkey/Italy/99 (H7N1)
19.	A/chicken/Chile/2002 (H7N3)
20.	A/chicken/The Netherlands/2003 (H7N7)
21.	A/chicken/Thailand/2004(H5N1)

- sudden death without any clinical sign;
- severe depression, inappetence and excessive thirst;
- production of eggs without shells or cessation of egg production;
- cyanotic wattles, combs and legs;
- oedema of head, neck, eyelids, comb, wattles and legs;
- nasal discharge, coughing, sneezing; and
- diarrhoea (begins with watery bright green and progresses to almost totally white)

Host range

Most avian species appear to be susceptible to at least some of the AI viruses. The host range for HPAI varies with the isolate as seen in some outbreaks, only one out of several avian species present on the farm became infected. Although AI viruses have been isolated from a large number of species covering 12 of the 50 Orders of birds[1], the number, variety and distribution of AI viruses have been far greater in waterfowl, Order *Anseriformes*, than in other birds.

AI viruses are perpetuated in free-living waterfowl through the passage of virus from adult to juvenile birds on lakes where the birds congregate before migration each year. Considerable quantities of the virus are excreted with the faeces to contaminate lake or pond water. AI virus may be isolated from untreated lake water where large numbers of waterfowl are found.

Pigs are also susceptible to AI viruses and have been involved in influenza infection of turkeys. Other mammals do not appear to be involved in the epidemiology of HPAI. However, since 1997, numerous human infections have occurred and even tigers have been reported to be infected[2].

Molecular basis of virulence

The haemagglutinin (HA) glycoprotein for influenza viruses has two important functions that are imperative for the infectivity of the virus. It brings about

1) attachment to host cell and
2) fusion between the host cell membrane and the virus membrane so that the viral genetic material is introduced into the host cell.

This glycoprotein is produced as a precursor, HA0, which requires cleavage by host proteases before it is able to induce membrane fusion and virus particles become infectious[3]. The HA0 precursor proteins of AI viruses of low virulence for poultry have a single arginine at the cleavage site and another at position -3 or -4. These viruses can only be cleaved by host proteases such as trypsin-like enzymes and thus restricted to replication at the respiratory and intestinal tracts of the host where such enzymes are found.

HPAI viruses possess multiple basic amino acids, arginine and lysine, at their HA0 cleavage sites either as a result of apparent insertion or apparent substitution[4] and appear to be cleavable by ubiquitous proteases. These viruses are able to replicate throughout the bird, damaging vital organs and tissues which results in disease and multiple organ failure leading to death[3].

For example, all H7 subtype viruses of low virulence have had the amino acid motif at the HA0 cleavage site of either -PEIPKGR*GLF- or -PENPKGR*GLF-, whereas examples of cleavage site amino acid motifs for HPAI H7 viruses are: -PEIPKKKKR*GLF-, PETPKRKRKR*GLF-, -PEIPKKREKR*GLF-, -PETPKRRRR*GLF-, -PEIPKGSRVRR*GLF-.

Current theories suggest that HPAI viruses emerge from viruses of low virulence by mutation[5]. It appears that such mutations occur only after the viruses have moved from their natural host to poultry. This is supported by phylogenetic studies of H7 subtype viruses, which indicate that HPAI viruses do not constitute a separate phylogenetic lineage, but appear to arise from non-pathogenic strains and the selection of mutants virulent for chickens from an avirulent H7 virus[6].

Spread of AI among birds

AI viruses circulate among birds worldwide. Certain birds, particularly water birds, act as natural reservoirs for influenza viruses by carrying the virus in their intestines and shedding it. Infected birds shed virus in saliva, nasal secretions, and faeces. Susceptible birds can become infected with AI virus when they have contact with contaminated nasal, respiratory, or faecal material from infected birds. Faecal-to-oral transmission is the most common mode of spread between birds. Most often, the wild birds that are host to the virus do not get sick, but they can spread influenza to poultry and other birds.

Primary introduction

All available evidence suggests that primary introduction of AI viruses into an area is by wild birds, usually waterfowl, but gulls and shorebirds have also been implicated. Domesticated birds may become infected with AI virus through direct contact with infected waterfowl. Infected waterfowl may take the viruses to an area and these may then be introduced to poultry through mechanical transfer of the virus in infective faeces and respiratory secretions. Surface water used for drinking water may also be contaminated and serve as a source of infection.

Apart from wild birds, other possibilities should not be ruled out. For example, H1N1 viruses pass readily between pigs, humans and turkeys and the introduction of H1N1 viruses to turkey flocks from infected pigs has been well documented.

Secondary spread

Secondary spread of AI viruses is mainly by mechanical transfer of infective faeces, in which virus may be present at high concentrations and may survive for considerable periods. Poultry may become infected through direct contact with infected birds or contact with surfaces (such as dirt or cages) or materials (such as water or feed) that have been contaminated with AI virus. People, vehicles, and other inanimate objects such as cages can be vectors for the spread of influenza virus from one farm to another.

Prevention, control and eradication

The main measures available to prevent, control and eradicate HPAI are:

- effective disease surveillance for early detection and reporting of outbreaks;
- enhanced biosecurity of poultry farms and associated premises;

- control of movement of birds and products that may contain virus, including controls at the interface of infected and uninfected areas;
- changes to industry practices to reduce risk;
- rapid, humane destruction of infected poultry and poultry at high risk of infection;
- disposal of carcasses and potentially infective material in a biosecure and environmentally acceptable manner; and
- the proper use of vaccination.

Each of the control measures reduces risk but if used in isolation, it will be insufficient. All available measures must be considered to determine the best combination to prevent incursion or to control and eradicate the disease[7].

Since wild birds are a source for primary introduction of AI viruses, it is preferable to design farms practices to minimise direct or indirect contact with wild birds, e.g. bird-proofing the farm or environmentally controlled farm. Since one of the major reservoirs of influenza viruses is in migratory waterfowl, ideally commercial farms should be located away from migratory flyways. Poultry may be less likely to become infected with AI viruses if kept indoors, but for some species, e.g. ostriches, it is a necessity to keep them outdoors. Use of surface drinking water and the presence of lakes that attracted waterfowl close to the farms were associated with the HPAI outbreaks in Australia and USA.

Stamping out policy will be enforced if a poultry farm in Singapore is infected with HPAI. Simulation exercises are regularly carried out to fine tune and sharpen the preparedness to control and eradicate HPAI should an incursion occur. Biosecurity in local poultry farms have been strengthened. This includes mandatory bird proofing, thorough disinfection of vehicles and personnel entering the farm, visitors and poultry or poultry products are not allowed into the farm. Border checks are tightened. Birds, poultry and poultry products are refused entry from countries or regions affected by HPAI. Surveillance for AI has been intensified at poultry farms, pet bird establishments, border check points, nature reserves and zoological gardens.

Vaccination

If birds are sufficiently well immunized against the HA subtype corresponding to that of the challenge virus they will be protected from the worst effects of the clinical disease and mortalities. Experience in Hong Kong indicates that H5N2 vaccines can be used successfully to help eliminate H5N1 HPAI virus. Vaccination has also been used successfully in other regions to control AI viruses. Most examples from Europe and North America relate to using vaccination to help control LPAI viruses.

However, some vaccinated birds continue to be infected with no or minor illnesses and shed viruses in their faeces. The existence of a large number of virus subtypes together with the known variation of different strains within a subtype pose serious problems when selecting strains to produce influenza vaccines. In addition, some isolates do not grow to a sufficiently high titre to produce adequately potent vaccines without costly prior concentration.

Most vaccines used to date for AI have been inactivated whole AI virus antigen in an oil based emulsion adjuvant. The inactivated vaccines are either autogenous (prepared from isolates specifically involved in an epizootic), or prepared from viruses possessing the same HA subtype that yield high concentrations of antigen. Recently, baculovirus derived H5 and H7 vaccines and recombinant fowlpox vectored vaccine with AI H5 gene insert have been used. Several novel vaccines have also been developed or are currently under development for AI. These include

- vaccines based on reverse genetics that provide an exact antigenic match with field strains of virus but which can be grown to high and consistent titre;
- adenovirus-vectored vaccines that can be delivered via drinking water; and
- Newcastle disease-vectored vaccines that can be delivered by aerosol.

Avian influenza infection in humans

Although avian influenza A viruses do not usually infect humans, several instances of human infections with AI have been reported since 1997. Most of the human cases are thought to have resulted from contact with infected poultry or contaminated surfaces. However, there is still a lot to learn about how different subtypes and strains of AI virus might affect humans. For example, it is not certain how the distinction between "low pathogenic" and "highly pathogenic" strains is related to the risk of disease in humans. Illnesses caused by highly pathogenic viruses appear to be more severe in humans.

Instances of avian influenza infections in humans

Confirmed instances of avian influenza viruses infecting humans since 1997 include:

- H5N1, Hong Kong, 1997: This was the first time an AI virus had ever been found to transmit directly from birds to humans. In this outbreak, 18 people were hospitalized and 6 of them died. Hong Kong authorities depopulated about 1.5 million chickens to remove the source of the virus to stop the outbreak. Scientists determined that the virus spread primarily from birds to humans, though very limited person-to-person spread was noted. A survey after the outbreak identified 17% seroprevalence in poultry workers in Hong Kong but without any known occurrence of clinical disease.
- H9N2, China and Hong Kong, 1999: H9N2 AI was confirmed in two children. Both patients recovered. The evidence suggested that poultry was the source of infection and the main mode of transmission was from bird to human. Several additional human H9N2 infections were reported from mainland China in 1998-99.
- H7N2, Virginia, 2002: Following an outbreak of H7N2 among poultry in the Shenandoah Valley poultry production area, one person was found to have serologic evidence of infection with H7N2.
- H5N1, China and Hong Kong, 2003: Two cases of H5N1 infection occurred among members of a Hong Kong family that had travelled to China. One of them died. Another family member also died of a respiratory illness in China, but no testing was done.
- H7N7, Netherlands, 2003: Outbreaks of H7N7 HPAI in poultry started in February in the Netherlands. Later, infections were reported among pigs and humans. In total, 89 people, mostly poultry workers, were confirmed to have H7N7 influenza virus infection associated with this poultry outbreak. The majority of the cases had conjunctivitis only and a few cases had influ-

enza-like illnesses with cough, fever, and muscle aches. One veterinarian died from acute respiratory distress syndrome and complications related to H7N7 infection after visiting one of the affected farms. The majority of these cases occurred as a result of direct contact with infected poultry; however, Dutch authorities reported three possible instances of transmission from poultry workers to family members.

- H9N2, Hong Kong, 2003: H9N2 infection was confirmed in a child in Hong Kong. The child was hospitalized but recovered.
- H5N1, Thailand and Vietnam, 2004: The ongoing outbreak of H5N1 HPAI across 10 Asian countries started in late 2003. Human cases were first reported in January 2004. Since then, 47 human cases involving 34 deaths have been reported in Thailand (17 cases/12 deaths) and Vietnam (30 cases/22 deaths) giving an extremely high case-fatality rate of 72%.
- H7N3 in Canada, 2004: In February 2004, human infections of H7N3 among poultry workers were associated with an outbreak in poultry. The illnesses were mild and consisted of eye infections.

Symptoms of avian influenza in humans

The reported symptoms of avian influenza in humans have ranged from typical influenza-like symptoms (e.g. fever, cough, sore throat, and muscle aches) to conjunctivitis, pneumonia, acute respiratory distress, other severe and life-threatening complications and death.

Antiviral agents for influenza

Two groups of antiviral drugs are used in the treatment and/or prophylaxis of influenza.

(1) ***M2 protein inhibitor***

The antiviral mechanism of amantadine and rimantadine is not clearly understood. It appears to prevent the release of infectious viral nucleic acid into the host cell by interfering with the viral M2 protein. It also prevents virus assembly during virus replication.

(2) ***Neuraminidase inhibitor***

Oseltamivir (Tamiflu) and zanamivir inhibit the influenza virus neuraminidase enzyme and prevent the release of virus particles from the host cell.

All four have activity against influenza A viruses. However, some of the 2004 H5N1 viruses isolated from poultry and humans in Asia have been found to be resistant to amantadine and rimantadine.

Zoonotic potential and pandemics

Influenza viruses have eight separate gene segments. The segmented genome allows viruses from different species to mix and create a new influenza A virus if viruses from two different species infect the same person or animal.

For example, since pigs have the receptors for both avian and human influenza viruses, it is possible for a pig to be infected with a human influenza virus and an avian influenza virus at the same time. These viruses could reassort and produce a new virus that had most of the genes from the human virus, but a haemagglutinin and/or neuraminidase from the avian virus. The resulting new virus might then be able to infect humans and spread from person to person, but it would have surface proteins (haemagglutinin and/or neuraminidase) not previously seen in influenza viruses that infect humans.

This type of major change in the influenza A viruses is known as antigenic shift. Antigenic shift results in a new influenza A subtype to which most people have little or no immune protection. If this new virus causes illness in people and can be transmitted easily from person to person, an influenza pandemic can occur.

It is also possible that the process of reassortment could occur in a human. For example, if a person were infected with avian influenza and a human strain of influenza at the same time, the viruses could reassort to create a new virus that had a haemagglutinin from the avian virus and other genes from the human virus. Theoretically, influenza A viruses with a haemagglutinin against which humans have little or no immunity that have reassorted with a human influenza virus are more likely to result in sustained human-to-human transmission and pandemic influenza. Thus, careful evaluation of influenza viruses recovered from humans who are infected with avian influenza is very important to identify reassortment if it occurs.

An influenza pandemic is a global outbreak of influenza and occurs when a new influenza A virus emerges among people, spreads, and causes disease worldwide. Past influenza pandemics have led to high levels of illness, death, social disruption and economic loss. Three pandemics occurred in the 20th century. All of them spread worldwide within 1 year of being detected. They are:

- **1918-19, "Spanish flu":** Influenza A (H1N1) caused the death of more than 500,000 people in the United States, and 40 million people worldwide. Many people died within the first few days after infection and others died of complications soon after. Nearly half of those who died were young, healthy adults.
- **1957-58, "Asian flu":** Influenza A (H2N2) caused about 70,000 deaths in the United States and 1 million deaths worldwide. First identified in China in late February 1957, the Asian flu spread to the United States by June 1957.
- **1968-69, "Hong Kong flu":** Influenza A (H3N2) caused approximately 34,000 deaths in the United States and a million deaths worldwide. This virus was first detected in Hong Kong in early 1968 and spread to the United States later that year.

Both the 1957-58 and 1968-69 pandemic viruses were a result of the reassortment of a human virus with an avian influenza virus and pigs acted as a "mixing vessel". The origin of the 1918 pandemic virus is not entirely clear but also thought to be of avian origin[8].

The current influenza A H5N1 meets 2 of the 3 important criteria for a new pandemic influenza virus – (1) the ability to replicate in humans and cause disease; and (2) the absence of immunity to the virus in the human population at large. The third criterion is the potential to rapidly spread from man to man, which has so far not been observed. No one can predict if or when the third prerequisite for the start of a pandemic will be met[9].

Conclusion

Since late 2003, outbreaks of HPAI among poultry have been reported in several parts of the world. In Vietnam and Thailand, H5N1 HPAI outbreaks among poultry have been associated with illness and death in humans. In British Columbia, Canada, an outbreak of H7N3 among poultry in 2004 was associated with human illness.

Because of concerns about the potential for more widespread infection in the human population, public health authorities are closely monitoring outbreaks of human illness associated with avian influenza. To date, human infections with avian influenza viruses detected since 1997 have not resulted in sustained human-to-human transmission. However, because influenza viruses have the potential to change and gain the ability to spread easily among people, the situation is sufficiently serious to warrant considerations to put in place pandemic preparedness plans.

[Reported by Dr Chua Sin Bin, Dy CEO, AVA, based on OIE. Avian influenza - brief review. Draft report of the meeting of the OIE ad hoc group on avian influenza, Paris, 2003, Appendix III.
(http://www.oie.int/eng/AVIAN_INFLUENZA/AHG_AI_Nov2003.pdf) and CDC. General information on avian influenza,2004
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A review of the avian influenza situation in the region

(As of 22 December 2004)

Background

Avian influenza is an infectious disease of birds caused by type A strains of the influenza virus. The disease, which was first identified in Italy more than 100 years ago, occurs worldwide. All birds are thought to be susceptible to infection with avian influenza, though some species are more resistant to infection than others. Infection causes a wide spectrum of symptoms in birds, ranging from mild illness to a highly contagious and rapidly fatal disease resulting in severe epidemics. The latter is known as "highly pathogenic avian influenza" (HPAI). This form is characterized by sudden onset, severe illness, and rapid death, with a mortality that can approach 100%. Direct or indirect contact of domestic flocks with wild migratory waterfowl has been implicated as a frequent cause of epidemics. Live bird markets have also played an important role in the spread of epidemics.

HPAI was considered a rare occurrence with only 21 outbreaks reported worldwide between 1959 and December 2003. Majority of these outbreaks were in Europe and the Americas, of which five significantly involved numerous farms, while only one was associated with spread to other countries

Recent research has shown that viruses of low pathogenicity, after circulation for short periods in a poultry population, could mutate into highly pathogenic viruses. During an epidemic in the United States of America in 1983–1984, the H5N2 virus initially caused low mortality, but within six months became highly pathogenic, with a mortality of 90%. Control of the outbreak required destruction of more than 17 million birds at a cost of nearly US$ 65 million. In another epidemic in Italy in 1999–2001, the H7N1 virus, initially of low pathogenicity, mutated within 9 months to a highly pathogenic form. More than 13 million birds died or were destroyed.

Avian influenza is now of grave public health concern as epidemics caused by the highly pathogenic H5N1 strain have been reported in many Asian countries. This strain is known to be directly transmissible to humans.

Current situation

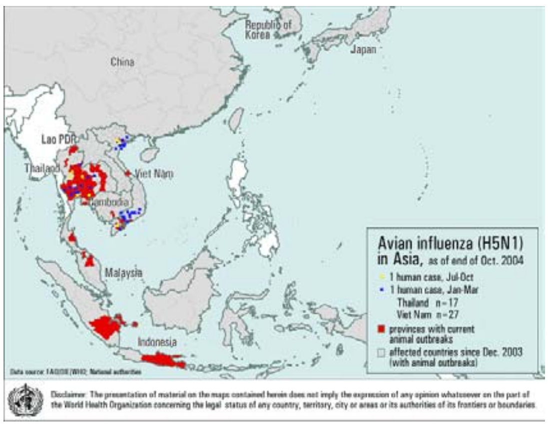
Since mid-December 2003, the H5N1 virus has been confirmed in nine Asian countries; namely Vietnam, Thailand, Malaysia, Indonesia, China (including Hong Kong), Japan, Republic of Korea, Cambodia and Lao People's Democratic Republic. Most of these countries were experiencing HPAI outbreaks for the first time.

The outbreaks dwindled in March 2004 but resurfaced around late June to July 2004 in China, Indonesia, Thailand and Vietnam (*Fig. 13*). As many of these outbreaks were not evidently linked to one another, it was believed that avian influenza was widely prevalent and could have become endemic.

A total of 44 laboratory-confirmed H5N1 human cases (including 32 deaths) were reported from Thailand and Vietnam between 28 January and 25 October 2004 (*Table 6*).

According to a WHO report on 29 October 2004, a recent laboratory study of domestic ducks

Fig 13
Avian influenza (H5N1) situation in Asia
(Dec 2003- end Oct 2004)



(Source: WHO)

infected with the H5N1 virus in 2004 showed that not only were these ducks shedding more virus and for longer periods, as compared with ducks infected with the H5N1 virus in 2003, but majority were asymptomatic as well. Moreover, the recent H5N1 virus could survive several days longer in the environment. These findings suggest an altered role for domestic ducks in avian influenza viral transmission.

Table 6

Laboratory confirmed human cases of H5N1 avian influenza in Asia

Country	Total cases	Deaths
Thailand	17	12
Vietnam	27	20
Total	44	32

Vietnam

Between end-October 2003 and 13 January 2004, 14 people have been hospitalised for severe respiratory illness, among whom 13 were children and the only adult was the mother of a deceased child. WHO announced on 13 January 2004 that specimens obtained from two children and the adult were positive for the H5N1 avian influenza virus. It was not known whether the same virus was responsible for the other cases.

On 2 February 2004, possible human-to-human transmission was described by WHO in a cluster of respiratory illness in Thai Binh province, involving two sisters, aged 23 and 30 years, their 31-year-old brother and his 28-year-old wife. Both sisters and the man had died, while his wife fully recovered. The man and one sister had a history of direct contact with poultry, while none was reported for his wife and other sister. Although the couple was not tested, H5N1 infection was confirmed in both sisters. Genetic sequencing results showed that the viruses isolated from both of them were of avian origin and did not contain human influenza genes.

A total of 27 human cases of H5N1 infection, including 20 deaths have so far been reported from Vietnam. Three of the fatal cases occurred in two separate provinces since early August 2004 and an additional death case from Hanoi was laboratory-confirmed for the influenza A (H5) virus. No further cases of human infections have been reported since early September. A total of 44 out of 64 provinces and municipalities have been affected by avian influenza as of 24 November, according to the World Organisation of Animal Health (OIE). Two recent outbreaks of H5 infection were reported in 2 provinces in late November and mid-December.

Thailand

As of 4 November 2004, Thailand has reported 17 human cases of H5N1 infection with 12 deaths. Five of these cases, including four deaths, occurred since early September.

In a report on 28 September, WHO released details of a probable human-to-human transmission within a family cluster. H5N1 infection was confirmed in a 32-year-old woman and her 26-year-old sister, after the latter's 11-year-old daughter had died in early September. She had cared for her daughter in Kamphaeng Phet province, after which she herself fell ill upon returning to Bangkok where she passed away on 20 September. As specimens from the daughter were not available for testing, laboratory confirmation was not possible and she has been regarded as a probable case. Both the girl and her aunt, who had since recovered, were reported to have had direct contact with dead chickens. The H5N1 virus was not detected in the aunt's 6-year-old son, who was hospitalised but had recovered as well. No further updates on the investigation of this family cluster have been provided by WHO since.

Although this incident suggested that human-to-human transmission might have occurred, WHO has reiterated that evidence of possible viral transmission among humans has been limited to family members so far, with no indication of wider transmission in the community.

There have been no further reports of suspected human cases since late October. According to OIE, at least 55 of 76 provinces have been affected by avian influenza in poultry as of 16 November. Two new outbreaks were recently confirmed in backyard chickens in two provinces on 13 December.

There were several reports of H5N1 infection in animals other than poultry. In February 2004, the virus was detected in two out of three dead domestic cats, belonging to a cluster of 14 cats that died within a single household of 15 cats. One of the affected cats was noticed to have had contact with dead chickens. This was the first reported occurrence of natural infection with the H5N1 virus in domestic cats.

Eight months later in mid-October 2004, the H5N1 virus was detected in tigers belonging to a zoo in Chon Buri province. More that 80 tigers in the zoo had either died or been culled. The probable cause of infection appeared to be feeding the tigers with chicken carcasses. No clinical illness or death has been observed in any species in the zoo since 28 October.

Between October and November 2004, 10 out of 1,011 samples (0.98%) collected from 68 local and migratory bird species were found H5N1 positive. The positive samples were obtained from six local bird breeds from four provinces.

Malaysia

HPAI was first reported in Malaysia on 19 August 2004, where the H5 avian influenza virus was detected in a Kelantan village. In total, outbreaks in poultry have been reported from nine villages in five districts of the state as of 30 September. Surveillance samples taken from chickens in additional two villages were positive for the H5 virus. No further outbreaks were reported until Malaysian officials confirmed on 1 December that H5N1 had been detected in another village in mid-November. All known incidents of HPAI have been restricted to Kelantan and no human cases have been reported.

Indonesia

On 2 February 2004, OIE was notified of 127 H5N1 avian influenza outbreaks in 11 provinces, with the first outbreak detected on 15 December 2003. As of 6 October, a total of 15 provinces, comprising 98 districts, have been infected. New occurrences of HPAI were recently reported on 13 December in several parts of West Nusa Tenggara. No human cases have been reported.

China

The first outbreak of H5N1 infection in poultry was reported in Guangxi province on 27 January 2004. Since then, 53 outbreaks have occurred in 16 provinces, of which 49 have been confirmed to be caused by the H5N1 virus. No outbreaks were notified from mid-February until 6 July, when OIE was informed of a H5N1 outbreak in Anhui province. No human cases have been reported.

In August 2004, at an international symposium on SARS and avian influenza held in Beijing, a researcher from China's Harbin Veterinary Research Institute presented preliminary evidence that pigs from farms in parts of China have been infected with the H5N1 strain of avian influenza. China's Ministry of Agriculture has since confirmed these findings, although it is unclear whether the virus is widespread in pigs in the country.

Hong Kong

A peregrine falcon was found dead in the New Territories on 19 January 2004. Tests of specimens from the wild bird carcass showed presence of H5N1. The virus was subsequently detected twice in another wild species - a migratory grey heron (*Ardea cinerea)* - in early November and early December 2004. No outbreaks in poultry or human cases have been reported.

Japan

HPAI was reported for the first time in Japan on 13 January 2004 since 1925. The H5N1 virus was detected in a commercial flock in Yamaguchi prefecture. Between mid-January and early March 2004, another 3 H5N1 outbreaks occurred in 2 separate prefectures. Since the last outbreak in March, there were no further reports of new cases of HPAI in poultry. However, on 5 March 2004, 3 crows were found dead in Kyoto prefecture, one of which was positive for the avian influenza virus.

According to media reports*, Japan's Health Ministry revealed on 22 December that at least one person had been infected with the avian influenza virus after an outbreak among chickens in February. Four others had probably also been infected with the virus. Although all five people have tested positive for antibodies to the virus, they have not developed symptoms of avian influenza. This case marks the first human infection of avian influenza virus in Japan.

Republic of Korea

The Republic of Korea had been HPAI-free until an outbreak was announced in mid-December 2003 at a farm in Chungbuk province. A total of 19 farms in seven provinces or metropolitan cities were subsequently confirmed with HPAI. The last case of the disease was confirmed on 21 March 2004. No human cases have been reported.

Cambodia

Between 24 January and 1 April 2004, 12 outbreaks of avian influenza H5N1 in poultry were reported in five provinces. A new H5N1 outbreak in a farm in Kandal province was reported later in the year on 22 September. No human cases were reported.

Lao People's Democratic Republic

An outbreak of H5 avian influenza in a farm close to Vientiane, the capital, was confirmed on 27

(An example of the report is available in ProMED-mail, dated December 22, 2004 [http://www.promedmail.org])*

[Reported by Goh H, Lum MY, Ye Tun, Communicable Diseases Division (Surveillance Branch), Ministry of Health]

January 2004. WHO was informed on 4 February that 17 out of 18 farms in Vientiane have tested positive for the H5 virus. The last known suspected or confirmed case from the country was reported on 13 February. No human cases were reported. There has been little information on the situation in Lao PDR.

Editorial comments

The Agri-Food and Veterinary Authority (AVA) of Singapore has taken all the necessary precautions to prevent the disease from entering Singapore by suspending the import of live birds from countries affected by avian influenza. There are strict controls at the points of entry and samples are taken from every imported live bird consignment. The local poultry farms are biosecured and bird-proofed. There is intensified surveillance at the farms to look out for any unusual deaths and signs of avian influenza. Workers of poultry slaughter houses are required to wear personal protective equipment and to strictly adhere to hygiene practices. As most avian influenza outbreaks originated from backyard farms which do not have proper biosecurity measures in place, residents at Pulau Ubin are prohibited to keep more than 10 poultry per household. In the event of an outbreak in any of the farms, AVA will take immediate action to control and eradicate the disease by culling all the poultry, and the farms will be placed under strict quarantine.

In July 2004, the Dept of Veterinary Services (DVS), Malaysia, notified AVA of chickens dying in a school in Perak. As the test was subsequently found to be negative for H5N1, AVA did not take any action. On 3 Aug 2004, a consignment of healthy ducks imported from a farm in Perak was suspected to be infected with the H5 subtype of low pathogenicity. The DVS was informed and import of ducks was suspended as an additional precaution to minimize risk of exposure of any avian influenza to local poultry farms. On 18 Aug 2004, when Malaysia reported detection of avian influenza in Kelantan, all imports of poultry, poultry products and eggs from Malaysia were suspended. In Sept 2004, Kelantan confirmed another outbreak of avian influenza 5 km from the first affected farm.

AVA worked closely with Malaysia to put in place stringent control measures to enable resumption of import of poultry and eggs from non-affected areas in Malaysia in stages.

On 30 Sept 2004, following satisfactory reports by 3 AVA field investigations to accreditated farms in Johor and Malacca between 7 Sept and 25 Sept, AVA allowed resumption of poultry and egg imports from these two states. The teams were satisfied with the intensive disease surveillance programme, adequate biosecurity measures, including establishment of buffer zones to isolate the avian influenza-free states from the affected areas and road blocks to control interstate movement of poultry and eggs, and stringent inspection and health certification system for each export consignment.

The Ministry of Health (MOH) has maintained heightened surveillance for early detection of suspected cases of avian influenza in humans. Medical practitioners are periodically updated on the current avian influenza situation in the region and advised to take all necessary precautionary measures, including vaccination against influenza for those travelling to the temperate countries and high-risk patients with co-morbid conditions.

MOH has in place an influenza surveillance system which covers both humans and birds. MOH monitors the number of polyclinic attendances for acute respiratory infections (ARI), atypical pneumonias and unexpected deaths occurring in hospitals, and influenza viruses detected in patients presenting with ARI at sentinel polyclinics and Kandang Kerbau Hospital. AVA monitors influenza viruses from animal sources by routinely collecting cloacal swabs from poultry in domestic farms and import consignment of poultry from processing plants and at the points of entry. The Dept of Pathology, Singapore General Hospital , is the National Influenza Centre (NIC) which participates in the WHO Global Influenza Surveillance Network. The NIC samples patients with influenza-like illness and submits representative isolates to the WHO Collaborating Centres in US, UK, Australia and Japan for antigenic and genetic analysis on a regular basis. This provides guidance to WHO in its recommendations on the virus strains to be used for the influenza vaccine for the northern and southern hemisphere winter periods.

During the northern hemisphere winter of 2003/4, MOH advised all healthcare workers and persons at high risk of complications from influenza to be vaccinated. In May/June 2004, the Ministry further advised all healthcare workers and persons at risk of complications from influenza infection to be vaccinated with the southern hemisphere vaccine. The Ministry will continue to provide advice to Singaporeans on influenza vaccination based on the influenza situation locally and worldwide.

MOH has developed a pandemic preparedness plan detailing actions to be taken before and during an influenza pandemic. The objective of the plan is to mitigate the socio-economic impact of a pandemic occurring in Singapore, and to reduce morbidity and mortality associated with the pandemic.

The plan is aligned with recommendations made by WHO in the document 'WHO consultation on priority health interventions before and during an influenza pandemic'. As part of the pandemic preparedness plan, MOH has built up an initial stockpile of antiviral medications (oseltamivir or Tamiflu) to provide prophylaxis to essential service personnel as well as treatment to those affected by the disease.

Singapore has also developed a contingency plan to manage a highly pathogenic avian influenza outbreak in chickens and birds occurring in Singapore. The aim of this plan is to control the outbreak by culling all live poultry in the country, and providing antiviral prophylaxis for exposed persons such as chicken farmers. Exercises were conducted on 18 Feb 2004 and 3 Sept 2004 to test the interagency operational readiness in responding to an outbreak of avian influenza.

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All information was obtained from the following 3 sources, unless otherwise stated

1. World Health Organization (WHO) (http://www.who.int)

2. Food and Agriculture Organization of the United Nations (FAO) (http://www.fao.org)

3. World Organization for Animal Health (OIE) (http://www.oie.int)

Epidemiological investigations into an outbreak of cholera, Oct 2004

Introduction

Cholera is an acute food-borne disease caused by the bacterium *Vibrio cholerae* O1 and O139. The O1 serotype exists as two biotypes, classical and El Tor. Asymptomatic infection is much more frequent than clinical illness. The infection has a short incubation period, which ranges from a few hours to five days. The causative organism elaborates an enterotoxin that results in copious painless, watery diarrhoea and vomiting. In severe cases, the infection can lead to severe dehydration, shock and death. *Vibrio cholerae* is often found in the aquatic environment [1] and the infection is commonly acquired through ingestion of contaminated seafood and water. Person-to-person transmission via the faecal-oral route is uncommon.

Cholera is uncommon in Singapore. However, occasional localised food-borne outbreaks have been reported [2-4]. Consumption of contaminated prawns, squids, mussels and raw fish has been implicated in some of the outbreaks[5-7].

In Oct 04, a sudden increase in the notification of cholera cases caused by *V. cholerae* O1 , biotype El Tor, serotype Ogawa, was noted and epidemiological investigations were immediately conducted to determine the source of infection and mode of transmission. We present the findings of our epidemiological investigations into the outbreak.

Notification

On 12 Oct 04, the Ministry of Health (MOH) was notified of two cases of cholera by the Department of Pathology, Singapore General Hospital (SGH). Both cases resided in Bedok and gave a history of having consumed a variety of food in Bedok five days prior to onset of illness. The first case developed repeated bouts of watery diarrhoea on 4 Oct 04 and was admitted to SGH on 7 Oct 04, while the second case developed similar symptoms on 6 Oct 04 and was admitted to Changi General Hospital on 7 Oct 04. Eight more cases, including a death case were subsequently notified.

Epidemiological investigations

Epidemiological investigation was carried out as soon as each notification was received. Information was obtained on the clinical symptoms, date of onset of illness, food items eaten, food establishments visited, medical treatment sought and other relevant epidemiological data. Active case detection for diarrhoeal illness among family members, workplace contacts and public food handlers in the implicated food establishments was conducted. Alert letters were also sent to medical practitioners in the Bedok area and they were asked to notify MOH of any suspected cholera cases immediately. Cases of diarrhoea detected through contact tracing were considered cholera suspects and referred to the Communicable Disease Centre (CDC) for further investigation.

The implicated food premises in Bedok and Tampines were inspected, raw and ready-to-serve food items as well as environmental swabs collected for microbiological analyses, and contacts and implicated foodhandlers sent to CDC for medical screening. As seafood was suspected, distributors of raw seafood items sold to the implicated eating establishments were traced. The National Environment Agency and Agri-Food & Veterinary Authority of Singapore were alerted to step up vigilance on food retail establishments and seafood import and distribution, respectively.

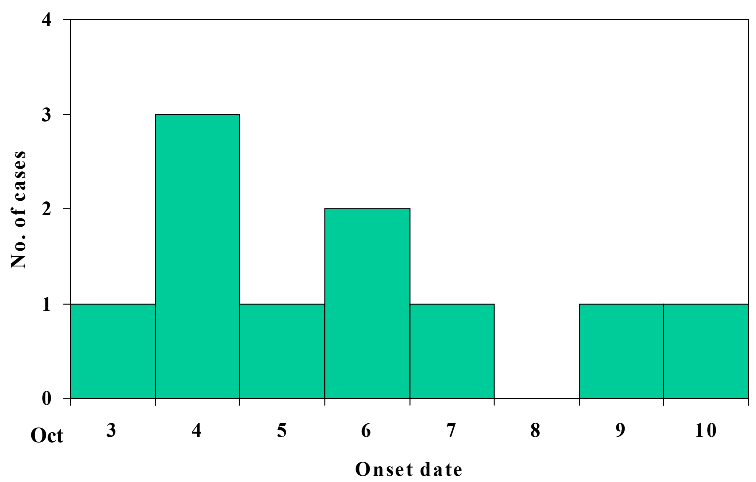
A case-control study was conducted using a standardised questionnaires form to determine the vehicle of transmission. A case of cholera was defined as a person who presented with symptoms of diarrhoea or vomiting from 3 -10 Oct 04 and in whom *Vibrio cholerae* O1, biotype El Tor, serotype Ogawa, was isolated from the stool or urine culture. Controls were chosen from asymptomatic household members whose stool or urine samples were tested negative for cholera organisms. Cases were interviewed on whether or not they had visited a list of food establishments and had consumed specified food items, in particular seafood, 5 days prior to their onset of illness. Controls were also asked identical questions within the same period.

Data from the questionnaires were analysed by SPSS base 12.0 (SPSS Inc., Chicago, IL). Chi Square and Fisher's Exact tests were used to determine significant differences between proportions. To quantify the extent of risk, we also computed the odds ratio, together with their 95% confidence intervals.

Results

A total of 10 cholera cases were confirmed with onset of illness between 3 - 10 Oct 04 (*Fig 14)*. The median age of the cases was 56 years (range: 20 years – 89 years) and 60% were females. The ethnic distribution of the cases was: Chinese (6 cases), Malays (3

Figure 14
Onset of illness of 10 reported cholera cases in Singapore, Oct 2004

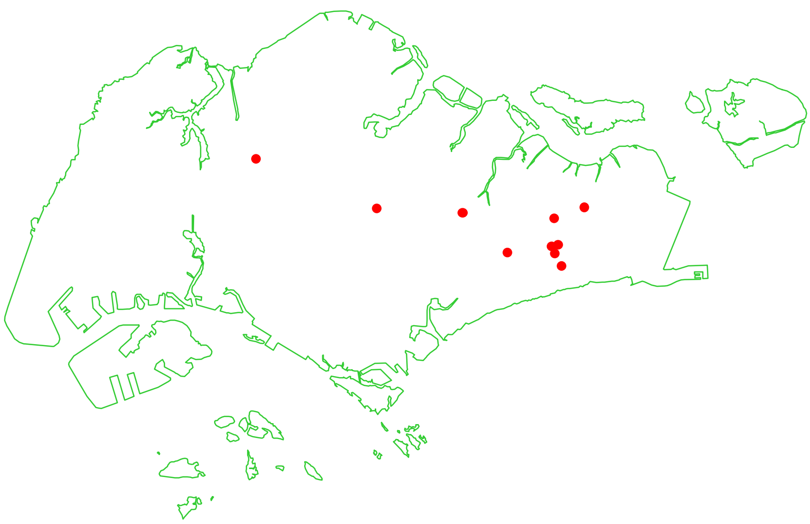


cases) and Thai (foreign resident)(1 case). The clinical symptoms were diarrhoea (90%), vomiting (50%), abdominal pain (40%) and nausea (20%). Nine cases were hospitalised, while one sought medical treatment from a general practitioner. *Vibrio cholerae* 01 was isolated from a 89-year-old Malay retiree with concurrent medical conditions who subsequently died. The cause of death was certified as 'acute renal failure secondary to diabetic nephropathy, contributing cause cholera'. Seven of the ten cases lived in Bedok and Tampines (*Fig 15*) and had taken their meals at Bedok. The remaining three cases (including the death case) were elderly patients with no known epidemiological links to Bedok.

Analysis of the case-control study did not implicate any specific eating establishments. Four specific cooked food items; viz. prawns in noodles, steamed prawns, cooked squid and fried fish were significantly associated with the illness (*Table 7*). In addition, three groups of seafood, namely fish, prawns and squids, were also implicated (*Table 8*).

Investigation into the preparation of seafood at the various implicated food establishments showed that there was no violation of food hygiene procedures. None of the food handlers in the food establishments frequented by the cases reported any recent episodes of gastroenteritis. None of the 271 food items and 22 environmental swabs taken from retail establishments and sent to the Food & Water Microbiology Laboratory, SGH, were positive for *Vibrio cholerae* O1, although a few samples were contaminated with *Salmonella, Vibrio cholerae* non-O1, *Vibrio parahaemolyticus, Staphylococcus aureus* and *Bacillus cereus*. Of 50 household contacts and 350 implicated food handlers referred to CDC for medical screening, the stool culture of one asymptomatic household contact was positive for *Vibrio cholerae* O1.

Figure 15
Residential locations of 10 reported cholera cases in Singapore, Oct 2004



Discussion

The epidemic curve for the ten confirmed cases was consistent with the pattern of a common source outbreak although its duration was longer than the known incubation period of cholera. A water-borne outbreak was excluded because such an incident tends to be explosive and many more cases would have been reported. Despite active case finding, no other case with an earlier onset date was identified. This showed that food contaminated at source rather than subsequently contaminated by an infected foodhandler had initiated the outbreak. The onset dates of the cases were between 3 and 10 Oct 04 and based on the known incubation period of 0.5-5 days, the period of exposure could be narrowed down to 2-5 Oct 04. The beginning of this period coincided with a weekend when majority of Bedok residents were likely to have dined out and done their marketing.

Investigations showed that virtually all the cases had consumed seafood in the five days prior to their onset of illness. However, no single food outlet or common prepared food item was identified. These findings increased the likelihood of raw seafood as the vehicle of transmission, and the inference was

Table 7

Association between consumption of specific cooked food items and cholera, Oct 2004

Food items	Case			Control			P value	OR	95% CI
	Ate	Did not eat	Ate %	Ate	Did not eat	Ate %			
Prawn in noodles	3	6	33.3	1	28	3.4	0.035	14.0	1.2-158.8
Steamed prawns	3	6	33.3	1	28	3.4	0.035	14.0	1.2-158.8
Cooked squids	4	5	44.4	2	27	6.9	0.020	10.8	1.5-75.7
Fried fish	7	2	77.8	9	20	31.0	0.023	7.8	1.3-45.1

NS = not significant

Table 8

Association between consumption of specific seafood and cholera, Oct 2004

Food items	Case			Control			P value	OR	95% CI
	Ate	Did not eat	Ate %	Ate	Did not eat	Ate %			
Fish	9	0	100	19	10	65.5	0.042	-	-
Prawn	6	3	66.7	5	24	17.3	0.009	9.6	1.8-51.9
Sotong/ Squid/ Cuttlefish	4	5	44.4	2	27	6.9	0.020	10.8	1.5-75.7
Shellfish (mussels, cockles, etc)	0	9	0	2	27	6.9	NS	-	-

NS = not significant

supported by the presence of both Chinese and Malay cases. Case-control study further implicated fish, prawn and squid. This finding of not one but three implicated groups of seafood, together with the fact they are not natural reservoirs of *Vibrio cholerae,* suggested that contamination had occurred either at source or subsequently along the chain of supply and distribution.

All raw sea catches into Singapore are delivered for wholesale to the two fishery ports at Senoko and Jurong. It is unlikely that the contamination had occurred at source delivered at either port because this would have led to an island-wide outbreak. On the retail end, the microbial findings confirmed that food handling practices were conducive to the spread of gastrointestinal infections.

Nonetheless, the wider distribution of cases showed that cross-contamination was more likely to have occurred prior to the point of retail. Hence, it is probable that a batch of seafood purchased by a fishmonger was contaminated during delivery on the way to Bedok. This is a known risk because a previous outbreak in Nov 1999 was traced to contaminated styrofoam ice boxes that had been used for transporting raw seafood[8].

Multiple neighbourhood food outlets were involved in this outbreak because it is a practice for fishmongers to subdivide lots obtained from the wholesale market, resulting in distribution of the produce to different locations. Stallholders in hawker centres are also known to buy their seafood from the neighbourhood wet market. *Vibrio cholerae* present in raw seafood would be killed if the food is cooked thoroughly. This could have been a reason for the absence of familial clusters among the reported cases. The extended tail of the epidemic curve can be explained by storage for a few days before the contaminated seafood was completely consumed. The period that *Vibrio cholerae* can survive in seafood is 2-5 days at room temperature (30-32^{O}C) and up to 9 days under refrigeration (5-10^{O} C)[9]. Sporadic occurrence of cases beyond Bedok could be expected as the contaminated seafood made its way through the eating establishments and some households. The three cases without specific links to Bedok were all elderly and it is likely that their relatives had not thoroughly cooked some contaminated seafood of unknown origin that was provided to them.

This outbreak highlighted a gap in the distribution chain among fishmongers. There is currently no clear accountability on the movements of seafood from the point it leaves the fishery port until the point it turns up in retail establishments. Some areas of improvement for the seafood industry would include better storage conditions of seafood during transportation, better traceability of seafood during distribution and maintenance of cold chain throughout the distribution system. In addition, food handlers and members of the public must be continually educated on the need to observe proper food and personal hygiene, to cook foods thoroughly, and as far as possible to avoid consuming seafood raw or partially cooked[9].

As part of outbreak management, the public were informed of the outbreak through press releases on 15, 18 and 27 Oct 04 and advised on the necessary precautionary measures. FAQs (Frequently Asked Questions) on cholera[10] were also posted on the MOH website. In line with the International Health Regulations, the World Health Organization was notified of the situation.

(Reported by Chan PP, Wong C, Yip R, Lim S, Ooi PL, Disease Control Branch, MOH)

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