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Tuberculosis surveillance in Singapore, 2006

The incidence rate of tuberculosis (TB) declined sharply from 307 per 100,000 population in 1960 to 56 per 100,000 in 1987. During the period 1987-1998, the incidence of new TB cases among Singapore citizens and permanent residents was fairly stable hovering around 50-55 per 100,000 population. Since then, the rate has shown a declining trend from 57 per 100,000 population in 1998 to 37 per 100,000 in 2005 and to its current rate of 34.8 per 100,000 in 2006 (*Fig. 1*).

During the year, there were 1,256 notified new cases of TB among Singapore residents. Majority (85.3%) of the cases had pulmonary TB (ie. TB of the lung parenchyma and included cases that had both pulmonary and extrapulmonary TB), the others (14.7%) were exclusively extrapulmonary TB. The most common site of extrapulmonary TB in males was the pleura (43 new cases); and in females, it was the lymphatic system (34 new cases). No case of TB meningitis was reported among Singapore residents below 15 years of age.

Age and gender distribution

As in previous years, TB continued to be mainly a disease of older males (*Fig. 2*). Of the notified cases, 691 (55.0%) were 50 years old and above, and 863 (68.7%) were males.

The TB incidence rates among males and females aged 80 years and above were 370.4 per 100,000 and 88.3 per 100,00, respectively. The rate for these elderly males was marginally lower compared to that of previous year (371.1 per 100,000). In the case of females, there was a marked reduction from 123.2 per 100,000 in 2005.

Figure 1
Incidence rate of tuberculosis among Singapore residents, 1960 – 2006

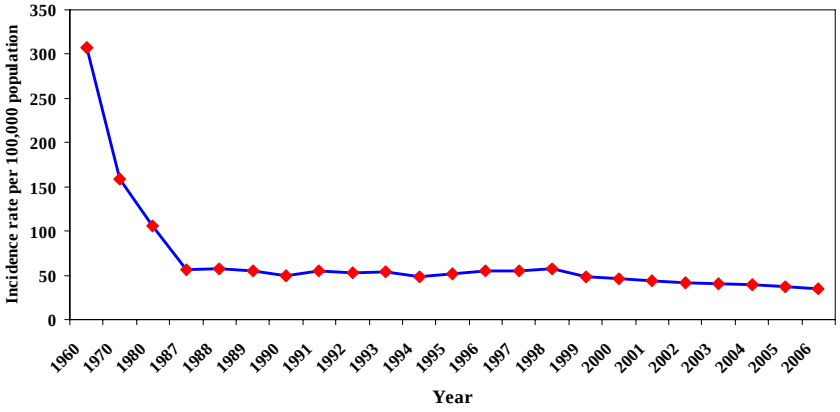
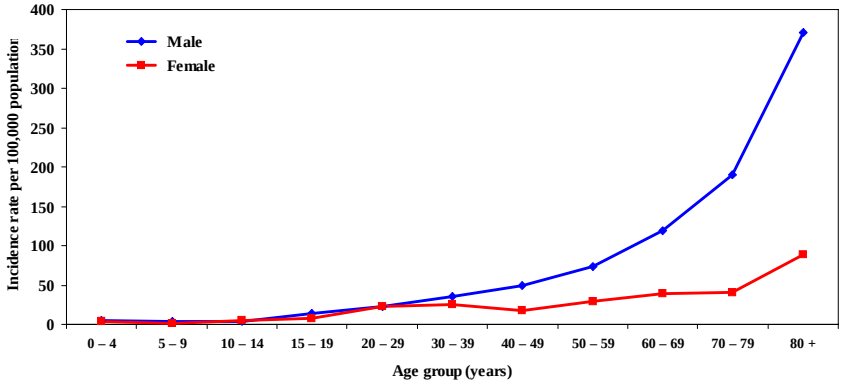


Figure 2
Incidence rates of reported tuberculosis by age and gender among Singapore residents, 2006



Ethnic distribution

The incidence rate among the Malays (50.4 per 100,000) was 1.5 times higher than that of the Chinese (33.0 per 100,000) and twice that of the Indians (23.8 per 100,000).

Clinical presentation and bacteriological status

Of the 1,071 newly notified Singapore residents with pulmonary TB, bacteriological tests were carried out on 1,034 (96.5%) cases. 85.6% were found to be bacteriologically positive.

Culture and drug sensitivity examination of *Mycobacterium tuberculosis* in sputum showed an increase in the incidence of single and multiple primary drug resistance among new TB cases in Singapore residents. In 2006, the overall drug resistance was 7.8%, with 5.5% (47 cases) being resistant to one drug and 2.4% (21 cases) being resistant to two or more drugs. Of the cases resistant to more than one

drug, three (0.3% of total examined) were multi-drug-resistant TB (MDRTB); i.e. resistant to at least rifampicin and isoniazid.

Relapsed TB cases

The number of relapsed TB cases notified among Singapore residents was 137 in 2006, the lowest number over the last 5 years. Most of these cases were seen in the older age groups and in the male population.

In 2006, of the 101 relapsed cases with pulmonary disease that had bacterial sensitivity tests done, 5 cases (4.9%) were resistant to one drug and 5 cases (4.9%) were resistant to two or more drugs, compared to 5.5% and 2.4%, respectively among the new cases. There were 3 cases of MDRTB, i.e. resistant to at least rifampicin and isoniazid.

TB in non-residents

TB among non-residents who were pass holders residing in Singapore (325 cases) and short-stay non-residents (391 cases) constituted 16.5% and 19.8%, respectively, of all new cases notified in 2006. Work permit holders constituted more than three-quarters of pass holders reported to have TB (251 cases), while foreign visitors made up over half of the number of short-stay non-residents with TB (216 cases). (Foreign visitors comprised those who came for medical treatment, those who come for medical consultation and were diagnosed to have TB, and those who fell ill with TB while on a social visit pass.)

TB mortality

There were 61 deaths from TB among Singapore residents giving a mortality rate of 1.7 cases per 100,000 population. The majority were males (68.9%) and those aged 60 years and above (78.7%). In 2006, TB accounted for 0.4% of all deaths in Singapore.

(Source: Tuberculosis Control Unit, Tan Tock Seng Hospital)

Editorial comments

The incidence of drug resistance to TB in Singapore remains low at less than 5% for previously untreated cases. Directly observed therapy (DOT) is recommended for all TB patients. Non-adherence because of adverse reactions and prolonged therapy is a major problem, as it leads to possible treatment failure and acquired drug resistance.

There are two forms of drug resistance: MDR-TB and XDR-TB. MDR-TB is a form of TB that does not respond to the standard treatments and is defined as TB resistant to the main first-line drugs, isoniazid and rifampicin.. XDR-TB occurs when there is resistance to all of the most effective anti-TB drugs, and is defined as TB with MDR-TB resistance as well as resistance to any one of the fluoroquinolone drugs and to at least one of the three injectable second-line drugs, amikacin, capromycin and kanamycin. In developing countries, multidrug resistance emerges when there is mismanagement of drugs and under-investment in quality TB control. Extensive drug resistance emerges through mismanagement of MDR-TB. The resistant strains can be spread from one person to another. Globally, there are an estimated 424 000 new cases of MDR-TB every year. The cost of treating MDR-TB can be 1000 times more than treating standard TB. WHO estimated that there are 25 000 to 30 000 new cases of XDR-TB every year. So far, 37 countries have confirmed cases of XDR-TB.

The world first became aware of XDR-TB in March 2006 after researchers reported on an emerging global threat of highly resistant TB strains. Concerns were heightened six months later by a cluster of 'virtually untreatable' XDR-TB cases in an area of South Africa with high prevalence of HIV. All but one of the 53 patients died in an average of 25 days after samples were taken for drug resistance tests. In May 2007, the case of an air passenger from the United States infected with XDR-TB also focused attention on the need to address the TB epidemic as an immediate international priority.

Reference

WHO News Release. WHO/32, 21 June 2007

Risk factors for tuberculosis mortality in Singapore

Introduction

Tuberculosis (TB) is still a major cause of death worldwide. According to the World Health Organisation (WHO), a total of 1.6 million people in the world died of TB in 2005[1]. Directly observed therapy (DOT) is recommended for all TB patients. Treatment outcome is important in assessing the performance of a national TB control programme[2,3].

Several studies have reviewed the mortality among tuberculosis patients as this is of relevant concern to the individual patients and doctors[3-6]. We undertook a study to identify possible risk factors for TB-associated mortality in patients diagnosed and treated for TB in Singapore for the period 2001-2004.

Methods

This was a retrospective cohort study which reviewed data obtained from the Tuberculosis Control Unit (TBC) in Singapore. The study population comprised patients notified and treated for TB between 2001 and 2004.

The Singapore Tuberculosis Elimination Programme (STEP) Registry provided data on TB patients notified and treated at all TB treatment centres in Singapore. Information was collected on demographics, dates of diagnosis and notification, treatment initiation dates, sputum and culture results, drug sensitivity tests, chest x-ray results, duration of treatment before death, and primary and secondary causes of death. Diagnoses were based on microbiological or histological evidence of TB or on the clinical judgment of the notifying physicians. The official cause of death was based on death certification by the Registry of Birth and Death and coded according to the ICD-9 codes.

Statistical analyses were performed using SPSS Software Version 13.0. The data was scrutinized for completeness and consistency. Differences in charac-

teristics of patients who died of TB and other causes were tested using the Chi-square test and Fisher's exact tests. A p-value of <0.05 was taken to indicate a significant difference. Univariate and multivariate logistic regression analyses were performed to identify risk factors associated with death due to TB.

Results

Between 2001 and 2004, there were 5898 patients notified and treated for TB within the same year. A total of 627 (10.6%) patients died. Of these, the official cause of death of 152 (2.6%) was TB (with ICD-9 death codes 010-1374), while the others were certified to have died from other reported causes. Of note, TB accounted for only a quarter of the deaths among the patients notified and treated for TB, followed by malignancy (20.1%) and pneumonia (15.0%). *Table 1* shows the distribution of TB patients who died each year during the period of review and *Table 2* lists the official causes of death. While most of the causes of death among the TB patients were also the principal causes of deaths for the total population in Singapore, TB was not ranked in the top 10 principal causes of deaths. Most of the patients who died of TB, as well as other causes of death, were aged 65 years and above (*Table 3*).

Table 4 shows the characteristics of patients who died due to TB and other causes. Of the 627 patients who died, 24.2% were due to TB and the remaining 75.8% due to other causes of death. According to the physicians' notifications, those who died of TB tended to suffer from co-morbidity other than the medical conditions listed on the notification forms MD532 and MD117 (i.e. diabetes, renal failure, steroid therapy, immuno-compromised state and cancer). This group was also more likely to have smear and culture results positive, cavity shown in their CXR and the duration from the commencement of TB treatment to death tended to last 8 weeks or less. The demographic and clinical characteristics of patients who died of TB and other causes were comparable with respect to gender, ethnic group, age at death, marital status, treatment status, pulmonary and extrapulmonary involvement and drug resistance.

Table 5 presents the results of the univariate and multivariate logistic regressions for association of death due to TB versus death due to other causes. Shorter time from commencement of treatment to death and positive smear and culture results were the strongest overall predictors for death due to TB, followed by absence of co-morbidity. These three predictors re-

Table 1

Distribution of TB patients who died from TB and other causes, 2001-2004

Year	No. of patients notified and started on TB treatment	No. of deaths due to other causes (%)*	No. of deaths due to TB (%)*
2001	1537	98 (20.6)	32 (21.1)
2002	1522	133 (27.9)	47 (30.9)
2003	1442	129 (27.1)	39 (26.3)
2004	1397	116 (24.4)	33 (21.7)

Note:

* These patients were Singapore residents who were notified and started on TB treatment within the same year. They were either new, uncertain, relapsed or reinstated cases; and had pulmonary, extrapulmonary or both pulmonary and extrapulmonary involvement.

Table 2
Reported causes of death among TB patients, 2003-2005

Type of disease	Number(%)*	Proportion of total deaths in Singapore in 2003 (%)	Proportion of total deaths in Singapore in 2004 (%)	Proportion of total deaths in Singapore in 2005 (%)
Tuberculosis	152 (24.2)	#	#	#
Malignancy	126 (20.1)	25.9	27.1	26.4
Pneumonia	94 (15.0)	14.6	14.1	14.9
Cerebrovascular disease	86 (13.7)	9.7	9.8	9.9
Cardiovascular disease	29 (4.6)	19.3†	18.8†	18.1†
Chronic obstructive pulmonary disease	22 (3.5)	3.3	3.1	3.5
Infection	16 (2.6)	#	#	#
Liver/Gastrointestinal disease	15 (2.4)	#	#	#
Diabetes mellitus	14 (2.2)	2.3	3.0	3.1
Renal disease	14 (2.2)	1.4‡	1.6‡	1.6‡
Others**	60 (9.6)	#	#	#

Note:
* Expressed as a proportion, with number of deaths due to TB or other causes as the numerator and no. of patients notified and started on treatment for TB as the denominator during the same year
** Includes venous thromboembolism, violent deaths etc
\# Not included in the top 10 prinicipal causes of death
† Ischaemic heart disease
‡ Nephritis, nephrotic syndrome and nephrosis

Table 3
Reported causes of death by age at death among TB patients

Cause of death	Age group (years)					Total
	25-34	35-44	45-54	55-64	65+	
Tuberculosis	3	5	18	25	101	152
Pneumonia	0	2	7	8	77	94
Malignancy	4	3	15	21	83	126
Cerebrovascular disease	0	0	6	14	66	86
Cardiovascular disease	1	0	2	4	22	29
Diabetes mellitus	0	0	1	4	9	14
Liver/ Gastrointestinal disease	1	3	2	3	6	15
Renal disease	0	0	1	3	10	14
Chronic obstructive pulmonary disease	0	1	1	4	16	22
lnfection	0	0	0	3	13	16
Others, incl violent death & VTE	4	17	9	12	17	59
All causes	13	31	62	101	420	627

VTE : venous thromboembolism

Table 4
Characteristics of TB patients who died due to TB and other causes

Characteristics	Death due to TB (n=152)	Death due to other causes (n=475)	*P**
Gender			
Male	124 (81.6%)	353 (74.3%)	0.08
Female	28 (18.4%)	122 (25.7%)	
Ethnic group			
Chinese	116 (76.3%)	393 (82.7%)	0.14
Malay	27 (17.8%)	55 (11.6%)	
Indian and others	9 (5.9%)	27 (5.7%)	
Age at death (years)			
25 — 34	3 (2.0%)	10 (2.1%)	0.75
35 — 44	5 (3.3%)	26 (5.5%)	
45 — 54	18 (11.8%)	44 (9.3%)	
55 — 64	25 (16.4%)	76 (16.0%)	
65 +	101 (66.5%)	319 (67.1%)	
Marital status			
Single	43 (28.3%)	102 (21.5%)	0.18
Married	93 (61.2%)	314 (66.1%)	
Divorced/Separated	6 (3.9%)	12 (2.5%)	
Widowed	10 (6.6%)	47 (9.9%)	
Treatment status			
New or uncertain	122 (80.3%)	401 (84.4%)	0.26
Relapsed or reinstated	30 (19.7%)	74 (15.6%)	
Presence of co-morbidity			
No	50 (32.9%)	97 (20.4%)	0.001
Yes – ≥1 specific condition**	60 (39.5%)	267 (56.2%)	
Yes – ≥ 1 other condition	42 (27.6%)	111 (23.4%)	
Number of sites			
1 site	137 (90.1%)	423 (89.1%)	0.77
> 1 site	15 (9.9%)	52 (10.9%)	
Pulmonary involvement			
Extrapulmonary only	9 (5.9%)	47 (9.9%)	0.23
Pulmonary only	131 (86.2%)	382 (80.4%)	
Both extrapulmonary and pulmonary	12 (7.9%)	46 (9.7%)	
Laboratory results			
Smear/Culture negative	20 (13.2%)	133 (28.0%)	<0.0005
Smear positive only	23 (15.1%)	59 (12.4%)	
Culture positive only	26 (17.1%)	140 (29.5%)	
Both smear and culture positive	83 (54.6%)	143 (30.1%)	
Drug resistance			
No	141 (92.8%)	452 (95.2%)	0.30
Yes	11 (7.2%)	23 (4.8%)	
CXR results			
No cavity	111 (73.0%)	390 (82.1%)	0.02
Cavity	41 (27.0%)	85 (17.9%)	
Time from treatment commencement to death			
≤ 8 weeks	111 (73.0%)	206 (43.4%)	<0.0005
> 8 weeks	41 (27.0%)	269 (56.6%)	

* Based on Fisher's exact test for binary variables and Chi-square test for other categorical variables.
** The specific conditions are diabetes, renal failure, steroid therapy, immuno-compromised state and cancer.

Table 5
Analyses of risk factors among TB patients who died from TB

Characteristics	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Gender						
Male	1.00	Referent		1.00	Referent	
Female	0.65	0.41 — 1.03	*0.07*	0.75	0.45 — 1.23	*0.25*
Age at death (years)			*0.76*			*0.81*
25 — 34	1.00	Referent		1.00	Referent	
35 — 44	0.64	0.13 — 3.20	0.59	0.63	0.11 — 3.60	0.60
45 — 54	1.36	0.34 — 5.54	0.67	1.02	0.22 — 4.66	0.98
55 — 64	1.10	0.28 — 4.30	0.90	0.72	0.16 — 3.15	0.66
65 +	1.06	0.29 — 3.91	0.94	0.69	0.17 — 2.82	0.60
Treatment status						
New or uncertain	1.00	Referent		1.00	Referent	
Relapsed or reinstated	1.33	0.83 — 2.13	0.23	1.33	0.79 — 2.25	0.29
Presence of co-morbidity			*0.001*			*0.003*
No	1.00	Referent		1.00	Referent	
Yes – ≥ 1 specific condition*	0.44	0.28 — 0.68	<0.0005	0.45	0.28 — 0.73	0.001
Yes – ≥ 1 other condition	0.73	0.45 — 1.20	0.22	0.80	0.47 — 1.38	0.42
Number of sites						
1 site	1.00	Referent		1.00	Referent	
> 1 site	0.89	0.49 — 1.63	0.71	1.80	0.38 — 8.43	0.46
Pulmonary involvement			*0.24*			*0.67*
Extrapulmonary only	1.00	Referent		1.00	Referent	
Pulmonary only	1.79	0.85 — 3.75	0.12	0.81	0.32 — 2.06	0.66
Both extrapulmonary and pulmonary	1.36	0.52 — 3.54	0.53	0.44	0.07 — 2.67	0.37
Laboratory results			*<0.0005*			*<0.0005*
Smear/Culture negative	1.00	Referent		1.00	Referent	
Smear positive only	2.59	1.32 — 5.08	0.01	1.94	0.92 — 4.12	0.08
Culture positive only	1.24	0.66 — 2.32	0.51	1.32	0.64 — 2.74	0.46
Both smear and culture positive	3.86	2.24 — 6.64	<0.0005	3.61	1.87 — 6.96	<0.0005
Drug resistance						
No	1.00	Referent		1.00	Referent	
Yes	1.53	0.73 — 3.22	0.26	1.56	0.68 — 3.60	0.30
CXR results						
No cavity	1.00	Referent		1.00	Referent	
Cavity	1.70	1.10 — 2.60	0.02	1.29	0.79 — 2.10	0.31
Time from treatment commencement to death						
≤ 8 weeks	1.00	Referent		1.00	Referent	
> 8 weeks	0.28	0.19 — 0.42	<0.0005	0.27	0.17 — 0.41	<0.0005

Overall p-values of the covariates are included in *italics*.
OR: Odds ratio
CI: Confidence interval
* The specific conditions are diabetes, renal failure, steroid therapy, immuno-compromised state and cancer.

mained in the multivariate model based on backward likelihood stepwise method (with p>0.10 for removal and p<0.05 for entry of variables, results not shown). With patients who had negative smear/culture results as the referent category, patients with smear result positive only, culture result positive only, and those with both smear and culture results positive were at increased risk of death due to TB with adjusted OR of 1.9 (95% CI 0.9—4.1), OR 1.3 (95% CI 0.6—2.7) and OR 3.6 (95% CI 1.9—7.0), respectively. Patients whose duration of commencement of TB treatment to death lasted more than 8 weeks were at a significantly lower risk of dying due to TB, with adjusted OR of 0.27 (95% CI 0.2—0.4).

It was observed that the risk of those who suffered from any of the medical conditions listed in the notification forms dying from TB was significantly lower (adjusted OR 0.4; 95% CI 0.3—0.7) compared to those who had no co-morbid conditions (referent category). This observation could be attributed partly to the fact that the likelihood of dying from other more serious co-morbid condition might be greater than death due to TB, in view of the competing risk of survival among patients with co-morbid conditions (including TB).

Comments

Our study showed that among TB patients, shorter time from commencement of treatment to death, positive smear and culture for *Mycobactrium tuberculosis*, and absence of specific co-morbidity were associated with an increased risk of death due to TB than other causes. These three risk factors remained significant after adjusting for various demographic and clinical characteristics, and may serve as useful indicators for prognosis of patients with TB.

There was evidence of a decrease in risk associated with death due to TB when the duration from treatment commencement to death was greater than 8 weeks. Hence, patients who had started on TB chemotherapy for less than 8 weeks and with positive smear and culture results should be carefully monitored.

In conclusion, regular review of the risk factors for mortality among TB patients could aid in the prognosis, patient care and treatment. Emphasis should be given to the crucial components of the TB control programme; ie. adherence to the full duration of treatment and ensuring that complete laboratory tests are carried out.

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

References

1. *World Health Organisation. Global tuberculosis control: surveillance, planning, financing. Geneva: WHO, 2007. Available at: www.who.int/tb/publications/global_report/2007/pdf/key_findings.pdf*
2. *World Health Organisation, Communicable Diseases Department. Treatment of tuberculosis: guidelines for national programmes. Third edition. WHO, Geneva, 2003. Available at: whqlibaoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng .pdf*
3. *Borgdorff MW, Veen J, Kalisvaart NA, Nagelkerke N. Mortality among tuberculosis patients in the Netherlands in the period 1993-1995.* Eur Respir J 1998*; 11:816-20.*
4. *Walpola HC, Siskind V, Patel AM, Konstantinos A, Derhy P. Tuberculosis-related deaths in Queensland, Australia, 1989-1998:characteristics and risk factors.* Int J Tuberc Lung Dis 2003*; 7:742-50.*
5. *Mathew TA, Ovsyanikova TN, Shin SS, et al. Causes of death during tuberculosis treatment in Tomsk Oblast, Russia.* Int J Tuberc Lung Dis 2006*; 10:857-63.*
6. *Caylà JA, Caminero JA, Rey R et al. Current status of treatment completion and fatality among tuberculosis patients in Spain.* Int J tubercu Lung Dis 2004*; 8:458-64.*

Is there a seasonal pattern for infectious diseases, including acute respiratory illnesses, in Singapore?

Introduction

Seasonality is a feature of infectious diseases common in temperate countries. Trend and seasonality are important aspects of disease manifestation as well as clues to the aetiology of diseases. Hence, we seek to understand whether seasonal patterns exist in selected infectious diseases, including acute respiratory illnesses, in Singapore which has a tropical climate with limited variation in temperature. The findings are important for enhanced surveillance and interventions of these infectious diseases.

Materials and methods

We did a retrospective study of monthly observations of selected infectious diseases, which included acute respiratory illnesses (ARI), chickenpox, hand-food-mouth disease (HFMD), dengue, melioidosis and mumps, aggregated from weekly polyclinic attendances for ARI, and MD-131 notifications for the other diseases during the 5-year period (2000 – 2004).

Time series analyses[1] were carried out using the multiplicative decomposition method. Different methods were used to study seasonal variability, which included Kruskal-Wallis test, one-way analysis of variance and R-square of first-order autoregression using Cochran-Orchutt method[2].

Results

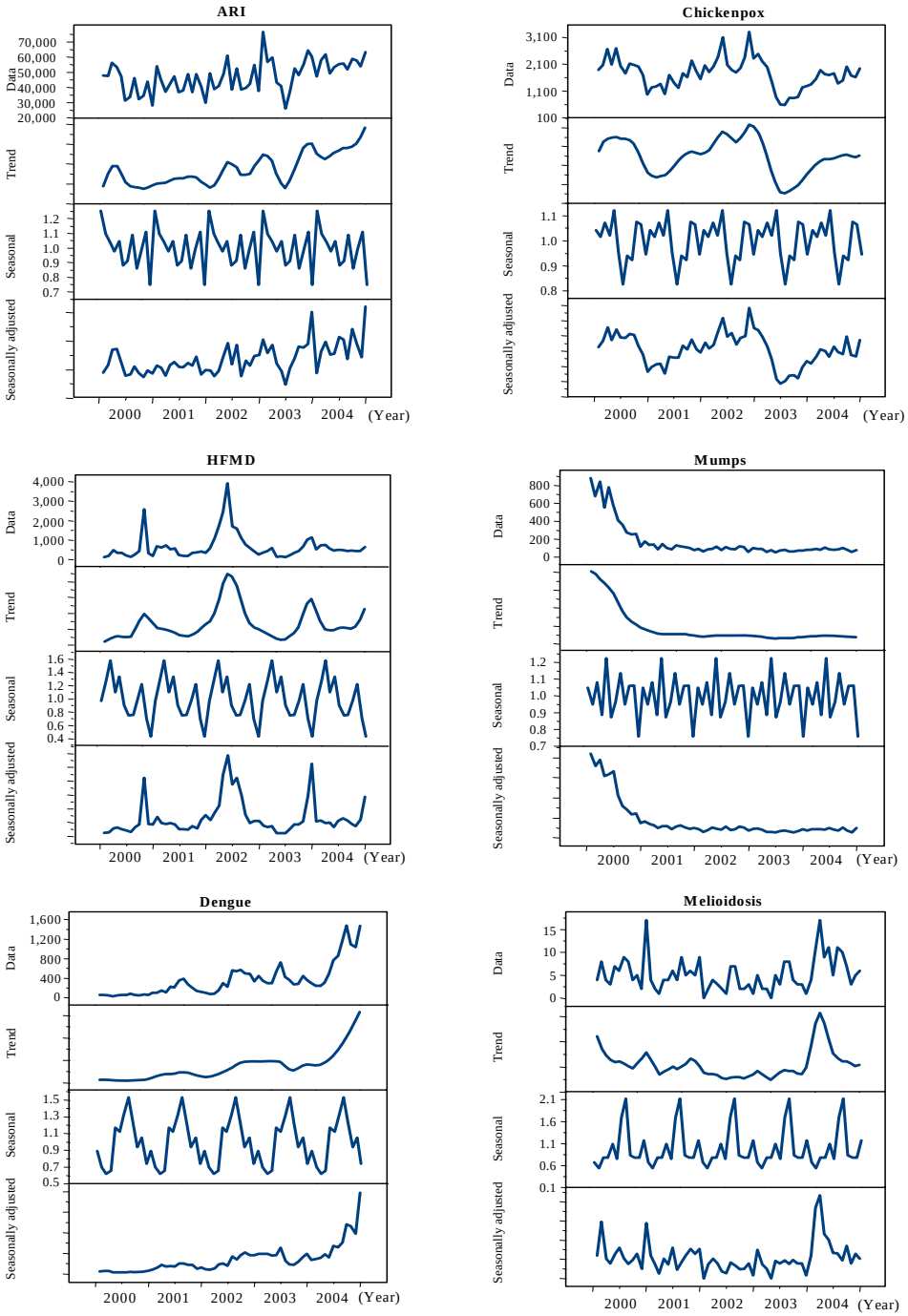
Fig. 3 shows the decomposition plots comprising a time series plot of the original data in the top panel followed by panels of the trend, seasonal factors and seasonally adjusted time series. Seasonally adjusted estimates were derived by removing the seasonal components from the original time series, so as to reveal the underlying non-seasonal features and hence this bottom panel represents the net effect of the underlying trend and irregular influences.

Some interesting patterns were observed for the trend panels, which provide some perspectives in the analysis and monitoring of the underlying direction of the specific infectious diseases. Polyclinic attendances for ARI depicted a rising trend during the period of review. Notifications for chickenpox reached a bimodal peak in year 2002 followed by a drastic drop in mid-2003. HFMD had similar pattern with one peak of different amplitude each year, with apparent outbreaks in years 2000 and 2002. Notifications for dengue rose at an exponential rate over the study period, while that of melioidosis followed a fluctuating trend and reached a peak in March 2004[3]. There was an outbreak of mumps in year 2000[4] and subsequently, the notifications were maintained at a fairly low level.

The seasonal panel showed that the normalized seasonal factor for all the diseases, including ARI, reached a trough in December except for melioidosis which climbed to a peak in the last month of the year. While seasonal factor of other diseases generally declined from January, that of HFMD showed an opposite pattern with subsequent increase from January. ARI and mumps also showed seasonal peaks in May,

Figure 3

Decomposition plots of 6 infectious diseases, including ARI



August and November, while dengue and melioidosis indicated a prominent unimodal spike in August. HFMD and chickenpox had the same seasonal peaks in March, May and October and seasonal troughs around mid-year and end of the year, which were the school holidays when contact among school-going age children were minimized.

The magnitudes of the seasonal factors (difference between the maximum and minimum seasonal factor in *Fig. 3*) were largest for melioidosis and HFMD, followed by dengue. *Fig. 4* shows the plots of median of monthly polyclinic attendances for ARI and MD-131 notifications for chickenpox, HFMD, dengue, melioidosis and mumps aggregated over the 5-year period, which corresponded somewhat to the observations of the seasonal factors. The movement from start to end of the study period for the 6 infectious diseases, including ARI, matched the observations made for the seasonal panel in *Fig. 3*.

In *Fig. 4*, the monthly aggregated time series over the 5-year period in terms of median indicated peaks in polyclinic attendances for ARI in March, August and November. Notifications for mumps showed a peak in May followed by a second peak in October. Notifications for melioidosis indicated a prominent unimodal spike in August while, dengue, a vector-borne disease, had 3 rising peaks. Conspicuous peaks in March and October were observed for HFMD and chickenpox with notifications reaching a trough around mid-year and end of the year.

Table 6 provides the results of statistical tests for seasonality of the 6 diseases, including ARI. Those with moderate and weak evidence of seasonality by Kruskal-Wallis test showed consistent findings with that of the stable seasonality test using one-way analysis of variance (ANOVA) on the de-trended series with month as a factor. The findings provided strong statistical evidence of seasonality for dengue.

The R-squared autoregression coefficients (R^2_{Autoreg}), the coefficients of determination of the autoregressive regression model fitted to the de-trended data, can be used for quantifying the strength of seasonality. The magnitude of R^2_{Autoreg} shows how well the next value can be predicted when the seasonal component is the only predictor. Based on the available interpretation for different values for R^2_{Autoreg}, values from 0 to less than 0.4 represent non-existent to weak seasonality, 0.4 to less than 0.7 moderate to strong seasonality, and 0.7 to 1 strong to perfect seasonality[2]. The R^2_{Autoreg} values of the 6 selected infectious diseases, including ARI, ranged from a high of 0.54 (mumps) to a low of 0.22 (HFMD). Mumps, dengue and ARI had a range of moderate to strong seasonality, while chickenpox, melioidosis and HFMD represented non-existent to weak seasonality.

Comments

The findings using the graphical representation and statistical tests indicated that among the 6 infectious diseases studied, seasonality was more apparent for dengue and mumps, followed by polyclinic attendances for ARI.

While the decomposition method enjoys conceptual simplicity, it assumes a "periodic" component for seasonality, that is, the same cycle occurs for each

Figure 4

Plots of median of monthly time series aggregated over the 5-year period for 6 infectious diseases, including ARI

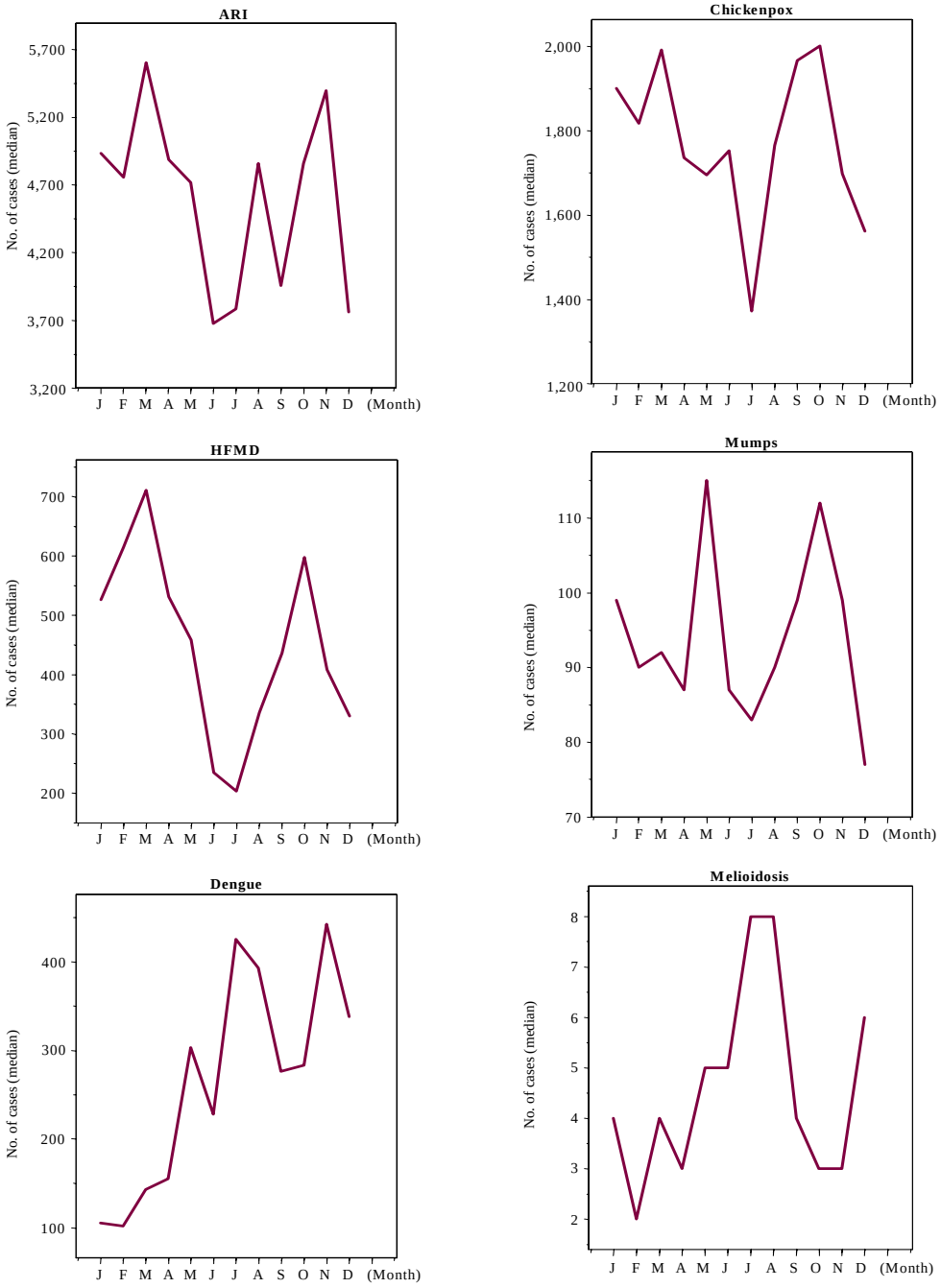


Table 6

Results of statistical tests for seasonality on the 6 infectious diseases, including ARI

Infectious diseases including ARI	Kruskal-Wallis Chi-square statistics* (*P*-value)	1-way ANOVA F statistics ** (*P*-value)	$R^2_{Autoreg}$
ARI	15.2 (0.18)	1.86 (0.08)	0.39
Chickenpox	10.3 (0.51)	1.04 (0.43)	0.36
HFMD	12.7 (0.32)	0.88 (0.57)	0.22
Dengue	25.7 (0.01)	3.89 (0.001)	0.49
Melioidosis	13.1 (0.29)	1.67 (0.12)	0.34
Mumps	17.4 (0.10)	2.10 (0.05)	0.54

* Kruskal-Wallis test is a non-parametric test, and the basis for the application of this test is that if the specific seasonals are purely random with no seasonality, their distribution should be the same in all seasons.

** One-way analysis of variance (ANOVA) is a parametric test applied here in addition to the Kruskal-Wallis test, as the tests for normality (i.e., Kolmogorov-Smirnov test and Shapiro-Wilk test of normality) on the de-trended time series showed that the distribution was normal for only ARI, chickenpox and mumps.

year of the series. Hence, a caveat is that the statistical tests used may fail to detect moving seasonality if the magnitude of seasonal factor changes over time. There is also a need to explore correlation of seasonal variation in the incidence of some infectious diseases, including ARI, with that of weather and environmental related factors, such as changes in temperature, humidity, moving calendar holidays, congregation of susceptible hosts, etc.

A retrospective study on acute respiratory viral infections based on laboratory reports for influenza viruses and other respiratory viruses showed seasonal variation in incidence for infections due to the influenza viruses, respiratory syncytial virus (RSV) and parainfluenzaviru type 1[5]. Another study had noted two seasonal peaks based on prospective laboratory surveillance for influenza viruses[6]. The existence of seasonal trends of acute viral respiratory infections was also demonstrated in a retrospective survey of laboratory virus isolation, serology and immunofluorescence microscopy[7]. Our time series analyses of polyclinic attendances for ARI includes influenza viruses, RSV, parainfluenzaviruses and other respiratory pathogens. Hence, if there are any seasonal patterns in these components of ARI which differ in their peaks and troughs, the overall seasonality would be attenuated when consolidated as one main group.

The focus on the seasonality of specific infectious diseases, including ARI, is important, as seasonal patterns provide a major pathway for the potentially drastic effects of climate changes and environmental driver on disease dynamics. In view of the above, further analyses will need to be carried out to address pertinent areas of concerns.

(Reported by Ang LW, Tun Y and Chow A, Communicable Diseases Division, Ministry of Health)

References

1. *Nicholas RF, LaVerne WS. Quantitative forecasting methods. Boston: PWS-Kent, 1989.*
2. *Moineddin R, Upshur RE, Crighton E, Mamdani M. Autoregression as a means of assessing the strength of seasonality in a time series. Popul Health Metr 2003;1:10-6.*
3. *Ministry of Health. Epidemiological investigations into an outbreak of melioidosis, Jan - June 2004. Epidemiol News Bull 2004; 30:24-8.*
4. *Goh KT. Resurgence of mumps in Singapore caused by the Rubini mumps virus vaccine strain. Lancet 1999; 354:1355-6.*
5. *Doraisingham S, Ling AE. Patterns of viral respiratory tract infections in Singapore: Ann Acad Med Singapore 1986;15:9-14.*
6. *Doraisingham S, Goh KT, Ling AE, Yu M. Influenza surveillance in Singapore: 1972-86. Bull W HO 1988;66:57-63.*
7. *Chew FT, Doraisingham S, Ling AE, Kumarasinghe G, Lee BW. Seasonal trends of viral respiratory tract infections in the tropics. Epidemiol Infect. 1998;121:121-8.*

Cervical cancer and human papillomavirus vaccine

Human papillomavirus (HPV) is one of the most common causes of sexually transmitted infection (STI) and the major cause of cervical cancer. More than half of all sexually active adults will become infected with HPV during their lifetime[1]. There are more than 100 different types of HPV, most of which are harmless. About 30 types of HPV are spread through sexual contact. Many people infected with HPV have no symptoms.

As with many viral diseases, infection with HPV will stay with the human host until it is eliminated by the host immune system. As such, HPV infection in many young females is usually transient and most will be eliminated by the age of 40-50 years old[2].

Although HPV infection usually resolves spontaneously, it may persist and precancerous cervical lesions may follow. If untreated, these may progress to cervical cancer over a period of 20 – 30 years.

HPV is divided into high-risk and low-risk categories. High-risk HPV may cause abnormal Pap smear results, and could lead to cancers of the cervix, vulva, vagina, anus, or penis. Low-risk HPV may also cause abnormal Pap smear results or genital warts. In general, about 10-20% of sexually active women are infected with the high-risk HPV[1].

About 70% of the high grade cervical dysplasia and cervical cancer are caused by HPV types 16 or 18 while more than 90% of genital warts are caused by HPV types 6 and 11. For cervical cancer, HPV 16 (the most common) accounts for 50%, HPV 18 about 20%, and the other HPV types about 30%.

Cervical cancer in Singapore

In Singapore, cervical cancer is the fifth most common cancer in females (5.3% of all cancers diagnosed in females) and was the sixth leading cause of

cancer deaths in females from 1998 to 2002 (4.9% all cancer deaths in females). The incidence of cervical cancer in Singapore has been consistently declining over the past 30 years. The annual incidence has dropped from 14.2 per 100,000 population (1993-1997) to 10.6 per 100,000 population (1998-2002)[3].

HPV vaccines

The first vaccine developed to prevent cervical cancer, precancerous genital lesions and genital warts in females is 'Gardasil' (manufactured by Merck). It is a recombinant quadrivalent vaccine that protects against four HPV types, HPV 6, 11, 16 and 18.

The vaccine was recommended by the U.S. Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) in June 2006 to be included in the Vaccines for Children Programs and it was recently licensed by the Food and Drug Administration (FDA) for use in female aged 9 to 26 years. The ACIP also recommended that the vaccine should not be given during pregnancy, but if pregnancy is detected after the vaccine has been given, the remaining doses of the series should not be given until the pregnancy is completed. This is due to the limited available data on vaccine safety for pregnant women and their developing fetus from studies conducted so far[1].

The recommended vaccine schedule is at month 0, month 2 and month 6 and the vaccine is to be administered intramuscularly. Studies in females aged 16 to 25 years have demonstrated 100% efficacy in preventing cervical precancer caused by the targeted HPV types. It has also been found to be almost 100% effective in preventing vulva and vagina precancers and genital warts that are caused by the targeted HPV types. For the full benefit of vaccination, the vaccine should be given to females before the onset of sexual activities, as the vaccine does not confer protection against disease due to HPV types already acquired prior to vaccination. The ACIP recommends it to be given to girls at age 11 or 12 years. The vaccine is proven to be safe. No vaccine related serious adverse event was reported and the most common side effect is brief soreness at the injection site[1].

A bivalent HPV vaccine, being developed by GSK, for protection against two types of HPV (16 & 18) is in the final stages of testing in females and may be available soon.

Concerns with the use of HPV vaccines

As for all new vaccines, it is not known at this moment the duration of protection against HPV and if a booster dose will be needed. Current studies indicate the vaccine is effective for at least five years. Since the vaccine does not protect against all types of HPV that cause cervical cancer, sexually active women who have been vaccinated still need regular screening with Pap smears. It is argued that if all sexually active women have regular Pap smears with proper follow-up, most cervical cancers could be prevented or detected early even without the use of a vaccine. Furthermore, it is not known if genotype replacement of cancer causing serotypes will occur following the commencement of vaccination[1].

Vaccinated women should continue to practise protective sexual behaviours because the vaccine will

not prevent all HPV types nor will it prevent other STIs. Parental acceptance for the use of a prophylactic vaccine against sexually transmitted virus for girls in their early adolescence and the optimal age for vaccination in different countries have to be determined[1].

At the moment, the usage of this vaccine is limited to females only. For boys, the vaccine has also been shown to be safe and immunogenic. Studies to determine if the vaccine is effective in preventing genital warts or anogenital cancers are being planned[1].

HPV vaccine use in Singapore

The HPV vaccine 'Gardasil' was approved for use in Singapore for females aged 9 to 26 years in December 2006. However, in view of the high cost of the vaccine, unknown duration of long-term protection, low disease burden from cervical cancer and the need for regular Pap smears (for sexually active females, first smear by age 25 years followed by three-yearly tests) despite vaccination, HPV vaccination for female adolescents for the prevention of cervical cancer has not been incorporated into the national childhood immunization programme in Singapore.

(Reported by Chan F, Communicable Diseases Division, Ministry of Health)

References

1. *Centers for Disease Control and Prevention. HPV and HPV vaccine: information for healthcare providers (content reviewed in June 2006). Available at http://www.cdc.gov/std/hpv/hpv-vacc-hcp-3-pages.pdf .*

2. *Tay EH. Human papilloma virus (HPV) & cervical cancer. The Singapore Family Physician 2005; 131: 18-21.*

3. *Seow A, Koh WP, Chia KS et al. Trends in cancer incidence in Singapore 1968-2002. Singapore Cancer Registry Report No.6, 2004.*

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Any comments or questions should be addressed to:

The Editor
Epidemiological News Bulletin
Communicable Diseases Division, Ministry of Health
College of Medicine Building, 16 College Road,
Singapore169854
E-mail : Goh_Kee_Tai@moh.gov.sg
Lyn_James@moh.gov.sg