Influenza surveillance in Singapore: 1972–86

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Prospective laboratory surveillance of influenza viruses has been carried out since 1973 in Singapore. The results indicate that antigenic shift variants caused epidemics at various times of the year over this period, whereas drift variants were associated with a regular increase in incidence during the second and fourth calendar quarters. Outbreaks due to influenza A virus occurred every year and to influenza B virus at intervals of 16–24 months. Between outbreaks, viruses belonging to either of the two types could be detected during most months, and certain variants appeared several months before the outbreaks they subsequently caused. The factors that contribute to the seasonal pattern are at present unknown.

The island of Singapore is a busy port situated at a crossroads of international air and sea travel. It has a total population of 2.5 million, an overall population density of 4000 persons per km², and a population of relatively young average age, a third of whom are less than 20 years old. These factors facilitate the importation and rapid dissemination of infections of the respiratory tract, so that influenza, not surprisingly, is one of the major viral diseases on the island.

There were apparently no notable outbreaks of influenza in the country between the end of the Second World War and the Asian influenza pandemic of 1957. Despite this, more than 80% of individuals tested during the pandemic in Singapore had antibody to influenza H1N1 virus, variants A/FM/1/47 and A/PR/8/34, indicating widespread circulation of these viruses in the population (1, 4). The H2N2 subtype caused an explosive epidemic of influenza in Singapore from May to June 1957, during which period the prototype influenza virus A/Singapore/1/57(H2N2) was isolated (1, 2). With the appearance of A/Hong Kong/1/68(H3N2) eleven years later, another major epidemic occurred in August 1968 (3–5).

Prospective surveillance for influenza has been carried out in Singapore since December 1973. Here, we describe the pattern of infection revealed by more than 14 years’ surveillance in this tropical, developing, and predominantly urban country.

MATERIALS AND METHODS

From October 1972 until December 1973 a study was carried out by the Department of Pathology in the Ministry of Health 5 and three private practitioners in Singapore to determine the incidence of influenza and β-haemolytic streptococcal infections in patients with acute pharyngitis. An average of 40 specimens were analysed each month. The findings indicated that the method could be useful for monitoring the incidence of influenza in the community, and when the study was completed in December 1973, prospective laboratory surveillance for influenza was begun. Throughout the year, 20–21 specimens for influenza virus isolation are collected weekly from patients with influenza-like symptoms attending government outpatient clinics. In the period 1973–82 two of the largest outpatient clinics in Singapore participated in the surveillance, but from September 1982 onwards this has involved three clinics in order to encompass a larger area of the island; seven specimens are sent for analysis from each clinic.

In addition, all specimens from patients with respiratory infections of suspected viral origin seen at hospitals and also, on occasion, specimens from cases with acute respiratory infections in army camps were included in the surveillance. The number of specimens varied considerably from 3 to 60 per month.

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Between 1973 and 1975, hens' eggs alone were used for virus isolation, but from 1975 to 1983 primary cynomolgus monkey kidney cells were also used. In 1983, Madin-Darby canine kidney (MDCK) cells replaced monkey kidney cells, which had become difficult to obtain.

Viruses were typed locally using antisera provided by the WHO Collaborating Centre for Reference and Research on Influenza, Atlanta, GA, USA, against prevailing influenza virus A and B strains. In addition, an average of 16% of the viruses isolated in a given year were typed by this Centre and the WHO Collaborating Centre for Reference and Research on Influenza in London, England.

From 1975 onwards, records have been maintained of weekly attendances of patients with acute respiratory infections at government polyclinics. An influenza outbreak was confirmed when an increase in the proportion of positive isolates coincided with an increase in outpatient attendances for acute respiratory infections, while the severity of the outbreak was measured by the number of influenza-pneumonia deaths reported to the Registrar of Births and Deaths.

RESULTS

Chronological appearance of the various antigenic variants

From May to July 1972 an epidemic of influenza in Singapore was caused by the variant A/England/42/72(H3N2) (Fig. 1). Four out of 16 isolates obtained during the epidemic were typed by the WHO Collaborating Centre for Reference and Research on Influenza, London, as being related to this strain. A second wave of infection due to the same virus occurred from October 1972 to March 1973. A/England/42/72-like viruses continued to be isolated until November 1973 when they were replaced by a new variant, A/Port Chalmers/1/73(H3N2), which was isolated from five patients in November and December of that year.

After laboratory surveillance was begun in December 1973, it was noted that a regular increase in influenza infection occurred every year in Singapore, the pattern usually being bimodal (Fig. 1). The first and major seasonal increase occurred from April to June and extended usually into July, while the second increase was during the last quarter and sometimes continued into the beginning of the next year. Outbreaks of influenza A occurred every year, while those of influenza B were spaced at intervals of 16–24 months, usually immediately preceding or following outbreaks of the A virus (6). Between outbreaks, the two types were frequently sporadically isolated.

The monthly distribution of influenza viruses isolated from 1972 to 1986 together with the corresponding attendances of patients with acute respiratory infections at government polyclinics from 1975 to 1986 are shown in Fig. 1. The major antigenic variants of influenza virus A that appeared in Singapore from 1972 to 1986 are shown in Fig. 2, which was plotted largely using data from the two WHO Collaborating Centres. The time of appearance of a variant was always (and that of its disappearance was usually) determined by reports from these Centres. The results of the strain-typing by the local laboratory were used to fill in gaps in the data from the two Collaborating Centres.

Influenza virus A/Port Chalmers/1/73(H3N2), which was first detected in November 1973, caused an epidemic from May to July 1974 in Singapore. At its peak in June, 1,500 new cases were seen daily at government polyclinics, and an associated increase in influenza-pneumonia deaths was also noted (7). A total of 79 isolates of type A virus were made during the epidemic, 7 of which were typed by the WHO Collaborating Centre in London. A second wave of infection, caused by the same virus, began in November 1974 and continued into the first quarter of 1975.

Throughout 1975, isolation rates of influenza A/H3N2 viruses were relatively high, with peaks from April to June and from October to December. A/Port Chalmers/73 was detected throughout the year, and in April, together with A/Scotland/840/74(H3N2) and intermediate strains. Another new variant, A/Victoria/3/75(H3N2), was first isolated in July, then repeatedly during the last quarter of 1975 when a third variant, A/England/864/75(H3N2), which is related to A/Texas/1/77, was also detected. Type B infection surged in July 1975 with the decline in that of type A, three isolated viruses being characterized as intermediate strains that showed some antigenic drift from B/Hong Kong/5/72.

A/Victoria/3/75(H3N2), which was first detected in July 1975, caused a major epidemic from April to June 1976 in Singapore. At its peak in May, 3,000 new cases were seen daily at government polyclinics, and a concomitant increase in influenza-pneumonia deaths was also noted (7). Of a total of 114 isolates obtained during the epidemic, nine were characterized by the WHO Collaborating Centre in London as A/Victoria/75-like. Following the epidemic, there was minimal influenza activity for the rest of 1976.

A/Victoria/75, A/Texas/77, and strains related to B/Hong Kong/5/72 were responsible for the seasonal increase in infection from April to July 1977. However, 1977 was marked by the re-emergence of the H1N1 subtype, and A/USSR/90/77(H1N1) was isolated in November of that year. Outbreaks due to this virus first began among national servicemen in a number of army camps in mid-December, but rapidly spread to the rest of the popu-
Fig. 1. Monthly distribution of influenza viruses in Singapore, 1972–86. (a) Number of outpatient attendances according to virus type. (b) Proportion of positive isolates according to virus type.

In 1978 the expected increase of influenza cases in the second quarter was not observed. Instead, another H1N1 outbreak occurred in September and October, viruses related to A/USSR/90/77 and A/Brazil/11/78(H1N1) being responsible.

Influenza B was dominant in 1979, and a major epidemic from April to June was caused by a new variant, B/Singapore/222/79, which was isolated from a 3-month-old infant in March of that year. Predominantly children and young adults under 25 years of age were affected. With the decline in type B infection in June 1979, type A surged, and the viruses isolated were related to A/Texas/77. During the last quarter of this year both H1N1 and H3N2 viruses co-circulated.
A/Texas/1/77(H3N2), the most persistent variant during the study period (Fig. 2), was responsible for most of the infection in the second quarter of 1980, while A/Philippines/2/82(H3N2) (first detected in July 1982) caused outbreaks in the third quarter of 1984 and the second quarter of 1985.

Successive H1 viruses (A/Brazil/11/78, A/England/333/80, A/Chile/1/83, and A/Singapore/6/86) caused outbreaks during the second or fourth quarters of 1980, 1981, 1983, and 1986 (Fig. 1).

Between April 1982 and December 1986, influenza B infection surged at approximately 18-month intervals in Singapore. In general, strain characterization of viruses responsible for such outbreaks was less satisfactory than that for outbreaks caused by influenza A virus because isolates of the B virus survived transportation to the Collaborating Centres only poorly and a representative number could seldom be recovered on each occasion.

**Age distribution of patients**

The age distribution of patients from whom influenza viruses were isolated during outbreaks between 1974 and 1986 is shown in Fig. 3. Type H1 outbreaks occurred in 1977, 1978, and 1986; type H3 in 1974, 1976, and 1985; and B infections in 1975, 1977, and 1979.

Data from the 1980 population census were used to calculate age-specific isolation rates, this year being chosen because it fell mid-way between 1974 and 1986. The number of isolations made during individual outbreaks was too small for annual rates to be calculated. Instead, rates were calculated using the age distribution of the whole population rather than that of outpatients who visited the government polyclinics, since detailed information about them was unavailable and hospitalized cases were also included.

The highest isolation rates for both type H1 and H3 viruses occurred among the 0–4-year and 15–24-year olds. While rates for H1 infections fell off sharply for those aged above 25 years, for H3 infections they declined only among those aged above 55 years. Peak rates for influenza B infections occurred among 5–14-year olds and declined rapidly among those older than 35 years.

During the outbreaks caused by A/Victoria/75 in 1976, B/Singapore/79 in 1979, and A/Singapore/86 in 1986, more isolates of influenza viruses were made among infants aged <2 years than at other times from 1972 to 1986.

**Clinical features**

The majority of isolates of influenza viruses in the surveillance study were from outpatients with acute respiratory infections. Hospitalized patients contributed usually between 0% and 21% (mean 8.5%) of the positive isolates obtained during successive outbreaks. The single exception to this occurred during the A/Singapore/6/86(H1N1) outbreak from March to May 1986, when 65% of the isolates were made from infants who had been hospitalized with febrile convulsions.

Variants A/Port Chalmers/1/73(H3N2), A/Victoria/3/75(H3N2), and B/Singapore/222/79 were more frequently associated with complications than other variants that appeared in Singapore between 1974 and 1986. An increase in the number of deaths from influenza–pneumonia by more than 50% occurred during the epidemics caused by these two influenza A viruses (7). Complications, which were both respiratory as well as non-respiratory, were recorded predominantly among children in the 0–4-year age range.
group: these included pneumonia, bronchiolitis, croup, myositis (seen only with influenza B infections), myocarditis, febrile convulsions, and encephalopathy (6-8).

During the period of surveillance the following influenza viruses were isolated after post-mortems of three patients: in March 1973, subtype H3N2 virus from the brain of a 42-year-old male; in October 1978, subtype H1N1 virus from the brain of a 20-year-old male who had been hospitalized with acute psychosis; and in May 1984, subtype H1N1 virus from the intestine of a 19-year-old male who died of gastroenteritis with dehydration.

**DISCUSSION**

The results of the prospective surveillance of influenza in Singapore indicate that, as in temperate zones, the infection occurs seasonally also in Singapore. However, two seasonal peaks occur in Singapore, a pattern also seen in Malaysia (S. K. Lam, personal communication, 1982). While antigenic shift variants such as A/Singapore/57, A/Hong Kong/68, and A/USSR/77 caused epidemics at different times of the year, with rare exceptions, drift variants gave rise to regular outbreaks during the second and fourth quarters of each year during the study period.

Seasonal outbreaks of influenza occurred against a background of almost year-long transmission. This has become more evident since 1982 when immunofluorescence microscopy was introduced in Singapore for the rapid diagnosis of influenza, positive isolates being made between outbreaks from hospitalized children.

The viruses responsible for most of the infection in the first seasonal peak of a given year usually differed from those that dominated in the second; certain variants could, however, be detected several months before they caused major outbreaks. This occurred, for example, with A/Port Chalmers/73 and A/Victoria/75, both of which were associated with "herald-wave" infections during the fourth quarter of one year, before causing a major epidemic in the second quarter of the following year. A/Texas/77 and A/Philippines/82 were also detected over a period of several months before they caused significant outbreaks.

From 1973 to 1986 influenza activity was lowest during the third quarter of the year, at which time infection with respiratory syncytial (RS) virus peaked. This virus, like influenza virus, is also associated with a seasonal increase in infection in Singapore, the peak occurring during the second half of the year (6). An especially prolonged outbreak of RS virus infection occurred from July to December 1985, during which period influenza virus was only occasionally detected (by immunofluorescence microscopy). Interference between outbreaks of RS virus infection and influenza has been reported previously (10, 11).

The reason for the seasonal pattern of influenza infection is unclear. Temperatures remain relatively constant throughout the year in Singapore. December and January are the coolest months when, for the period 1973-85, mean monthly temperatures ranged from 24.8 °C to 26.6 °C. May and June are usually the warmest months and over the same period the mean monthly temperature ranged from 26.4 °C to 28.2 °C. The first and major seasonal peak occurred during the warmest period of the year and the second, during the "coolest".

November and December are usually the wettest and January to March the driest months of the year. However, the relative humidity is high throughout the year, and from 1973 to 1986 was in the range 83-91% in November-December, and 79-89% in April-June. It should be noted that this is inconsistent with the finding of Hemmes et al. that influenza viruses in aerosols become inactivated more rapidly at high relative humidities (9). The only climatic feature that appears to be related to the pattern of influenza infection is that the first and major seasonal outbreak (April-June) is regularly preceded by a period when daily fluctuations in temperature are greatest (Y.C. Chan & T.W. Wong, personal communication, 1987). Possibly these fluctuations, like chilling in cold climates, may have a detrimental effect on the host's defense mechanisms.

Although Singapore is a busy air- and seaport, the influenza seasons appear not to be affected by fluctuations in the number of visitors to the country. The monthly average of approximately 250 000 visitors increases by about 12% in August and December but not immediately before the onset of the seasonal peaks in influenza outbreaks.

The age distribution of laboratory-confirmed cases of influenza was generally similar to that of such cases in temperate countries: H1N1 viruses were infrequently isolated from patients over 25 years of age, while influenza B infection peaked among schoolchildren.

Like Hong Kong, Singapore is a densely populated and busy port, and influenza variants introduced into (or arising in) the population would spread more efficiently here than in less populous areas. This and possible climatic factors ensure a higher rate of transmission throughout the year than in temperate regions of the world. The sampling of small numbers of suspected cases (100-130 per month) is therefore usually sufficient for the detection of circulating viruses. City-ports like Singapore are ideal global sentinels for the detection of new antigenic influenza variants.
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RÉSUMÉ

SURVEILLANCE DE LA GRIPPE À SINGAPOUR: 1972–1986

Une surveillance prospective de la grippe, consistant en une mise en culture de 20 prélèvements par semaine provenant de cas suspects ambulatoires a été mise en place à Singapour en décembre 1973. Les prélèvements de malades hospitalisés atteints d’infections respiratoires aiguës ont également été mis en culture.

Des examens de laboratoire ont montré que des variants par casseur antigénique tels que A/Singapour/1/57(H2N2), A/Hong Kong/1/68(H3N2) et A/URSS/90(H1N1) provoquaient des épisodes en toutes saisons mais que les variants par glissement antigénique étaient associés à une augmentation saisonnière régulière de l’incidence de la grippe au cours des deuxième et quatrième trimestres de l’année civile, la principale flambée étant celle du deuxième trimestre. Des flambées dues au virus grippal A ont eu lieu chaque année, tandis que les flambées dues au virus grippal B survenaient à intervalles de seize à vingt-quatre mois. Entre les flambées, des virus appartenant à l’un ou l’autre type étaient détectés tout au long de l’année par isolement et, plus récemment, par immunofluorescence.

Pour une année donnée, les virus responsables de la majeure partie des infections de la première flambée saisonnière diffèrent habituellement des virus de la deuxième flambée. Toutefois, certains variants ont pu être détectés plusieurs mois avant une flambée majeure; par exemple, les variants A/Port Chalmers/1/73(H3N2) et A/Victoria/3/75(H3N2) ont été associés à de petites flambées "annonciatrices" au quatrième trimestre d’une année avant de provoquer des épisodes importants au deuxième trimestre de l’année suivante. Le variant A/Texas/1/77(H3N2), le mieux conservé pendant toute la période couverte par la surveillance, et le variant A/Philippines/2/82(H3N2), ont également pu être détectés longtemps avant d’être à l’origine d’une flambée importante.

Les raisons de l’apparition saisonnière de la grippe à Singapour sont peu claires. Les conditions climatiques varient peu au cours de l’année et l’hygrométrie reste élevée pendant les deux flambées saisonnières; toutefois, la principale saison grippale, au deuxième trimestre de chaque année, est précédée d’une période de fortes variations diurnes de la température de l’air. Les augmentations saisonnières sont en revanche sans rapport avec les variations de l’afflux de visiteurs étrangers.

Il existe une interférence entre les infections par le virus respiratoire syncytial (VRS) et la grippe. L’incidence de la grippe est en effet la plus faible au cours du troisième trimestre, période à laquelle culminent les infections à VRS.

Le répartiion par âge des malades présentant des isolements positifs était analogue à celle qu’on observe dans les régions tempérées. Les taux d’isolement des virus H1N1 et H3N2 étaient les plus élevés chez les 0–4 ans et les 15–24 ans tandis que le virus grippal B frappait principalement les 5–14 ans. Les virus H1 n’étaient que rarement isolés chez les sujets de plus de 25 ans et les virus grippaux B, chez les sujets de plus de 35 ans. Certains variants antigéniques, tels que les variants A/Victoria/75(H3N2), A/Singapour/86(H1N1) et B/Singapour/79, ont été isolés plus fréquemment que les autres chez les enfants de 0–2 ans. Les variants A/Port Chalmers/73(H3N2), A/Victoria/75(H3N2) et B/Singapour/79 entraînent davantage de complications que les autres variants, notamment chez l’enfant.

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